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JOURNAL OF DRUGS IN DERMATOLOGY

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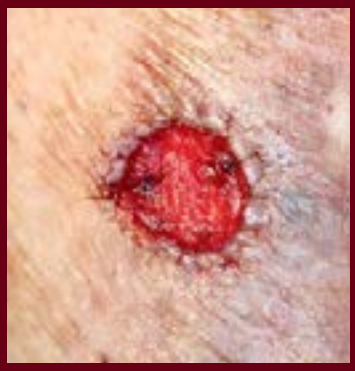

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Single Center, Observational Experience With a Bovine Collagen Wound Dressing for Distal Lower Extremity Surgical Defects

Jenna Wald MD, Mihir Shah MD, C. William Hanke MD MPH

Laser and Skin Surgery Center of Indiana, Indianapolis, IN

ABSTRACT

Background: Biologic dressings help treat many dermatologic conditions. Their use in dermatologic surgery continues to expand as new dressings are developed.

Objective: To discuss the authors' experience with a bovine-derived collagen wound dressing in surgical defects on the distal lower extremity.

Methods and Materials: Over a 9-month period, 24 surgical defects in 20 patients were treated with a bovine-derived collagen wound dressing. All surgical defects were located below the knee. The average defect was 6.9 cm^2 (range 1.0 - 18.0 cm^2). The mean duration until healing completion was 117.3 days (range 63-183).

Results: The treated surgical defects demonstrated shortened healing time, improved cosmetic outcome, decreased wound drainage, and decreased pain compared with that traditionally seen in second intention healing. Bovine-derived collagen wound dressings should be considered to facilitate the healing of surgical defects on the distal lower extremity that would otherwise be left to heal by the second intention.

J Drugs Dermatol. 2023;22(12):1149-1152. doi:10.36849/JDD.5404

INTRODUCTION

Surgical treatment, with Mohs micrographic surgery (MMS) or standard surgical excision, is the standard of care for nonmelanoma skin cancers and primary cutaneous melanomas.[1,2,3] The surgical defects created by tumor extirpation may range from a few millimeters to several centimeters. Depending on the defect size, location, and cosmetic goals of the patient, repair options include second intention healing (SIH), primary closure, skin flaps, and skin grafts. In addition, a plethora of biologic dressings have been introduced over the last 40 years to facilitate healing, with variable evidence supporting their use.

Many skin cancers develop on the distal lower extremities and feet, especially in fair-skinned individuals who have had heavy sun exposure. Surgical defects in these areas are often difficult to close primarily and pose a reconstructive conundrum. For patients with poor skin quality, older age, limited skin laxity, or vascular disease, more conservative approaches such as SIH may be appropriate. SIH has many advantages, including reduced initial procedure time, avoidance of secondary wound or larger surgical site, smaller scar due to contraction, and better cosmetic and functional outcomes when compared with full-thickness skin graft.[4]

SIH is an easy, low-cost repair option that should be considered for surgical defects of the distal lower extremity, but it does have disadvantages that include prolonged healing and wound care and the risk of postoperative bleeding.[4,5] Because of these limitations, placement of biologic dressings should be considered for patients who would otherwise undergo SIH.

Biologic dressings (also known as skin substitutes or biologic skin substitutes) are helpful for healing burns, chronic wounds, blistering diseases, and postsurgical defects. The dressings are designed to accelerate wound healing by replacing components of the extracellular matrix.[6] They are categorized as composite, dermal, or epidermal, and can be further divided based on their origin. The ever-expanding variety and availability of biologic dressings have led to multiple review articles and exploration of their utility in acute surgical wounds.[6-18] Biologic dressings are reported to decrease postoperative pain and healing time compared with SIH; however, most lack controlled trials to

verify these findings.[7,11] The most common limitations of their use are the high cost, storage, and shelf life.[6,7]

Through experience with various biologic dressings, the authors have found the microscaffold™ collagen wound dressing (Puracol®; Medline Industries, Inc; Mundelein, IL) to be a useful biologic dressing in SIH due to the long shelf-life, affordability, ease of use, and clinical results. Clinically it has been shown to decrease wound drainage, shorten healing time, and decrease pain in chronic wounds.[13,14] Its use has additionally been described in post-surgical scalp defects, including defects with exposed calvarium, and was shown to decrease healing time compared with SIH.[15] We have successfully used the bovine-derived collagen wound dressing (BCWD) in various locations and find it particularly helpful in facilitating SIH of the distal lower extremity, an area with a traditionally prolonged healing course. We present a single center, observational experience of the use of BCWD in lower extremity surgical defects that would otherwise have been healed by SIH.

MATERIALS AND METHODS

Puracol® (Medline Industries, Inc; Mundelein, IL, USA) is a 100% pure native bovine-derived microfibrous type 1 collagen sponge in its native triple-helix format; it is comprised of 88.4% collagen.[19] It is indicated for use in full- and partial-thickness wounds, pressure and venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, burns, donor sites, cuts and abrasions, surgical wounds, and dehisced wounds.[20] Contraindications include known sensitivity to collagen and wounds with active vasculitis.[18] It is available in 5.1 cm x 5.1 cm, 10.2 cm x 10.8 cm, and 20.3 cm x 20.3 cm sheets. Its shelf life is 3 years and it costs ~$5 to $40 per BCWD depending on the size.

Surgical defects were created by treatment of cutaneous malignancies with excision or MMS. The sterile BCWD was stored at room temperature. Immediately prior to application, the BCWD was hydrated in room temperature sterile saline for < 1 minute. The BCWD was draped over the surgical defect as a single layer to ensure complete coverage. If extra dressing allowed for the surgical defect to be covered more than once, the BCWD was folded on itself. Surgical defects were completely covered with 1 to 4 layers of BCWD until the defect was filled or the BCWD was completely used up. The number of layers was determined by the depth of the surgical defect and the excess amount of BCWD. The edges were trimmed so that the BCWD would not extend beyond the defect. All BCWD were secured with 4-0 or 5-0 chromic gut. Post operative wounds were treated as a skin graft (1 week of application of petroleum jelly only, followed by gentle cleansing and petroleum jelly with non-stick dressing) or covered with an Unna boot. Patients were encouraged to elevate their leg when resting and wear compression stockings as tolerated.

RESULTS

All patients with a surgical defect treated with a BCWD on the lower extremity during a 9-month period (July 12, 2018, through April 11, 2019) were followed through their healing course. A total of 25 patients were identified. Five patients were excluded due to the inability to follow healing completion. Of the 20 patients with follow-up, 4 had 2 surgical defects treated with a

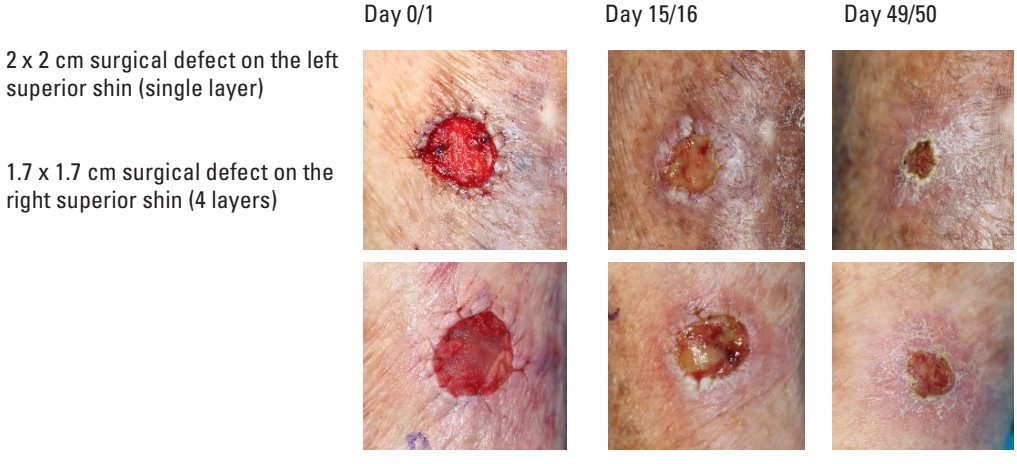
TABLE 1.

Patient Demographics		
	N=20	
Age, mean years	77.2	(Range 34-91)
Gender		
Female	17	85%
Male	3	15%
Impaired wound healing		
Tobacco Use		
Former/Never	19	95%
Current	1	5%
Diabetes	3	15%
>1 surgical defect treated	4	20%

TABLE 2.

Surgical Defects Treated		
	N=24	
Location		
Foot	6	25%
Distal Lower extremity	18	75%
Defect Size (mean cm²)	**6.9**	**(Range 1.0-18.0)**
Follow-up		
Number of visits (mean)	4.1	(Range 1-13)
Duration (mean days)	117.3	(Range 63-183)
Treatment Course		
Antibiotics		
Prophylactic	21	87.5%
> 1 course	5	16.7%
Pain medication	0	0%
Incorporation	24	100%
Unna boot		
Yes	9	37.5%
Number of applications (mean)	4.3	(Range 1-13)
Follow-up visits (mean)	6.4	(Range 3-13)
Follow-up duration (mean days)	116.1	(Range 14-182)
No	15	62.5%
Follow-up visits (mean)	2.7	(Range 1-5)
Follow-up duration (mean days)	118.0	(Range 63-178)

FIGURE 1. Surgical defects on the bilateral superior anterior shin of a 91-year-old woman treated with bovine-derived collagen wound dressing. The left leg was treated with a single layer of the dressing. The right leg was treated with 4 layers of the dressing. The right was treated 1 day prior to the left. Follow-up at days 0 and 1, 15 and 16, and 49 and 50 respectively.



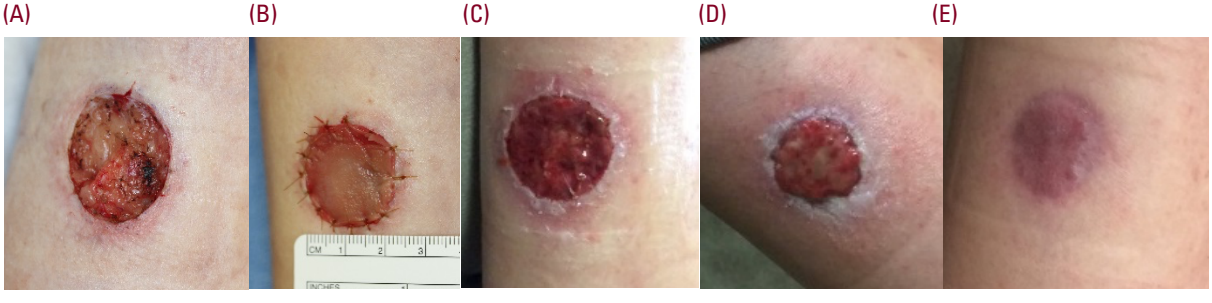
BCWD. The surgical defects treated with a BCWD would have otherwise been allowed to heal by SIH. Patients were selected due to concern for poor wound healing, cosmetic outcome, healing time, and overall healing experience. The total number of surgical defects treated with BCWD was 24.

All surgical defects were located on the distal lower extremity or foot and extended to the subcutaneous fat. The average defect was 6.9 cm^2. Patients were followed until completely healed, as demonstrated by scar with no granulation tissue, eschar, erosions, or crusting. The mean duration until healing was 117.3 days (N=14, range 63-183 days). The mean number of follow-up visits was increased in patients who were treated with Unna boots (6.4 vs 2.7); however, the mean duration of follow-up between patients treated with Unna boots and traditional wound care was similar (116.1 vs 118.0). Factors influencing Unna boot application included the presence of edema, concern for infection, inability to care for the wound, and patient preference. All patients were given prophylactic antibiotics for 7 days unless contraindicated; 5 patients received a second course of antibiotics despite no evidence of active infection due to patient concern. Two patients reported pain throughout healing, which correlated with increased physical activity or prolonged standing; though no patients required prescription pain medication. All BCWD were fully incorporated into the healing wound. (Table 2)

In the authors' experience, all treated defects healed at a faster rate than is seen with SIH, but additional studies are needed to better quantify this finding. A single patient with 2 surgical defects on the bilateral superior shins was treated by application of 1 and 4 layers of BCWD to the respective defects. There was no variability noted throughout the healing process (Figure 1); this suggests that the number of layers may not alter the healing course. Two patients demonstrated excessive granulation tissue that was treated with silver nitrate or removed via shave biopsy to exclude recurrence. Factors that appeared to increase the healing rate included the use of Unna boots and compliance with compression.

Physician and patient impressions throughout the treatment course were that patients experienced limited to no pain throughout healing. Surgical defects treated with BCWD healed at a more rapid rate than traditionally observed in

FIGURE 2. A 34-year-old woman with a surgical defect to the subcutaneous fat treated with bovine-derived collagen wound dressing. The surgical defect is shown before (A) and after (B) dressing placement, and at 14 days (C), 42 days (D), and 98 days (E) post-operatively.



SIH with excellent cosmetic outcomes (Figure 2). Although few patients were concerned about infection due to slight inflammation, likely due to the chromic gut suture, no patients demonstrated evidence of active infection. Patients reported and demonstrated little or no wound drainage compared with that seen in SIH. Furthermore, the Unna boot application allowed for approximately equivalent healing time in patients who traditionally heal at a slower rate.

DISCUSSION

Biologic dressings are useful tools in dermatology for many different conditions. As new dressings continue to emerge, the role of their use in dermatologic surgery has been increasingly explored. Collagen is a key component of wound healing and is a component of many biologic dressings including dermal xenogenic, dermal allogenic, and composite dressings.[7,8] Its popularity in wound healing has led to its commercial availability as partially purified skin, collagen sponges, fibers and powders, composite dressings, and hydrolyzed collagen.[21] Pure collagen dressings absorb exudate prevent desiccation and inhibit wound breakdown by sequestering matrix metalloproteases.[14] Pure collagen xenografts, such as the BCWD used, are beneficial because they are incorporated into the wound.[14,19] This feature limits wound manipulation from dressing removal and allows for repeated application as needed.[19] This also results in a less morbid clinical course with equal, if not superior, aesthetic outcomes to SIH. Multiple bovine collagen dressings have been successfully used in the management of surgical defects.[12,15,17,18]

We present a successful experience of a BCWD facilitated SIH of surgical wounds on the distal lower extremity. In the authors' opinions, the 24 surgical defects treated with the BCWD demonstrated less drainage, decreased pain, and shortened healing time, which is consistent with reports of other bovine collagen products shown to similarly shorten healing time and improve the healing experience.[12,13,15,17,18] The concurrent use of Unna boots facilitated healing, as would be expected, but increased the number of visits.[22]

CONCLUSION

In conclusion, the BCWD appears to be a well-tolerated biologic dressing. It facilitates wound healing with acceptable aesthetic outcomes. We observed shortened healing time, good cosmetic outcome, decreased wound drainage, and decreased pain compared with that seen in SIH. Additional studies are needed to better quantify and verify the change in the duration of healing as well as patient experience during the healing process. The use of biologic dressings prevents the creation of morbidity associated with the secondary surgical defect of a skin graft or skin flap while providing wound protection. Additionally, it is a feasible treatment because it is relatively inexpensive, stored at room temperature, and has a long shelf-life, which makes it suitable to keep on hand. Its use should be considered to augment healing in surgical defects on the lower extremity that would otherwise heal by secondary intention.

DISCLOSURES

This article has no funding source. The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

International Dermatology Outcome Measures (IDEOM): Report From the 2022 Annual Meeting

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ABSTRACT

Background: The International Dermatology Outcome Measures (IDEOM) is a non-profit organization dedicated to the advancement of evidence-based, consensus-driven outcome measures in dermatological diseases. Researchers and stakeholders from various backgrounds collaborate to develop these objective benchmark metrics to further advance treatment and management of dermatologic conditions.

Summary: The 2022 IDEOM Annual Meeting was held on June 17-18, 2022. Leaders and stakeholders from the hidradenitis suppurativa, acne, vitiligo, actinic keratosis, alopecia areata, itch, cutaneous lymphoma, and psoriatic disease workgroups discussed the progress of their respective outcome-measures research. This report summarizes each workgroup's updates from 2022 and their next steps as established during the 2022 IDEOM Annual Meeting.

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INTRODUCTION

International Dermatology Outcome Measures (IDEOM) is a non-profit organization founded in 2013. IDEOM's mission is to establish patient-centered outcome measures within dermatology through consensus-driven efforts.[1] Such outcome measures greatly benefit healthcare providers and researchers in determining patient progress and appropriate treatments in addition to healthcare payers in determining optimal payment policies. Therefore, IDEOM offers a unique opportunity for key patient, physician, industry, government, and insurer stakeholders to contribute to the establishment of such outcome measures.

To best achieve IDEOM's mission, IDEOM has created workgroups dedicated to a number of dermatologic conditions. The workgroups are composed of key stakeholders in psoriasis, psoriatic arthritis (PsA), hidradenitis suppurativa (HS), acne, vitiligo, actinic keratosis (AK), alopecia areata (AA), itch, and cutaneous lymphoma. The methodology followed by the workgroups is informed by evidence-based resources published by Outcome Measures in Rheumatology (OMERACT), Core Outcomes Measures in Effectiveness Trials (COMET), and COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN) initiatives.[2,3] These

initiatives assist in determining what disease domains should be measured (selection of core domain) and how to measure these domains (instrument selection/development).[4,5]

Each year, individual IDEOM workgroups convene to present progress updates and engage in focused discussions to collaborate on ongoing projects and determine future directions. In this report, we summarize the progress made by each IDEOM workgroup as presented at the 2022 IDEOM Annual Meeting (Table 1).

WORKGROUP UPDATES

Psoriatic Disease – Treatment Satisfaction Workgroup

Vibeke Strand MD and April Armstrong MD presented on the development of the Psoriasis and Psoriatic Arthritis Treatment Satisfaction Instrument. The instrument was created to evaluate patients' satisfaction with a therapy used to treat both their psoriasis and PsA given that PsA occurs in approximately 30% of patients with psoriasis.[6]

The Psoriasis and Psoriatic Arthritis Treatment Satisfaction Instrument is based on the DermSat-7 questionnaire. It retains the DermSat-7 questions pertaining to a treatment's ability to treat psoriasis and improve skin appearance and symptoms. Additionally, the instrument evaluates patients' satisfaction with a treatment's effectiveness at reducing tenderness, swelling, redness, stiffness, and pain related to PsA. Nominal discussions with patients, patient association representatives, dermatologists, rheumatologists, and industry partners were held to refine the syntax of analogous PsA questions to ensure questions were clear and applicable to patients. Patient and non-patient stakeholders agreed it was necessary to distinguish how a treatment improves physical functionality specifically related to PsA (ie, increased ability to use one's hands, walk, and/or climb stairs). All respondents were supportive of the instrument assessing patients' overall satisfaction with a therapy's ability to treat their psoriasis, PsA, and both psoriasis *and* PsA. The next step is further evaluation of the proposed instrument by IDEOM physicians, methodologists, and patients.

Psoriatic Disease – Psoriatic Arthritis Workgroup

Joseph Merola MD MMSc and Lourdes Perez-Chada MD MMSc presented the status of the development of the IDEOM Musculoskeletal Questionnaire (IDEOM MSK-Q), a measurement tool to assess musculoskeletal (MSK) symptoms in patients with psoriatic disease. The content validity (ie, relevance, comprehensiveness, and comprehensibility) of the IDEOM MSK-Q was evaluated in a multi-phase pilot testing study: (1) an online survey distributed to patient-research partners with psoriatic disease, (2) a discussion of survey results and voting on steps to improve content validity among key stakeholders at the IDEOM 2021 Annual Meeting, (3) further content validity assessment via 3-step test interviews among patients with psoriatic disease, (4) targeted questionnaire evaluation via survey polling and discussions with key stakeholders at this IDEOM 2022 Annual Meeting, (5) and final interviews with patients with psoriatic disease to confirm data saturation. Content validity assessment results were largely reaffirming. There were no concerns related to relevance; however, participants offered suggestions for improving comprehensiveness (eg, include an item about joint swelling), general comprehensibility (eg, layout format), and item-specific comprehensibility (eg, item wording). The IDEOM MSK-Q consists of 9 items organized into 3 subscales: Intensity of MSK symptoms (pain; joint swelling; joint stiffness), Impact of MSK symptoms (work and/or school activities; family, social, and/or leisure activities; physical activity; sleep; emotional state), and Intensity of fatigue. The instrument is currently being validated in multiple settings.

Acne Workgroup

The Acne Core Outcomes Research Network (ACORN) workgroup, led by Diane Thiboutot MD, discussed the overall progress to date within each of the 6 core domains: Satisfaction with Treatment, Satisfaction with Appearance, Health-related Quality of Life (HrQOL), Signs and Symptoms, Long-term Control and Extent of Scars and Dark Marks.

Systematic reviews using the COSMIN criteria have been completed for Satisfaction with Treatment and Health related Quality of Life. No instruments measuring treatment satisfaction were deemed suitable based on COSMIN criteria according to Jerry Tan MD.[7] However, the Acne-Q and Comprehensive Acne Quality of Life Scale (CompAQ) were found to be validated to a sufficient standard to support recommendations for consideration as measures for acne-associated quality of life ("A" grade). The Acne-specific Quality of Life (AcneQoL) and Acne Symptom and Impact Scale (ASIS) could be considered with additional evaluation of content validity as reported by John Barbieri MD MBA.[8]

The workgroup's systematic review of Satisfaction with Appearance is nearly complete. Twenty-two scales have been identified; however, it is uncertain as to whether they are well-suited for acne. Thematic analysis revealed that negative self-image, negative self-concept/belief, and self-consciousness/self-conscious emotions were predominant. The next steps are to elicit patient input on scaled and conduct patient-focused interviews on relevant aspects relating to satisfaction with appearance.

For each of the 3 remaining domains, additional preliminary discussions are needed before conducting systematic reviews. For example, Jonette Keri MD PhD raised the question as to whether a systematic review for both scars and dark marks should be conducted or if these should be separate reviews. A preliminary assessment of the volume of available literature

TABLE 1.

Workgroup Updates and Overview From the 2022 IDEOM Annual Meeting

Workgroup	Aim(s)	Presenter(s)	Key Discussion Points	Action Plan
Psoriatic Disease - Treatment Satisfaction	Develop an instrument to measure patient treatment satisfaction for psoriasis and psoriatic arthritis	Vibeke Strand MD April W. Armstrong MD MPH	Overview of the Psoriasis and Psoriatic Arthritis Treatment Satisfaction Instrument Revision of PsA-specific questions following nominal discussion amongst stakeholders	Hold additional nominal discussions with IDEOM physicians, methodologists, and patients to further evaluate the proposed instrument
Psoriatic Disease - Psoriatic Arthritis	Develop an instrument to measure musculoskeletal symptoms in patients with psoriatic disease	Joseph F. Merola MD MMSc Lourdes Perez-Chada MD MMSc Alice B. Gottlieb MD PhD	Overview of the IDEOM Musculoskeletal Questionnaire (IDEOM MSK-Q) created for patients with psoriatic disease Presentation of the multi-phase pilot study evaluating the content validity of the instrument	Validate the IDEOM MSK-Q in multiple settings among patients with psoriasis and/or psoriatic arthritis
Acne (ACORN)	Develop multiple core outcome sets (ie, appearance/ treatment satisfaction, long term acne control, HrQOL, extent of scars and dark marks) for use in acne clinical trials	Diane Thiboutot MD	Overview of ACORN's work to date Systematic reviews completed or in process on satisfaction with appearance, satisfaction with treatment and HrQOL	Conclude ongoing study to evaluate measurement properties of HrQOL instruments and DermSat
Vitiligo	Identify core domains for use in vitiligo Develop core outcome sets (ie, HrQOL, repigmentation) for use in vitiligo	Nanette Silverberg MD David Rosmarin MD FAAD	Overview of Vitiligo's work to date Stakeholder discussion to refine a core domain group and intake information pertinent to domains	Further evaluate core domains for potential inclusion Establish proprietary intake forms
Actinic Keratosis	Develop multiple core outcome sets (ie, treatment satisfaction) for use in AK	Richard Torbeck MD	Overview of AK's work to date, specifically on the AK treatment satisfaction instrument Discussion to further refine the existing questionnaire	Design study to validate the AK treatment satisfaction questionnaire
Alopecia Areata (AAROW)	Establish areas of unmet needs in alopecia areata Identify core domains for use in alopecia areata	Arash Mostaghimi MD MPA MPH	Overview of systematic review of current outcome measures used in alopecia areata clinical trials Stakeholder discussion to articulate the goals of the workgroup	Integrate European colleagues into workgroup Perform DELPHI study to determine potential gaps in current management and identify a core set of domains
Hidradenitis Suppurativa	Develop multiple core outcome sets for use in HS	Antonio Martorell MD PhD Tarannum Jaleel MD Samuel Williams BA	Overview of HS's work to date, specifically with the Telehealth, Tape-strip Biomarker Diagnosis, and Tunnel Immunology/Scarring projects Discussion to refine Novartis HS screening tool Stakeholder dialogue on integrating telehealth into HS standard-of-care	Further develop telehealth standards-of-care Conduct DELPHI survey to identify key disease outcome measures Hold virtual meeting in preparation for Scarring workgroup's progressor biomarker study
Itch	Establish areas of unmet needs in itch Identify core domains for use in itch Improve awareness of pruritic disorders	Sonja Ständer MD	Overview of Itch workgroup's work to date Discussions on definition of itch and areas of unmet need in chronic nodular prurigo	Collaborate on and devise new definition of itch
Cutaneous Lymphoma Quality of Life (CL-QL) Consortium	Establish areas of unmet needs in CTCL Identify core domains for use in CTCL	Cecilia Larocca, MD Michi M. Shinohara MD	Overview of the CL-QL's work to date Identification of research priorities, potential barriers to core outcome set development, need for additional resources to facilitate expansion, and importance of early engagement of healthcare providers and patients	Develop educational programs on the importance of PROMs Stakeholder collaboration for core outcome set development

on these topics will be conducted to help determine if there should be a single review or 2 separate reviews. Preliminary discussions with providers and patients are needed to agree on definitions of long-term control.

In collaboration with Dr. Armstrong, the ACORN workgroup has also incorporated the DermSat-7 in its ongoing study to assess measurement properties of CompAQ, Skindex-16, and DermSat-7 in acne patients on isotretinoin. This study will include a patient global assessment and the Comprehensive Acne Severity Scale (CASS) IGA.

Vitiligo Workgroup

Nanette Silverberg MD and David Rosmarin MD led the vitiligo workgroup. The IDEOM vitiligo workgroup is a growing, new workgroup and is currently seeking to further expand its membership. Workgroup projects this year include completion of a literature review of scoring systems used to assess vitiligo in articles reporting topical corticosteroid and topical calcineurin inhibitor therapies. This has been written up for publication and presented at the Revolutionizing Vitiligo (ReV) Conference. During the 2022 breakout session, the vitiligo workgroup refined a core domain group and intake information pertinent to these domains. The following core domains met 75% consensus threshold: health-related quality of life, extent of depigmentation, treatment satisfaction including treatment burden, location, color matching, and maintenance of pigmentation. Two domains (comorbidities and subtyping) only met 50% threshold and will be further refined for potential inclusion. These core domains, agreed upon by workgroup members, were presented at the 2022 ReV Conference.

In the interim, the workgroup is working on the core domains that met inclusion via stakeholder voting during the 2022 ReV Conference and the intake parameters and forms related to these core domains. In the next year, the workgroup plans to address core domains previously used in systemic medication trials and produce its proprietary intake forms addressing patient parameters of mutual concern to the patient-practitioner-industry triad.

Actinic Keratosis Workgroup

The actinic keratosis (AK) workgroup was led by Richard Torbeck MD and Daniel M. Siegel MD. After the group discussion, changes were made to 2 of the AK treatment satisfaction instrument questions. Since there are no injectable treatments for AK, the word "injection'' was removed from the question regarding treatment convenience. In the question *How bothered are you by the out-of-pocket cost of this treatment for your actinic keratosis?*, the phrase "out-of-pocket costs" was replaced with "impediment to treatment" to broaden the scope of the question.

Given AK is a chronic disease that should be treated repeatedly, the 2 following questions were added to the instrument: (1) *If your doctor told you that you need another therapy course, would you do this again?* and (2) *Would you be willing to do this 2-4 times a year?* Additionally, since the questionnaire did not capture cosmetic outcomes, the workgroup decided to add the question: *Did your treatment make you look better?*

The next step is to design a study to validate the questionnaire. The workgroup discussion focused on when the patients should be surveyed. The workgroup decided that patients will be surveyed at 3 timepoints: (1) immediately after starting treatment, (2) 1 month after initiating treatment, and (3) 3 months following treatment completion to assess long-term overall satisfaction with the treatment.

Alopecia Areata Workgroup

Arash Mostaghimi MD MPH and Aaron Drucker MD led the meeting of the Alopecia Areata core Outcomes Working group (AAROW). The primary objective of the meeting was to present preliminary data on a systematic review of current outcome measures used in AA clinical trials, which demonstrated substantial heterogeneity in both the quality and utilization of existing measures. Group discussions including key stakeholders from industry focused on the need for creation of measures that enable consistent evaluation of individual lesions of hair loss to facilitate clinical trials for localized therapeutics. The next steps for the workgroup include integration of European colleagues and performance of a DELPHI survey to determine potential gaps in current management and to identify a core set of domains.

Hidradenitis Suppurativa Workgroup

At the 2022 hidradenitis suppurativa workgroup, workgroup leaders discussed their progress with telehealth, tape-strip biomarker diagnosis, and tunnel immunology/scarring. All 3 research groups had made significant progress and were in different stages of analysis of results and expansion of projects. Antonio Martorell MD PhD presented on the Scarring group's study that aims to characterize tunnel progressor biomarkers during the progression from dermal to dermoepidermal, complex scarring tunnels.[9-10] Tarannum Jaleel MD led the Best Practices in TeleHealth group and presented the successes and challenges of implementing telehealth in a busy HS clinic. Samuel Williams MD reported on the progress made by the Tape-Stripping Biomarkers project in patient recruitment and sample collection to find new biomarkers of disease activity using a non-invasive sample without need for biopsy.

In the breakout section, the workgroup discussed a Novartis screening tool for patients and providers to use to help diagnose HS or provide useful background information on

disease progression. Stakeholders provided suggestions to the company for improving this intake form to better address issues important to providers and patients. The workgroup also discussed the potential benefits of telehealth visit integration into HS standard-of-care given the cyclical nature of disease flares and the limited availability of dermatology appointments. Some of the next steps identified at the meeting included further development of telehealth standards of care and identifying domains that are important to patients and clinicians using a DELPHI survey. Additionally, the Scarring workgroup will be hosting a virtual meeting to define the materials and methods for its study to analyze progressor biomarkers. The study will evaluate the main triggers of scarring tissue development given that the different ultrasound, genetic, epigenetic, microbiologic, and cytokine tunnel profiles may explain both scarring proliferation and different therapeutic outcomes observed in clinical assays.

Itch Workgroup

Sonja Ständer MD presented updates from the Itch Workgroup Steering Committee. The IDEOM itch group was founded in 2021 to identify barriers to recognition of chronic pruritic disorders as disease entities and to enhance itch awareness in all stakeholder groups. Itch is the most common symptom in dermatology and approved therapies are a highly unmet need. To enable high quality randomized controlled trials, validated instruments for itch measurement are needed. These instruments are still in development, and it is one aim of the itch group to support this process.

Stakeholders discussed how the definition of itch, the unpleasant sensation leading to the desire to scratch, dates back to 1660 and does not capture the complexity of the sensation.[11,12] Nowadays, definitions of sensory symptoms consist of information related to symptoms and disease stage as well as emotional and causal attributes. This is largely missing in the current itch definition. The sensory facets of itch were discussed, and it was decided to work on a new definition that will account for itch as its entity.

The workgroup also discussed chronic nodular prurigo (CNPG). CNPG is a neuroimmune disease with severe itch and multiple pruriginous nodules.[13] As lesions persist for many years and patients scratch continuously, CNPG is a model disease for the itch-scratch-cycle. The patients are highly burdened and effective therapies are largely missing. In the breakout sessions, working fields for this entity were identified and consisted of clinical phenotypes, the severity definition and scoring instruments.

In terms of next steps, a group composed of all stakeholders shall be formed involving patients and representatives from itch and pain societies to collaborate on a new definition of itch. The workgroup plans to assemble participants in several DELPHI conferences and publish its new definition in 2024.

Cutaneous Lymphoma Quality of Life (CL-QL) Consortium

Cecilia Larocca MD and Michi M. Shinohara MD led the cutaneous lymphoma quality of life (CL-QL) workgroup session. The CL-QL steering committee outlined tasks for key projects, which will lay the foundation for the development of a core outcome set (COS) of patient-reported outcome measures (PROMs) for cutaneous T-cell lymphoma (CTCL) research. Stakeholders provided feedback on potential barriers to COS development and resource allocation. The following research priorities were identified: (1) systematic literature review (SLR) of existing qualitative studies and quantitative studies to identify candidate domains related to the concept of health-related quality of life, (2) SLR to evaluate measurement properties and quality of content validity studies of relevant PROMs, (3) qualitative study of underrepresented groups, (4) content validity study of the leading HrQOL tool(s) in CTCL, and (5) protocol development for a core outcome domain set. The CL-QL committee refined its methodology for the SLRs and core domain development. Stakeholders identified the need for a dedicated IDEOM research fellow to help support multicenter collaborative research efforts and planned to expand the steering committee to include colleagues in Europe. The workgroup also identified the importance of early engagement of healthcare providers and patients internationally to ensure optimal COS development and adoption. As part of its next steps, the CL-QL committee will develop educational programs on the importance of PROMs and collaboration of all stakeholders for COS development through professional societies and patient research partners.

Speaker Talks

The 2022 IDEOM Annual Meeting also featured Mark Kaufmann MD, who president of the American Academy of Dermatology during the 2022 Annual Meeting, who gave an informative talk entitled, "Why Do Drugs Cost So Much- The Answer Might Surprise You." Dr. Kaufmann elaborated on the role of Pharmacy Benefits Managers (PBMs) as intermediaries in the US pharmacy marketplace and discussed how these PBMs may employ different strategies (ie, copay clawbacks, spread pricing, rebates, copay accumulator cards, and step edits/prior authorizations) that lead to increased costs of medical treatments.

CONCLUSION

IDEOM is an organization dedicated to advancing evidence-based, patient-centered dermatologic outcome measures. The 2022 IDEOM Annual Meeting allowed clinicians, patients, and industry stakeholders from diverse backgrounds to collaborate on matters related to dermatologic outcome measures. Workgroups in psoriatic disease, acne, actinic keratosis, vitiligo, itch, hidradenitis suppurativa, cutaneous lymphoma, and alopecia areata presented their progress made in 2022 and discussed plans for future directions. This report details each workgroup's respective updates. Further workgroup progress will be presented at the 2023 IDEOM Annual meeting.

DISCLOSURES

Kathryn Lee, Michael J. Woodbury, Melissa Peri Zundell, Rosario Agüero, Jenna Yousif, Samuel C. Williams, Cecilia Larocca, Richard L. Torbeck, and Lourdes M. Perez-Chada have no conflicts of interest to disclose.

David Rosmarin has received honoraria as a consultant for AbbVie, Abcuro, AltruBio, Arena, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Concert, CSL Behring, Dermavant, Dermira, Incyte, Janssen, Kyowa Kirin, Lilly, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, UCB, VielaBio; has received research support from AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Dermira, Galderma, Incyte, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals Inc; and has served as a paid speaker for AbbVie, Amgen, Celgene, Incyte, Janssen, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi.

Nanette Silverberg is an advisory board member for Vyne, Amryt, Regeneron/ Sanofi, and Incyte and is a speaker for Pfizer, Regeneron/ Sanofi, and Novartis.

Diane Thiboutot has served as a consultant to Novartis, LaRoche Posay and Biofrontera.

Michi M. Shinohara is the principal investigator of clinical trials involving Aztex and Cabaletta Bio and is a member of the NCCN T-cell Lymphoma Panel.

Arash Mostaghimi has received consulting fees from Pfizer, hims and hers, Fig. 1, Digital Diagnostics, Concert, Lilly, Abbvie, and Bioniz.

Sonja Ständer has been an advisor, speaker, or investigator for Abbvie, Almirall, Beiersdorf, Bellus Health, Benevolent, Bionorica, Cara, Celldex, Clexio, Dermasence, DS Biopharma, Eli Lilly, Galderma, GSK, Integrity CE, Kiniksa, Klinge Pharma, Leo Pharma, Menlo, Novartis, Omnicuris, Pfizer, P. G. UCB, Unna Academy, Sanofi, TouchIME, Trevi, Vanda, Vifor, and WebMD.

Antonio Martorell has acted as a consultant, advisory board member, and investigator and received honoraria from Novartis, AbbVie, Janssen Cilag, UCB, Lilly, LEO Pharma, L´Oreal, Sanofi, Sandoz and Amgen.

Tarannum Jaleel is an investigator for UCB and Eli Lilly. She reports consulting for Eli Lilly, Novartis and Chemocentryx and receiving honoraria. She has received funds from Pfizer for research fellow support. She also has received funds from Dermatology Foundation, Skin of Color Society, and NIH K12 (grant number: K12HD043446).

Daniel M. Siegel has served as a consultant for Avita, Cara, DermaSensor Inc., Lazarus Enterprises Inc., Logical Images, MedX Health, Strata Skin Sciences, UCB, SciBASE, Pulse Biosciences, Sol-Gel Technologies, Verrica Pharmaceuticals, and Seapire Skincare. Dr. Siegel has also served on the advisory board of Avita, MycoMedica Life Sciences, Tetros Group, SkinVision, Greenway Therapeutix, Palmm, and Modernizing Medicine. He holds stock in Biofronterra, Greenway Therapeutix, Novascan, Plasmend, RaMedical, and Skinvision.

Vibeke Strand has served as a consultant for Abbvie, Alpine Immune Sciences, Alumis, Amgen Corporation, Aria, AstraZeneca, Atom Biosciences, Bayer, Bioventus, Blackrock, BMS, Boehringer Ingelheim, Celltrion, Endo, Equillium, Ermium, Fortress Biotech, Genentech / Roche, Gilead, GSK, Horizon, Inmedix, Janssen, Kiniksa, Lilly, Merck, MiMedx, Novartis, Omeros, Pfizer, R-Pharma, RAPT, Regeneron, Samsung, Sandoz, Sanofi, Scipher, Setpoint, Sorrento, Spherix, Tonix, and Urica.

April W. Armstrong has served as a research investigator, scientific advisor, and/or speaker to AbbVie, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Mindera, Nimbus, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, and Pfizer.

Joseph F. Merola declares he has received consultant and/or investigator honorarium from Amgen, Bristol-Myers Squibb, Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Sun Pharma, Biogen, Pfizer and Leo Pharma.

Alice B. Gottlieb has received honoraria as an advisory board member and consultant for Amgen, AnaptypsBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Dermavant, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, Sun Pharma, UCB, and Xbiotech and has received research/educational grants from AnaptypsBio, Moonlake Immunotherapeutics AG, Novartis, Bristol-Myers Squibb, and UCB Pharma, (all paid to Mount Sinai School of Medicine).

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ORIGINAL ARTICLE

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Efficacy of Topical Cholesterol and Statin Combination Therapy in the Treatment of Porokeratosis: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Porokeratosis is a group of disorders characterized by aberrant skin keratinization secondary to genetic alterations in the mevalonate pathway, which participates in cholesterol synthesis. While a rare disorder, malignant transformation to squamous cell carcinoma is seen in up to 11% of cases. Recently, topical cholesterol and topical statin therapy have been suggested as a pathogenesis-directed treatment for porokeratosis.

Methods: A PubMed/MEDLINE and Embase literature search was performed using the search terms: "porokeratosis" AND "cholesterol" OR "lovastatin" OR "simvastatin" OR "atorvastatin" OR "fluvastatin" OR "pitavastatin" OR "pravastatin" OR "rosuvastatin" OR "statin." Peer-reviewed clinical trials, case series, and case reports of all porokeratosis subtypes were included.

Results: Eleven articles were included in the systematic review and 9 articles in the meta-analysis. The systematic review consisted of an aggregate of 33 patients, most of whom (n=31, 93.9%) applied the treatment twice daily for an average of 9.4 weeks (median=8 weeks), with 93.9% (n=31) experiencing improvement or resolution of porokeratosis. Sixteen patients (48.5%) used lovastatin and 16 (48.5%) used simvastatin with concurrent cholesterol therapy. Mild adverse events including erythema and contact dermatitis were experienced by 12.1% of patients. Our meta-analysis yielded a random effects model supporting a robust reduction in porokeratosis severity (*OR* = .076, 95% CI [0.022, 0.262]).

Conclusion: This underpowered meta-analysis provides limited, preliminary evidence supporting the efficacy of topical cholesterol/statin therapy. Overall, quality studies and aggregated sample size are limited; future large clinical trials are needed to further elucidate the role of topical cholesterol/statin therapy in the treatment of porokeratosis.

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INTRODUCTION

Porokeratosis is a group of disorders characterized by inherited or acquired dysregulation of skin keratinization.[1] Lesions classically present as annular plaques with raised, hyperkeratotic borders and an area of central atrophy.[2] While several clinical subtypes vary in morphology, distribution, and clinical course, all reliably exhibit the presence of cornoid lamella on histopathology.[1,2] The global incidence of porokeratosis is unknown, but a 2023 Swedish study estimated a national disease incidence of 1.2/100,000 person-years and prevalence of 24.2/100,000.[3] Additionally, the exact mechanism of pathogenesis remains unknown.[1,3]

Observational studies have linked porokeratosis to ultraviolet radiation, with a higher incidence in areas of high sun exposure.[1] Also, acquired cases have been linked to immunosuppression, particularly in those with solid organ and bone marrow transplants, where the incidence can be as high as 10%.[1] Moreover, cases of porokeratosis have been seen in relation to specific drugs and infections, and are associated with autoimmune and systemic diseases.[1,4] Porokeratosis may also be a genetic disorder, given significant numbers of familial cases are inherited as an autosomal dominant condition with variable penetrance and recently described mutations in the mevalonate pathway.[1,3,4]

Porokeratosis is considered a premalignant lesion, with malignant transformation seen in 7.5% to 11% of cases across all subtypes.[4] Histologically, the parakeratotic cells of the cornoid lamella possess similarities to the cells seen in squamous cell carcinoma, including abnormal DNA ploidy.[4] Given this transformation risk, treatment of porokeratosis remains an active area of discovery.

Current treatment modalities include several topical therapies, systemic therapies, and destructive therapies.[1] The recent link of genomic variations in the mevalonate pathway has sparked interest in a pathogenesis-directed therapy with topical cholesterol and topical statin therapy.[5–8] The mevalonate pathway is essential for the production of cholesterol, an integral component of the extracellular lipid matrix in the stratum corneum, which maintains the skin's barrier function.[5]

In theory, this treatment option replenishes cholesterol and uses a statin to prevent the accumulation of toxic metabolites from dysfunctional pathway enzymes.[5] From this review, we aim to highlight the current evidence surrounding the use of topical cholesterol and statin therapy to assist clinicians in their choice of treatment for porokeratosis.

MATERIALS AND METHODS

A primary literature search was conducted in January 2023 using the PubMed/Medline and Embase bibliographical databases with the following search terms: "porokeratosis" AND "cholesterol" OR "lovastatin" OR "simvastatin" OR "atorvastatin" OR "fluvastatin" OR "pitavastatin" OR "pravastatin" OR "rosuvastatin" OR "statin," according to PRISMA reporting guidelines for systematic reviews.[9] Additionally, the MOOSE reporting guidelines were followed for the meta-analysis.[10] English, peer-reviewed articles and studies conducted in human subjects were considered for inclusion. There was no restriction on porokeratosis subtype. Basic science articles, reviews, study protocols, and editorials/commentaries were excluded. Quality of evidence assessment was conducted using the modified version of the 2011 Oxford Centre for Evidence-Based Medicine Scheme.[11]

To perform a meta-analysis, articles with quantitative results (eg, use of assessment scales or odds ratios) were included. For articles without quantitative results (ie, included only lesion descriptions and pre-and-post clinical photographs), 2 physicians (FC and AP) independently rated the severity of porokeratosis using a Physician's Global Assessment (PGA) scale and a standardized rating sheet. All discrepancies in PGA scoring were resolved by consensus.

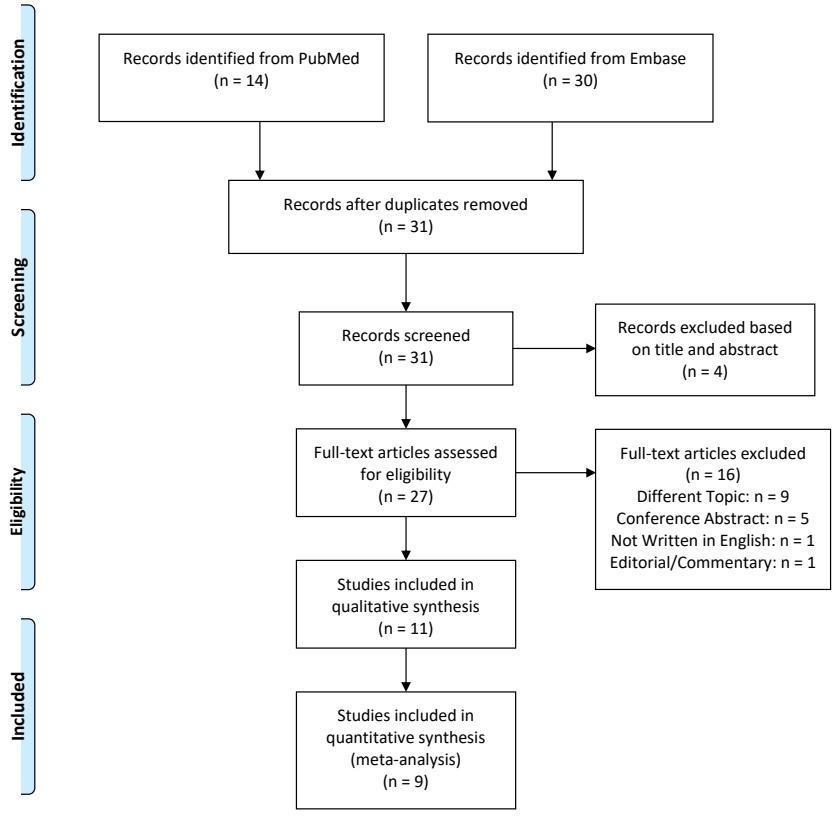
The raters used the PGA scale to rate the overall lesional severity, erythema intensity, scale severity, and lesional extent. The PGA scale was as follows: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe. Studies where PGA scores were unable to be assigned were excluded. Primary analyses were conducted using a random effects model, as this conservative approach is more appropriate for a diverse group of studies.[12] Given the substantial limitations in participants across studies, no potential moderator variables were identified for individual studies. Regarding the 2 RCTs included in the final analysis, both articles were coded for variables required to calculate aggregate effect size (eg, participants, means, standard deviations).

RESULTS

Systematic Review

There were 44 total articles initially retrieved and 13 duplicates removed (Figure 1). Eleven articles met the inclusion criteria for the systematic review, consisting of 2 randomized controlled trials (RCTs), 3 case series, and 6 case reports, with an aggregate

FIGURE 1. PRISMA flow diagram for review of topical cholesterol/statin therapy for porokeratosis.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

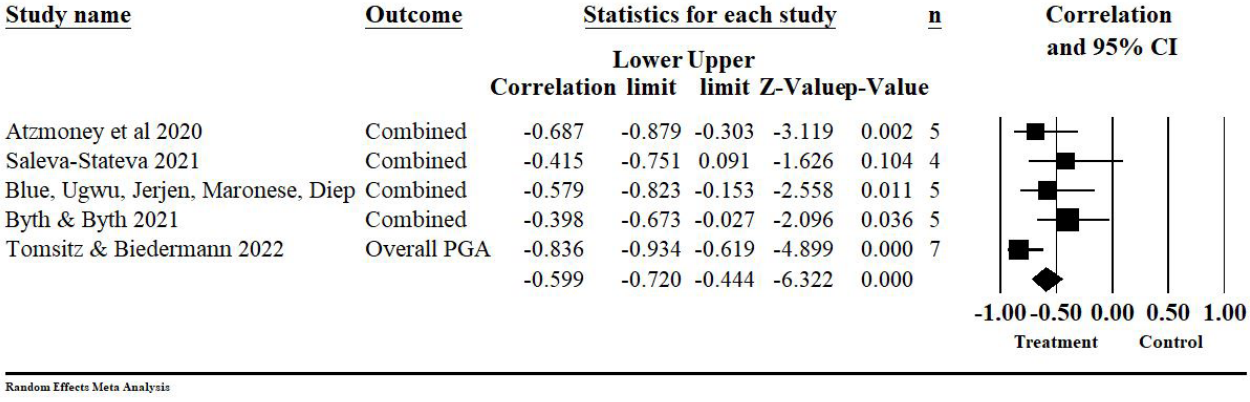
TABLE 1.

Summary of Included Studies

Author (Year)	Study Design	Level of Evidence	Subjects	Intervention	Treatment Duration	Outcome Measured	Outcome Results
Aerts et al. (2022)[21]	Case Report	5	70-year-old male with DSAP	Simvastatin (2%) / Cholesterol (2%), twice daily	24 weeks	N/A	Gradual improvement. After 24 weeks, developed strongly pruritic contact dermatitis, requiring treatment cessation.
Buhle et al. (2022)[18]	Case Report	5	30-year-old male with biopsy-proven LP	Lovastatin (2%) / Cholesterol (2%), unknown frequency of application	Unknown	N/A	Partial improvement of lesions; patient discontinued therapy due to effort of application. No adverse reactions.
Diep et al. (2022)[19*]	Case Report	5	61-year-old male with biopsy-proven LP	Lovastatin (2%) / Cholesterol (2%), twice daily to only one extremity	12 weeks	N/A	Significant reduction in erythema and scaling compared to baseline and the untreated upper extremity. No adverse reactions.
Tomsitz and Biedermann (2022)[13*]	RCT, 2 arms	1	7 patients (4 males; 3 females) with biopsy-proven DSAP	Arm 1: Lovastatin (2%) / Cholesterol (2%), twice daily on half of body Arms 2: vehicle on half of body	12 weeks	Measurement of lesion clearance using Physician's Global Assessment (PGA)	2 patients experienced complete remission and 5 experienced improvements in PGA scores; vehicle did not experience improvements. No adverse reactions.
Blue et al. (2021)[17*]	Case Report	5	17-year-old female with biopsy-proven LP	Lovastatin (2%) / Cholesterol (2%), twice daily	12 weeks	N/A	Complete resolution on the arm and forearm with significant decrease in the erythema and hyperkeratosis on the dorsal hands and fingers. No adverse reactions.
Byth L and Byth J (2021)[13*]	RCT, 2 arms	1	8 patients (1 male; 7 females) with clinical diagnosis of DSAP	Arm 1: Simvastatin (2%) / Cholesterol (2%), twice daily to one extremity Arm 2: Bland emollient to contralateral affected extremity	6 weeks	Lesion number, erythema and scale measured on prespecified ordinal scales, analyzed using Bayesian logistic regression and Odds Ratios (OR)	Significant improvement in number of lesions (OR = 0.12), erythema (OR = 0.25), scale (OR = 0.18), and patient-reported disease activity (OR =0.33). 3 patients experienced increased erythema after 1 week of treatment.
Jerjen et al. (2021)[15*]	Case Series	4	2 patients with clinically diagnosed DSAP (a 63-year-old female and a 52-year-old female)	Simvastatin (2%) / Cholesterol (2%), twice daily	12 weeks	N/A	Objective and subjective reduction in the number of lesions, with a markedly fainter appearance. No adverse reactions.
Maronese et al. (2021)[20*]	Case Report	5	66-year-old male with biopsy-proven DSAP	Lovastatin (2%) / Cholesterol (2%) applied daily	8 weeks	N/A	Marked improvement noticed; reduction of lesional extent and number
Saleva-Stateva et al. (2021)[16*]	Case Series	4	5 patients with biopsy-and-mutation-analysis-proved LP (3 females, 2 males)	Simvastatin (2%) / Cholesterol (5%), twice daily. One patient applied Simvastatin (5%) / Cholesterol (5%) twice daily for 9 months. All patients concurrently applied urea 10% cream for verrucous lesions	4 – 36 weeks	N/A	4 patients experienced some improvement (less pruritus/pain; softer skin; flattening of verrucous plaques; decrease in erythema and scale). 1 patient experienced initial improvement followed by worsening keratotic lesions
Atzmony et al. (2020)[5*]	Case Series	4	5 patients with biopsy-and mutation analysis-proven DSAP (n=1), PPPD (n=2), and LP (n=2)	Lovastatin (2%) / Cholesterol (2%), twice daily	5 – 12 weeks	N/A	Marked decreases in erythema and scaling in all patients. 2 patients experienced improved lesion thickness. 2 patients did not experience improvement in number of lesions. No adverse reactions.
Ugwu et al. (2020)[22*]	Case Report	5	36-year-old male with biopsy-and mutation analysis-proven DSAP	Lovastatin (2%), twice daily	6 weeks	N/A	Complete resolution of lesions. No adverse reactions.

DSAP, disseminated superficial actinic porokeratosis; LP, linear porokeratosis; N/A, not applicable; PPPD, porokeratosis palmaris et plantaris disseminate; RCT, randomized controlled trial.
*Indicates inclusion in meta-analysis.

FIGURE 2. Forest Plot of random effects model of overall change in porokeratosis lesions (combined changes in severity of the lesions, erythema intensity, scale severity, and lesional extent).



of 33 patients (21 with DSAP, 10 with LP, and 2 with PPPD). Most patients (n=31, 93.9%) applied the treatment twice daily for an average of 9.4 weeks (median=8 weeks), with 93.9% (n=31) experiencing improvement or resolution; 2 patients (6.1%) experienced no improvement, both of whom had LP. Of those who experienced improvement, 12.1% (n=4) experienced complete resolution (DSAP=3, LP=1). Sixteen patients (48.5%) used lovastatin and 16 (48.5%) used simvastatin with their concurrent cholesterol therapy; one patient (3%) used lovastatin monotherapy.

The highest quality evidence comes from 2 RCTs.[13,14] One RCT was an open-label, split-body trial that included 8 patients (7 females, 1 male; median age=65-years) with a clinical diagnosis of DSAP and symmetrical involvement of at least one set of extremities, who applied topical 2% cholesterol/2% simvastatin twice daily for 6 weeks.[13] Treatment response was assessed using an ordinal scale from 0 to 4, with 0 being clear skin and 4 being severe features. Using odds ratios (OR) to compare treated limbs with untreated limbs, they found significant reductions in lesion number (OR=0.12, 95% Confidence Interval [CI] 0.01-0.72), reduction in erythema (OR=0.25, 95% CI 0.05-0.79), reduction in scale (OR=0.18, 95% CI 0.03-0.64), and improvements in patient-reported disease activity (OR=0.33, 95% CI 0.09-0.89). Similarly, a second open-label, split-body RCT involving 7 patients (3 females, 4 males; age range, 48 to 85-years) with biopsy-proven DSAP were treated with topical 2% cholesterol/2% lovastatin cream (applied twice daily, for 12 weeks) on one half of the body, and compared treatment response to lesions treated with vehicle.[14] After 12 weeks, 2 patients achieved complete remission, and the remaining 5 patients experienced visible improvements in detectable disease, as noted by decreasing PGA scores following treatment.

Among the 18 patients reported from observational studies, 2 experienced complete resolution (DSAP=1, LP=1), and 14 experienced a qualitative improvement in erythema, scale, and lesion size/number. Three small case series contribute to the evidence suggesting treatment efficacy.[5,15,16] A case series with 5 patients (2 females, 2 males, and one unspecified gender; age range, 5 to 53 years) with different porokeratosis subtypes (3 familial cases with varied presentations, including DSAP [n=1], PPPD [n=2], and LP [n=2]) assessed the efficacy of twice-daily topical 2% cholesterol/2% lovastatin therapy after 6 to 12 weeks.[5] Erythema, scale, thickness, and lesion size and number were assessed each visit. The patient with DSAP experienced decreased scale, erythema, and lesion size; the patient tried an additional 4 weeks of solitary 2% cholesterol topical therapy without any lesion improvement. The patients with PPPD experienced improvement in scaling but no change in the number or size of the lesions, and the LP patients experienced decreased erythema and lesional thickness.

Similarly, a case series with 2 female patients with DSAP (aged 52 and 63 years) were treated twice daily with topical 2% cholesterol/2% simvastatin.[15] The authors noted subjective and objective improvements after 12 weeks of therapy, with the 52-year-old patient specifically experiencing reduced lesion number and a markedly reduced appearance of lesions.

Interestingly, a third case series with 5 patients (3 females, 2 males; age range, 9 to 51 years) with histologic and mutation analysis-confirmed LP were treated with 5% cholesterol/2% simvastatin twice daily with adjuvant urea 10% cream to assist with the treatment delivery to thick verrucous lesions.[16] After 4 weeks, one patient saw no improvement, and her simvastatin concentration was increased to 5%; after an additional 9 months, the patient experienced decreased pruritus and pain, and improved skin texture compared to untreated regions. One patient experienced flattening of the verrucous plaques after 4 weeks, and 2 additional patients saw minor decreases in erythema and scaling. The treatment was ineffective for 2 of the 5 patients.

Additional evidence comes from 5 case reports regarding topical statin/cholesterol therapy,[17–21] and one case report of topical statin monotherapy.[22] Three case reports document 3 patients (1 female, 2 males; age range, 17 to 61 years) with LP who were treated with 2% cholesterol/2% lovastatin for up to 12 weeks; each experienced clinical improvement, with complete resolution of arm lesions,[17] significant reductions in lesion erythema and scaling,[17,19] and unspecified partial improvement of lesions.[18] Two patients with DSAP (2 males; age range, 61 to 66-years) were treated with 2% cholesterol/2% lovastatin or 2% cholesterol/2% simvastatin for 8 to 12 weeks and saw significant reductions in lesional extent and number,[20] and unspecified gradual improvement.[21] Interestingly, a 36-year-old male with DSAP was treated with topical lovastatin 2% monotherapy twice daily for 6 weeks and achieved complete remission of all lesions.[22] Notably, one patient stopped treatment due to the effort of application.[18]

Adverse Events

Few mild adverse events were experienced by 12.1% of patients (n=4), including erythema (n=3), contact dermatitis (n=1), and nausea (n=1); no adverse side effects were experienced by the patients who used statin monotherapy. The incidences of erythema in treated areas arose within the first week of therapy and were suspected to be an irritant response; one patient discontinued treatment after 2 weeks due to this erythema and was noted to have porokeratotic lesions on a background of atopic dermatitis.[13] One patient reported an episode of nausea that spontaneously resolved.[13] The patient who developed contact dermatitis necessitated treatment cessation after 24 weeks on 2% cholesterol/2% simvastatin.[21]

Meta-Analysis

Two studies provided quantitative data for inclusion,[13,14] and an additional 7 qualitative studies were included following the assignment of PGA scores. Two studies were excluded from the analysis due to the inability to assign PGA scores.[18,21] Two additional patients were excluded from the final analysis due to poor clinical descriptions and no clinical photographs.[15,16] A total of 9 studies, encompassing data from 29 patients, were included in the meta-analysis. Studies included in the meta-analysis are denoted with an asterisk in Table 1. Moderator analyses were not performed as the limited power derived from the dearth of data in the field did not warrant further analyses. Given that most studies in the field used odds ratios, odd ratios were used to maintain continuity and ease of understanding. As shown in Figure 2, a random effects model supported a robust reduction in porokeratosis severity among 26 participants across 5 studies (*OR* = .076, 95% CI [0.022, 0.262]); this analysis encompassed all changes in pre-post treatment lesion number, lesion severity, erythema intensity, scale severity, and lesional extent. Given that primary analyses included a combined study consisting of single-participant case reports, a subsequent analysis was performed removing this combined study, which yielded a similar effect to the initial analysis (*OR* = .068, 95% CI [.013, .343]).

Publication Bias

Given the well-established tendency to publish studies with significant results, an attempt to quantify potential publication bias included a "fail-safe" analysis.[23] The results of 2-tailed *z* value for observed studies was -5.158, *P*<.001, suggesting a strong indication of publication bias. Given the robust reported effects, a *failsafe N* revealed that 30 similarly-sized missing studies would be required to bring *P*-values above .05. However, it is worth noting that the present body of literature is marked by small sample sizes and few studies. As such, a singular large study could easily shift the weight of the present findings, where patients found not to improve.

DISCUSSION

This systematic review and meta-analysis provide preliminary evidence supporting topical cholesterol/stain therapy as an efficacious treatment of porokeratosis. The systematic review revealed that 93.9% of patients achieved improvement in their porokeratotic lesions. While only 12.1% of patients experienced complete resolution, a prior study noted that only 16% of patients experienced complete resolution among available treatment modalities (eg, retinoids, laser treatment, cryotherapy, etc.), not including topical cholesterol/stain therapy.[1,24] Furthermore, this systematic review demonstrates efficacy with the use of both topical simvastatin and lovastatin and improvement across all subtypes of porokeratosis.

A conservative approach to the meta-analysis similarly supported the robustness of these results, showing significant reductions in the severity of porokeratosis lesions and symptoms. However, due to the limited sample size of the analysis, the true efficacy of topical cholesterol/stain therapy is subject to significant publication bias. Notwithstanding this fact, these results suggest that further investigation into topical cholesterol/statin therapy may find this treatment modality to be both highly effective and safe, as only 12.1% of patients experienced mild and transient adverse effects, mostly commonly increased lesional erythema.

While the exact pathogenic mechanism of porokeratosis remains to be elucidated, the efficacy of topical cholesterol/statin therapy supports the theory that this is a new pathogenesis-directed treatment modality. Porokeratosis is linked to heterozygous germline mutations in the mevalonate pathway, including mevalonate decarboxylase (*MVD*), mevalonate kinase, phosphomevalonate kinase (*PMVK*), farnesyl diphosphate synthase (*FDPS*), and solute carrier family 17 member 9 (*SLC17A9*).[25,26] Recent evidence suggests LP specifically is associated with both germline and second-hit postzygotic mutations in genes encoding mevalonate pathway enzymes.[26]

Alterations in the mevalonate pathway affect cell growth and differentiation, cytoskeleton assembly, and post-translational protein modification for intracellular signaling.[27] Cholesterol, one of the downstream end-products in this pathway, is a component of the stratum corneum, which maintains the skin barrier. Depleted cholesterol levels have been linked to increased keratinocyte apoptosis, and interestingly, porokeratosis lesions have been shown to have both dysregulated keratinocyte differentiation and premature apoptosis.[26] Therefore, it is theorized that topical cholesterol/statin therapy functions to replenish the end-product of the mevalonate pathway while also inhibiting keratinocyte 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a precursory step in the mevalonate pathway, to prevent accumulation of toxic metabolites.[5,26] However, given the incomplete resolution of some lesions, it is theorized that additional end-products need to be attenuated to optimally correct for the mevalonate pathway dysregulation leading to the porokeratotic phenotype.[5]

The evidence supporting the use of topical cholesterol/statin therapy for the treatment of porokeratosis is mainly derived from poor quality, underpowered split-body RCTs, and several low-level evidence case series and reports. Additional limitations of this review include small sample sizes, lack of quantitative evidence, incorporation of mainly observational studies, and a largely underpowered meta-analysis. In addition, publication bias potentially contributes to the low number of published studies. Though underpowered, this meta-analysis offers preliminary evidence that topical cholesterol/statin therapy is efficacious in the treatment of porokeratosis and serves as a valuable part of the therapeutic armamentarium.

CONCLUSION

This systematic review and meta-analysis highlight the limited evidence supporting the treatment of porokeratosis with topical cholesterol/statin therapy. While the therapy appears to be efficacious, the evidence is mainly derived from low-quality RCTs, low-level of evidence observational studies, and an underpowered meta-analysis. However, this preliminary analysis suggests a robust response to treatment and beckons further large clinical trials to evaluate to elucidate the true treatment efficacy.

DISCLOSURES

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Cryosurgery and 5-Fluorouracil Combination Therapy for Treatment of Bowen's Disease and Superficial Basal Cell Carcinoma

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ABSTRACT

Background: Non-melanoma skin cancer (NMSC), which includes both Bowen's disease (BD) and superficial basal cell carcinoma (sBCC), is the most commonly diagnosed cancer in Canada. BD and sBCC are amenable to minimally invasive treatments; however, large-scale studies assessing long-term outcomes are lacking, particularly regarding the timing and duration of non-invasive combination treatments.

Objective: To examine the clinical cure rate of BD and sBCC using a combination treatment consisting of a single cycle of cryotherapy followed by a 3- to 4-week course of topical 5-fluorouracil (5-FU).

Methods: Retrospective chart review at a single center. Inclusion criteria included histology-proven sBCC or BD treated with either a combination protocol, cryosurgery, or 5-FU alone.

Results: 310 biopsy-confirmed cases of BD and 176 biopsy-confirmed cases of sBCC were analyzed. Of these, 229 cases of BD and 61 cases of sBCC were treated with cryosurgery and immediate 5-FU application, yielding a clearance rate of 90% and 86.9% at 6 months from initial treatment.

Conclusion: Cryosurgery followed by immediate 5-FU use may be an effective mode of treatment for BD and sBCC, negating the need for invasive procedures and allowing for increased accessibility. Further studies with longer follow-up intervals, comparisons with other non-invasive treatments, and evidence of histologic cure are required.

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INTRODUCTION

Non-melanoma skin cancer (NMSC) is the most commonly diagnosed cancer in Canada, with incidence rates continuing to rise.[1–3] Basal cell carcinoma is the most common of these skin cancers, with superficial basal cell carcinoma (sBCC) making up between 10% to 17% of all basal cell cancers. Squamous cell carcinoma (SCC) is the second most common cutaneous neoplasm, with in situ SCC, referred to as Bowen's disease (BD), accounting for close to 12% of all SCCs.[4] Collectively, sBCC and BD represent a substantial percentage of malignant cutaneous neoplasms in Canada, although morbidity secondary to NMSC is uncommon, leaving it untreated can result in significant disfigurement, functional impairment, and progression to SCC that may lead to distant metastases.[5]

Superficial basal cell carcinoma is confined to or is contiguous with the epidermis, and, similarly, BD does not invade the underlying dermal layer.[4] Thus, there is a question as to whether surgical interventions are required for treatment given the more invasive nature of the procedure, longer wait and recovery times, risk of associated morbidities, and aesthetic appearance of the final scar site.[6] As the incidence of NMSC continues to rise, with rates expected to triple by 2031,[1] there remains a need to evaluate less invasive treatment options that can more easily be implemented in community settings.

A variety of non-surgical interventions can be used to treat sBCC and BD including photodynamic therapy, cryosurgery, imiquimod cream, and 5-fluorouracil (5-FU). Using these therapeutic options may negate some of the risks presented with surgical interventions, but often yield higher recurrence rates and may prove to be intolerable in some individuals due to adverse effects. Emerging studies have begun to evaluate combination therapies to reduce the side effects of a single

treatment regimen while preserving recovery rates.[7–10] To date, the combination of liquid nitrogen cryotherapy with 5-FU for the treatment of BD and sBCC has been reported in several smaller observational studies, making it difficult to estimate the true rate of cure or complications.[7–10] As this treatment modality is commonly employed in many community dermatology clinics, more data are needed to guide dermatologists about its effectiveness and adverse effects. In the current retrospective chart review, we evaluate 290 biopsy proven cases of BD and sBCC treated with a combination of cryosurgery and immediate 5-FU therapy. We compare these results to an additional 196 cases of BD and sBCC treated with cryosurgery alone and 19 treated with solely topical 5-FU. In addition, we examined the outcomes of several other modalities.

MATERIALS AND METHODS

Patients with histologically confirmed BD or sBCC with one of 3 treatment protocols were included in this study: 1) cryosurgery followed by an immediate 3- to 4-week course of 5-FU topical treatment applied twice daily 2) cryosurgery alone 3) a 3- to 4-week course of 5-FU topical treatment applied twice daily. All patients had a minimum 6 months follow-up. This was a single-center retrospective study in Guelph, Ontario with treatment carried out by the same dermatologist. A chart review was conducted to identify patients treated with any of the 3 treatment protocols, and records between January 1, 2016, and September 1, 2020, were reviewed. 197 patients with a total of 359 cases of BD and 115 patients accounting for 176 total cases of sBCC were included in this study. Patients with multiple scalp NMSCs were not included in the current study as they were difficult to landmark and follow based on clinical documentation.

Lesions treated with cryosurgery were exposed to liquid nitrogen for 10 seconds, approximately one centimeter from the surface of the lesion, and with clinical margins of 5 millimeters. Patients in the combination category were instructed to subsequently complete a 4-week course of 5-FU applied twice daily to the lesion and surrounding site. If patients were unable to tolerate treatment, they were instructed to stop the 5-FU after 3 weeks, and reactions were managed with topical steroids and topical antibiotics. If there was suspicion of recurrence, the case was documented as a clinical recurrence or sent for a repeat biopsy to confirm diagnosis. As a secondary endpoint, we also assessed other treatment modalities (Table 5).

RESULTS

Combination Treatment

A total of 229 biopsy-confirmed cases of BD were included in this branch of the study (Table 1). The overall cure rate, noted after a follow-up of at least 6 months, was 90.0%, with the lowest cure rate of 78.3% (n=23) being noted for lesions located on the neck. The average time of recurrence was 10.7 months. Some patients did experience local site reactions; however, no systemic adverse events were noted. Patients that were noted to have recurrence were managed with either repeat cryosurgery and/or 5-FU or underwent surgical management, depending on patient factors, size, and anatomic site involved. There were no major complications with any of the sites examined, with none leading to compromised cosmesis, compromised function, or requiring extensive revision surgery.

A total of 61 biopsy-confirmed cases of sBCC treated with a combination of cryosurgery and 5-FU were analyzed (Table 2).

TABLE 1.

Results for Biopsy Proven Cases of Bowen's Disease Treated with Cryosurgery and 5-Fluorouracil Combination Treatment. Cure Rates and Time of Recurrence Rounded to the Closest Tenth Decimal

Anatomic Location	Total	Recurrence	Cure Rate (%)	Average Time of Recurrence (months)
Scalp	33	3	90.9	24
Forehead	38	2	92.9	10.5
Cheeks/jaw/chin	40	4	90	7.5
Ears	24	3	87.5	7.3
Nose	6	--	100	--
Neck	23	5	78.3	8
Arm/shoulder	18	3	83.3	6
Hands	7	1	85.7	7
Chest/abdomen	8	1	87.5	25
Back	15	1	93.3	11
Legs	17	--	100	--
TOTAL	229	23	90.0	10.7

TABLE 2.

Results for Biopsy Proven Cases of Superficial Basal Cell Carcinoma Treated with Cryosurgery and 5-Fluoruracil Combination Treatment. Cure Rates and Time of Recurrence Rounded to the Closest Tenth Decimal

Anatomic Location	Total	Recurrence	Cure Rate (%)	Average Time of Recurrence (months)
Scalp	--	--	--	--
Forehead	8	1	97.5	5
Cheeks/jaw/chin	6	2	66.7	7.5
Ears	4	--	100	--
Nose	4	--	100	--
Neck	3	--	100	--
Arm/shoulder	7	1	85.7	6
Hands	--	--	--	--
Chest/abdomen	8	2	75.0	14
Back	18	2	88.9	5.5
Legs	3	--	100	--
TOTAL	61	8	86.9	8.1

TABLE 3.

Results for Biopsy Proven Cases of Bowen's Disease Treated with Cryosurgery Alone. Cure Rates and Time of Recurrence Rounded to the Closest Tenth Decimal

Anatomic Location	Total	Recurrence	Cure Rate (%)	Average Time of Recurrence (months)
Scalp	10	1	90	8
Forehead	10	3	70	23
Cheeks/jaw/chin	5	1	80	3
Ears	4	1	75	24
Nose	1	0	100	--
Neck	9	2	77.8	6
Arm/shoulder	19	1	94.7	4
Hands	2	1	50	30
Chest/abdomen	7	0	100	--
Back	7	3	57.1	11
Legs	7	2	71.4	10.5
TOTAL	81	15	81.5	13.5

TABLE 4.

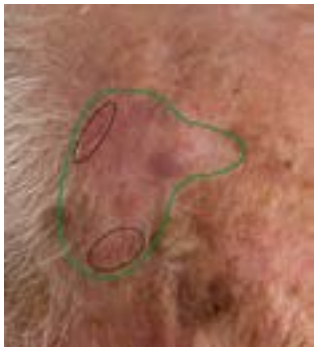
Results for Biopsy Proven Cases of Superficial Basal Cell Carcinoma Treated with Cryosurgery Alone. Cure Rates and Time of Recurrence Rounded to the Closest Tenth Decimal

Anatomic Location	Total	Recurrence	Cure Rate (%)	Average Time of Recurrence (months)
Scalp	1	0	100	--
Forehead	6	0	100	--
Cheeks/jaw/chin	4	0	100	--
Ears	3	0	100	--
Nose	4	0	100	--
Neck	8	0	100	--
Arm/shoulder	30	8	73.3	15.2
Hands	--	--	--	--
Chest/abdomen	17	7	58.8	15
Back	30	10	66.7	10.9
Legs	12	2	83.3	8.5
TOTAL	115	27	76.5	13.7

TABLE 5.

Results for Other Treatment Modalities for Treatment of Biopsy Proven Cases of Bowen's Disease			
Treatment Modality	**Total Treated**	**Recurrence**	**Cure Rate (%)**
Photodynamic therapy in combination with cryotherapy and 5% 5-fluorouracil	11	0	100
Imiquimod 4-week course	12	1	91.2
5% 5-fluorouracil 4 weeks after cryosurgery	19	4	78.9
Surgical excision	7	0	100

FIGURE 1. Recurrence (denoted by black circles) at the edge of a scar of Bowen's disease (original outline denoted in green) on the forehead after treatment with cryosurgery.



The overall cure rate was 86.9%, with an average recurrence time of just over 8 months. Patients with recurrence were re-treated with cryosurgery, with or without the addition of 5-FU, or were referred for further surgical intervention. There were no major complications with any of the sites examined. It was noted that lesions on the cheeks/jawline/chin had a lower cure rate (66.7%).

Cryosurgery Alone

A total of 81 cases of BD (Table 3) and 115 cases of sBCC (Table 4) were treated with cryosurgery alone. The overall cure rate for BD was 81.5% and 76.5% for sBCC. The average time to recurrence for sBCC and BD with a single modality treatment was 13.7 months and 13.5 months, respectively. An example of recurrence of BD treated with cryosurgery is shown in Figure 1 in which there is evidence of clinical recurrence at the edge of the scar, which is amenable to a second course of cryosurgery, especially in the context of no prior 5-FU use. If signs of clinical recurrence, the lesion was re-treated with cryosurgery or the patient was referred for surgical management. There were no major complications with any of the sites examined, with none leading to compromised cosmesis, compromised function, or requiring revision surgery.

Other Treatments

17 total cases of BD and 2 cases of sBCC were treated with 5-FU alone (Table 5). There was inadequate in-person follow-up to determine curative rates for this treatment modality. In addition, several cases were treated with alternate treatment protocols. In one scenario, 11 total cases of BD were treated with a combination of cryosurgery, 5-FU, and photodynamic therapy, with none showing clinical relapse (Table 5). Another assessed treatment modality involved 13 patients with BD treated with Imiquimod 3.75% once daily immediately after cryosurgery resulting in a 91.2% cure rate. Other modalities assessed included treatment of 23 lesions with 5-FU at an interval of 4 weeks after cryosurgery (78.9% cure rate) and surgical excision in 7 cases (100% cure rate).

DISCUSSION

The incidence of NMSC continues to rise alongside an aging population and the economic burden secondary to BCC and SCC has been estimated to be over $90 million in Canada alone.[1] As a result, there is a need to evaluate the efficacy and limitations of different modalities of treatment. Surgical therapies, which include excision and Mohs micrographic surgery (MMS) often yield the highest rates of clearance, with cure rates of MMS ranging from 93.5% to 99%.6,[11–15] However, use of such modalities depends on a variety of factors including existing comorbidities, patient preference, risk of treatment, and cosmesis. Canadian guidelines recommend that the use of topical therapies, cryosurgery, and photodynamic therapy be considered in cases of low-risk BCC and BD and similarly recommend cryosurgery, and radiation therapy and acknowledge the utility of photodynamic therapy and topical therapies in treating BD.[16,17]

Cryosurgery is a versatile treatment modality that induces tissue injury via cell freezing and subsequently development of vascular stasis. Cryosurgery has been shown to provide a clinical clearance of upwards of 99%, but this requires freezing durations nearing 60 seconds and a minimum of 2 cycles resulting in decreased tolerability secondary to local reactions and an increased potential for scarring.[8,18] In the current study, patients treated with a single 10-second cycle of cryosurgery demonstrated a clearance rate of just over 81% for BD and 76% for sBCC which is in keeping with previous reports. Patients elected for this option for a variety of reasons, but most commonly due to the side effect profile associated with 5-FU or negative experiences with 5-FU treatment in the past. These cure rates remain lower than the rates that were seen with combination treatment.

5-FU is a pyrimidine analog that acts as an antimetabolite and is available as a topical treatment. Prolonged durations of up to nine weeks have been preferred to achieve adequate penetration and reach acceptable NMSC cure rates;[19] however, this is associated with increased pain and irritation to the treatment site as well as risk of hypopigmentation. These side effects ultimately lead to decreased patient compliance, with one study finding close to 50% of patients not being able to tolerate the 9-week course.[19] Alternatively, studies evaluating shorter courses of 5-FU treatment yield higher rates of recurrence, suggesting that perhaps an adjunctive treatment may be required. In the current study, we had a total of 19 patients undergoing only 5-FU treatment for 3 to 4 weeks. Many of these cases were in light of the COVID-19 pandemic, as patients were unable to come into clinic for cryosurgery, and thus these patients had inadequate in-person follow-up, making it difficult to track the cure rates of a shorter course of 5-FU.

Emerging studies have begun to evaluate the efficacy of combination therapies to limit the adverse effects of any one therapeutic strategy while maintaining acceptable recovery rates. As this remains an area of active study, there are currently no agreed upon guidelines addressing combination regimens and duration of treatment.

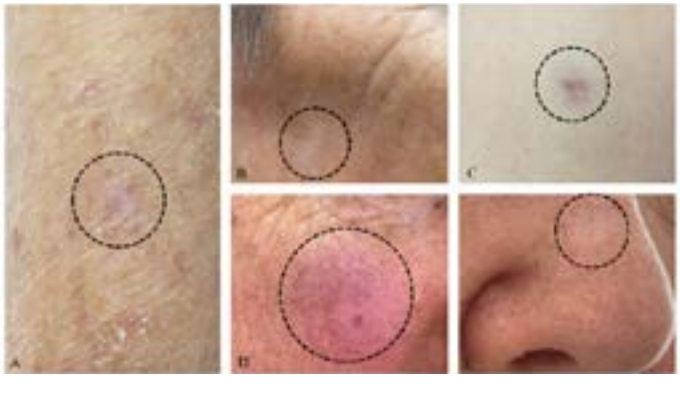
In this retrospective chart review, patients were treated with a single 10-second cycle of cryosurgery with an immediate start of a 3 to 4 week course of 5-FU. This is in contrast to a similar study that started combination treatment 4 weeks after the cryosurgery treatment.[8] Previous studies evaluating combination therapies with cryosurgery hypothesize that it may have a sensitizing role in subsequent topical treatments.[20] By minimizing time between cryosurgery and initiation of 5-FU treatment, the skin does not have an opportunity to re-epithelialize potentially allowing for deeper penetration of topical therapies. In line with this hypothesis, there was a group of patients who were unable to start treatment with 5-FU immediately after the procedure and/or preferred to do it four weeks after the treatment with cryosurgery. While the sample size is relatively small, the cure rate of 78.9% is in keeping with previous findings.[8] The caveat with decreasing the recovery time between cryosurgery and 5-FU is the risk of increased irritation, burning, and erythema. In cases such as these, patients were asked to continue 5-FU treatment for three weeks if clinical resolution was evident, rather than completing the full four-week course. In many patients, 5-FU did cause some degree of mild discomfort with local irritation and crusting, but this resolved shortly following treatment completion. Steroid creams and antibiotic ointments were prescribed if required, to manage the secondary effects. Future studies to determine the long-term clearance for these patients will be essential to determine lasting efficacy.

Immediate treatment with 5-FU following cryosurgery was well-tolerated in the patient population, with some noting erythema and irritation to the treated area, but all included patients were able to complete a minimum of 3 weeks of 5-FU treatment. The cure rate of 229 biopsy proven BD lesions with this protocol was close to 90%, with a mean time of recurrence at just under 11 months. In a total of 61 cases of sBCC treated with this approach, we were able to achieve a cure rate of 86.9%, with a mean time of recurrence just over 8 months.

The characteristics that predict the recurrence of BD and sBCC remain unknown. A recent systematic review found that immunosuppression was the only variable with a statistically significant association with the recurrence of BD.[21] In the current study, at least two patients who demonstrated recurrence after combination treatment were known to be immunosuppressed. In addition, although certain anatomical locations, including the head and neck, are believed to have a higher risk of developing BD, there remains insufficient evidence to correlate location and recurrence risk. Our results showed that BD located on the neck carried the highest risk of recurrence following combination therapy, and future studies aimed at further evaluating this risk may help to stratify treatment options. Finally, there is a paucity of data evaluating the relationship between tumor size and recurrence risk, with some studies showing no association between the two.[13,21] Multiple factors are likely associated with understanding the risk of recurrence of these lesions and will have to be taken together to guide treatment.

While cure rates with this combination protocol did not match the cure rates observed with MMS, the cryosurgery and 5-FU combination were similar to those seen with other surgical modalities, while also providing additional benefits in the context of a condition that usually is slow to progress and carries low risk of mortality. For one, treatment can be carried out as soon as biopsy results are available and do not require visits to tertiary centers. Additionally, local treatment negates

FIGURE 2. Bowen's disease and superficial basal cell carcinomas treated with combination therapy. Circle represents site of original lesion (A) triceps (B) face (C) upper arm (D) face (E) nose.



the use of skin closure techniques and results in acceptable aesthetic outcomes for patients (Figure 2). Furthermore, none of the recurrences led to significant complications and were easily treated with either a repeat course of treatment or surgically. Thus, for low and moderate risk NMSC, combination treatment provides an alternative to surgical interventions, with more invasive treatment options being available for recurrent lesions and those classified as high risk or for lesions in more sensitive areas such as near the eyes and lips.

Limitations of this study include its retrospective nature. Inclusion criteria was follow-up for at least 6 months, and with mean recurrence being shown to be greater than this, recurrence rates may be higher than reported, thus, there is great utility for future studies with longer follow-up periods to ensure lasting clearance. Additionally, high risk areas, such as the face and neck, did have a higher rate of recurrence, and a smaller sample size, so these results should be interpreted with caution secondary to study limitations. For patients with multiple NMSCs, especially those on the scalp, it was difficult to ascertain whether new lesions were indeed new occurrences of NMSC or rather recurrences of previously treated cancers. Thus, multiple NMSCs treated on the scalp were not included in the current study as they were difficult to landmark and follow based on clinical documentation. Finally, confirmation of resolution was assessed clinically and not histologically which may affect final clearance rates.

Our results show that cryosurgery and 5-FU combination treatment with no recovery time between modalities is an effective option when treating sBCC and BD and may be more accessible to clinicians while providing fewer adverse effects for patients. There is a need to evaluate longer follow-up periods to ensure lasting clearance using this protocol. Furthermore, it may be of value to consider additional combination treatment approaches to increase cure rates as 11 cases of BD treated with 5-FU, photodynamic therapy, and cryosurgery, showed no clinical signs of recurrence. More studies are needed to assess the optimal treatment approach for BD and sBCC in the community setting where access to MMS and tertiary care hospitals is limited.

DISCLOSURES

The authors have no conflicts of interest to disclose. Informed consent was obtained.

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ORIGINAL ARTICLE

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A Salicylic Acid-Based Dermocosmetic is Effective as an Adjunct to Benzoyl Peroxide for Mild to Moderate Acne and as Monotherapy in Maintenance Post Benzoyl Peroxide

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ABSTRACT

Background: A dermocosmetic (DC) containing salicylic acid, niacinamide, and thermal spring water has been developed for the management of mild to moderate acne.

Aim: To assess the efficacy of DC as an adjunct to benzoyl peroxide (BPO) every other day compared with BPO over 3 months, and its efficacy as maintenance post-BPO care compared with vehicle for another 3 months.

Methods: Single-center, randomized, double-blind study in 100 patients with mild to moderate facial acne according to the Global Acne Severity (GEA) Scale. During phase 1, subjects received either BPO + vehicle (vehicle group) or BPO + DC (DC group) for 12 weeks. During phase 2, patients were re-randomized to receive either the vehicle or the DC for 12 weeks. Assessments included inflammatory and non-inflammatory lesion count, acne severity using the GEA Scale, local tolerance, quality of life, and quantity of product used.

Results: During phase 1, both groups, DC and vehicle, reached the same level of efficacy at month 3, although the quantity of BPO used was significantly reduced in the DC group (P=0.0001). During phase 2, acne continued to significantly improve (all P<0.05) in the DC group, as did clinical signs and symptoms; while patients randomized to vehicle reported relapses of their acne and related symptoms.

Conclusion: The use of DC significantly reduces the need for BPO with no impact on the efficacy of mild to moderate acne. The use of DC as a maintenance post-BPO allowed a significant reduction of acne relapse compared with vehicle after 3 months of follow-up, with a good tolerance.

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INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicle. The main factors of acne pathophysiology are hyperkeratinization of the pilosebaceous infundibulum, leading to the formation of comedones, increased sebum production, and dysbiosis or alteration of the skin microbiota.This is mainly through changes in the microbiome diversity including *Cutibacterium acnes (C. acnes)* strains, and ultimately activation of the innate immunity leading to inflammation.[1] The disease is highly prevalent in adolescents but can be seen in adults as well, with an increased prevalence of adult female acne these past years.[2-4] Acne severity and response to treatment may be influenced by various external or environmental factors.[2,5-9]

To date, several topical and systemic treatments exist to manage acne, such as topical retinoids, oral isotretinoin, benzoyl peroxide (BPO), fixed drug combination of topical retinoids and BPO or topical antibiotics, systemic antibiotics, and hormonal treatments.[4,10-12] BPO is an oxidizing agent that is bactericidal against *C acnes*. In addition to its primary bactericidal properties, BPO shows anti-inflammatory and mild comedolytic activities.[13,14] However, the use of BPO may cause skin irritations, including erythema, pruritus, and skin burning, as well as skin allergies.[15]

With acne being a chronic disease, maintenance care is currently recommended to avoid flare-ups of the condition.[11,12,16] In addition to the different pharmacological classes of acne treatment, several dermocosmetics have been developed over the last decades to be used as adjuvant care, limiting treatment-related side effects or managing the milder forms of acne when used alone.

A topical comprehensive dermocosmetic formulation (DC) containing salicylic acid and one of its derivatives C8-lipohydroxy acid (C8-LHA), niacinamide, zinc, and La Roche-Posay Thermal Spring Water has been developed to manage the milder forms of acne as both a standalone treatment and an adjunct to pharmacological treatments.[17-21] Indeed, salicylic acid-based formulations are part of the international acne guidelines for the management of mild acne.[22] In addition to its keratolytic properties, it decreases the quantity of skin lipids and possesses anti-inflammatory properties.[21,23,24] La Roche-Posay Thermal Spring Water shows both probiotic and prebiotic properties, thereby maintaining a healthy skin barrier.[25]

This study aimed to assess the efficacy of DC as an adjunct to BPO every other day compared with BPO over 3 months, and its efficacy as maintenance post-BPO care compared with vehicle for another 3 months.

MATERIALS AND METHODS

This was a randomized, vehicle-controlled, double-blind clinical study. The study complied with the principles of the Declaration of Helsinki and Good Clinical Practices, as well as with local regulations for the conduct of clinical studies. The study received approval from the local ethics committee (AB/BB CPP N°451/2009) prior to its initiation. All patients provided written informed consent to participate.

Suitable subjects for this study were to be Caucasian, aged between 15 and 30 years, and presenting with mild to moderate facial acne, defined as the presence of 20 to 50 non-inflammatory and 10 to 40 inflammatory lesions according to the Global Evaluation of Acne (GEA) tool.[26] Subjects should not have received any topical acne treatment for 15 days or any systemic treatment for at least 4 weeks prior to inclusion in this study. The study planned for 100 patients to be included.

During (phase 1), suitable patients received either BPO 5% topical formulation to be applied every other day in the evening (EOD) and the DC (DC group) or the emollient vehicle (vehicle group) every morning for 12 weeks. During the maintenance phase (phase 2), all subjects who finished phase 1 were re-randomized into 2 subgroups to receive either the vehicle or the DC as maintenance care once a day every morning for 12 weeks.

Clinical evaluations were performed at baseline, week 6, and week 12 during phase 1 and at baseline, week 6, and week 12 during phase 2. They included inflammatory and non-inflammatory lesion count and GEA scoring (on a scale from 0=no lesions to 6=severe acne) by a dermatologist.[26] The investigator also assessed erythema and desquamation on a scale from 0=no issue to 4=important issue, and local tolerance on a scale from 0=not tolerated to 4=excellent tolerance at all visits.

Patients assessed pruritus, stinging, and burning sensations and global tolerance on a scale from 0=no issue to 4=serious issue, and local tolerance on a scale from 0=not tolerated to 4=excellent tolerance. Assessments were made at all visits.

The patients' quality of life (QoL) was assessed using the Cardiff Acne Disability Index (CADI) at baseline, week 12 (end of treatment phase 1), and week 24 (end of maintenance phase 2).[27]

The quantity of BPO applied during phase 1 was assessed by weighing the tubes at baseline and week 12.

Statistical analyses were performed using Statview 5.0 (SAS Institute). Quantitative variables (ie, acne lesion counts, weighing, and scores) were descriptively presented through means and standard deviations, and qualitative variables were presented through raw data and percentages. The Kruskall-Wallis test was used to compare groups during phase 1 and phase 2 at all visits. Quantitative variables were compared using the t-student or the Mann-Whitney test; for qualitative variables, the chi-square test was used. The composite score was calculated. Significance levels were set at 5%.

RESULTS

Population and Baseline Data

In total, 100 patients with mild to moderate acne were included in this study – 60 women and 40 men. The mean patient age was 20.0 ± 4.0 years, ranging from 15 to 30 years. The median acne duration was 5.0 years [3.0; 9.0] in the vehicle group and 6.0 years [3.0; 9.0] in the DC group. More patients in the DC group (12.0%) than in the vehicle group (4.0%) reported previous acne treatment.

At study baseline, mean inflammatory lesion counts were 21.9 ± 1.1 in the vehicle group and 19.9 ± 1.1 in the DC group, while mean non-inflammatory lesion counts were 30.8 ± 0.9 in the vehicle group and 29.1 ± 1.0 in the DC group. Mean GEA scores were 1.38 ± 0.61 and 1.42 ± 0.50 in the vehicle and DC groups, respectively. The mean erythema score was 0.8 ± 01 in the vehicle group and 0.9 ± 0.1 in the DC group; the mean desquamation score was 0.04 ± 0.03 and 0.1 ± 0.04 in the vehicle and DC groups, respectively. Mean pruritus, stinging, and burning sensation scores given by the patients were very low and similar in both groups. Baseline demographic and disease data were similar in both groups. Mean global QoL scores at baseline were 5.0 ± 0.4 and 4.2 ± 0.4 in the vehicle and DC groups, respectively. Detailed patient demographic and baseline data are provided in Table 1.

Efficacy

Phase 1: After 12 weeks of adjuvant use, the mean number of inflammatory lesions had decreased by 15.4 ± 1.0 and by 14.5 ± 1.0 in the vehicle and DC groups, respectively, as had mean non-inflammatory lesion counts (-18.2 ± 1.2 in the vehicle group and

TABLE 1.

Patient Demographic and Baseline Data for Phase 1 (Treatment Phase) and Phase 2 (Maintenance Phase)		
	N=100	
Gender		
Female	60 (60.0%)	
Male	40 (40.0%)	
Age (years)		
Mean ± SD	20.0 ± 4.0	
Min; Max	(15.0; 30.0)	
Acne history (years)		
Median (interquartiles)	5.0 [3.0; 9.0]	
Phase 1	**Vehicle Group**	**Dermocosmetic Group**
Mean inflammatory lesion count	21.9 ± 1.1	19.9 ± 1.1
Mean non-inflammatory lesion count	30.8 ± 0.9	29.1 ± 1
Mean GEA score	2.8 ± 0.1	2.6 ± 0.1
Mean erythema score	0.80 ± 0.10	0.90 ± 0.10
Mean desquamation score	0.04 ± 0.03	0.10 ± 0.04
Mean pruritus score	0.10 ± 1.10	0.10 ± 0.10
Mean stinging sensation score	0.10 ± 0.03	0.10 ± 0.05
Mean burning sensation score	0.04 ± 0.04	0.10 ± 0.04
Mean CADI score	5.0 ± 0.4	4.2 ± 0.4
Phase 2	**Vehicle Group**	**Dermocosmetic Group**
Mean inflammatory lesion count	5.64 ± 4.60	5.58 ± 4.85
Mean non-inflammatory lesion count	10.44 ± 4.43	10.24 ± 6.25
Mean total lesion count	15.8 ± 10.1	16.1 ± 8.4
Mean GEA score	1.42 ± 0.50	1.38 ± 0.61

CADI, Cardiff Acne Disability Index; GEA, Global Acne Severity Scale; SD, standard deviation.

-19.7 ± 0.9 in the DC group). The mean GEA score had decreased from 2.6 ± 0.1 to 1.4 ± 0.1 in the DC group and from 2.8 ± 0.1 to 1.5 ± 0.1 in the vehicle group. Evolution over time of mean lesion counts is given in Figure 1.

Overall, the investigator rated the efficacy as good or excellent in 80.0% of patients in the DC group compared with 59.0% in the vehicle group (P=0.02).

Patients in the DC group applied significantly (P=0.0001) less BPO (32.0 ± 3.8 g) than those in the vehicle group (54.8 ± 4.8 g); no difference was observed for the quantity of vehicle (47.3 ± 3.7 g) and DC (45.9 ± 3.5 g) used.

Overall, 65.0% and 61.0% of patients in the DC and vehicle groups, respectively, rated the efficacy of their treatment as good or excellent at week 6. This incidence increased in the DC group to 80.0% and 71.0% in the vehicle group at week 12.

The mean CADI score had decreased in the DC group by 0.61 ± 1.17 from 2.61 ± 2.26 at baseline to 2.00 ± 2.03, and in the vehicle group by 0.30 ± 1.88 from 4.00 ± 3.05 at baseline to 3.70 ± 03.25 at week 12. The improvement of the CADI score from baseline was significant (P=0.0007) after 12 weeks of use of the DC compared with the vehicle.

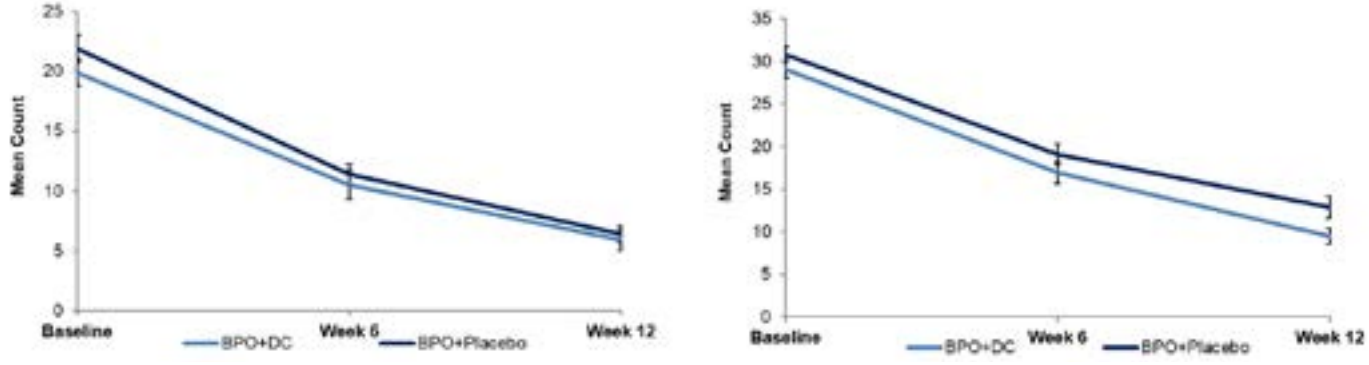
Phase 2: Baseline values for mean inflammatory, non-inflammatory, and total lesion count, as well as for the mean GEA score, are given in Table 1.

The mean inflammatory lesion count of patients in the DC group was 5.58 ± 4.85 in the DC group and 5.64 ± 4.60 in the vehicle group. After 12 weeks of use, it decreased to 3.55 ± 5.23 in the DC group and increased to 6.98 ± 5.44 in the vehicle group (both P<0.0001).

At baseline, the mean non-inflammatory lesion count in the DC group was 10.24 ± 6.25, and in the vehicle group 10.44 ± 4.43. After 12 weeks of use, it decreased to 6.68 ± 7.12 in the DC group and increased to 12.84 ± 8.14 in the vehicle group (both P<0.0001).

The mean number of total lesions decreased with the DC from 15.8 ± 10.1 at baseline to 10.2 ± 10.9 after 12 weeks, while it

FIGURE 1. Mean lesion count during the treatment phase (benzoyl peroxide + dermocosmetic or vehicle). (1A) Inflammatory lesions. (1B) Non-inflammatory lesions.



increased from 16.1 ± 8.4 at baseline to 19.8 ± 11.8 with vehicle (both P <0.0001).

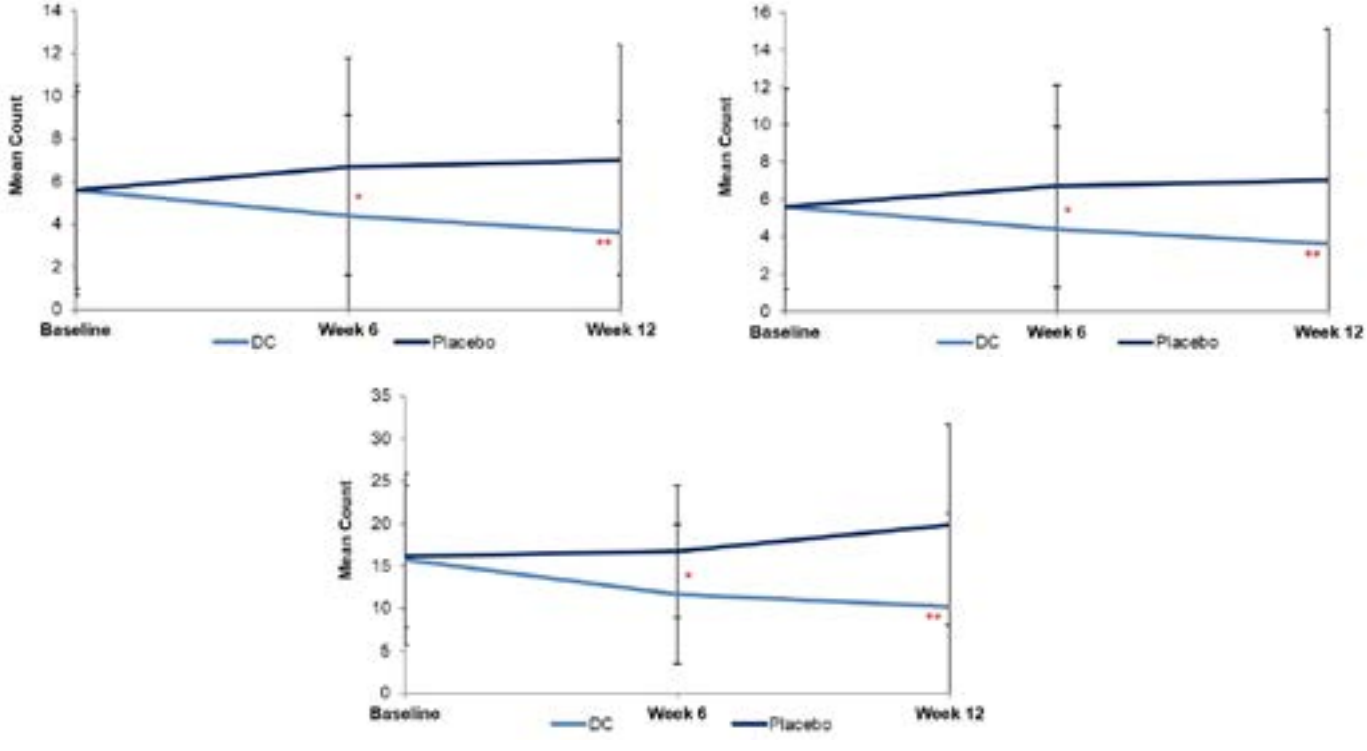
Evolution over time for lesion counts of phase 2 is provided in Figure 2.

The GEA score increased with the vehicle from 1.42 ± 0.50 to 1.91 ± 0.78 (P=0.0009) at week 12, while it continued to decrease with the DC (week 12: 1.27 ± 0.66 vs baseline: 1.38 ± 0.61).

The percentage of a good or excellent efficacy of the DC was significantly more highly rated by the investigators (week 6: 93.3%%, P<0.0017; week 12 90.9%, P=0.0002) than vehicle (week 6: 71.1%; week 12: 67.4%). Patient satisfaction (good or excellent) was more important with the DC after 12 weeks (DC: 86.4%, vehicle: 74.1%), although the difference was not significant.

The CADI score decreased in both groups. The decrease with the DC was more important (-0.61 ± 1.17, baseline: 2.61 ± 2.26, week 12: 2.00 ± 2.03) compared with that of vehicle (-0.30 ±

FIGURE 2. Mean lesion count during maintenance (dermocosmetic or vehicle). (2A) Inflammatory lesions. *P<0.0074, **P<0.0001 in favor of dermocosmetic compared with vehicle. (2B) Non-inflammatory lesions. *P<0.0401, **P<0.0001 in favor of dermocosmetic compared with vehicle. (2C) Total lesions. *P<0.00024, **P<0.0001 in favor of dermoscosmetic compared with vehicle.



1.88, baseline: 4.00 ± 3.05, week 12: 3.70 ± 3.25), although the difference was not significant between the 2 groups. The improvement of the CADI score from baseline was significant (*P*=0.0007) after 12 weeks of use of the DC, but not with the vehicle.

Local Tolerability

Phase 1: Mean erythema scores assessed by the investigator were 0.9 ± 0.1 in the DC group and 0.8 ± 0.1 in the vehicle group at baseline. After 12 weeks, scores had decreased to 0.6 ± 0.1 in both groups. Mean desquamation scores at baseline were 0.1 ± 0.04 in the DC group and 0.04 ± 0.03 in the vehicle group. Mean scores were 0.02 ± 0.02 after 12 weeks. Local tolerance scores were 2.7 ± 0.1 at baseline and 2.8 ± 0.1 at week 12. Overall, the investigator rated the tolerance to treatment as good or excellent: 48.0% in the vehicle group and 46.0% in the DC group. According to the patients, pruritus, stinging, and burning-sensation mean scores had decreased from baseline (0.1 ± 0.1, 0.1 ± 0.05 and 0.1 ± 0.04 in the DC and 0.1 ± 1.1, 0.1 ± 0.03and 0.04 ± 0.04 in the vehicle group) after 12 weeks.

Global tolerance scores were almost identical in both groups (DC: 100%; vehicle: 96.0%).

Phase 2: The percentage of patients with mild acne after 12 weeks of maintenance care was significantly (*P*=0.0309) higher with the DC (79.5% vs 55.6% at baseline) than the vehicle (58.1% vs 62.2% at baseline). No change from baseline mean scores were observed for pruritus, tingling sensation, and burning sensation after 12 weeks of maintenance. Global local tolerability to the DC was better (100%) compared with vehicle (95.3%).

DISCUSSION

Results from this randomized, double-blind study conducted in 100 patients with mild to moderate acne showed that the DC used daily in combination with BPO applied every other evening was as effective as BPO used every day with a vehicle. While both combinations were very well tolerated, the DC used adjuvant to BPO EOD significantly (*P*=0.03) improved the patients' quality of life and significantly (*P*=0.0001) reduced the quantity of BPO to be used by 50%, compared with the group using BPO QD and vehicle.

The use of BPO has been reported to induce in some patients desquamation, erythema, and patient-reported symptoms.[28] Adding a DC to help reduce the quantity of BPO applied has resulted in a good tolerance profile for BPO, without impacting its clinical efficacy in patients with mild to moderate acne when used instead of a traditional emollient. This observation is of importance as acne is a long-lasting condition requiring permanent and adapted care. Adding a well-tolerated DC that allows a decrease in the number of BPO applications may thus improve treatment adherence.

Results from the maintenance phase showed that the daily use of DC in patients continued to decrease the inflammatory, non-inflammatory, and total lesion count, while an increase was observed with vehicle after 6 and 12 weeks of maintenance care. So did the GEA score; however, with a significant difference (*P*=0.0002) between the DC (week 12: -0.09 and vehicle (week 12: 0.51). After 12 weeks of follow-up, significantly (*P*=0.0309) more patients with DC had their erythema improved (mild erythema: 79.5%) compared with vehicle patients (mild erythema: 58.1%).

This study highlights the interest of a DC to maintain the treatment success after topical therapy with BPO was stopped. Although acne is a chronic disease requiring long-term management, the use of pharmacological treatments as maintenance may not always be necessary for the management of milder forms of acne, and specifically developed dermocosmetics may provide adequate care. Moreover, in addition to their benefit in maintaining control of acne lesions, they may also improve local tolerance compared with topical drugs; and thus adherence. The tested DC maintained the treatment outcome and was well tolerated. It may thus be a good alternative to pharmacological treatments in the care of milder forms of acne. Moreover, the significant (*P*<0.05) decrease of CADI observed during phase 1 in the combination of the DC and BPO EOD was maintained in patients who received the DC during the maintenance phase. This was possibly due to the good efficacy and good to excellent local tolerance profile of the DC, already confirmed in a previous study.[23]

In conclusion, the tested DC in adjunct to BPO EOD had the same efficacy as BPO QD, allowing less use of BPO without any impact on acne efficacy. Used in monotherapy as a maintenance post BPO, DC proved its superior efficacy vs vehicle, with good tolerance.

DISCLOSURES

Sophie Seité, Ann'Laure Demessant-Flavigny, and Delphine Kerob are employees of La Roche-Posay Laboratoire Dermatologique. Brigitte Dréno is a consultant to La Roche-Posay Laboratoire Dermatologique and received honoraria from them to conduct the study. Amir Khammari has no conflicts of interest to disclose.

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Data Availability Statement: The data that support the findings of this work are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

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Recombinant Zoster Vaccine Reduces 3-Year Cardiovascular Risk: Insights From a Multi-Centered Database

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ABSTRACT

Background: Herpes zoster increases the risk for stroke and myocardial infarction. Zoster vaccination's impact on this risk is understudied. This retrospective work sought to determine if prophylactic herpes zoster vaccination may reduce the risk of stroke, myocardial infarction, and/or mortality.

Methods: A cohort analysis utilized TriNetX, a national, federated database. In one analysis, patients who received 2 doses of recombinant zoster vaccine (RZV) were compared to adults without RZV. A 1:1 propensity-score match analysis was conducted to adjust for demographics and comorbidities in calculating adjusted Relative Risks (aRR) with 95% confidence intervals. First-time incidences for myocardial infarction, stroke, and mortality were assessed after 3 years. A subgroup analysis between RZV and zoster vaccine live (ZVL) was also assessed.

Results: Matched cohorts of 7,657 patients revealed that adults who received 2 doses of RZV were at lower risk of MI (aRR [95% CI])= (0.73 [0.55,0.96]) and mortality (0.7 [0.57,0.88]) while having similar risk for stroke (0.97 [0.75,1.26]). Further subgroup analysis also revealed a reduced risk of 3-year mortality when compared to the ZVL cohort (0.84 [0.74,0.95]). Sample size and comorbidities included in the analysis were limited by using a large database.

Conclusions: RZV reduces the 3-year risk for myocardial infarction and mortality.

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INTRODUCTION

Approximately one in three people within the United States of America (US) will develop herpes zoster in their lifetime.[1] Herpes zoster (shingles) is a reactivation of latent Varicella-Zoster Virus (VZV), which is responsible for varicella (chickenpox).[2] Zoster is often seen in individuals over 50 or with compromised immune systems.[3] Reactivation of VZV manifests as painful rash and potential medical complications such as Post-Herpetic Neuralgia (PHN), and vision loss due to Herpes Zoster Opthalmicus (HZO) may occur.[4]

Age and immunosuppression can increase the risk of herpes zoster. In the US, the number of Americans above the age of 60 increased by 34% between 2009 and 2019, and the population aged 65 and older numbered 54.1 million in 2019 (16% of the total population).[5] Immunosenescence occurs with aging and correlates to decreased or absent T-lymphocyte response to VZV antigen, increasing the risk of herpes zoster.[6] In the US, the incidence of herpes zoster is approximately 4 cases per 1,000 annually and the incidence among people 60 years and older is about 1 case per 100 annually.[7] A high incidence of herpes zoster has also been reported in immunocompromised or immunosuppressed patients of any age.[8,9]

Studies report that herpes zoster increases the risk of cardiovascular and cerebrovascular events, including stroke and myocardial infarction.[10,11,12] Herpes zoster vaccination's impact on these events is understudied. Given the growing population at risk for herpes zoster reactivation and the reported relationship between herpes zoster and other health issues, prevention is important to boost VZV-specific immunity.

The importance of vaccination in reducing herpes zoster disease burden and the immunological mechanism of action is well understood.[13] Until November 2020, two herpes zoster vaccines were available in the US: the single-dose live-attenuated vaccine (Zoster Vaccine Live [ZVL], Zostavax® [Merck & Co., Inc.]), and the two-dose adjuvanted vaccine (Recombinant Zoster Vaccine [RZV], Shingrix® [GlaxoSmithKline]).The US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommends RZV vaccination for individuals ≥50 and previously recommended ZVL for individuals ≥60.[14,15] Currently, only RZV is available in the US. RZV's efficacy after 3 years has been studied for the prevention of herpes zoster in individuals aged 50-59 to be 96.6% (95% Confidence Interval [CI] = 89.6–99.3) and 97.4% (95% CI = 90.1–99.7) in individuals aged 60–69 years.[16] In July 2021, the US Food and Drug Administration (FDA) expanded the indication of RZV for immunosuppressed and immunocompromised patients, and in January 2022, the ACIP recommended the two-dose RZV for this population ≥19.[17,18]

This retrospective work sought to determine if prophylactic herpes zoster vaccination may reduce the risk of stroke, myocardial infarction, and/or mortality. Further, we analyzed a subgroup of individuals who received either RZV or ZVL to study their outcomes.

MATERIALS AND METHODS

This retrospective cohort analysis utilized TriNetX, a national, federated database composed of Electronic Medical Records (EMR) from 103+ million patients across 63+ healthcare organizations in the US. Search queries were used to identify the populations for the study based on age, zoster vaccination status, or zoster vaccination type.

TABLE 1.

Summary of Baseline Characteristics for Individuals With or Without RZV Before and After Propensity Matching

Before Propensity Matching			
Characteristic Name	**Shingrix (N=7,657)**	**General Population (N=7,222,905)**	**Standard Mean Difference**
Age at Index	56.33±3.61	53.56±4.62	0.669
BMI	29.86±6.5	29.87±6.72	0.001
White	5857 (76.49%)	4282239 (59.29%)	0.375
Female	4071 (53.17%)	4079009 (56.47%)	0.066
Black or African American	1132 (14.78%)	990777 (13.72%)	0.031
Disorders of lipoprotein metabolism and other lipidemias	3886 (50.75%)	925092 (12.81%)	0.892
Essential (primary) hypertension	3837 (50.11%)	1099791 (15.23%)	0.801
Diabetes mellitus	1884 (24.61%)	462809 (6.41%)	0.519
Other diseases of liver	726 (9.48%)	146495 (2.03%)	0.324
Other chronic obstructive pulmonary disease	409 (5.34%)	127643 (1.77%)	0.194
Acute kidney failure	293 (3.83%)	88440 (1.22%)	0.166
Rheumatoid arthritis with rheumatoid factor	83 (1.08%)	13063 (0.18%)	0.114
Systemic lupus erythematosus (SLE)	38 (0.5%)	23693 (0.33%)	0.026
After Propensity Matching			
Characteristic Name	**Shingrix (N=7,657)**	**General Population (N=7,657)**	**Standard Mean Difference**
Age at Index	56.33±3.61	56.31±3.62	0.005
BMI	29.86±6.5	30.24±6.73	0.058
White	5857 (76.49%)	5856 (76.48%)	<0.001
Female	4071 (53.17%)	4067 (53.12%)	0.001
Black or African American	1132 (14.78%)	1143 (14.93%)	0.004
Disorders of lipoprotein metabolism and other lipidemias	3886 (50.75%)	3891 (50.82%)	0.001
Essential (primary) hypertension	3837 (50.11%)	3841 (50.16%)	0.001
Diabetes mellitus	1884 (24.61%)	1888 (24.66%)	0.001
Other diseases of liver	726 (9.48%)	722 (9.43%)	0.002
Other chronic obstructive pulmonary disease	409 (5.34%)	398 (5.2%)	0.006
Acute kidney failure	293 (3.83%)	288 (3.76%)	0.003
Rheumatoid arthritis with rheumatoid factor	83 (1.08%)	78 (1.02%)	0.006
Systemic lupus erythematosus (SLE)	38 (0.5%)	43 (0.56%)	0.009

Each cohort underwent 1:1 propensity score matching analysis to balance the cohorts by demographics (age, body mass index, race, and sex) and comorbidities (hyperlipidemia, essential hypertension, diabetes mellitus, liver disease, COPD, acute kidney failure, rheumatoid arthritis, and systemic lupus erythematosus). Patients with a prior history of a stroke, myocardial infarction, mortality, or COVID-19 infection were excluded from this analysis.

TABLE 2.

Summary Of Baseline Characteristics for Individuals Vaccinated With RZV Or ZVL Before and After Propensity Matching			
Before Propensity Matching			
Characteristic Name	**Shingrix (N=14,578)**	**Zostavax (N=252,194)**	**Standard Mean Difference**
Age at Index	62.07±7.7	66.85±7.85	0.615
BMI	29.59±6.29	29.27±6.15	0.052
White	11465 (78.65%)	187762 (74.48%)	0.098
Female	7601 (52.14%)	146454 (58.1%)	0.12
Black or African American	1867 (12.81%)	31092 (12.33%)	0.014
Disorders of lipoprotein metabolism and other lipidemias	8337 (57.19%)	130921 (51.93%)	0.106
Essential (primary) hypertension	8203 (56.27%)	132591 (52.6%)	0.074
Diabetes mellitus	3659 (25.1%)	52838 (20.96%)	0.098
Other diseases of liver	1351 (9.27%)	10959 (4.35%)	0.196
Other chronic obstructive pulmonary disease	916 (6.28%)	17380 (6.89%)	0.025
Acute kidney failure	672 (4.61%)	8503 (3.37%)	0.063
Rheumatoid arthritis with rheumatoid factor	161 (1.1%)	526 (0.21%)	0.111
Systemic lupus erythematosus (SLE)	72 (0.49%)	1066 (0.42%)	0.011
After Propensity Matching			
Characteristic Name	**Shingrix (N=14,536)**	**Zostavax (N=14,536)**	**Standard Mean Difference**
Age at Index	62.1±7.69	62.3±7.53	0.027
BMI	29.58±6.29	29.61±6.24	0.004
White	11427 (78.61%)	11493 (79.07%)	0.011
Female	7580 (52.15%)	7601 (52.29%)	0.003
Black or African American	1864 (12.82%)	1871 (12.87%)	0.001
Disorders of lipoprotein metabolism and other lipidemias	8302 (57.11%)	8383 (57.67%)	0.011
Essential (primary) hypertension	8172 (56.22%)	8216 (56.52%)	0.006
Diabetes mellitus	3637 (25.02%)	3664 (25.21%)	0.004
Other diseases of liver	1326 (9.12%)	1440 (9.91%)	0.027
Other chronic obstructive pulmonary disease	916 (6.3%)	975 (6.71%)	0.016
Acute kidney failure	662 (4.55%)	800 (5.5%)	0.043
Rheumatoid arthritis with rheumatoid factor	143 (0.98%)	240 (1.65%)	0.059
Systemic lupus erythematosus (SLE)	72 (0.5%)	85 (0.59%)	0.012

Each cohort underwent 1:1 propensity score matching analysis to balance the cohorts by demographics (age, body mass index, race, and sex) and comorbidities (hyperlipidemia, essential hypertension, diabetes mellitus, liver disease, COPD, acute kidney failure, rheumatoid arthritis, and systemic lupus erythematosus). Patients with a prior history of a stroke, myocardial infarction, mortality, or COVID-19 infection were excluded from this analysis.

Three populations were analyzed for this study: those vaccinated with RZV or ZVL, and those who were unvaccinated. International Classification of Diseases 10th Revision (ICD-10) and Current Procedural Terminology (CPT) codes were utilized to identify patients with herpes zoster vaccination and outcomes of interest.

We performed two analyses to assess the risk for stroke, myocardial infarction, and/or mortality (RZV vs control and RZV vs ZVL). Given the high efficacy rate for RZV reported at 3 years, outcomes were assessed after 3 years of obtaining two doses of RZV. A 1:1 Propensity Score Matching (PSM) analysis was used to balance each cohort for demographics and comorbidities (Table 1 and Table 2). Comorbidities analyzed in this study included: obesity, hyperlipidemia, essential hypertension, diabetes mellitus, other diseases of the liver, COPD, acute kidney failure, rheumatoid arthritis, and systemic lupus erythematosus. Cohorts were matched to study the effects of patients who either received two doses of RZV (between October 20, 2017, and July 1, 2019; aged 50-65) or received no herpes zoster vaccine (control; aged 50-65) and patients who received either two doses of RZV (between October 20, 2017, and July 1, 2019; ≥50) or one dose of ZVL (before July 1, 2019; ≥60). After PSM, adjusted Relative Risk (aRR) for stroke, myocardial infarction, and mortality were calculated with 95% CI.

RESULTS

7,489,677 patients were used in the analysis. 7,222,905 patients made up the control cohort and did not receive either vaccine, 14,578 patients made up the RZV cohort and were fully vaccinated, and 252,194 patients made up the ZVL cohort and were fully vaccinated.

FIGURE 1. Myocardial infarction and mortality risk decreased for patients who received two doses of RZV compared to the general population (aRR [95% CI])=(0.73 [0.55,0.96]) *P*<0.025 and mortality (0.7 [0.57,0.88]) *P*<0.001 while having similar risk for stroke (0.97 [0.75,1.26]) *P*<0.829 when compared to the general population cohort.

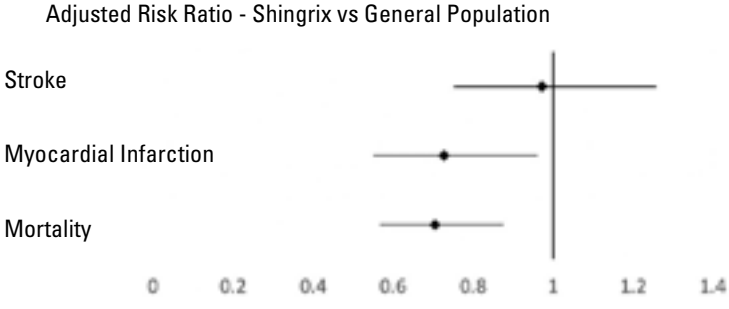
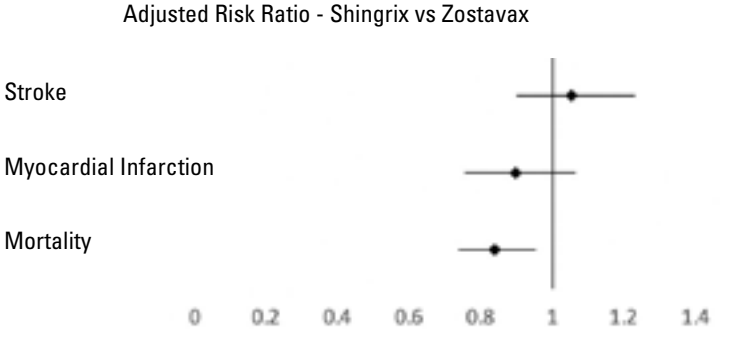


FIGURE 2. Mortality decreased for patients who received two doses of RZV compared to ZVL (aRR [95% CI])=(0.84 [0.74,0.95]) *P*<0.006.



After PSM, matched cohorts (N=7,657) of patients revealed that adults aged 50-65 who received two doses of RZV were at lower risk of myocardial infarction (aRR [95% CI])=(0.73 [0.55,0.96]) *P*<0.025 and mortality (0.7 [0.57,0.88]) *P*<0.001 while having similar risk for stroke (0.97 [0.75,1.26]) *P*<0.829 [Figure 1] when compared to the general population cohort.

A propensity-matched subgroup analysis based on type of zoster vaccination (N=14,536) also revealed that RZV reduced the risk of 3-year mortality when compared to the ZVL cohort (aRR [95% CI])=(0.84 [0.74,0.95]) *P*<0.006 [Figure 2]. Further, matched cohorts who received RZV with hyperlipidemia (N=3,426) had a smaller risk of mortality (aRR [95% CI])=(0.5 [0.37,0.67]) *P*<0.001 while having similar risk of myocardial infarction (1.8 [1.08,2.99]) *P*<0.022 or stroke (1.28 [0.87,1.87]) *P*<0.204, when compared to patients who received RZV and did not have hyperlipidemia.

CONCLUSION

As the adult population in the US ages, the risk for herpes zoster will compound and vaccination will increasingly become an important public health and policy topic. Additionally, those with hyperlipidemia, who may be at increased risk for cardiovascular events, may see a decreased risk of mortality if they receive zoster vaccination. Widespread vaccination against herpes zoster has the potential to decrease the risk of myocardial infarction, mortality, and decrease health care expenditures.

Our study used a large nationally representative database that has inherent limitations. To limit the risk of coding discrepancies, we identified patients with stroke and myocardial infarction through entries of ICD-10 and CPT codes for each, a method that has been previously validated in claims-based studies.[19-21] Discontinuous enrollment may lead to interventions or outcomes outside of the TriNetX dataset and a large sample size allows for even distribution across study cohorts. To account for the level of healthcare contact, we used PSM to balance patients with common comorbidities. Additionally, it is unknown how coronavirus could affect these results as it is also known to increase the risk of thromboembolic phenomenon.[22] Future considerations may include diagnosis with COVID-19 or vaccination for COVID-19 into matching criteria to assess outcomes when also vaccinated for herpes zoster. Further study is needed to understand if herpes zoster vaccination may also reduce the risk of cardiovascular or cerebrovascular events in immunocompromised and immunosuppressed patients.

This retrospective cohort study suggests that zoster vaccination,

specifically RZV, reduces the 3-year risk for myocardial infarction in those aged 50-65, particularly in those with hyperlipidemia, and demonstrates additional benefit of RZV over ZVL. The benefits of zoster vaccination extend beyond primary prevention of zoster.

DISCLOSURES

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Off-Label Use of Janus Kinase Inhibitors in Inflammatory Cutaneous Diseases

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ABSTRACT

Dysregulation of Janus kinase (JAK) pathways from uncontrolled cytokine signaling comprises the pathological basis for many complex inflammatory cutaneous disorders. Oral JAK inhibitors, upadacitinib, tofacitinib, and baricitinib targeting JAK 1 and JAK 1/3, respectively, are currently US Food and Drug Administration (FDA)-approved for several rheumatic conditions. However, studies have shown that JAK-mediated signaling pathways are involved in many immune-related dermatologic conditions. As a result, for recalcitrant diseases, JAK inhibitors are potential alternative therapies due to their broad targeted inhibitory mechanisms.

In this case series, we present the successful off-label treatment of 6 cases across dermatomyositis, hidradenitis suppurativa, cutaneous lupus, and cutaneous Crohn's disease, which failed conventional therapies with upadacitinib or tofacitinib. In the 3 dermatomyositis cases, use of upadacitinib or tofacitinib demonstrated positive clinical outcomes, with no recurrent symptoms in cases where upadacitinib was used. In treatment-resistant hidradenitis suppurativa, upadacitinib demonstrated reduced systemic flares and moderate cutaneous symptom improvement. In the case of cutaneous Crohn's disease, upadacitinib resulted in reduced cutaneous symptoms without new flares. Tofacitinib resulted in completed resolution of cutaneous symptoms in our patient's case of cutaneous lupus erythematosus. JAK inhibitors upadacitinib and tofacitinib may be potential drug candidates in patients with treatment-resistant disease, especially in cases of inflammatory cutaneous conditions such as dermatomyositis, hidradenitis suppurativa, cutaneous lupus, and cutaneous Crohn's disease. Further studies with larger sample sizes among these conditions are warranted to assess potential broader applicability of the positive results demonstrated in our patient cases.

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INTRODUCTION

Dysregulation of Janus kinase (JAK) pathways from uncontrolled cytokine signaling comprises the pathological basis for many complex inflammatory disorders.[1] Since JAK-family receptors are activated by numerous ligands, including several interleukins (IL), interferons (IFN), and hematopoietic growth factors, JAK inhibition can interfere with many different cellular pathways, potentially resulting in both desired efficacy as well as side effects.[2]

While most JAK inhibitors are US Food and Drug Administration (FDA)-approved for treating rheumatic conditions and are often used in patients not responding to disease-modifying antirheumatic drugs and biologics, there are several other inflammatory indications for which JAK inhibitors have demonstrated clinical promise.[3,4] For example, JAK-mediated signaling pathways are involved in many immune-related dermatologic conditions, including atopic dermatitis (IL-4/5/13), psoriasis (IL-23/17), dermatomyositis (IFN-α/β, IL-6/15), and vitiligo (IFN-γ), among others.[1,4] Additionally, in cases of cytokines that do not involve JAK pathways, JAK inhibitors have demonstrated utility by indirectly suppressing related molecules including upstream precursors that are later involved with JAK mechanisms, suggesting broader benefits of this drug class.[4]

Upadacitinib is an oral JAK inhibitor associated with reductions in IL-6 and IFN-γ that selectively targets JAK1, and is an example of an agent approved for use in rheumatoid arthritis, atopic dermatitis, and psoriatic arthritis, in addition to non-cutaneous autoimmune conditions.[3,5,6]Tofacitinib is an oral JAK 1/3 inhibitor disrupting IL-2/4/15/21 signaling, and is approved for broader use in rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis.[3,7]

In this report, we present different inflammatory systemic disorders that failed conventional treatment but were treated successfully with upadacitinib or tofacitinib, including dermatomyositis (DM), hidradenitis suppurativa (HS), cutaneous lupus, and cutaneous Crohn's disease.

Dermatomyositis

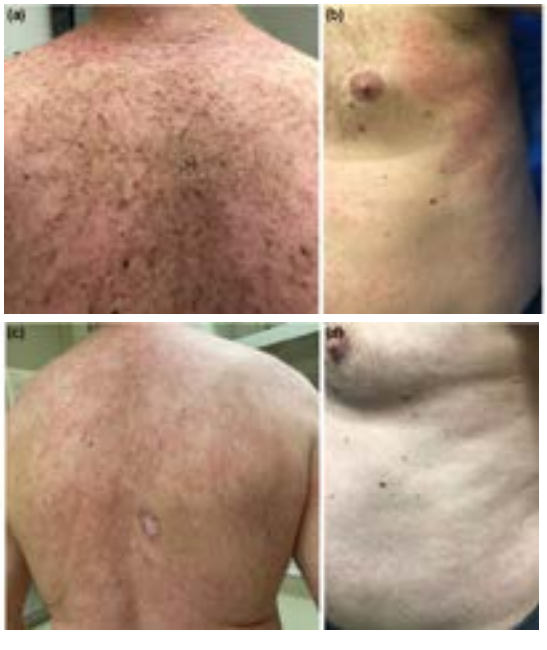
Dermatomyositis is a rare muscular inflammatory condition presenting with proximal muscle weakness, as well as cutaneous manifestations including heliotrope rash and Gottron's sign; however, it may also be accompanied by findings such as poikiloderma, periungual telangiectasia, and non-scarring alopecia.[8] Due to the immunosuppressive nature of therapies for DM, there is a high risk of malignancy associated with the disease, particularly lung, ovarian, and gastrointestinal cancers.[9] The etiology of this disorder has not been elucidated but is believed to have a genetic basis in patients of different backgrounds with particular human leukocyte antigen haplotypes.[10]

There is evidence that type I IFN (IFNα/β) activity may be involved in the pathogenesis of DM, which may indicate a role of JAK inhibitors as type I IFN is associated with JAK1.[11] Furthermore, skin and muscle biopsies of DM patients have found elevated levels of plasmacytoid dendritic cells (pDCs), which have been linked to elevated type I IFN signaling.[12] This implication of type 1 IFN signaling in DM is suggestive of a potential alternative for therapy with JAK inhibitors that requires further exploration.

CASE 1

A 59-year-old male presented with scaly erythematous plaques on the arms, trunk, and legs with body surface area (BSA) >15%. The patient also reported joint swelling and pain in the hands and knees. He was initially treated with ustekinumab 90 mg once every 3 months, apremilast 30 mg twice daily, and triamcinolone 0.1% ointment by an outside provider for suspected psoriasis and psoriatic arthritis. Given the inadequate response, a skin biopsy was done, which showed interface dermatitis suggestive of connective tissue disease including systemic lupus erythematous (SLE) or DM. He subsequently presented to our academic center for further management and treatment.

FIGURE 1. Erythematous macules and papules of the upper back and erythematous patches of the left trunk (A, B) before tofacitinib and (C, D) 5 months after tofacitinib.



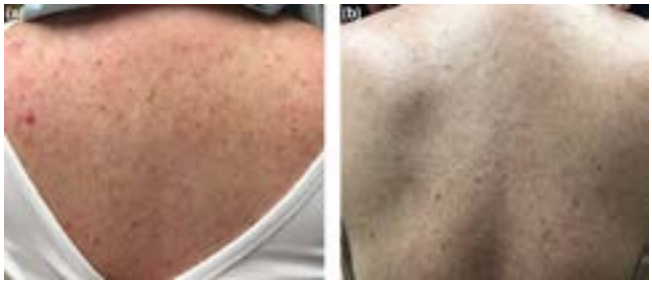
Autoimmune workup was significant for positive antinuclear antibody (ANA) with speckled pattern 1:1,280, and myositis panel positive for Ro-52. After an acute flare of skin lesions, low-dose prednisone taper for 2 weeks and off-label tofacitinib 11 mg extended-release daily was initiated. After 5 months of tofacitinib, the patient was stable and almost clear of skin lesions (Figure 1); however, recurrent flares of inflammatory arthritis of the hands and knees persisted.

CASE 2

A 75-year-old female presented with erythema of the hands, face, scalp, back, and chest, and dilated nail fold capillaries for over a year. Skin biopsy findings revealed interface dermatitis with increased dermal mucin. Labs showed ANA positive with 1:320 speckled pattern, SS-A positive, Ro-52 positive, and elevated creatine kinase (CK). The patient received intravenous immunoglobulin every 6 to 8 weeks for one year and hydroxychloroquine 200 mg twice daily for 2 years.

Despite therapy, examination revealed erythematous macules and papules of the face, trunk, arms, and legs, an acute flare of swollen joints of the hands, and morning stiffness. The patient was tapered off hydroxychloroquine and off-label tofacitinib 11 mg extended-release daily was started. Examination revealed decreased erythematous papules on the trunk and throughout the body after 4 months of tofacitinib (Figure 2). Due to persistent joint pains, tofacitinib was discontinued and switched to low-dose oral prednisone and off-label upadacitinib 15 mg daily. At her 3-month follow-up, the patient reported an overall improvement in joint pains and stiffness, with no new lesions to date.

FIGURE 2. Generalized erythematous macules and papules on the back (A) before tofacitinib and (B) 4 months after tofacitinib.



CASE 3

A 30-year-old female with a history of Raynaud's presented to our clinic for treatment of biopsy-proven DM. Additional workup was significant for ANA positive 1:160 speckled pattern, normal CK, normal aldolase, negative myositis panel, and positive electromyography consistent with myositis. An examination revealed erythematous patches on the chest, thighs, elbows, and hands with violaceous patches on both lower eyelids and knees. The patient also reported morning stiffness and proximal muscle weakness.

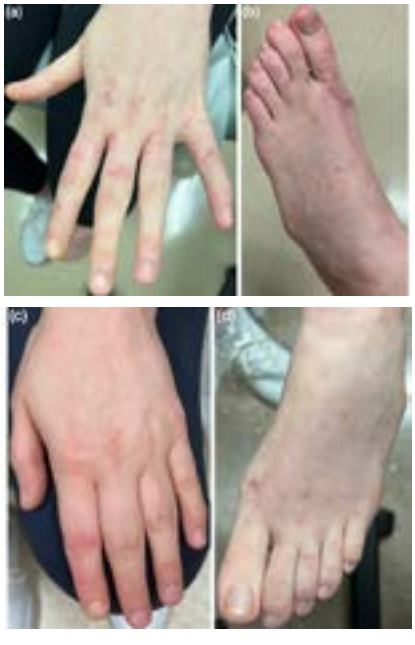
The patient had failed multiple therapies over 1.5 years, listed in Table 1, due to either inadequate response or intolerable adverse effects. Slight improvement in skin findings and muscle weakness were noted while on mycophenolic acid 720 mg twice daily and rituximab infusions. However, after a second infusion of rituximab, the patient developed herpetic oral blisters and was started on valaciclovir. Due to inadequate treatment response, the patient was started on off-label upadacitinib 15 mg daily, and near-clearance of the skin lesions was evident after 3 weeks (Figure 3). Upadacitinib was increased to 30 mg daily, and

TABLE 1.

Clinical Characteristics					
Cases	**Past Therapies**	**Physical Exam Findings**	**Additional Tests**	**Current Management**	**Clinical Response**
Dermatomyositis					
Case 1	Ustekinumab 90mg q3 months, Apremilast 30mg BID, Triamcinolone 0.1% ointment, Prednisone	Joint pain/swelling of hands, knees, photosensitivity, erythema of face, erythematous papules/ plaques of chest, trunk, arms, legs, morning stiffness, motor strength 5/5 all extremities	ANA positive with speckled pattern 1:1280, positive Ro-52, Chest CT- findings consistent with COPD	Tofacitinib 11mg XR daily low dose prednisone taper	Improvement of skin lesions, recurrent flares of inflammatory arthritis
Case 2	Clobetasol 0.05% cream, Triamcinolone 0.1% ointment, IVIg, Hydroxychloroquine 200mg BID, Tofacinitib11mg XR daily	Erythema of hands, face, scalp, back, and chest, photosensitivity, dilated nail fold capillaries, joint pains, swelling of hands, morning stiffness, motor strength 5/5 all extremities	ANA positive with 1:320 speckled pattern, positive SS-A, positive Ro-52, elevated CK, Chest CT- no ILD, PFT negative	Low dose prednisone taper, Upadacitinib 15mg daily	Clearance of skin lesions and decreased joint pain/ stiffness
Case 3	IVIg, Methotrexate 20mg once weekly, Mycophenolate mofetil 1000mg BID, Mycophenolic acid, 720mg BID, Azathioprine 50mg daily, Low dose prednisone Rituximab	Muscle weakness, morning stiffness, motor strength 3/5 all proximal extremities	CK, Aldolase, LDH, myositis panel negative, EMG consistent with myositis, ANA positive 1:160 speckled pattern, Chest CT- no ILD, PFT negative	Mycophenolic acid taper, Rituximab taper, Upadacitinib 15 mg daily increased to 30mg daily	Clearance of skin lesions with improvement in muscle weakness
Hidradenitis Suppurativa					
Case 4	Spironolactone 100mg BID, Doxycycline 20mg BID, Clindamycin 1% solution, Metformin 500mg daily, Norgestimate and ethinyl estradiol, Adalimumab 40mg q weekly, IL Triamcinolone injections, Infliximab, Low dose prednisone	Inflamed cysts/ nodules, extensive scarring on axillae and inguinal regions, joint pains/stiffness of knees and elbows	CBC, CMP, hepatitis panel negative, ANA positive, rheumatoid factor negative	Spironolactone 100mg BID, Doxycycline 100mg BID, Clindamycin 1% solution, Upadacitinib 15mg daily	Decrease flares of HS, improvement in joint pain/stiffness
Cutaneous Lupus Erythematosus					
Case 5	Tacrolimus 0.1% ointment, Prednisone 20mg daily, Methotrexate*, Azathioprine 100mg daily, IL Triamcinolone injections, Clobetasol 0.05% solution	Diffuse hair thinning, malar rash, follicular plugging on ears, indented hyperpigmented atrophic plaque on the frontal and occipital scalp, discoid rash, and a hyperpigmented plaque on the nose	ANA positive with speckled pattern 1:1280, positive anti-dsDNA, positive anti-smith, positive anti-histone, positive anti-SS-A	Hydroxychloroquine 200mg BID, Tofacitinib 5mg BID, IL Triamcinolone injections q6-8 weeks	Clearance of skin lesions, hair regrowth, improvement of joint pains
Cutaneous Crohn's Disease					
Case 6	Adalimumab*, Cyclosporine 100mg daily, Infliximab, 5-ASA, Prednisone, Hyperbaric Oxygen Therapy, Azathioprine*, Methotrexate*, Oral Metronidazole*, Clobetasol 0.05% ointment, Tacrolimus 0.1% ointment, Mercaptopurine 50mg daily	Swelling and proliferation of the labia majora and minora, tender erosions on the intergluteal cleft	Surgical pathology of rectum and anus, total proctectomy active Crohn's anoproctitis with fissuring mucosal ulcers	Ustekinumab 90mg q4 weeks, Upadacitinib 15 mg daily	Overall improvement in cutaneous findings with no new lesions or flares

ANA, anti-nuclear antibody; IL, intralesional; BID, twice daily; XR, extended release; IVIg, intravenous immunoglobulin; CK, creatine kinase; ILD, interstitial lung disease; PFT, pulmonary function test; COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; EMG, electromyography
*specific dosing is unknown.

FIGURE 3. Erythematous papules on dorsum of hands and feet (A) before upadacitinib and (B) 3 weeks after upadacitinib.



mycophenolic acid and Rituxan infusions were tapered, with no new lesions or flares in symptoms reported after 2 months.

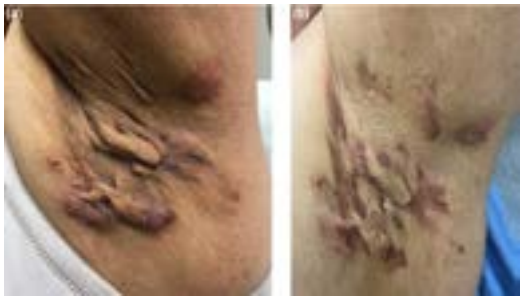
Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic cutaneous disorder demonstrating nodules, abscesses, and sinus tracts in apocrine gland regions.[13] While the pathogenesis of HS is still unclear, IL-17 has been shown to have a role in triggering HS.[14] Studies have shown the downregulation of IL-17 by JAK inhibitors, albeit indirectly through regulation of the IL-23 STAT-dependent cytokine; thus, targeting JAK/STAT signaling represents a potentially important therapeutic target for HS.[3,15,16]

CASE 4

A 28-year-old female with a long-standing history of refractory HS demonstrated inflamed cysts, nodules, and extensive scarring of the bilateral axillae and groin on examination. After multiple failed therapies, listed in Table 1, the patient was started on infliximab. There was an overall marked improvement in skin lesions with decreased flares of HS after 2 infliximab infusions. However, infliximab was discontinued due to insurance coverage issues. The patient ultimately was restarted on infliximab after 5 months and had minimal to no clinical response the second time. She began to have flares of symptoms and was treated with intralesional steroid injections once every 4 weeks. Due to the acute onset of inflammatory arthritis of the lower back, the patient was started on upadacitinib 15 mg daily. At the 2-month follow-up visit, there was an overall moderate decrease in inflammation and erythema of cysts and nodules (Figure 4). The patient also reported an improvement in joint pain and

FIGURE 4. Tender inflamed cysts and nodules of the left axillae (A) before upadacitinib and (B) 2 months after upadacitinib.



decreased HS flares. Upadacitinib, however, was held prior to getting the COVID-19 booster vaccine, and the patient did note a flare of symptoms while off treatment.

Cutaneous Lupus Erythematosus

Systemic lupus erythematosus is a multisystem autoimmune condition, presenting most commonly with cutaneous, musculoskeletal, renal, and neurological manifestations, which typically affects females aged 15 to 44.[17] Skin presentations range from a generalized, localized, or malar rash present in a photosensitive distribution, with specific types such as discoid lupus having unique characteristics such as scarring and cicatricial alopecia.[18] Naso-oral ulcers are also common, and some non-specific cutaneous presentations of SLE include vasculitis, urticaria, and bullae.[17,18]

Treatments for cutaneous lupus generally include topicals like corticosteroids and calcineurin inhibitors, as well as systemic treatments including antimalarials and oral steroids; however, long-term use of systemic agents often results in treatment-associated complications.[19,20] Pathogenesis of cutaneous lupus involves many cytokines, including TNFα, IL-1α/β, IL-6, and IFN-α/κ/λ, as well as IL-12/23 from pDC activation, many of which signal through the JAK/STAT signaling pathway, thereby suggesting a potential therapeutic role for JAK inhibitors.[21]

CASE 5

A 35-year-old female with a history of SLE presented to our clinic with an erythematous malar rash, intermittent generalized joint pains, hyperpigmented plaque on the left nasal ala, and atrophic hair loss patches on the frontal and occipital scalp. Autoimmune workup was significant for positive ANA with speckled pattern 1:1,280, positive anti-dsDNA, positive anti-Smith, positive anti-SS-A, and low C4 level. She was diagnosed with SLE in 2012 and failed multiple therapies over the years as listed in Table 1. At her initial visit, she was on hydroxychloroquine 200 mg twice daily, azathioprine 100 mg daily, and prednisone 20 mg daily, and she received monthly intralesional steroid injections for the scalp. Tacrolimus 0.1% ointment twice daily was recommended for the hyperpigmented plaque on the nose and clobetasol 0.05% solution for the scalp.

FIGURE 5. Hair loss patch on the crown of the scalp with diffuse hair thinning (A) before tofacitinib and (B) 3 months after tofacitinib.

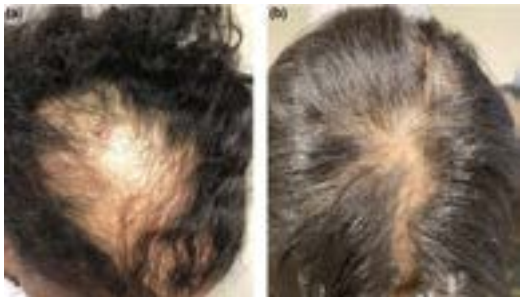
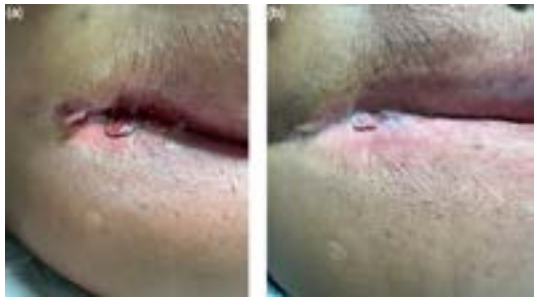


FIGURE 6. Tender erythematous erosions of the intergluteal cleft (A) before upadacitinib and (B) 2 months after upadacitinib.



As a result of progression in symptoms, including prominent diffuse hair thinning of the scalp, acute intermittent episodes of chest pain, and increased joint pains of the hands, azathioprine was increased to 150 mg by rheumatology. A punch scalp biopsy revealed findings consistent with alopecia areata and off-label tofacitinib 5 mg twice daily was initiated for hair loss, persistent inflammatory arthritis, and cutaneous lupus lesions that were nonresponsive to azathioprine. Azathioprine was discontinued once tofacitinib was started.

At the 3-month follow-up, the exam revealed improvement of erythematous papules and malar rash of the face and moderate hair regrowth on the crown of the scalp (Figure 5). After 5 months, the hyperpigmented plaque on the nose and malar rash completely resolved, with no flares in joint pains and no new lesions.

Cutaneous Crohn's Disease

Crohn's disease (CD) is a chronic inflammatory condition affecting the gastrointestinal tract, with skin involvement being present in up to 40% of cases.[22] Perianal fissures, ulcers, and vegetative plaques are common findings in cutaneous Crohn's.[22] Non-caseating granulomatous lesions may be seen at distant sites in metastatic CD, in addition to extraintestinal manifestations including erythema nodosum, aphthous ulcers, and pyoderma gangrenosum.[22,23] Studies have shown that the pathogenesis of CD and/or ulcerative colitis is mediated by IFN-γ, IL-9, IL-12, and IL-23, which are implicated in JAK/STAT signaling.[24] To date, some clinical trials evaluating the efficacy and safety profile of oral JAK inhibitors in CD and ulcerative colitis have shown promising results.[24,25]

CASE 6

A 35-year-old female with biopsy-proven cutaneous CD presented to our clinic with multiple erosions of the intergluteal cleft and labia minora. The patient was diagnosed with metastatic CD in 2002 and had failed multiple therapies as listed in Table 1, with slight improvement in cutaneous lesions following an exploratory laparotomy colectomy with end ileostomy and rectal resection in 2020.

When she presented to our clinic, she was on ustekinumab 90 mg every 4 weeks, with minimal improvement of her cutaneous Crohn's. Intralesional steroid injections and oral prednisone were offered as treatment options, but the patient deferred as she felt her symptoms were stable. At a follow-up appointment, examination revealed significant swelling and proliferation of the labia majora and minora, and tender erythematous erosions on the intergluteal cleft. Due to the progression of symptoms, off-label upadacitinib 15 mg daily was initiated, in combination with ustekinumab. After 2 months, there was overall improvement with less erythema and swelling of the labia majora and minora, as well as thin plaques and dry eroded areas on the intergluteal cleft (Figure 6). To date, the patient denies new lesions or flares of symptoms.

RESULTS AND DISCUSSION

As the molecular pathogeneses of various immune conditions continue to be elucidated, there may be a role for JAK inhibitors in their treatment such as those we present here. Many dermatological conditions and presentations involve inflammatory mediators that are involved in the JAK/STAT pathway, and JAK inhibitors have demonstrated considerable clinical improvement in patients where traditional treatments have failed.[4,16,19,26,27] The cases presented represent successful off-label use of upadacitinib or tofacitinib in dermatomyositis, hidradenitis suppurativa, cutaneous lupus, and cutaneous Crohn's disease.

In DM treatment, tofacitinib and ruxolitinib have most commonly demonstrated clinical benefit.[26,28,29] However, in our patients, upadacitinib or tofacitinib demonstrated positive clinical outcomes in all 3 cases of DM, with no recurrent symptoms or flares in the 2 cases where upadacitinib was used. Despite a restricted sample size, our findings suggest potentially greater utility of JAK1 inhibition in DM, though it must be confirmed in larger randomized clinical trials.

Various cases of recalcitrant HS have previously been treated with tofacitinib in combination with oral antibiotics and other immunosuppressive drugs, and recent phase II studies have also

indicated the utility of targeting JAK1 with the new experimental agent INCB054707.[30,31] In our patient with treatment-resistant HS, upadacitinib, preferentially targeting JAK1, was used alone and demonstrated moderate clinical benefit for cutaneous findings, with an overall reduction in systemic symptoms and flares. While results of a clinical trial for designated upadacitinib use in moderate to severe HS are currently pending, our case demonstrates a potential early indication of utility in recalcitrant HS.[32]

Cutaneous lupus erythematosus (CLE) consists of heterogeneous subtypes ranging from localized discoid plaques to severe and widespread erythematous papulosquamous lesions.[33] Dysregulation of JAK/STAT signaling has been implicated in both serum and skin biopsy studies in patients with CLE, prompting the use of JAK inhibitors.[12,34-37] Numerous case reports and case series have reported clearance of cutaneous lesions or significant clinical improvement as measured by cutaneous lupus erythematosus disease area and severity index following the use of tofacitinib and other systemic JAK inhibitors.[38-42] The case we present provides clinical evidence of successful tofacitinib use resulting in complete resolution of skin findings in SLE with no new flares and successful hair regrowth. This further suggests that oral JAK inhibitors may be an alternative therapy for refractory CLE and non-scarring alopecia when other agents are ineffective or contraindicated, although randomized clinical studies with larger study populations are warranted.

A phase II study evaluated the efficacy of upadacitinib in moderate-to-severe Crohn's disease and significantly demonstrated endoscopic remission in a dose-dependent manner, but did not report or assess the clinical response of cutaneous findings.[43,44] Cutaneous manifestations occur in approximately 22% to 44% of patients with Crohn's disease, and are often refractory to treatment.[45] Current therapies are limited by drug resistance or significant adverse effects after long-term use, so an unmet need for new alternative therapies remains.[25,46] The case we present provides evidence for clinical improvement with the use of upadacitinib as demonstrated by overall reduction in cutaneous manifestations after 2 months and no new flares to date. Therefore, upadacitinib merits consideration as an alternative therapy for refractory cutaneous CD. Similarly, phase II trial data of filgotinib, a selective JAK1 inhibitor, demonstrated clinical improvement in treating perianal fistulae,[3,27,47,48] further supporting the use of selective JAK1 inhibition in cutaneous CD.

In this report, we demonstrate the clinical benefit of upadacitinib and tofacitinib in various inflammatory cutaneous conditions. It is also important to consider the potential utility of other related agents when investigating off-label use, especially during a period of significant exploration for broader applications for this drug class. Other globally approved agents in the JAK inhibitor family include abrocitinib, baricitinib, delgocitinib, fedratinib, filgotinib, oclacitinib, pacritinib, peficitinib, and ruxolitinib.[49-51] Importantly, in off-label use, the risks for adverse events must be assessed on an individual basis, as the immune suppressive actions of JAK inhibitors increase the likelihood for lung, heart, and gastrointestinal disease or cancers; so agents should be selected judiciously.[52,53] Mindful of these considerations, the JAK inhibitors upadacitinib and tofacitinib continue to demonstrate potential in the management of inflammatory skin conditions, and could be potential drug candidates in patients with treatment-resistant disease.

DISCLOSURES

Saakshi Khattri is an employee of Mount Sinai and a consultant for AbbVie, Eli Lilly, Glenmark, Ichnos Sciences, Janssen, and Novartis. She serves on the Advisory Boards for Eli Lilly, Glenmark, Ichnos Sciences, Janssen, Novartis, and UCB. The other authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Topical Stabilized Super-Oxidized Hypochlorous Acid for Wound Healing in Hair Restoration Surgery: A Real Time Usage-Controlled Trial Evaluating Safety, Efficacy, and Tolerability

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ABSTRACT

Objective: Assess the perceived efficacy of stabilized, super-oxidized hypochlorous acid (HOCl) in hair transplant surgical procedures intraoperative and post-operative.

Background: Stabilized, super-oxidized hypochlorous acid (HOCl), is highly effective against bacterial, fungal, and viral microorganisms. In addition, topical HOCl, will increase tissue oxygenation of wound sites to aid in healing. This molecule represents an ideal agent for intraoperative and postoperative use in hair restoration procedures which involve thousands of small wounds.

Methods: 35 patients were enrolled in a multi-site study following repeat or initial hair restoration surgery. Surgeons were provided a 500mL trigger spray bottle of HOCl spray liquid for use prior to and throughout the surgical procedure. Patients were provided with a ten-day supply of HOCl for post-operative care. Two formulations were utilized, one was applied to the recipient sites while the other to the donor area postoperatively. Patients and surgeons were provided with observational surveys regarding healing and usage of the products.

Results: Statistical analysis found 56% had significant reduction in the amount of erythema compared to their current wound healing regimen. More than half of the patients (54%) had significant improvement of pruritus. The compliance rating for this study was 97% among patients. Surgeons were queried on the overall efficacy. There were no incidence of donor or recipient tissue necrosis.

Conclusion: The evolution of hair restoration surgery has been accompanied by large numbers of grafts being implanted. This change necessitates the requirement for optimum intraoperative and postoperative care. Topical, stabilized hypochlorous spray represents a major advance in wound cleansing and healing and offers the theoretical benefits of reducing tissue necrosis through oxygenation.

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INTRODUCTION

Surgeons performing hair restoration procedures routinely create thousands of micro incisions in the donor and recipient areas. This procedure creates a very unique set of challenges. Intraoperative bleeding control can become as issue. No spray solutions have shown a benefit regarding hemostasis. Hypochlorous acid (HOCl) may be the exception. Postoperative complications in hair restoration surgery are infrequent, but include infection, swelling, bleeding, and, rarely, tissue necrosis. There are many types of topical products available for post-operative wound care but few have been evaluated in clinical trials.[1] There is scant evidence that any one topical agent speeds healing of surgical wounds by secondary intention more than another agent.[1] Compelling evidence exists in the literature which demonstrates that topical HOCl represents an ideal agent of choice for postoperative care in hair restoration surgery patients.[7-10]

Stabilized Hypochlorous

HOCl is a naturally occurring molecule whose mechanism of action is achieved through white blood cells. Specifically, neutrophils augment host immunity when they release HOCl to aid in the destruction of pathogenic organisms such as bacteria, fungi, and yeast. Unlike antibiotics, when used topically as a stabilized formula, there is no evidence microbial resistance will emerge.[8]

Antimicrobial Properties

Studies show HOCl exhibits broad spectrum antimicrobial properties at concentrations of 0.1 ug/mL to 2.8 ug/mL.[11] The literature regarding its efficacy in the reduction of staph aureus is abundant.[21-25] A closer look at these various studies (which were performed with HOCl gels, sprays, and solutions) reveals that topical HOCl is impacted by both pH and formulation stability.[11,12] Degradation and instability issues of the HOCl

molecule have been solved with advanced manufacturing, chemistry, and storage techniques. Regardless of the vehicle, the antimicrobial properties are attributed to a direct cytotoxic reaction to microbial organisms. This includes both gram-positive and gram-negative bacteria. Biofilm breakdown is known to be essential to effectively combat wound infection [21,27-28] HOCl is shown to be effective in preventing biofilm formation and aiding in biofilm breakdown.[26]

HOCl as a Disinfectant

HOCl has emerged in the current SARS-CoV-2 pandemic as the most potent and environmentally safe disinfectant available.[33,34] Super-oxidized HOCl has demonstrated a wide range of efficacy against many human pathogens, including: coronavirus, BSE prions, and HPV. Some pathogens susceptible to stabilized HOCl are resistant to all other known disinfectants.[29,30] According to the Application for Inclusion in the 2021 WHO Essential Medicines List *"Unprecedented efficacy is matched with a benign safety profile that makes authentic homogeneous HOCl eminently suited to contemporary public health needs."*[10]

Anti-Inflammatory and Anti-Pruritic Qualities

Postoperative pain management and wound care go hand-in-hand. A study by XU on postoperative laser patients demonstrated that substance P increased gradually over time in the postoperative period with the usage of different wound healing ointments.[9] Substance P is a neuropeptide which provides a good basis for wound healing.[31] Optimal wound care can up regulate the expression of substance P. When wounds improve quickly patients are highly satisfied with the appearance and judge the procedure accordingly.[32] The pathways for pain and itch are similar.[2,3] Post-operative hair restoration surgery is traditionally associated with a fair amount of pruritus that is bothersome to patients. While this does not generally affect wound healing, there are instances in which scratching the donor and recipient site can be of concern.[16] Additional inflammation and subsequent increase in scar formation should be avoided if at all possible. Pelgrift published an overview of the anti-inflammatory effects of HOCl.[12] Anti-pruritic properties were attributed to a reduction in the release of histamine, leukotriene B4, and Interleukin-2. He further theorized that a reduction of pathogens, such as staph aureus, also plays a role.[12] Some authors suggest that HOCl acts like a mast cell membrane stabilizing inhibitor, decreasing granule secretion.[13] The literature is replete with citations documenting the anti-inflammatory effects that come in part from controlling the mast cell response.[8] Dharap demonstrated HOCl produced a significant reduction in the signs of inflammation in ulcer wounds.[14]

Hemostasis

Superoxidized, HOCl solution has been reported to have anti-coagulation properties. In an observational study of 60 dental procedures, the reported average blood loss was 500 cc to 600 cc with the HOCl and 900 cc to 1200 cc without.[35] The extrapolation of an anticoagulant effect on scalp tissue cannot be made without further studies. Hair transplant surgeons in the hypochlorous study group and technicians did report observing hemostatic properties of the HOCl spray solution intraoperatively. The limitations of this statement would be lack of a control observation group.

Tissue Oxygenation

Transcutaneous oximetry (TcPO2) can detect viable tissue with the highest probability of healing. Bongiovanni is often referenced when discussing micro-circulatory oxygenation and super-oxidized HOCl.[15] These data demonstrated that most venous leg ulcer (VLU) patients had elevated TcPO2 values immediately after exposure to HOCl. Important to note, TcPO2 levels remained elevated for 72 hours.[15] Perfusion is directly related to the delivery of oxygen. This effect on O^2 levels is of critical concern to all hair transplant surgeons because necrosis of both the donor and recipient tissue has been observed post operatively. Most commonly, this tissue death is attributed to a disruption of the micro circulation. There have been no forthcoming studies using topical HOCl that have demonstrated a reduction of this uncommon complication following hair restoration surgery. Future studies comparing the TcP02 levels of pre and post-hair transplant surgical regions after topical application of HOCl are warranted. Wasserbauer reported a small pilot study using stabilized HOCl spray intra-operatively and postoperatively for both donor area and recipient area, in 16 patients. No complications of compromised perfusion were reported.[7] The potential benefits of increased perfusion and oxygenation remains to be proven in hair restoration procedures, but the logical contributions to favorable outcomes are clear.

Scarring

Unsightly scarring is of major concern following a hair restoration procedure. Some patients are genetically predisposed to hypertrophic scars and keloids.[4,5,6] For wound care management, HOCl demonstrates both anti-inflammatory properties and anti-biofilm activity; but no definitive studies exist on the usage of this molecule in the prevention of abnormal scarring. Some authors have stated a theoretical advantage of early intentional use of HOCl after incisional surgery, to reduce the itch scratch cycle and subsequent scarring.[8,16]

Safety

The optimal post-surgical wound product should be of very low risk. As previously stated, a Cochrane review did not find any evidence that one topical agent speeds up healing of surgical wounds by secondary intention more than another agent.[1] Topical antibiotics can cause contact dermatitis and bacterial

resistance, and their use as prophylaxis for infection is no longer recommended by the American Academy of Dermatology.[17] Topical antiseptics have demonstrated excellent antimicrobial properties, but unfortunately may impede wound healing and have otologic and ocular toxicity.[17] In regard to the safety of HOCl, a review by Thorne et al[18] describes a large body of evidence available on safety. The Murine model demonstrated no adverse effects of HOCl after a single oral dose and 28-day repeated oral dosing.[18] A 2011 study by Morita et al evaluated the risk of biological toxicity in a murine model when HOCl was ingested as drinking water for 8 weeks. Visual inspection, gastrointestinal histology, inflammatory markers, mucosal thickness, periodontal tissue, tooth enamel, and other metrics were evaluated and no changes from controls were observed. Their conclusion was that HOCl has no systemic effects and would be safe if used as a mouthwash in humans, even if ingested.[19]

MATERIALS AND METHODS

Study participants: Thirty-five subjects who were scheduled for an upcoming hair transplant procedure were enrolled by the hypochlorous solution study group. Eligible subjects included healthy men or healthy women. The study population was diverse, with Caucasian, African-American, and Hispanic subjects all participating. Subjects signed an informed consent and agreed to follow the study requirements and provide survey data at day 1, day 3, day 5, and day 10.

Study Population and Design

An open label, single arm, controlled trial evaluated the intraoperative and post-operative use of topical stabilized hypochlorous spray in the donor and recipient areas of hair restoration patients. Patients were included into the study if they had a previous surgical hair restoration procedure or were undergoing an initial surgical procedure.

After a detailed explanation of the trial, all patients consented and agreed to participate. Surgeons were provided with a 500 mL trigger spray bottle of stabilized, super-oxidized hypochlorous spray liquid for intra-operative use. The technicians also used this HOCl spray intraoperatively. Post-surgically, the patients were provided with a 10-day supply of stabilized, super-oxidized hypochlorous solution for post-operative care (two 3 oz liquid spray bottles for the recipient site and two 3 oz hydrogel spray bottles for the donor site). The spray hydrogel product was applied to the donor area and the spray liquid was applied to the recipient sites. This was a 10-day, post-operative usage period in which various wound healing parameters were independently assessed by both the surgeon and the patient. Neither the participants in the study nor the surgeons were made aware of the recorded responses of either party until the conclusion of the study.

Patients were excluded from the study if they withdrew informed consent. All patients were shown proper usage of the spray formulations prior to beginning the study. The surgeons' survey results were averaged and recorded separately from the patients' survey results for statistical analysis.

Statistical Methods

Through proper design, focus, and agile document-driven methodology, logical edits using SAS software programs were used for cleaning raw data and preparing question frequencies for both the physician and the patient questionnaires. Survey findings including highlights and question attributes are provided to translate the data into meaningful and actionable information.

RESULTS

The key findings of the physician survey were as follows:

1. Evaluating the overall efficacy of HOCl on their patients, results indicate that HOCl worked very well at healing the surgical wounds in 97% of patients.
2. 86% of physicians reported that they were very pleased with the performance of the HOCl spray solution and intend to change from their current regimen.
3. 100% of physicians found the HOCl spray solution easy to incorporate into their surgical practice and instructing the patients on use.
4. 69% of physicians reported that patients were found to have returned to daily activities faster than expected.
5. 80% of the physicians and technicians reported a moderate to significant hemostatic effect when applying HOCl during the surgical procedure.
6. When asked to evaluate the post-operative wound erythema in HOCl treated patients, over half (56%) reported significant improvement/reduction in the amount of erythema compared with current wound healing regimen in similar patients.

The key findings of the patient survey were as follows:

1. 100% of patients reported the HOCl spray product was easy to use.
2. 95% of patients reported an overall reduction in itching symptoms by day 10, with 55% reporting a significant reduction in pruritis.
3. 90% of patients reported the HOCl spray was nonirritating.
4. Compliance was very good, with 95% of patients reporting to have applied the HOCl spray at least 5 times daily throughout the 10-day study duration.

Limitations

The study's limitations include its small trial size and the absence of a vehicle control group or comparator arm. The data presented fulfil the unmet need for more factual information on

FIGURE 1. Day 10 data. Physician Survery: Overall opinion on the stabilized, super-oxidized HOCl spray as an intraoperative wound cleansing and healing regimen.

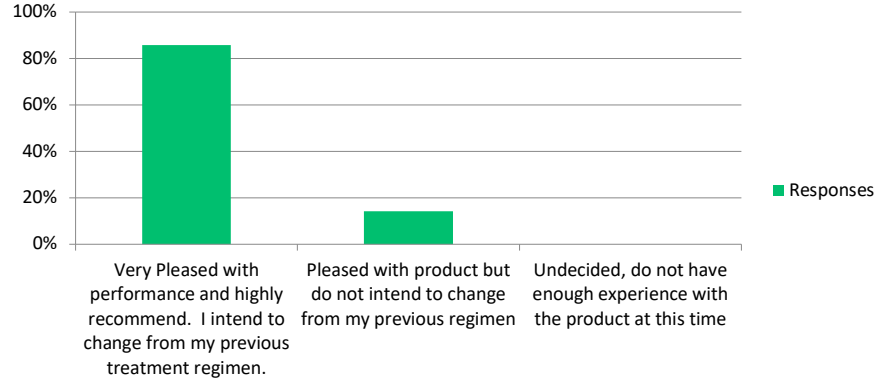


FIGURE 2. Day 10 data. 100% reported product was easy to incorporate into surgical practice and easy to instruct patients on use. Physician Survey: The ease of use of stabilized, super-oxidized HOCl spray compared with other treatment products and regimens.

FIGURE 3. Day 10 data. Patient Survey: Stabilized, super- oxidized HOCl and ease of use.

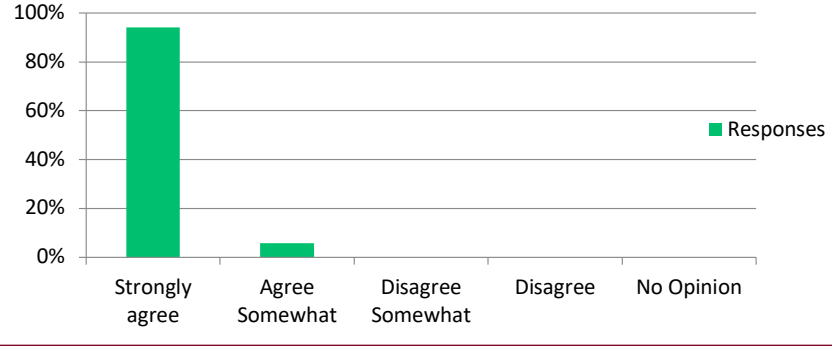
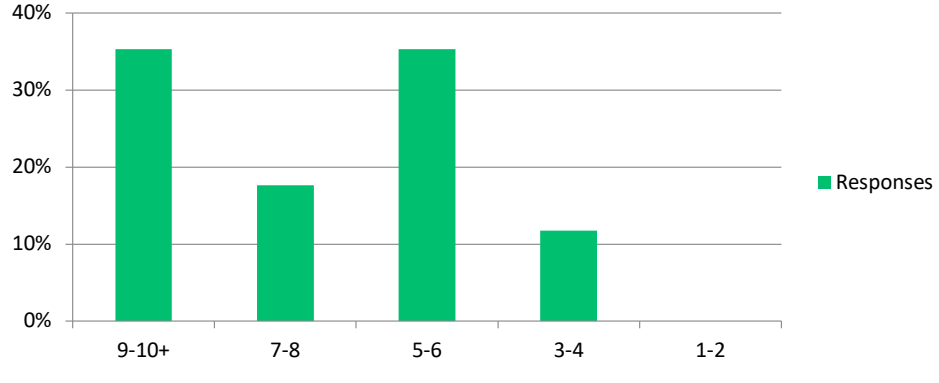


FIGURE 4. Day 10 data. Patient Survey: How many times per day did you apply stabilized, superoxidized HOCl spray post-operatively.



the efficacy, safety, and side effect profile of topical, stabilized, superoxidized HOCl intraoperatively and post operatively in hair restoration surgical procedures.

DISCUSSION

Stabilized, super-oxidized HOCl in a liquid or hydrogel medium has a large body of evidence available to support its safety, antimicrobial effects, anti-inflammatory activity, and clinical use in wound cleansing and healing. It is extensively used in diabetic foot ulcers, venous ulcers, burns, and cutaneous surgery.[20] A manuscript by Gold et al described the HOCl molecule as the future gold standard for wound care and scar management in dermatology and plastic surgery procedures.[8] The use of HOCl in hair restoration surgery has been minimal, but there are compelling reasons that this agent will find a favorable niche.[7] The study presented here gives statistical support for the use of stabilized, super-oxidized HOCl in hair restoration surgery. Our data did not analyze its use in scar management or prevention of abnormal scarring. The hemostasis effect of HOCl will be confirmed with future studies. Finally, there is a theoretical advantage of stabilized, super-oxidized HOCl spray to elevate oxygenation and subsequent prevention of tissue necrosis.

FIGURE 5. Day 10 data. Patient Survey: Pruritis reduction after applying stabilized, super-oxidized HOCl spray.

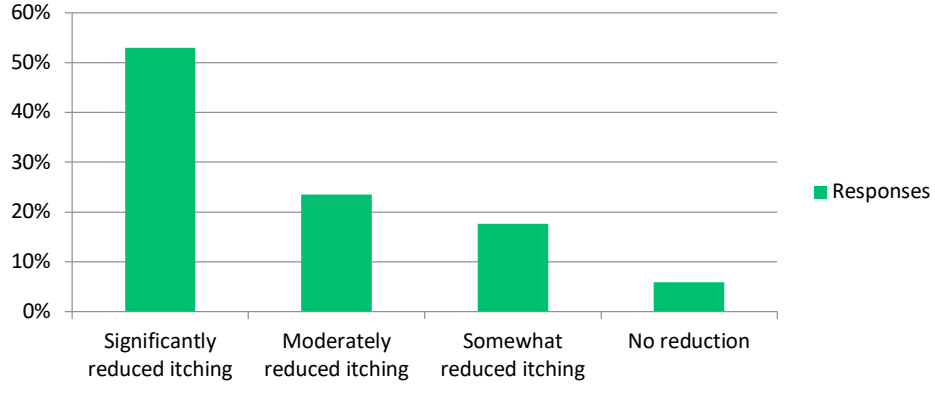


FIGURE 6. Day 10 data. Patient Survey: Stabilized, super-oxidized HOCl spray was non-irritating to my skin.

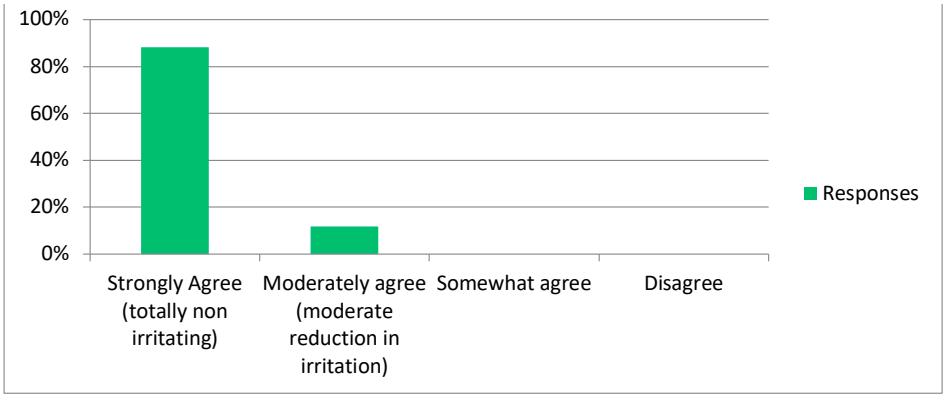


TABLE 1.

Demonstrated Benefits Of HOCL In Wound Cleansing and Healing
Extensive studies demonstrate superior and broad-spectrum bactericidal properties without evidence of creating microbe resistance.[20]
Anti-inflammatory and anti-pruritic properties documented in mild-to-moderate seborrheic dermatitis, atopic dermatitis, and facial acne vulgaris.[20]
Significantly shorter medium healing time demonstrated in infected diabetic wound ulcers and venous leg ulcers.[15, 20]
Superior patient satisfaction compared with traditional regimens in hair restoration surgery, when evaluated in a one-month observational pilot study.[7]
Hemostasis from previous reports have been validated by surgeons and technicians in hair restoration and oral surgery.[7,35]
Advanced manufacturing and storage capabilities enhance stability and create extended shelf-life.[11]
Stabilized, super-oxidized HOCl increases tissue oxygenation.[15]

DISCLOSURES

Dow Stough MD has no conflicts of interest to declare. Neither surgeons nor patients received financial compensation for their participation in this clinical trial. Surgeons were provided with 1 bottle of SurgiHEAL PRO 500mL trigger spray and patients were given 2 bottles of SurgiHEAL PRO 3 oz spray liquid and 2 bottles of SurgiHEAL PRO 3 oz. spray hydrogel. Products provided by Surgical Health Solutions, Inc.

ACKNOWLEDGMENT

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ORIGINAL ARTICLE

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Innate Error Immunities of the Th17 Immune Pathway Associated With Chronic Mucocutaneous Candidiasis: A Systematic Review

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ABSTRACT

Background: *Candida albicans* is an opportunistic pathogenic yeast commensal in human mucosa. In individuals with compromised immune systems, it can present as chronic mucocutaneous candidiasis (CMC) or systemic infection. CMC often exists in the presence of other infectious phenotypes due to dysfunction of the Th17 immune response.

Objective: To examine innate error immunities (IEI) of the Th17 immune response associated with CMC.

Methods: MEDLINE PubMed, Embase, and Web of Science were searched for keywords and Medical Subject Headings (MeSH) related to the subject of interest. Nonapplicable and non-primary research methodologies were excluded.

Results: We identified 266 articles; 89 were removed for being a duplicate, 108 for irrelevance, and 51 for being a review. We examined 18 studies, 5 on murine models, and 13 human studies.

Conclusion: Case reports in patients with CMC have identified a range of mutations in IL-17F, IL-17RA, IL-17RC, and ACT1. Mouse models confirm the role of IL-17A and IL-17F in disease susceptibility.

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INTRODUCTION

Candida albicans is an opportunistic pathogenic yeast that can cause thrush, intertrigo, and genital candidiasis. Individuals with compromised immune systems can present with chronic mucocutaneous candidiasis (CMC) or systemic infection.[1-4]

CMC is a chronic infection of the skin, nails, oropharyngeal, and genital mucosae classified as syndromic or CMC disease (CMCD).[2] Syndromic CMC is CMC in addition to other infectious phenotypes. This includes autosomal-dominant (AD) hyper IgE syndrome (HIES), autosomal-recessive (AR) autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED/APS-1), and mutations in signal transducer and activator of transcription 1 (STAT1), interleukin (IL)-12 receptor β1 (IL-12Rβ1), IL-12p40, caspase recruitment domain-containing protein 9 (CARD9), or retinoic acid-related orphan receptor γT (RORγT). CMCD is CMC independent of other immune disorders.[1-6]

Both types of CMC relate to the dysfunction of Th17 cells and their cytokines. Six cytokines (IL-17A-E) and 5 receptors (IL-17RA-RE) make up the IL-17 family. Important to the IL-17Rs is the ACT1 adapter molecule required for cell signaling. To date, there are 8 innate error immunities (IEI) in the IL-17 pathway: (1) IL-17A, (2) IL-17F, (3) IL-17AF, (4) IL-17C, (5) IL-17E (IL-25), (6) IL-17RA, (7) IL-17RC, and (8) ACT1/TRAF3 interacting protein 2 (TRAF3IP2).[1-6]

In this review, we examine each of the IEIs as relates to CMC.

MATERIALS AND METHODS

The search was developed in collaboration with a Wake Forest University Health Sciences librarian. It was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered on PROSPERO (CRD42022384733).

TABLE 1.

Studies Analyzing the Role Of IL-17 Cytokines and Receptors in Chronic Mucocutaneous Candidiasis Diseases

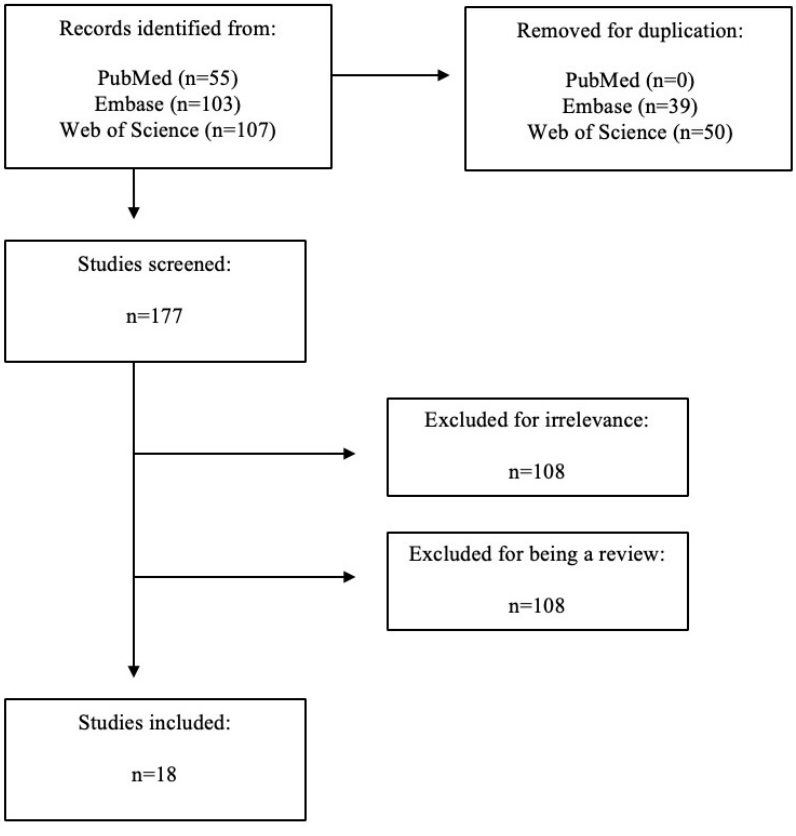
IL-17-related deficiency	Disease	Subject model	Subject (n)	Kindred (n)	Mutation	Result
IL-17A, IL-17F	OPC	Murine	--	--	--	Homozygous *Il17fS65L/S65L* and *Il17a*$^{-/-}$ mice have a higher oral fungal burden than WT mice. Homozygous *Il17f*$^{-/-}$ and heterozygous Il17f$^{-/}$ S65L do not.[3]
IL-17A, IL-17F	ECC	Murine	--	--	--	Combined deficiency in IL-17A and IL-17F *(Il1af*$^{-/-}$*)* resulted in increased fungal burden and skin inflammation compared to *Il17a*$^{-/-}$, *Il1f*$^{-/-}$, or WT mice.[7]
ACT1, IL-17RA, IL-17A, IL-17F, IL-17AF	OPC	Murine	--	--	--	IL-17RA$^{-/-}$ and Act1$^{-/-}$ mice are more susceptible to OPC than IL-17A$^{-/-}$ and anti-IL-17A-treated mice. Anti-IL-17A-treated mice are more susceptible than ILA$^{-/-}$ mice. Anti-IL-17A-treated mice are more susceptible than anti-IL-17F mice, but less susceptible than combined anti-IL-17A and anti-IL-17F-treated mice.[8]
IL-17RA	Systemic candidiasis	Murine	--	--	--	IL-17RA$^{-/-}$ mice had increased systemic fungal burden. IL-17RA$^{-/-}$ and WT mice had increased expression of IL-17A in response to *C. albicans*.[11]
IL-17C, IL-17RE	OPC, ECC, systemic candidiasis	Murine	--	--	--	IL-17C$^{-/-}$ and IL-17RE$^{-/-}$ mice have similar susceptibility to OPC, ECC, and systemic candidiasis as WT mice.[15]
IL-17F	CMC	Human	7	1	$^{n1-7}$c.284 C >T, (S65L)	Partial loss of response to IL-17A and IL-17F homo- and heterodimers.[9]
IL-17F	CMC	Human	1	1	^{n1}c.3777A>G, (E126G)	The heterozygous mutation leads to defected Th17 response and decreased IL-17F production.[10]
IL-17RA	CMC	Human	1	1	^{n1}c.805C >T, (Q284X)	Complete loss of response to IL-17A and IL-17F homo- and heterodimers.[9]
IL-17RA	CMC	Human	7	3	^{n1,2}c.196C>T ^{n3,4}missense mutation ^{n5,6}frameshift mutation n7c256C>A	Patients present with CMC and *S. aureus* infections with loss of IL-17RA signaling.[12]
IL-17RA	CMC	Human	21	12	^{n1,2}c.850C >T, (Q284X) ^{n3,4}c.1302_1318dup, p.N440Rfs*50 ^{n5,6}c.1159G > A (D387N) ^{n7,8}c.166_169dup, p.C57Yfs*5 ^{n9,10}c.196C >T, (R66X) ^{n11,12}c.112_119del, p.H38Afs*15 ^{n13}c.163+1G > A ^{n14}c.1152C > A, (Y384X) $^{n15-18}$c.268del, p.L90Cfs*30 ^{n19}c.1770_1771dup, p.Y591Sfs*29 ^{n20,21}c.769_773del, p.P257Rfs*16	Complete loss of response to IL-17A and IL-17F homo- and heterodimers.[4]
IL-17RA	CMC	Human	2	1	^{n1,2}22q11.1 770 kb deletion	Increased proinflammatory cytokines (IL-1b and TNF-a) and impaired IL-17 signaling.[13]
IL-17RA	CMC	Human	1	1	^{n1}c.1696insAG causing a frameshift mutation (p.Q566fs)	Patient presents with recurrent *Candida spp.* and *S. aureus* infection.[14]
IL-17RC	CMC	Human	3	3	^{n1}c.412C >T (Q138*) ^{n2}c1126C >T, (R376*) ^{n3}c1132C >T, (R378*)	Loss of response to IL-17A and IL-17F homo- and heterodimers, but not to IL-17E.[16]
ACT1	CMC	Human	2	1	^{n1,2}c.1607C >T, (T5361I)	Reduced activity of IL-17RA, IL-17RB, IL-17RC despite increased IL-17 T cell populations.[17]
ACT1	CMC	Human	1	1	^{n1}c.847C >T, (R238*)	Patient presents with CMC and recurrent pneumonia.18
ACT1	CMC	Human	2	2	^{n1,2}c.559C >T, (R187*)	Defective signaling between ACT1 and all IL-17Rs.[19]
ACT1	CMC	Human	1	1	^{n1}c.1498C >T/ c.1352A >T, (R500*/D451V)	Defective signaling between ACT1 and IL-17Rs results in loss of IL-17 response.[20]
ACT1	CMC	Human	2	1	^{n1,2} R542W	Siblings with AR ACT1 deficiency present with mutation in SEFIR domain leading to defective IL-17 receptors response.[21]

Abbreviations: AD: autosomal dominant; AR: autosomal recessive; CMC: Chronic Mucocutaneus Candidiasis; ECC: epicutaneous candidiasis; HMZ: homozygous; HTZ: heterozygous; MUT: mutation.

TABLE 2.

	Search Strategy	
PubMed		
1	("**Interleukin-17" [Mesh] OR "IL17A protein, human" [Supplementary Concept] OR "Interleukin-17" [tw] OR** "Interleukin 17" [tw] OR IL-17 [tw] OR IL 17 [tw] OR Interleukin-17A [tw] OR Interleukin 17A [tw] OR IL-17A [tw] OR IL 17A [tw] OR Interleukin-17B [tw] OR Interleukin 17B [tw] OR IL-17B [tw] OR IL 17B [tw] OR Interleukin-17C [tw] OR Interleukin 17C [tw] OR IL-17C [tw] OR IL 17C [tw] OR Interleukin-17D [tw] OR Interleukin 17D [tw] OR IL-17D [tw] OR IL 17D [tw] OR "Interleukin-27"[Mesh] OR Interleukin 27 [tw] OR IL-27 [tw] OR IL 27 [tw] OR Interleukin-17E [tw] OR Interleukin 17E [tw] OR IL-17E [tw] OR IL 17E [tw] OR Interleukin 25 [tw] OR IL-25 [tw] OR IL 25 [tw] OR "**IL17F protein, human" [Supplementary Concept]** or Interleukin-17F [tw] OR Interleukin 17F [tw] OR IL-17F [tw] OR IL 17F [tw] **OR "IL25 protein, human" [Supplementary Concept] OR "IL17F protein, human" [Supplementary Concept]** OR "Receptors, Interleukin-17"[Mesh] OR "Interleukin-17 Receptor" [tw] OR Interleukin-17 Receptors [tw] OR "Interleukin 17 Receptor" [tw] OR Interleukin 17 Receptors [tw] OR IL-17 Receptor [tw] OR IL 17 Receptor [tw] OR IL-17 Receptors [tw] OR IL 17 Receptors [tw] OR Interleukin-17 Receptor A [tw] OR Interleukin 17 Receptor A [tw] OR Il-17 Receptor A [tw] OR Il 17 Receptor A [tw] OR Interleukin-17RA [tw] OR Interleukin 17RA [tw] OR IL-17RA [tw] OR IL 17RA [tw] OR Interleukin-17 Receptor B [tw] OR Interleukin 17 Receptor B [tw] OR Il-17 Receptor B [tw] OR Il 17 Receptor B [tw] OR Interleukin-17RB [tw] OR Interleukin 17RB [tw] OR IL-17RB [tw] OR IL 17RB [tw] OR Interleukin-17 Receptor C [tw] OR Interleukin 17 Receptor C [tw] OR Il-17 Receptor C [tw] OR Il 17 Receptor C [tw] OR Interleukin-17RC [tw] OR Interleukin 17RC [tw] OR IL-17RC [tw] OR IL 17RC [tw] OR Interleukin-17 Receptor D [tw] OR Interleukin 17 Receptor D [tw] OR Il-17 Receptor D [tw] OR Il 17 Receptor D [tw] OR Interleukin-17 Receptor E [tw] OR Interleukin 17 Receptor E [tw] OR Il-17 Receptor E [tw] OR Il 17 Receptor E [tw] OR Interleukin-17RE [tw] OR Interleukin 17RE [tw] OR IL-17RE [tw] OR IL 17RE [tw] OR Interleukin-17RF [tw] OR Interleukin 17RF [tw] OR IL-17RF [tw] OR IL 17RF [tw] OR Interleukin-17 Receptor F [tw] OR Il-17 Receptor F [tw] OR Il 17 Receptor F [tw] OR Interleukin-17RF [tw] OR Interleukin 17RF [tw] OR IL-17RF [tw] OR IL 17RF [tw] OR "**IL-25 receptor protein, human" [Supplementary Concept]** OR ACT1 [tw] OR TRAF3IP2 [tw])	33,816
2	Deficiency [tw]	486,256
3	#1 AND #2	2,317
4	("Interleukin-17/deficiency"[Mesh])	192
5	#3 OR #4	2,317
6	**"Candidiasis, Chronic Mucocutaneous"[Mesh]** OR "chronic mucocutaneous candidiasis"[tw] OR (chronic [tw] AND mucocutaneous [tw] AND candidiasis [tw]) OR (chronic [tw] AND mucocutaneous [tw] AND candidiases [tw])	1,121
7	#5 AND #6	55
Embase		
1	**'interleukin 17'/exp** OR 'interleukin 17' OR **'il17a protein human'/exp** OR 'il17a protein human' OR 'interleukin-17':ab,ti OR 'interleukin 17':ab,ti OR 'il-17':ab,ti OR 'il 17':ab,ti OR 'interleukin-17a':ab,ti OR 'interleukin 17a':ab,ti OR 'il-17a':ab,ti OR 'il 17a':ab,ti OR **'interleukin 17b'/exp** OR 'interleukin 17b' OR 'interleukin-17b':ab,ti OR 'interleukin 17b':ab,ti OR 'il-17b':ab,ti OR 'il 17b':ab,ti OR **'interleukin 17c'/exp** OR 'interleukin 17c' OR 'interleukin-17c':ab,ti OR 'interleukin 17c':ab,ti OR 'il-17c':ab,ti OR 'il 17c':ab,ti OR 'interleukin-17d':ab,ti OR 'interleukin 17d':ab,ti OR 'il-17d':ab,ti OR 'il 17d':ab,ti OR **'interleukin 27'/exp** OR 'interleukin 27' OR 'interleukin-27':ab,ti OR 'interleukin 27':ab,ti OR 'il-27':ab,ti OR 'il 27':ab,ti OR **'interleukin 25'/exp** OR 'interleukin 25' OR 'interleukin-17e':ab,ti OR 'interleukin 17e':ab,ti OR 'il-17e':ab,ti OR 'il 17e':ab,ti OR 'interleukin 25':ab,ti OR 'il-25':ab,ti OR 'il 25':ab,ti OR **'interleukin 17f'/exp** OR 'interleukin 17f' OR **'il17f protein human'/exp** OR 'il17f protein human' OR 'interleukin-17f':ab,ti OR 'interleukin 17f':ab,ti OR 'il-17f':ab,ti OR 'il 17f':ab,ti OR **'interleukin 17 receptor'/exp** OR 'interleukin 17 receptor' OR 'interleukin-17 receptor':ab,ti OR 'interleukin-17 receptors':ab,ti OR 'interleukin 17 receptor':ab,ti OR 'interleukin 17	78,582
2	**'deficiency'/exp** OR deficiency:ab,ti	444,852
3	**'mucocutaneous candidiasis'/exp** OR 'chronic mucocutaneous candidiasis':ab,ti OR 'chronic mucocutaneous candidiases':ab,ti OR (chronic:ab,ti AND mucocutaneous:ab,ti AND candidiasis:ab,ti) OR (chronic:ab,ti AND mucocutaneous:ab,ti AND candidiases:ab,ti)	2,787
4	#1 AND #2	3,082
5	#3 AND #4	103
Web of Science		
1	**TS**=("IL17A protein" OR "Interleukin-17" OR "Interleukin 17" OR "IL-17" OR "IL 17" OR "Interleukin-17A" OR" Interleukin 17A" OR "IL-17A" OR "IL 17A" OR "Interleukin-17B" OR "Interleukin 17B" OR "IL-17B" OR "IL 17B" OR "Interleukin-17C" OR "Interleukin 17C" OR "IL-17C" OR "IL 17C" OR "Interleukin-17D" OR "Interleukin 17D" OR "IL-17D" OR "IL 17D" OR "Interleukin-27" OR "Interleukin 27" OR "IL-27" OR "IL 27" OR "Interleukin-17E" OR "Interleukin 17E" OR "IL-17E" OR "IL 17E" OR "Interleukin 25" OR "IL-25" OR "IL 25" OR "IL17F protein, human" or "Interleukin-17F" OR "Interleukin 17F" OR "IL-17F" OR "IL 17F" OR "IL25 protein, human"] OR "IL17F protein, human" OR "Receptors, Interleukin-17" OR "Interleukin-17 Receptor" OR "Interleukin-17 Receptors" OR "Interleukin 17 Receptor" OR "Interleukin 17 Receptors" OR "IL-17 Receptor" OR "IL 17 Receptor" OR "IL-17 Receptors" OR "IL 17 Receptors" OR "Interleukin-17 Receptor A" OR "Interleukin 17 Receptor A" OR "Il-17 Receptor A" OR "Il 17 Receptor A" OR "Interleukin-17RA" OR "Interleukin 17RA" OR "IL-17RA" OR "IL 17RA" OR "Interleukin-17 Receptor B" OR "Interleukin 17 Receptor B" OR "Il-17 Receptor B" OR "Il 17 Receptor B" OR "Interleukin-17RB" OR "Interleukin 17RB" OR "IL-17RB" OR "IL 17RB" OR "Interleukin-17 Receptor C" OR "Interleukin 17 Receptor C" OR "Il-17 Receptor C" OR "Il 17 Receptor C" OR "Interleukin-17RC" OR "Interleukin 17RC" OR "IL-17RC" OR "IL 17RC" OR "Interleukin-17 Receptor D" OR "Interleukin 17 Receptor D" OR "Il-17 Receptor D" OR "Il 17 Receptor D" OR "Interleukin-17 Receptor E" OR "Interleukin 17 Receptor E" OR "Il-17 Receptor E" OR "Il 17 Receptor E" OR "Interleukin-17RE" OR "Interleukin 17RE" OR "IL-17RE" OR "IL 17RE" OR "Interleukin-17RF" OR "Interleukin 17RF" OR "IL-17RF" OR "IL 17RF" OR "Interleukin-17 Receptor F" OR "Interleukin 17 Receptor F" OR "Il-17 Receptor F" OR "Il 17 Receptor F" OR "Interleukin-17RF" OR "Interleukin 17RF" OR "IL-17RF" OR "IL 17RF" OR"IL-25 receptor protein" OR "ACT1" OR "TRAF3IP2")	103
2	TS=deficiency	505,012
3	#1 AND #2	1,645
4	**TS**=("chronic mucocutaneous candidiasis" OR (chronic AND mucocutaneous AND candidiasis) OR (chronic AND mucocutaneous AND candidiases) OR "mucocutaneous candidiasis")	1,547
5	#4 AND #3	107

FIGURE 1. Flow chart of systematic literature search.



The search consisted of keywords and Medical Subject Headings (MeSH) related to the subject of interest. It was translated to MEDLINE PubMed, Embase, and Web of Science (Table 2). Eligibility criteria were predetermined by the authors. Search restrictions included language of publication (English).

Two authors independently reviewed articles. Titles and/or abstracts were reviewed for relevancy. Nonapplicable and non-primary research methodologies were excluded. The remaining articles were read as full texts. References for each article were reviewed for the sake of completion. For discrepancies that may have appeared, a consensus among authors was made.

RESULTS

The literature search resulted in 266 articles; 89 were removed for being a duplicate, 108 for irrelevance, and 51 for being a review. We examined 18 studies, 5 on murine models, and 13 human studies (Figure 1).

IL-17A

There are no case reports on IL-17A mutations in patients with CMC. There are 3 studies on murine models. This includes 2 on oropharyngeal candidiasis (OPC) and 1 on epicutaneous candidiasis (ECC).[3,7,8] IL-17a [AQ: should this be Il12a or IL-17A?] mRNA expression was analyzed in mice tongues of $Il17f^{S65L/S65L}$ mice with OPC. Despite increased IL-17a expression, IL-17A did not compensate for the lack of IL-17F signaling given treatment with anti-IL-17A antibodies did not increase the oral fungal load.[3]

Whibley et al (2016) investigated the significance of blocking IL-17A, IL-17F, IL-17AF, 1L-17RA, ACT1 in WT mice infected with *C. albicans*. Expression of *Il17a* mRNA post inoculation was higher than *Il17f, Il17c, Il17e, Il17b,* and *Il17d*. Blocking IL-17A with anti-IL-17A antibodies resulted in an increased fungal load. This was augmented by treatment with both anti-IL-17A and anti-IL-17F, despite treatment with anti-IL-17F alone having no significant impact. Levels of fungal growth returned to normal once blocking ceased.[8]

IL-17F

There is 1 case report on IL-17F mutations in 7 patients (1 kindred) and 1 patient with CMCD and 3 studies on murine models (2 OPC and 1 ECC).[3,7-10] Similar to IL-17A compensation in $IL\text{-}17F^{S65L/S65L}$ mice, $IL\text{-}17^{-/-}$ mice had higher levels of IL-17F. However, treatment with anti-IL-17F post-infection with *C. albicans* had no impact on OPC susceptibility.[3,8]

The case report details an AD heterozygous missense mutation (S65L) with incomplete penetrance. Six of the 7 patients carried the mutation, and 1 of the patients did not have genetic analysis. Five of the 7 patients had symptoms of the disease.[9] In ex vivo studies of the same report, the S65L mutant IL-17F protein formed homo- and heterodimers with IL-17A but failed to bind IL-17RA on fibroblasts.[3]

IL-17RA

There are 4 reports on IL-17RA deficiency in patients with CMC and 2 on murine models (1 OPC and 1 systemic candidiasis).[4,8,9,11-14] IL-17RA$^{-/-}$ and WT mice had increased expression of IL-17A in response to infection with *C. albicans*. Compared to WT mice, IL-17RA$^{-/-}$ mice had increased systemic fungal burden.[8] IL17RA$^{-/-}$ mice also had delayed neutrophil response and impaired neutrophil migration.[8,12]

A patient with CMCD, *C. albicans* dermatitis in the neonatal period, and *Staphylococcus aureus (S. aureus)* at 5 months of age had a homozygous c.850C>T nonsense mutation (Q284X) in the IL-17RA gene. IL-17RA was undetectable on the patient's fibroblasts, monocytes, peripheral blood mononuclear cells (PMCs), CD4+ T or CD8+ T cells, and following stimulation with IL-17 cytokines (IL-17A, IL-17F, IL-17AF), there was no response in fibroblasts or leukocytes.[9]

Twenty-one patients (12 kindreds) with AR IL-17RA deficiency presented with CMC before 6 months of age. Fourteen of 21 CMC patients also presented with recurrent *S. aureus* cutaneous infections (eg, folliculitis, furunculosis, crusted papules). Eight of the 12 mutations (1 splice variant, 3 nonsense, 4 frameshift) resulted in a premature stop codon upstream of the IL-17RA transmembrane domain. Four of the 12 mutations affected the "similar expression to fibroblast growth factor genes and IL-17R" (SEFIR) domain required for ACT1 signaling, 3 intracellularly of the SEFIR domain (1 nonsense, 1 missense, 1 frameshift) and 1 downstream of the SEFIR domain (1 frameshift). Each of these mutations resulted in a complete loss of response to IL-17A and IL-17F homo- and heterodimers in fibroblasts.[4]

IL-17C

There is 1 study on OPC, ECC, and systemic candidiasis on murine models deficient in IL-17C/IL-17RE. IL-17C mRNA expression is increased in response to *C. albicans*, however IL-17C$^{-/-}$, IL-17RE$^{-/-}$, and WT mice clear infection in the oral mucosa, skin, and bloodstream at similar rates.[15]

IL-17RC

One study on 3 patients (3 kindreds) identified 3 homozygous nonsense mutations in exon 3 of 1 patient and exon 11 of 2 patients of the IL-17RC gene. Patients presented with intertrigo and oral thrush, but no signs of other bacterial, viral, or fungal infection. There was loss of fibroblast response to IL-17A and IL-17F homo- and heterodimers, but not to IL-17E in ex vivo and in vivo differentiation.[16]

ACT1

There are 4 reports (6 patients with CMC, 5 kindreds) and 1 animal study (1 OPC) on ACT deficiency.[8,17-21] Compared to IL-17A$^{-/-}$ mice and WT treated with anti-IL17A, anti-IL17F, or anti-IL17AF, ACT$^{-/-}$ mice had the highest susceptibility to OPC following *C. albicans* inoculation.[8]

A missense mutation c.1607C >T, (T5361I) in the SEFIR domain of the ACT1 molecule was identified in 2 patients (1 kindred) with recurrent *C. albicans* and *S. aureus* infection.[17] There was lack of ACT1 binding to IL-17RA, IL-17RB, and IL-17RC in ACT1 deficient cells of ex vivo studies of the same report.[18] Defective signaling between ACT1 and IL-17 receptors was identified in a similar study of 2 patients (1 kindred) with recurrent *C. albicans* infection who had a nonsense mutation c.559C >T, (R187*) in the same gene.[19]

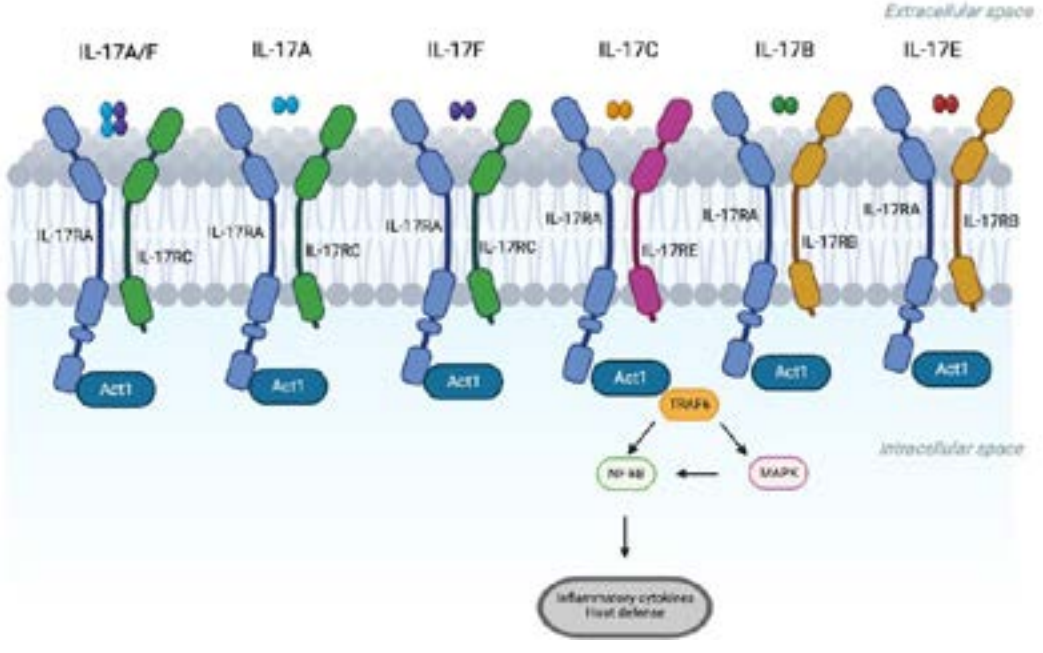
A heterozygous mutation c.1498C > T/ c.1352A > T, (R500*/D451V) in the SEFIR domain of the ACT1 gene was identified in a non-consanguineous born male with recurrent *C. albicans* infection since the age of 6 months. His medical history was also remarkable for atopic dermatitis, seborrhea, and recurrent blepharitis. There was complete loss of signaling between IL-17A and IL-17 receptors in ex vivo and in vitro differentiation ACT1D451V/R500* fibroblasts.[20]

DISCUSSION

IL-17 signaling stimulates intercellular adhesion molecule 1 (ICAM-1), IL-8, C-X-C Motif Chemokine Ligand 1 (CXCL1), CXCL5, CXCL2, and granulocyte-colony stimulating factor (G-CSF) to activate neutrophil upregulation in response to infection.[9,22-23] Essential in this signaling cascade is the adapter molecule ACT1. In response to IL-17 cytokine receptor binding, ACT1 activates nuclear factor-kappa B (NF-kB), mitogen-activated protein kinases (MAPKs) p38, and proinflammatory cytokines in fibroblasts, epithelial cells, endothelial cells, and immune cells.[2-4]

IL-17RA, IL-17RC, and ACT1 are important in host defense against infection. There were 1, 4, and 4 case reports in patients with CMC with IL-17RC, IL-17RA, and ACT1 deficiency, respectively. Mutations varied, but common among most was their impact on the SEFIR transmembrane binding domain. Individuals with IL-17RC and IL-17RA deficiency had a complete loss of response to IL-17A and IL-17F homo- and heterodimers while individuals with ACT1 deficiency had reduced cell signaling response across all IL-17 cell receptors.[4,9,12-13,16-21] Despite similar presentations of CMC, concomitant *S. aureus* infection was only present in those with mutations in IL-17RA.4[9,12-13]

FIGURE 2. IL-17 cytokine and receptor cell signaling.



IL-17A and IL-17F exists as homo- or heterodimers. Each isoform (IL-17A, IL-17F, IL17A/F) binds to IL-17RA:IL-17RC receptor complex. IL-17C, IL-17B, and IL-17E exists as homodimers, and bind to IL-17RA:IL-17RE, IL-17RA:IL-17RB, and IL-17RA:IL-17RB, respectively. For each IL-17 cytokine and receptor interaction, ACT1 is recruited for downstream signaling.

IL-17RA and IL-17RC form a heterodimeric complex to bind IL-17A, IL-17F, and IL-17AF (Figure 2). Each of these isoforms bind to IL-17RA: IL-17RC with varying potency (IL-17A > IL-17AF > IL-17F).[2-4] Each pair also responds differently to neutralization. IL-17A and IL-17AF are both neutralized by anti-IL-17A while anti-IL-17F inhibits IL-17F alone. This indicates the significant role of IL-17A in the heterodimer and its role in CMC as anti-IL-17A mice had higher susceptibilities to OPC than anti-IL-17F treated mice.[8] Despite differences in *C. albicans* susceptibility, IL-17A and IL-17F have a synergistic effect in reducing burden of disease. Mice treated with both anti-IL-17A and anti-IL-17F had higher susceptibilities than did mice treated with either alone.[7,12]

Other IL-17 cytokine receptor combinations include IL-17C to IL-17RA: IL-17RE and IL-17E to IL-17RA: IL-17RB.[2-4] While no studies identified IL-17C or IL-17E deficiency in humans, murine models of IL-17C and IL-17E deficient mice demonstrate similar susceptibilities to OPC, ECC, and systemic candidiasis as WT mice suggesting their lack of involvement in *C. albicans* defense.[15]

The increased risk of candidiasis in patients on anti-IL17 therapeutics confirms the role of IL-17 in *C. albicans* immunity.[24,25] Candidiasis occurred in psoriasis patients receiving antil-IL17A (secukinumab, ixekizumab), anti-IL17AF (bimekizumab), and anti-IL17F (brodalumab) therapy.[24,25] The most common site of involvement was oral candidiasis, followed by oropharyngeal and skin infection, respectively.[25]

CONCLUSION

Case reports in patients with CMC have identified a range of mutations in IL-17RA and ACT1. IL-17RA and ACT1 deficiency also caused CMC in mouse models, which supports the role IL-17A has on susceptibility to candidiasis. The role of IL-17 in protection against candidiasis is seen in the frequency of candidiasis in patients treated with IL17 inhibitors.

DISCLOSURES

Feldman has received research, speaking, and/or consulting support from Eli Lilly and Company, GlaxoSmithKline/Stiefel, AbbVie, Janssen, Alovtech, vTv Therapeutics, Bristol-Myers Squibb, Samsung, Pfizer, Boehringer Ingelheim, Amgen, Dermavant, Arcutis, Novartis, Novan, UCB, Helsinn, Sun Pharma, Almirall, Galderma, Leo Pharma, Mylan, Celgene, Ortho Dermatology, Menlo, Merck & Co, Qurient, Forte, Arena, Biocon, Accordant, Argenx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Teladoc, BMS, Ono, Micreos, Eurofins, Informa, UpToDate and the National Psoriasis Foundation. He is the founder and part owner of Causa Research and holds stock in Sensal Health. Mirza and Zaino report no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Pilot Study to Evaluate the Efficacy and Tolerability of a Topical Combination Serum for the Improvement of Aged Skin

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ABSTRACT

Background: With intrinsic aging, the epidermis becomes thinner and fine wrinkles appear. Extrinsic aging, or photoaging, is characterized by deep wrinkles, skin laxity, and hyperpigmentation.

Objective: To evaluate the efficacy and safety of a novel combination serum with retinol, hyaluronic acid, and trichloroacetic acid (Test Product) for the improvement of aged facial skin.

Methods: Female subjects (n=22) enrolled in the single-site, open-label, pilot study. Subjects had mild to moderate fine lines and wrinkles and mild to moderate photodamage. Subjects applied the Test Product, cleanser, and moisturizer-sunscreen combo once daily to the face during the 12-week study. Radiance, skin tone, skin smoothness, skin texture, red/blotchy, dryness, overall appearance, skin quality, and tolerance were evaluated at each visit.

Results: Skin radiance, tone, smoothness, texture, and overall appearance improved significantly with continued use of the Test Product up to week 12. Subjective improvement was significant for texture, tone, glow, smoothness, youthful appearance, pores, and satisfaction. More than half of subjects showed improvement in skin elasticity, redness/broken capillaries, and dryness. The treatment was well tolerated.

Conclusions: The combination serum with retinol, hyaluronic acid, and trichloroacetic acid has been shown to improve aged facial skin and is well tolerated when used daily for up to week 12.

J Drugs Dermatol. 2023;22(12):1204-1209. doi:10.36849/JDD.6835

INTRODUCTION

With aging, the natural rejuvenation process of human skin decelerates and the skin becomes thinner, drier, and less elastic.[1] Manifestations include wrinkles, discoloration, uneven texture, and alterations in pore size. Hyaluronic acid (HA) and collagen are also reduced in the dermal matrix.[2]

Intrinsic aging occurs with advancing age; the epidermis becomes thinner and fine wrinkles appear. Extrinsic aging, or photoaging, is due to chronic sun exposure and is characterized by deep wrinkles, skin laxity, and hyperpigmentation. The skin becomes coarse, the epidermis thickens, and then becomes thinner. There is also laxity, sallowness, wrinkles, irregular hyperpigmentation, lentigines, and telangiectasias. With either type of aging, wrinkles and reduced elasticity are typical manifestations and the result of progressive atrophy of the dermis.[3]

A youth-engaging skin serum (Y.E.S.S.®, Induction Therapies, Louisville, KY) is a novel collagen-building, tone-improving product with all-trans retinol, HA, and trichloroacetic acid (TCA) designed for the treatment of skin aging, discoloration, and hydration. Squalene and shea butter are also present.

The primary objective of the present study was to evaluate the efficacy and safety of this Test Product for the improvement of (1) fine lines and wrinkles, (2) appearance of discoloration, and (3) uneven texture of facial skin after week 12 of use. The secondary objective was to assess the improvement of moisture level and pore size during the same period.

MATERIALS AND METHODS

Subjects

Female subjects (n=22) aged 41 to 60 years (mean SD = 53.3 ± 5.4) and Fitzpatrick skin types II (n=12), III (n=8), and IV (n=2)

enrolled in the single-site, open-label, pilot study. Subjects had mild to moderate fine lines and wrinkles and mild to moderate photodamage. Wrinkles were grade 2 (class I) to 6 (class II) on the Fitzpatrick Wrinkles scale and photodamage was Glogau grade II or III. Subjects of child-bearing potential provided negative urine pregnancy test results. All subjects were willing to remain on their current skin-care regimen and to not use products other than the dispensed skin cleanser, moisturizer/sunscreen, and Test Product, the Youth Engaging Skin Serum (Y.E.S.S.) of Induction Therapies, Louisville, KY). All subjects provided written informed consent to participate in the study and to have facial photographs taken for potential use in media or scientific publications.

Subjects were excluded if they had excessive facial exposure to sunlight or ultraviolet (UV) light; recent history or active presence of any facial skin condition/disease which, in the opinion of the principal investigator (PI), might interfere with diagnosis or evaluation of study parameters (ie, moderate to severe acne vulgaris, atopic dermatitis, psoriasis, rosacea, seborrheic dermatitis, excessive facial hair or coloration, suspicious lesion); or invasive or non-invasive skin treatments, surgeries on the face, hair removal, light treatment, or filler or toxins performed in the treatment area within the previous 3 months. Other criteria were history of allergy or hypersensitivity to any of the product ingredients; pregnancy, breastfeeding, planning to become pregnant, or unwillingness to use an accepted form of birth control; participation in a drug or other research study currently or within the previous 30 days; unwillingness to have facial photographs used for media or scientific publications; recent use of medication that may interfere with skin characteristics; and, per the PI's discretion, any other mental or physical condition that might make it unsafe for the subject to participate in this study.

Procedure

Qualified subjects were evaluated at each visit by a trained evaluator. At the screening or baseline visit, informed consent, medical history and demographics, Fitzpatrick skin typing, inclusion/exclusion criteria, medications, wrinkles and photodamage, and pregnancy test results were evaluated. The schedule of other procedures is shown in Table 1.

Product Distribution

Test product, cleanser, moisturizer, and sunscreen were given to subjects at baseline. The trained evaluator instructed each subject on their proper use and how to record product application, new medications, and adverse events in their diary to ensure compliance. Products dispensed included the Test Product, cleanser (IT Cleanse), and moisturizer-sunscreen combo (Block IT-SPF30). Subjects were instructed to apply all products once daily, each evening, during the study.

Photography

Full-face, right side (45°), and left side (45°) images were obtained from each subject at each visit using a Visia CR facial imaging system (Canfield Scientific, Parsippany, NJ). The subject wore no makeup and removed all jewelry for photographs.

Assessments

Wrinkles

Wrinkles were evaluated at screening, using the Fitzpatrick Wrinkle Scale below. Qualified subjects were between grade 2 and grade 6.

TABLE 1.

Schedule of Study Procedures				
Procedure	**Baseline**	**Week 4[1]**	**Week 8[1]**	**Week 12[1]**
Dispense products	D	--	--	--
Dispense/Reconcile/Collect diary	D	R	R	C
Adverse event query	x	x	x	x
Medication query	x	x	x	x
Photographs	x	x	x	x
Investigator objective assessment[2]	x	x	x	x
Subject skin quality assessment	x	--	--	x
Tolerability assessments[3]	x	x	x	x
Investigator GAIS[4]	--	--	--	x

[1]±3 days.
[2]Radiance, fine lines/wrinkles, smoothness, firmness, and overall appearance.
[3]Objective (erythema, edema, dryness, peeling) and subjective (stinging, tingling, itching, burning).
[4]Global Aesthetic Improvement Scale.

TABLE 2.

Investigator's Objective Assessments									
Clinical Parameter	*P*-Value (Wilcoxon Test)[1] (wks 4, 8, 12 vs baseline)			Subjects Improved (%)			Median Improvement (%) (min. max)		
	wk 8	wk 12	wk 4	wk 8	wk 12	wk 4	wk 8	wk 12	wk 4
Radiance	0.0002	0.0001	<0.0001	61.9	66.7	85.7	50.0 (0, 200)	50.0 (0, 200)	50.0 (0, 200)
Tone	0.0005	<0.0001	<0.0001	57.1	76.2	85.7	33.0 (0, 50)	33.0 (0, 67)	50.0 (0, 67)
Smoothness	0.0005	0.0005	<0.0001	57.1	57.1	90.5	33.0 (0, 50)	33.0 (0, 50)	50.0 (0, 67)
Texture	0.0002	<0.0001	<0.0001	61.9	76.2	90.5	33.0 (0, 50)	50.0 (0, 67)	50.0 (0, 100)
Red/Blotchy	0.0977 (ns)	0.0171	0.0017	38.1	52.4	61.9	0.0 (0, 100)	41.5 (-100, 100)	83.5 (0, 100)
Dryness	0.0156	0.5000	1.000 (ns)	0	0	0	0 (0, 0)	0 (0, 0)	0 (0, 0)
Overall	0.0020	0.0001	<0.0001	47.6	66.7	90.5	0 (0, 50)	33.0 (0, 50)	50.0 (0, 67)

[1]*P*=0.017 as cut-off value for significance.

Photodamage
Photodamage was evaluated at screening, using the Glogau scale above.

Investigator Objective Assessments for Full Face
Radiance, skin tone, skin smoothness, skin texture, red/blotchy, dryness, and overall appearance were graded (0-4) at each visit. Low values indicated improvement, except for radiance, in which 0 denoted dull skin and 4 indicated skin that glowed.

Subjective Assessments for Full Face
Using a 0 to 10 severity scale, subjects completed the Subjective Skin Quality Questionnaire at baseline (before product application) and at the end of study (week 12). Subjects were asked to rate fine lines and wrinkles, elasticity, texture, tone, redness and broken blood capillaries, glow, smoothness, youthful appearance, dryness, discoloration, pores, and satisfaction with the look of their skin.

Tolerability for Full Face
The investigator objectively rated erythema, edema, dryness, and peeling of the full face, using a 0 to 4 (minimal to severe) scale, at each visit. Subjects rated stinging, tingling, itching, and burning, using the same scale, at each visit.

Global Aesthetic Improvement Scale (GAIS)
Using a 5-point scale for improvement (none, minimal, mild, moderate, marked) the investigator qualitatively assessed improvement at the end of the study.

Data Analysis
Since assessment scales had a small range and data were in small whole numbers, non-parametric statistics were used to analyze data, using P=0.05 as the cutoff value for significance. For multiple comparisons, the Bonferroni correction was used to adjust the cutoff value. For example, if the median scores at weeks 4, 8, and 12 were each compared with the median baseline score, the cut-off value (*P*=0.05) was divided by 3, the number of non-independent comparisons. In this case, the corrected *P*-value is 0.05/3 = 0.017.

RESULTS

Twenty-one subjects completed the study. One subject withdrew consent due to a scheduling conflict.

Investigator's Objective Assessments
The investigator's objective assessment results are shown in Table 2. The scores at weeks 4, 8, and 12 were compared with the scores at baseline using the paired Wilcoxon signed rank test. After applying the Bonferroni correction, improvements compared with baseline were significant at all time points for radiance, tone, smoothness, texture, and overall appearance. For red/blotchy, 4-week improvement was not significant, 8-week improvement was of borderline significance (0.0171), and 12-week improvement was significant (*P*=0.0017). Improvement in dryness was significant at week 4 and non-significant at weeks 8 and 12 due to low values (0 and 1) throughout the study for all subjects.

TABLE 3.

Subjective Skin Quality Assessments						
Question		Baseline Grade (median, min, max)	Wk 12 Grade (median, min, max)	Median % Diff (min, max)	P-value (baseline vs wk 12)	Subjects Improved (%)
1	lines and wrinkles	5.0 (2, 9)	5.0 (1,8)	0.0 (-40, 80)	0.1230	38.1
2	elasticity	5.0 (2, 9)	5.0 (2, 9)	12.0 (-100, 67)	0.4413	52.4
3	texture	5.0 (2, 10)	4.0 (1, 10)	33 (-100, 71)	0.0013	71.4
4	tone	7.0 (4, 10)	5.0 (1, 9)	25.0 (-20, 89)	0.0002	71.4
5	redness, broken capillaries	5.0 (2, 9)	4.0 (2, 8)	17.0 (-200, 71)	0.1084	61.9
6	glow	6.0 (3, 9)	5.0 (1, 9)	20.0 (-100, 75)	0.0013	76.2
7	smoothness	5.0 (2, 10)	4.0 (1, 10)	17.0 (-67, 75)	0.0031	57.1
8	youthful appearance	7.0 (3, 9)	5.0 (2, 7.33)	14.0 (-20, 60)	0.0026	66.7
9	dryness	5.0 (3, 8)	4.0 (2, 8)	14.0 (-100, 75)	0.2522	52.4
10	discoloration	5.0 (3, 8)	5.0 (2, 9)	0.0 (-60, 167)	0.5619	38.1
11	pores	4.0 (1, 7)	6.0 (2, 9)	40.0 (-40, 400)	0.0038	66.7
12	satisfaction	7.0 (3, 10)	5.0 (0,9)	29.0 (-67, 100)	0.0002	85.7

The percentage of subjects improved increased steadily from week 4 to week 12 for all parameters except for dryness. At week 12, smoothness, texture, and overall appearance showed the highest percentage of subjects improved at 90.5%.

Median percent improvement scores compared with baseline ranged from 33% to 50% at weeks 4, 8, and 12 for radiance, tone, smoothness, texture, and overall appearance. Values were more variable for red/blotchy and consistently 0 for dryness, the latter due to the small range of scores (0 to 1). Percent improvement for weeks 4, 8, and 12 compared with baseline was calculated by the following formula, using week 12 as an example.

Percent improvement = ([week 12 score – baseline score]/ baseline score) x 100

Investigator Tolerability

For erythema, edema, dryness, and peeling, grades were generally low (0-2) and varied randomly between baseline and week 12. All scores were 0 at baseline and week 12, except for a single subject with a grade of 1 for dryness at week 12. Five subjects were graded 2 at week 4 and all decreased to 0 or 1 at week 8 and week 12. These adverse events were study-related and were all mild to moderate, temporary, and resolved without treatment.

Subjective Tolerability

All subjects were graded 0 at baseline and week 12 for stinging, tingling, itching, and burning. Three subjects were graded 1 or 2 at week 4 and all decreased to 0 or 1 at week 8 and 0 at week 12. These adverse events were study-related and were all mild to moderate, temporary, and resolved without treatment.

Subjective Skin Quality

The subjective skin quality assessment results are shown in Table 3. For each question, the subject grades at week 12 were compared with the subject grades at baseline by the paired Wilcoxon signed rank test. Since this was a single comparison, the Bonferroni correction was not applied. Lower median grades at week 12 indicated improvement over baseline for all questions except 10 (discoloration) and 11 (pores).

Improvements at week 12 were significant for texture (P=0.0013), tone (P=0.0002), glow (P=0.0013), smoothness (P=0.0031), youthful appearance (P=0.0026), pores (P=0.0038), and satisfaction (P=0.0002). The percentage of subjects improved for these parameters ranged from 57.1% to 85.7%. For the remaining skin parameters, percentages of subjects improved at week 12 ranged from 38.1% (lines and wrinkles, discoloration) to 61.9% (redness and broken capillaries).

Global Aesthetic Improvement Scale (GAIS)
Mild to moderate improvement was observed in 76.2% of subjects.

The median improvement was 3.0 (mild) with a minimum value of 1 (none) and maximum value of 4 (moderate).

DISCUSSION

As stated earlier, the Test Product is a combination of all-trans retinol, HA, and TCA for the treatment of skin aging, discoloration, and hydration. Squalene and shea butter are also present. All-trans retinol (1%) supports collagen with little or no irritation and is encapsulated for stability and skin penetration. TCA improves the appearance of skin discoloration, pore size, and uneven texture. HA restores and improves skin moisture.

The findings of the present study support these expected clinical benefits and tolerability. The Investigator's objective assessments show that use of the Test Product as in the present study provides significant improvement in radiance, tone, smoothness, texture, and overall appearance; and that improvement increases with continued use up to week 12.These results are paralleled by the steady increase in the percentage of subjects improved during the study period. Improvement in red/blotchy became significant at week 8 and remained significant at week 12 with 61.9% of subjects improved.

Subjective skin quality assessments addressed changes in the same skin parameters (texture, tone, radiance [glow], smoothness, dryness, discoloration), with consideration also given to pores and overall satisfaction. As with the Investigator's objective assessments, improvement at week 12 was significant for texture, tone, glow [radiance], and smoothness. Improvement was also significant for youthful appearance, pores, and satisfaction. More than half of subjects showed improvement in skin elasticity, redness/broken capillaries, and dryness, although the week 12 scores for these parameters did not achieve significance.

Finally, the investigator and subjective tolerability data showed that the procedure was well tolerated by all subjects. Clinical examples are shown in Figures 1 to 3.

All-trans retinol is a precursor for the synthesis of endogenous retinal and retinoic acid (tretinoin). Retinol's potential for the treatment of photoaging was explored in a series of studies which showed that topical retinol had beneficial effects similar to tretinoin but with minimal erythema and skin irritation. Subsequent studies showed that, compared with tretinoin, retinol produced less transepidermal water loss, erythema, and scaling, and it stimulated collagen biosynthesis in photoaged skin. Retinol also improved fine wrinkles, reduced collagenase, and lowered gelatinase expression while increasing fibroblast growth and collagen synthesis in tissue specimens. These and other findings led to the conclusion that retinol should be effective in the treatment of aging and photoaging.[1]

FIGURE 1. A 60-year-old non-Hispanic Caucasian female of Fitzpatrick skin type 2 before (A) and after (B) week 12 of treatment with the Test Product. At the end of study, the subject's baseline investigator's objective assessments showed improvement in radiance, skin tone, smoothness, texture, red/blotchiness, and overall assessments. The subject's self-assessed skin quality improved in elasticity, smoothness, evenness, redness, radiance, softness, youthfulness, hydration, and pores. The investigator's aesthetic improvement assessment was 3 (mild). The subject was very satisfied with the treatment

(A) (B)

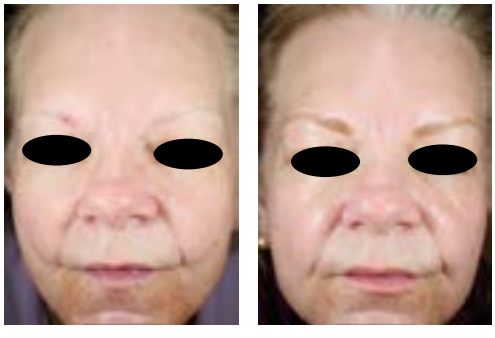
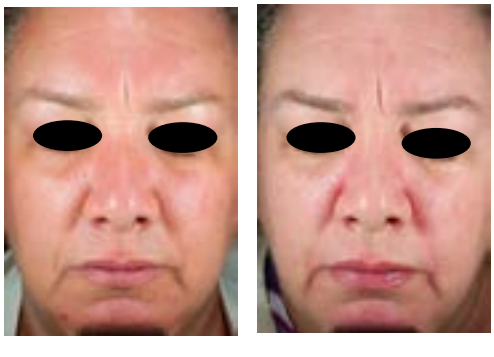


FIGURE 2. A 52-year-old non-Hispanic Caucasian female of Fitzpatrick skin type 2 before (A) and after (B) week 12 of treatment with the Test Product. At the end of study, the subject's baseline investigator's objective assessments showed improvement in smoothness and texture. The subject's self-assessed skin quality improved in fine lines and wrinkles, elasticity, smoothness, evenness, redness, radiance, youthfulness, and pores. The investigator's aesthetic improvement assessment was 2 (minimal). The subject was satisfied to very satisfied with the treatment.

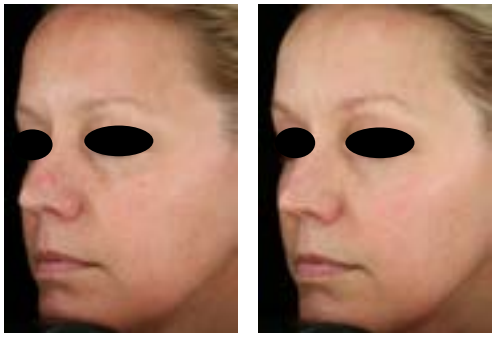
(A) (B)



In human skin, HA is a key contributor to water retention and mechanical support.[2] Found at the periphery and interfaces of collagen and elastin fibers, HA helps to hold collagen and elastin in a proper configuration. In aged skin, these connections with HA are absent, which may lead to the disorganized collagen and elastin fibers and the formation of fine lines, wrinkles, and nasolabial folds.[4]

FIGURE 3. A 43-year-old non-Hispanic Caucasian female of Fitzpatrick skin type 2 before (A) and after (B) week 12 of treatment with the Test Product. At the end of study, the subject's baseline investigator's objective assessments showed improvement in smoothness and texture. The subject's self-assessed skin quality improved in fine lines and wrinkles, elasticity, smoothness, evenness, redness, radiance, softness, youthfulness, hydration, and pores. The investigator's aesthetic improvement assessment was 4 (moderate). The subject was very satisfied with the treatment.

(A) (B)



HA is well known for its ability to hold a large amount of moisture. As skin ages, the amount of HA decreases to approximately 5% of baseline. HA is also a scavenger of free radicals and has anti-inflammatory properties. With these specific properties, HA should be a prime component of cosmetic products.[4]

For skin aging, trichloroacetic acid (TCA) has been considered a gold standard as it is stable, does not cause systemic toxicity, and does not need to be neutralized when applied to skin.[5] The main indications for TCA peels are melasma, photoaging, acne scars, under-eye circles, frictional melanosis, actinic keratosis, actinic cheilitis, xanthelasma, flat warts, seborrheic keratosis, and acanthosis nigrans.[6] Side effects include redness, herpes, hyperpigmentation, and lentigines.[7] These side effects were not observed in the present study.

Squalene, the main component of skin surface polyunsaturated lipids, offers advantages for the skin as an emollient and antioxidant, and for hydration. As in the Y.E.S.S. product, squalene is also used as a material in topically applied vehicles such as lipid emulsions and nanostructured lipid carriers.[8] Shea butter is used in the cosmetic industry due to its high percentage of compounds (triterpenes, tocopherol, phenols, and sterols), which possess potent anti-inflammatory and antioxidant properties.[9]

The results of the present study show that when applied daily for up to 12 weeks, the Test Product, cleanser, and moisturizer-sunscreen combo improves many of the manifestations of aged skin with high subject satisfaction and minimal adverse effects. As for limitations, a placebo-controlled clinical trial with a larger sample size should be performed to verify the results of this pilot study. The future study should include skin biopsy results to further define the observed clinical effects of the Test Product.

CONCLUSION

The combination serum with retinol, HA, and TCA has been shown to improve aged facial skin and is well tolerated when used daily for up to 12 weeks.

DISCLOSURES

Dr. Gold is a consultant to Induction Therapies, and Tennessee Clinical Research Center was compensated for performing the research.

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ORIGINAL ARTICLE

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Underrepresented Groups and Perceived Educational Barriers for Residency and Fellowship Success

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ABSTRACT

Background: The study aimed to compare barriers perceived by medical students and resident physicians identifying as of underrepresented groups in medicine (UIM) and/or as sexual and gender minorities (SGM) to individuals not identifying with these groups, especially for trainees with an interest in dermatology.

Methods: Cross-sectional survey of medical students and resident physicians based in the United States from February 2021 to July 2021, with subgroup analysis of trainees with interest in dermatology.

Findings: Among trainees interested in dermatology, the most notable barriers for the UIM group were 1) lack of home program in specialty/fellowship of interest (4.71±1.73); 2) lack of connections/networking opportunities (4.14±1.29); 3) lack of opportunity to obtain AOA membership (4.00±1.96); 4) obtaining mentorship (4.00±1.47); and lack of diversity in specialty/fellowship of interest (3.93±1.14).

Conclusions and Relevance: Increasing focused mentorship programs and fostering environments that embrace diversity are key to reducing perceived barriers for minority candidates.

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INTRODUCTION

As the United States (US) continues to rapidly diversify (racially/ethnically), the field of dermatology remains slow to follow suit. African Americans and Hispanics account for 13% and 16% of the US population, respectively, but only comprise 3% and 4% of dermatologists.[1] Insufficient representation of underrepresented groups in medicine (UIM) and sexual and gender minorities (SGM) may perpetuate health disparities for minority patient populations.[2] Studies have suggested that physicians from underrepresented groups are more likely to provide care for underserved populations and individuals of lower socioeconomic status, which can help alleviate health disparities and improve clinical outcomes for minority patient populations.[2–5]

The American Academy of Dermatology made a call to action in 2017, with proposals to address a lack of diversity.[6] This was an instrumental step toward achieving greater diversity within dermatology; nevertheless, there is a need for further characterization of the barriers that limit representation within the field.

As a result, the primary objective of this study was to compare perceived barriers for US-based medical students and resident physicians who self-identify as UIM or SGM to students and physicians who do not self-identify with these groups, with a special emphasis on the perceived barriers for dermatology applicants compared to applicants pursuing other medical specialties.

MATERIALS AND METHODS

Study Design

A cross-sectional survey study was performed of US-based medical students and resident physicians (Doctor of Medicine [MD], Doctor of Osteopathic Medicine [DO], MD/PhD, DO/PhD candidates). The primary objective was to identify differences in barriers to advancing in different medical specialties experienced by physician trainees who identify as UIM and/or as SGM, compared to non-UIM and non-SGM physician trainees. The study protocol was exempted by the Institutional Review Board at the University of California, Irvine. In accordance with the Association of American Medical Colleges, UIM is defined as individuals identifying with one of the following racial/ethnic groups: African American, Black, LatinX, Native American, Alaska Native, or Hawaiian American; and, SGM as individuals who identify as lesbian, gay, bisexual, transgender, queer, asexual, and pansexual.[7,8] Participants were stratified by UIM and SGM status, then further grouped by medical specialty of interest. A Likert scale score, with 1 being "Strongly Disagree" and 5 being "Strongly Agree" was used to assess barriers perceived by survey participants.

Survey Tool

A 54-question survey was developed to identify educational barriers faced by medical students/resident physicians identifying as UIM or SGM. The survey was evaluated by eight attending/faculty physicians in dermatology (n=7) and psychiatry (n=1) to obtain face validity. All US medical schools were contacted for assistance with survey distribution through REDCap (Research Electronic Data Capture).[9] The survey was also dispersed through the Skin of Color Society, Student National Medical Association, National Medical Association (NMA), Women's Dermatologic Society, and Association of Professors of Dermatology electronic listservs.

Statistical Methods

Statistical analyses were conducted using Stata/SE 16.1. Participants were stratified by UIM, SGM, and non-UIM/non-SGM status. Chi-squared tests and student t-tests (2-sided) were used to measure differences in prevalence rates and means between groups for categorical variables and continuous variables, respectively. Subgroup analyses of participants with an interest in dermatology were performed. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Participant Characteristics

Of 301 total respondents, 65 identified as UIM, 56 as SGM, and 281 as neither UIM nor SGM (non-UIM/non-SGM; Table 1). Among subjects identifying as SGM, 51.8% were bisexual. 57.8% of the UIM group indicated Hispanic or LatinX ethnicity, and 35.4% identified as Black or African American.

Barriers: Participants With Interest in Dermatology

In a subgroup analysis of participants with an interest in dermatology (n=61), the top 5 barriers for the non-UIM/non-SGM group were lack of home program in specialty/fellowship of interest (4.37±1.71), probability of matching (4.12±1.12), lack of connections/networking opportunities (3.85±1.31), lack of opportunity to obtain AOA membership (3.80±1.83), and obtaining multiple peer-reviewed research publications (3.54±1.38). For the UIM group, lack of home program in specialty/fellowship of interest (4.71±1.73), lack of connections/networking opportunities (4.14±1.29), lack of opportunity to obtain AOA membership (4.00±1.96) were also among the top 5 barriers; however, obtaining mentorship (4.00±1.47), specialty's perceptions of SGM students (3.93±2.02), and lack of diversity in specialty/fellowship of interest (3.93±1.14) were notable barriers for the UIM group but not the non-UIM/SGM group. Similar to the non-UIM/non-SGM group, lack of home program in specialty/fellowship of interest (4.83±1.47), probability of matching (4.67±0.52), and obtaining multiple peer-reviewed publications (4.17±0.75) were also top 5 barriers for the SGM group. Obtaining specialty-specific letters of recommendation (4.17±1.33) and USMLE Step 1 score (4.00±1.55) were also among the top 5 barriers for the SGM group in contrast to the non-UIM/SGM group (Table 2).

Participant Comments

Several themes emerged from qualitative analysis of participant comments including mentorship/networking, academic barriers, DO/foreign medical graduate-specific barriers, mental health, physical disabilities, early exposure to competitive specialties, SGM/UIM identity, gender bias, school/program-specific barriers, and socioeconomic barriers. When analyzing participant suggestions to improve barriers, numerous comments were made regarding remote mentorship opportunities, mentors with similar backgrounds, mentorship programs within medical schools/residency programs, resident/medical student mentorship, incentives for mentors, early initiation of mentorship, and strategies to reduce specific barriers for UIM/SGM students (Table 3).

TABLE 1.

Medical Student and Resident Physician Participant Characteristics

Characteristic	Non-UIM and Non-SGM (n=281)	UIM (n=65)	*P* value[a]	SGM (n=56)	*P* value[b]
Gender, n (%)	--	--	0.024	--	<0.001
Cisgender Female	186 (66.2)	38 (58.5)	--	38 (67.9)	--
Cisgender Male	95 (33.8)	25 (38.4)	--	14 (25)	--
Genderqueer	0 (0)	0 (0.0)	--	2 (3.57)	--
Decline to Answer	0 (0)	1 (1.5)	--	0 (0.0)	--
Other[c]	0 (0)	1 (1.5)	--	2 (3.57)	--
Sexual Orientation, n (%)	--	--	<0.001	--	<0.001
Heterosexual	281 (100)	53 (81.5)	--	0 (0.0)	--
Gay	--	1 (1.5)	--	11 (19.4)	--
Lesbian	--	0 (0.0)	--	3 (5.4)	--
Bisexual	--	5 (7.7)	--	29 (51.8)	--
Queer	--	2 (3.1)	--	6 (10.7)	--
Asexual	--	1 (1.5)	--	3 (5.4)	--
Pansexual	--	1 (1.5)	--	4 (7.1)	--
Decline to Answer	--	2 (3.1)	--	0 (0.0)	--
Specialty of Interest, n (%)	--	--	0.078	--	0.003
Internal Medicine	42 (15.0)	9 (13.9)	--	10 (17.9)	--
Dermatology	41 (14.6)	14 (21.5)	--	6 (10.7)	--
Emergency Medicine	27 (9.6)	3 (4.6)	--	0 (0.0)	--
Family Medicine	24 (8.5)	7 (10.8)	--	6 (10.7)	--
Pediatrics	24 (8.5)	5 (7.7)	--	0 (0.0)	--
General Surgery	19 (6.8)	3 (4.6)	--	3 (5.4)	--
Obstetrics/Gynecology	17 (6.1)	3 (4.6)	--	4 (7.1)	--
Psychiatry	13 (4.6)	1 (1.5)	--	4 (7.1)	--
Radiology	11 (3.9)	1 (1.5)	--	3 (5.4)	--
Ophthalmology/Otolaryngology/ Plastic Surgery	10 (3.6)	3 (4.6)	--	4 (7.1)	--
Anesthesiology	9 (3.2)	2 (3.1)	--	2 (3.6)	--
Other[d]	44 (15.7)	14 (21.5)	--	14 (25.0)	--
Race, n (%)	--	--	<0.001	--	<0.001
Caucasian or White	176 (62.6)	25 (38.5)	--	40 (71.4)	--
Black or African American	0 (0.0)	23 (35.4)	--	3 (5.4)	--
Asian	107 (38.1)	10 (15.4)	--	12 (21.4)	--
Native Hawaiian or Other Pacific Islander	0 (0.0)	8 (12.3)	--	2 (3.6)	--
American Indian or Alaskan Native	0 (0.0)	6 (9.2)	--	0 (0.0)	--
Other Race	9 (3.2)	2 (3.1)	--	2 (3.6)	--
Decline to Answer	3 (1.1)	5 (7.7)	--	2 (3.6)	--
Ethnicity, n (%)	--	--	<0.001	--	<0.001
Hispanic or Latino	0 (0.0)	37 (57.8)	--	6 (11.1)	--
Not Hispanic or Latino	281 (100)	27 (42.2)	--	48 (88.9)	--
Year in Training, n (%)	--	--	0.535	--	0.039
Resident Physician	76 (27.1)	18 (27.7)	--	9 (16.1)	--
MS3-MS4[e]	125 (44.5)	30 (46.2)	--	21 (37.5)	--
MS1-MS2	71 (25.3)	13 (20.0)	--	20 (35.7)	--
MD/PhD or MD/Master's Student	3 (1.1)	3 (4.6)	--	3 (5.4)	--
Post-Graduate Research Fellow	4 (1.4)	1 (1.5)	--	0 (0.0)	--
Other	2 (0.7)	0 (0.0)	--	2 (3.6)	--
Degree Type, n (%)	--	--	0.077	--	0.341
Doctor of Medicine (MD)	173 (61.6)	49 (75.4)	--	40 (71.4)	--
Doctor of Osteopathic Medicine (DO)	97 (34.5)	13 (20.0)	--	15 (26.8)	--
Foreign Medical Graduate	11 (3.9)	3 (4.6)	--	1 (1.8)	--
Geographic Location, n (%)	--	--	0.092	--	0.778
Northeast	26 (9.3)	4 (6.2)	--	5 (8.9)	--
Midwest	25 (8.9)	2 (3.1)	--	4 (7.1)	--
South	78 (27.8)	12 (18.5)	--	21 37.5)	--
West	89 (31.7)	27 (41.5)	--	14 (25.0)	--
Northwest	18 (6.4)	3 (4.6)	--	4 (7.1)	--
Southwest	45 (16.0)	17 (26.2)	--	8 (14.3)	--

[a]*P*-value comparing non-UIM/non-SGM group to UIM group; [b]*P*-value comparing non-UIM/non-SGM group to SGM group; [c]Transgender female (n=0), transgender male (n=1), gender nonconforming (n=1), gender fluid (n=0), gender expansive (n=0), gender non-binary (n=0); [d]Neurologic surgery (n=1), neurology (n=14), orthopedic surgery (n=10), pathology (n=11), physical medicine and rehabilitation (n=9), radiology/radiology oncology/intervention (n=16), thoracic surgery/vascular surgery (n=3), urology (n=3), other (n=7), unsure (n=13); [e]Includes student research fellows. *UIM,* Underrepresented in Medicine, *SGM,* Sexual and Gender Minority, *MS,* Medical Student, UIM and SGM categories not mutually exclusive; Statistically significant values are bolded.

TABLE 2.

Subgroup Analysis of Participants With Interest in Dermatology (n=61); Likert Scale Score

Potential Barriers (Likert Scale Score, Mean ± SD)	Non-UIM and Non-SGM (n=41)	UIM (n=14)	*P* value	SGM (n=6)	*P* value
Personal/Familial Obligations	2.39±1.22	2.36±1.39	0.933	3.00±1.22	0.255
Financial Status	2.20±1.14	2.36±1.34	0.663	3.67±1.03	0.005
Available Opportunities at Medical School/Residency Program	3.49±1.50	3.21±1.76	0.576	3.83±1.47	0.601
USMLE Step 1 Score	3.20±1.81	3.86±1.61	0.230	4.00±1.55*	0.306
Lack of Opportunity to Obtain Alpha Omega Alpha Membership	3.80±1.83*	4.00±1.96*	0.737	3.67±1.63	0.862
Lack of Opportunity to Obtain Multiple Honors, Awards, Scholarships, or Distinctions	3.29±1.72	2.93±1.33	0.475	3.17±1.67	0.864
Third-Year Clerkship Grades	3.29±1.62	3.50±1.74	0.686	3.50±1.78	0.771
Obtaining Specialty Specific Letters of Recommendation	3.32±1.65	3.14±1.66	0.735	4.17±1.33*	0.236
Obtaining Multiple Peer-Reviewed Research Publications	3.54±1.38*	3.21±1.72	0.482	4.17±0.75*	0.283
Obtaining Multiple Posters/Presentations	3.29±1.40	3.14v1.79	0.749	4.00±0.63*	0.233
Lack of Opportunity to Participate in Multiple Volunteer Experiences	2.27±1.14	2.21±1.19	0.880	3.33±1.21	0.040
Probability of Matching	4.12±1.12*	3.71±1.38	0.274	4.67±0.52*	0.251
Internalized and/or Social Perceptions of the Field	3.07±1.49	3.36±1.45	0.538	3.67±1.03	0.353
Specialty's Perception of UIM Students	3.02±1.88	3.36±1.39	0.546	3.00±1.55	0.976
Specialty's Perception of SGM Students	2.88±1.89	3.93±2.02*	0.083	3.00±1.79	0.882
Racial/Ethnic Background	2.61±1.36	3.14±1.23	0.200	2.17±0.41	0.435
Sexual Orientation and/or Gender Identity	2.12±1.23	3.21±1.97	0.018	2.50±0.84	0.472
Lack of Home Program in Specialty/Fellowship of Interest	4.37±1.71*	4.71±1.73*	0.515	4.83±1.47*	0.530
Obtaining Mentorship	3.37±1.39	4.00±1.47*	0.152	3.67±1.51	0.627
Lack of Diversity in Specialty/Fellowship of Interest	2.66±1.30	3.93±1.14*	0.002	2.83±0.75	0.750
Lack of Connections/Networking Opportunities	3.85±1.31*	4.14±1.29*	0.479	3.83±1.47	0.972

UIM, Underrepresented in Medicine, *SGM*, Sexual and Gender Minority. Statistically significant values are bolded. Likert scale: 1 = "Strongly Disagree", 2 = "Disagree", 3 = "Neutral", 4 = "Agree", 5 = "Strongly Agree", 6 = "N/A". *Top five barriers

TABLE 3.

Participant Suggestions for Overcoming Perceived Barriers

Suggestion	Example Comments*
Remote Mentorship Opportunities	"Tinder app for mentors/mentees. Mentorship via Zoom."
	"Remote mentoring opportunities through local/national organizations open to all medical students."
	"It would be helpful to have a centralized database to search for mentors on a local and national level because without your faculty having connections, attending conferences, or joining professional organizations, it is difficult to network with other potential mentors."
	"May want to have a list of contacts or a centralized hub where students/residents could find mentors and research projects in their field of interest."
Mentors with Similar Backgrounds	"Mentorship from physicians with disabilities."
Mentorship Programs within Medical Schools/Residency Programs	"The university leadership could match local mentors with students in the field of interest."
	"Pairing an alumnus in a specific field with a student with interest in that field is a good possible method."
	"Smaller class sizes at medical schools, and/or mandatory advisors having less of a load of mentees so that it feels more personal."
Resident-Medical Student Mentorship	"The frequency of interaction between the mentor and the resident should increase and the resident should be approached by the mentor as much as the student/resident is expected to approach -(them)."
Incentives for Mentors	"Incentivize attendings to mentor students and residents from the top down."
	"Encourage alumni to engage in mentorship programs at their medical schools."
	"Reach out to residents, especially first years who may serve as big brother/sister to the medical students. Provide educational resources available free of charge."
Initiate Mentorship Early	"I think it could be helpful to have mentorship programs for younger age groups, like pre-medical undergraduate students or perhaps even high school students."
	"Have attendings (from various backgrounds, such as private vs academic, etc.) discuss with medical students and pre-meds how they got their position."
Decreasing Barriers for UIM/ SGM Students	"Pairing URG students with mentors of the same URG at an early stage."
	"All program directors should be members on Diversity Equity and Inclusion committees at their institution."
	"More accessibility by working with programs to excuse UIM to actually attend conferences/ group meetings etc. directly created for them."
Other	"Residency programs should reach out more to schools without a home program and at least clarify expectations and explain how applications are evaluated."

*Edited for readability. *URG*, underrepresented group, *UIM*, underrepresented in medicine, *SGM*, sexual and gender minority

DISCUSSION

Access barriers (eg, board examination scores, AOA status, research, networking, etc.) perceived by medical students and resident physicians, are poorly characterized in the literature. This is concerning given that lack of diversity (racially/ethnically and sexual/gender) in certain medical specialties, may be in part due to these perceived access barriers from applicants.[10] Our study addresses this knowledge gap, providing insight into which access barriers are more burdensome for medical students and resident physicians, with specific participant-proposed solutions.

The lack of connections/networking opportunities and lack of diversity in specialty/fellowship of interest emerged as unique barriers for the UIM group in our study. Similar barriers have been noted in studies from over a decade ago. A survey of the Deans of Student Affairs of all US allopathic and osteopathic medical schools in 2002 found that lack of UIM faculty and/or role models were among the three most commonly reported barriers.[11] In 2015, Peek et al noted the presence of UIM role models and the access to established, experienced mentors to junior UIM faculty were important for recruiting and retaining UIM faculty.[12] Recently, a study evaluated the distribution of UIM among US medical school faculty for 16 clinical academic medicine departments using the Association of American Medical Colleges Faculty Roster from 1990 through 2019 and found an increase for UIM faculty in only 8/16 specialties.[13] Therefore, UIM residency and fellowship candidates likely lack mentors due to low UIM faculty and representation within health professional schools. Mentorship for UIM candidates is integral as mentors can help candidates navigate the resident selection process, and additionally in creating and facilitating networking experiences.[14]

Our results are consistent with prior reports that SGM medical students and residents are influenced by perceptions of inclusivity when discerning their choice of specialty. A prior study found that SGM physicians felt strongly that their sexual and gender identity influenced specialty choice, in addition to concerns about perceived inclusivity within a specialty.[15] Furthermore, among SGM physicians, 65% have heard derogatory lesbian, gay, bisexual, and transgender comments in the workplace and 15% reported being harassed by heterosexual colleagues.[16] The same study also reported SGM would likely avoid training in geographic areas of high prejudice or avoid pursuing careers in certain specialties; however, they did not delineate which specialties SGM felt least welcome.[16] To help combat these barriers, medical centers must continue to implement new policies to promote a safe and supportive training environment, as well as new recruitment processes to ensure a diverse and competent workforce of physicians, which includes SGM individuals.

Regarding dermatology-specific barriers, a cross-sectional study comparing UIM and non-UIM applicants who applied to the University of Texas Southwestern Dermatology Residency Program noted lack of equitable resources, lack of support, financial constraints, and lack of group identity as barriers to matching.[17] Moreover, a 2020 study, which included 67 medical students interested in applying to dermatology residency, found a lack of diversity, perceived negative perceptions of minority students by residencies, socioeconomic factors, and lack of mentors as major barriers for minority students.[18] Our study similarly found lack of diversity in specialty/fellowship of interest and obtaining mentorship to be important barriers for UIM candidates. Other notable barriers faced by UIM candidates, uniquely identified by our study, include lack of home program in specialty/fellowship of interest, lack of connections/networking opportunities, and lack of opportunity to obtain AOA membership. Lack of a home program and networking may have emerged in our study given limited away rotations amid the SARS-CoV-2 or coronavirus disease 2019 (COVID-19) pandemic.[19]

Overall, our study showed increased barriers for various groups including UIM, SGM, and osteopathic candidates, thus warranting action. While national organizations, such as the Dermatology Interest Group Association and NMA have created opportunities to increase equity, more accessible and effective mentorship is needed. For example, participants recommended a "Tinder (dating) application" specifically for networking to facilitate mentorship compatibility matching, as well as a centralized open-access resource of mentors. Moreover, virtual networking opportunities should be advertised and easily accessible to UIM and SGM medical students starting the first year of medical school. It would also be helpful for medical schools and residencies to establish alumni mentorship programs, where UIM/SGM students and alumni, with similar backgrounds, are matched early on in medical school/residency. Another solution, requiring coordination between medical schools and residency programs, is to establish opportunities that allow UIM/SGM students/residents to gain early exposure to all specialties, including dermatology. Moreover, to increase the comfort of SGM candidates in pursuing any medical specialty, medical school and resident lecture series are needed to increase awareness, dispel misconceptions, and increase sensitivity within the workplace for this group. Lastly, to reduce barriers for students lacking home programs, partnerships with local residency programs are needed to increase transparency and access to opportunities, making the process more equitable to all applicants.

Our study was strengthened by surveying a wide range of medical schools and organizations, while limitations include cross-sectional design and a short data collection period. Additionally,

our project was only able to capture 301 participants which is a small portion of medical school graduates. Of note, our findings may have been influenced by the COVID-19 pandemic that created unique stressors and obstacles for medical students/residents.

CONCLUSION

Increased representation and support of minority groups could encourage the recruitment of individuals who identify as part of these groups and further improve patient outcomes. Significant barriers among UIM trainees interested in dermatology include lack of home program in specialty/fellowship of interest, lack of connections/networking opportunities, lack of opportunity to obtain AOA membership, lack of connections/networking opportunities, and lack of diversity in dermatology. Our study also uniquely identified participant-proposed solutions such as a "Tinder (dating) application" for mentorship and local partnerships for greater transparency/support for students who lack affiliated hospitals and home programs. We look forward to further discussion regarding implementation of these solutions in efforts to reduce perceived access barriers for medical school and dermatology residency applicants.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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BRIEF COMMUNICATION

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Do the Words We Choose Matter When Prescribing Medications?

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ABSTRACT

Background: Caregivers are often apprehensive about treating childhood atopic dermatitis (AD) with topical corticosteroids but may find comfort if treatments are presented in a patient-centered manner.
Objective: We assessed caregivers' willingness to treat AD with either a "topical steroid," "topical medication," or "treatment, similar to the all-natural signals produced by the adrenal glands in the body."
Methods: A survey randomized 874 caregivers of children with AD to receive a "topical steroid," "topical medication," or "treatment, similar to the all-natural signals produced by the adrenal glands in the body." A scenario-only dataset received these descriptions, while a descriptive heading dataset and expanded scale dataset also received headings of "Topical Steroid Use," "Topical Medication Use," and "All-Natural Treatment Use," respectively. Responses were recorded on a 6-point Likert scale or 0-100 slider scale. Whole and dichotomized responses were evaluated using 2-tailed, independent sample *t*-tests.
Results: For the descriptive heading and expanded scale datasets, those presented with a "topical medication" reported greater willingness to treat than those presented with a "topical steroid" and "all-natural treatment" in the descriptive heading dataset ($P<0.05$). For the dichotomized scenario-only dataset, those presented with a "treatment, similar to the all-natural signals produced by the adrenal glands in the body," reported greater willingness than those presented with a "topical medication" ($P<0.05$).
Conclusion: Initially presenting caregivers with a "topical medication" rather than a "topical steroid" may improve willingness to treat AD for some caregivers. However, tailoring the discussion to best fit caregivers' understanding of treatment may be the most beneficial approach.

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INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory dermatologic condition, affecting upwards of 20% of children worldwide.[1] Although AD typically responds quickly to treatment, nonadherence is a common barrier to treatment success in the pediatric population, with up to two-thirds of patients and their caregivers not utilizing topical medications exactly as prescribed.[2] Common reasons for treatment nonadherence in AD include cost, unclear or difficult to understand treatment instructions and concerns about side effects.[3-5]

Health literacy, "the ability to read, understand and use health information to make appropriate healthcare decisions," is an essential aspect for health care providers to consider in their patients.[6,7] Low caregiver health literacy has been linked to deleterious health outcomes for many children.[8] Therefore, a caregiver's understanding of treatment, influenced by the provider's specific phrasing, may be associated with their willingness to treat childhood AD. In clinical practice, topical corticosteroids are often initially presented to caregivers as either a "topical medication" or "topical steroid." Some caregivers may benefit from education that topical corticosteroids share many similarities with the glucocorticoids produced naturally by the adrenal glands in the body.

Tailoring the language used when presenting topical corticosteroids to caregivers to best address their unique needs and understanding of treatment may increase willingness to initiate treatment; however, substitute language framing has not been well defined in this population. The purpose of this study was to assess caregivers' willingness to treat childhood AD with either a "topical steroid," "topical medication," or "treatment, similar to the all-natural signals produced by the adrenal glands in the body."

TABLE 1.

Survey Script Scenario Variants		
Groups 1,4,7	Topical Steroid Use (This heading only included in groups 4 and 7)	Your doctor suggests the following to you, "This topical steroid that works by bringing the skin's immune system into balance has an 80% chance of greatly improving your child's eczema if applied consistently on a twice daily basis."
Groups 2,5,8	Topical Medication Use (This heading only included in groups 5 and 8)	Your doctor suggests the following to you, "This topical medication that works by bringing the skin's immune system into balance has an 80% chance of greatly improving your child's eczema if applied consistently on a twice daily basis."
Groups 3,6,9	All-Natural Treatment Use (This heading only included in groups 6 and 9)	Your doctor suggests the following to you, "This treatment, similar to the all-natural signals produced by the adrenal glands in the body, that works by bringing the skin's immune system into balance has an 80% chance of greatly improving your child's eczema if applied consistently on a twice daily basis."

Participant questionnaire contained unformatted text. Assessment: How willing would you be to treat your child's eczema with this topical steroid or topical medication or treatment, similar to the all-natural signals produced by the adrenal glands in the body?
Groups 1-6, the scenario-only and descriptive heading datasets, responded using a 6-point Likert scale with 1 – definitely not willing and 6 – definitely willing. Groups 7-9, the expanded scale dataset, responded using a 0-100 sliding scale with 0 - definitely not willing and 100 - definitely willing.

MATERIALS AND METHODS

Following Wake Forest School of Medicine Institutional Review Board approval, a prospective parallel arm survey study was performed on eligible caregivers of children under 18 years of age with a self-reported diagnosis of AD. Subjects were required to have a working knowledge of English. If subjects did not meet inclusion criteria after answering the survey eligibility screening questions, they could not complete the remainder of the survey and were excluded from the analysis. 874 subjects were recruited through Amazon Mechanical Turk (MTurk), an online crowdsourcing platform. MTurk is a validated tool for conducting research in psychology and other social sciences and is considered diverse and perhaps more representative than traditional samples.[9,10] Subjects received a fact sheet and were taken to the survey hosted on Qualtrics, a secure web-based survey software that supports data collection for research studies. MTurk requires some amount of compensation to subjects; therefore, recruited subjects were compensated $0.05. Caregivers were randomized to 1 of 9 groups assessing their willingness to treat AD with either a "topical steroid," "topical medication," or "treatment, similar to the all-natural signals produced by the adrenal glands in the body" (for specific language used, see Table 1). Subjects in the first three groups (scenario-only dataset) read hypothetical scenarios, and responses were collected on a 6-point Likert scale ranging from 1 (definitely not willing) to 6 (definitely willing). Subjects in the next three groups (descriptive heading dataset) read the same scenarios, but with the addition of a descriptive heading of "Topical Steroid Use," "Topical Medication Use," or "All-Natural Treatment Use" at the beginning of each prompt. These headings were included to emphasize the unique phrasing of each information assignment group and potentially increase the sensitivity of detecting differences in caregiver willingness to treat childhood AD depending on the specific phrasing used.

Subjects in the final three groups (expanded scale dataset) read the same scenarios and headings, but responses were collected on a 0-100 slider scale, a tool where subjects can slide from left to right to set a numeric value to their answer. Demographic information, including sex, age, ethnicity, and education level, was also collected.

Outcome measures were recorded as caregivers' responses regarding their willingness to treat their child's eczema on either the 6-point Likert scale or slider scale. Additionally, responses were dichotomized into "not willing" or "willing". Data were analyzed using 2-tailed, independent sample *t*-tests, $\chi 2$, and ANOVA.

RESULTS

There were no significant differences between the groups' baseline characteristics (Table 2). For the dichotomized scenario-only dataset, 9.5% of caregivers reported being "not willing" to treat with a "topical steroid," 12.4% with a "topical medication," and 4.3% with a "treatment, similar to the all-natural signals produced by the adrenal glands in the body" (Figure 1). For the dichotomized descriptive heading dataset, 13.5% of caregivers reported being "not willing" to treat with a "topical steroid," 6.1% with a "topical medication," and 8.9% with a "treatment, similar to the all-natural signals produced by the adrenal glands in the body." For the dichotomized expanded scale dataset, 21.9% of caregivers reported being "not willing" to treat with a "topical steroid," 12.4% with a "topical medication," and 16.2% with a "treatment, similar to the all-natural signals produced by the adrenal glands in the body."

For the descriptive heading dataset, those presented with a "topical medication" reported a greater willingness to treat than those presented with a "topical steroid" (P=0.03) or "all-

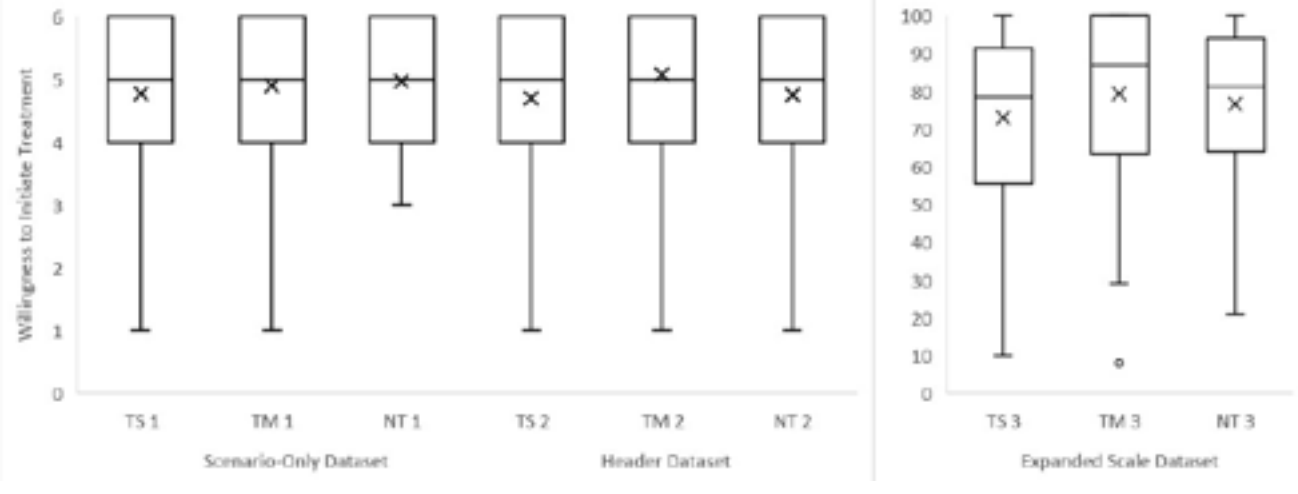
TABLE 2.

Summary of Baseline Characteristics and Demographic Information

Variable	Group 1 n = 95	Group 2 n = 97	Group 3 n = 94	Group 4 n = 89	Group 5 n = 98	Group 6 n = 101	Group 7 n = 96	Group 8 n = 105	Group 9 n = 99
Caregivers									
Age, y, mean ± SD	35.5 ± 10.1	34.4 ± 10.0	34.3 ± 8.1	35.2 ± 11.5	32.0 ± 10.0	34.5 ± 11.7	34.1 ± 10.9	33.6 ± 8.4	34.0 ± 9.6
Male sex, n (%)	38 (40.0)	40 (41.2)	34 (36.2)	43 (48.3)	52 (53.1)	47 (46.5)	39 (40.6)	39 (37.1)	34 (34.3)
Ethnicity, n (%)									
White	59 (62.1)	54 (55.7)	64 (68.1)	61 (68.5)	57 (58.2)	62 (61.4)	58 (60.4)	69 (65.7)	66 (66.7)
Black or African American	18 (18.9)	19 (19.6)	13 (13.8)	9 (10.1)	16 (16.3)	11 (10.9)	13 (13.5)	13 (12.4)	13 (13.1)
Hispanic or Latino	9 (9.5)	9 (9.3)	4 (4.3)	5 (5.6)	6 (6.1)	14 (13.9)	6 (6.3)	8 (7.6)	12 (12.1)
Asian or Pacific Islander	7 (7.4)	7 (7.2)	11 (11.7)	6 (6.7)	14 (14.3)	8 (7.9)	7 (7.3)	7 (6.7)	5 (5.1)
Native American or American Indian	1 (1.1)	5 (5.2)	2 (2.1)	7 (7.9)	4 (4.1)	3 (3.0)	10 (10.4)	5 (4.8)	1 (1.0)
Other	1 (1.1)	3 (3.1)	0 (0)	1 (1.1)	1 (1.0)	3 (3.0)	2 (2.1)	3 (2.9)	2 (2.0)
Education level, n (%)									
Bachelor's degree	37 (38.9)	45 (46.4)	40 (42.6)	38 (42.7)	45 (45.9)	42 (41.6)	33 (34.4)	49 (46.7)	40 (40.4)
High school graduate	27 (28.4)	26 (26.8)	30 (31.9)	27 (30.3)	24 (24.5)	26 (25.7)	36 (37.5)	23 (21.9)	32 (32.3)
Master's degree	21 (22.1)	19 (19.6)	13 (13.8)	12 (13.5)	16 (16.3)	23 (22.8)	18 (18.8)	26 (24.8)	13 (13.1)
Professional degree	4 (4.2)	6 (6.2)	6 (6.4)	6 (6.7)	10 (10.2)	4 (4.0)	6 (6.3)	6 (5.7)	9 (9.1)
Doctorate degree	3 (3.2)	1 (1.0)	4 (4.3)	2 (2.2)	1 (1.0)	1 (1.0)	3 (3.1)	1 (1.0)	1 (1.0)
No schooling completed	3 (3.2)	0 (0)	1 (1.1)	4 (4.5)	2 (2.0)	5 (5.0)	0 (0)	0 (0)	4 (4.0)

SD, Standard deviation.
Group 1: Scenario-only dataset (6pt scale) – "topical steroid"
Group 2: Scenario-only dataset (6pt scale) – "topical medication"
Group 3: Scenario-only dataset (6pt scale) – "treatment, similar to the all-natural signals produced by the adrenal glands in the body"
Group 4: Descriptive heading dataset (6pt scale) – "Topical Steroid Use"
Group 5: Descriptive heading dataset (6pt scale) – "Topical Medication Use"
Group 6: Descriptive heading dataset (6pt scale) – "All-Natural Treatment Use"
Group 7: Expanded scale dataset (0-100 scale) – "Topical Steroid Use"
Group 8: Expanded scale dataset (0-100 scale) – "Topical Medication Use"
Group 9: Expanded scale dataset (0-100 scale) – "All-Natural Treatment Use"

FIGURE 1. Comparison of the reported willingness to treat childhood atopic dermatitis (AD).



Reported willingness to treat childhood AD varied based on the information assignment group. Boxes indicate 25th and 75th percentiles; the horizontal line in the box indicates the group median; the "X" in each box indicates the mean; the error bars indicate minimum and maximum values, with outliers indicated with a circle.
TS, Topical Steroid; TM, Topical Medication; NT, Natural Treatment.

natural treatment" (*P*=0.04). For the expanded scale dataset, those presented with a "topical medication" reported a greater willingness to treat than those presented with a "topical steroid" (*P*=0.04). For the dichotomized data, subjects in the scenario-only dataset presented with a "treatment, similar to the all-natural signals produced by the adrenal glands in the body," reported a greater willingness to treat than those presented with a "topical medication" (*P*=0.04). Overall, the differences in reported willingness within each dataset were minor.

CONCLUSIONS

There was considerable overlap in the wording used between the nine survey prompts that caregivers were assigned to read in this study. Although the minor differences in wording resulted in some statistically significant differences, none of the wordings were associated with large absolute differences in reported willingness to treat childhood AD compared to other wordings. However, similar to prior studies, the phrase "topical steroid" often resulted in statistically lower caregiver willingness to treat than alternative phrasing.[3] For many of these caregivers, steroid phobia may be the underlying reason behind this phenomenon. For others, depending on their degree of health literacy, using the phrase "topical steroid" may be misleading, as caregivers may perceive initiating therapy with the proposed treatment as similar to giving their child anabolic steroids.

In most circumstances, using the phrase "topical medication" when presenting treatment to caregivers for childhood AD may be a simple, cost-free, effective strategy in improving caregivers' willingness to initiate treatment compared to presenting treatment as a "topical steroid." However, based on the responses recorded in this study, describing treatment as "similar to the all-natural signals produced by the adrenal glands in the body" would not be expected to have a large beneficial effect on caregivers' willingness to take treatment. Additionally, labeling that therapy as an "all-natural treatment" may negate any positive effects of this potentially reassuring description. Many caregivers may mistrust the notion that a medication prescribed by a physician and picked up at a traditional pharmacy could truly be an "all-natural treatment" despite an explanation of its similarity to the all-natural signals produced by the adrenal glands.

Although some of our findings were statistically significant, it is unclear whether the minor differences in reported willingness are clinically significant. Despite this, slight variations in phrasing appear to impact the perceptions of caregivers of children with AD. Since providers must consciously choose how to present treatment, using phrasing tailored to each caregiver's understanding of and concerns surrounding treatment may encourage caregiver primary adherence, potentially leading to improved clinical outcomes. Although these descriptions alone may have a role in promoting a willingness to use topical corticosteroids, these interventions do not replace the need for shared-decision making by discussing risks, benefits, and alternative treatments in childhood AD treatment.

DISCLOSURES

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CASE REPORT

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Successful Treatment of Keloids and Hypertrophic Scars With Systemic and Intralesional Dupilumab

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ABSTRACT

Keloids and hypertrophic scars negatively impact the quality of life for millions of people in the world. Unfortunately, though many therapeutic approaches are used to treat scars, they are often limited in efficacy with high rates of recurrence. Lately, a better understanding of the immune dysregulation of several dermatologic conditions has led to the emergence of multiple cytokine-targeted therapies for numerous conditions. Several studies have implicated T helper 2 (Th2) immune dysregulation in the development of scars and keloids, with interleukins (IL)-4 and -13 identified as pro-fibrotic mediators. Dupilumab is an IL-4 receptor alpha antagonist that inhibits the expression of both IL-4 and -13. Herein, we describe a 44-year-old woman who developed numerous disfiguring hypertrophic scars and keloids after suffering from a severe herpes zoster infection. Given the number of scars, intralesional corticosteroid injections were not feasible. Therefore, treatment with systemic dupilumab was initiated. Many scars flattened, several even developing a cigarette-paper-like texture due to rapid involution. The largest and most recalcitrant keloid was further treated with intralesional dupliumab injections every 2 weeks with an even more dramatic improvement noted in 2 months. To our knowledge, this is the first report of treating multiple keloids and hypertrophic scars with both systemic and intralesional dupilumab. Dermatologists may want to consider treating keloids that cover a large area with systemic dupilumab, a therapy with an established, reassuring safety profile. The most recalcitrant areas may further benefit from concentrating dupilumab by intralesional delivery.

J Drugs Dermatol. 2023;22(12):1220-1222. doi:10.36849/JDD.6385

INTRODUCTION

Keloids and hypertrophic scars negatively impact millions of people in the world each year. In addition to cosmesis, functional impact and symptomatic complaints (pruritus and pain) contribute to poor quality of life.[1] Intralesional corticosteroid injections remain the mainstay of therapy; however, several other treatment strategies (ie, scar revision, laser therapy, cryotherapy, 5-fluorouracil, and bleomycin) are utilized. Unfortunately, they are all limited in efficacy with high rates of recurrence.[1]

A better understanding of the pathogenesis of scars has raised the possibility of targeted treatment.[2,3] Herein, we report the benefits of treating keloids and hypertrophic scars with both systemic and intralesional dupilumab, a monoclonal antibody that inhibits the expression of interleukin (IL)-4 and IL-13.

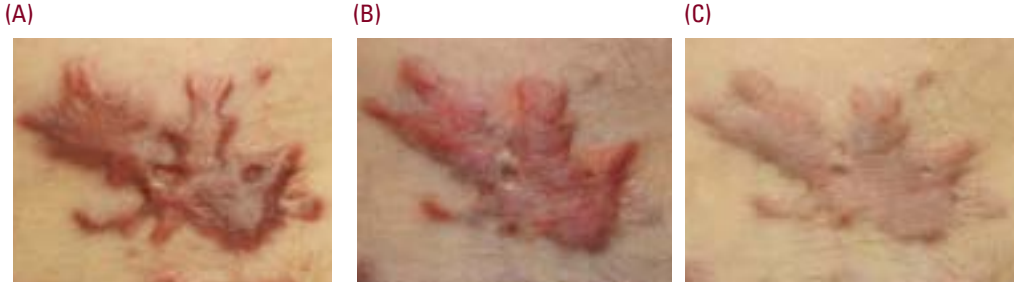
CASE REPORT

A 44-year-old woman with history of keloid scarring presented with firm nodules and plaques on her right flank and abdomen. A few months prior, she had developed numerous painful vesicles on her right lower trunk. Due to the coronavirus disease 2019 pandemic, she had not sought medical care, but it was suspected that she had suffered from herpes zoster. Vesicles resolved but were replaced with multiple firm lesions. These lesions became progressively indurated, large, and painful, with focal ulcerations, consistent with hypertrophic scars and keloids (Figure 1a). A biopsy confirmed the diagnosis.

Given the number of scars, monthly intralesional triamcinolone injections were not feasible. Dupilumab 600 mg followed by 300 mg subcutaneous injections every 2 weeks was initiated. Five months later, the patient noted significant improvement with

FIGURE 1. Hypertrophic scars and keloids before and after systemic dupilumab. (A) At baseline, erythematous and violaceous nodules coalescing into large, irregularly shaped plaques were present on the right lower abdomen, with ulceration along the inguinal fold (star). (B) Following 5 months of systemic dupilumab, smaller peripheral hypertrophic scars resolved (arrows), ulceration fully healed (star), and larger keloids softened. (C) Due to rapid involution, scars on the right flank developed an atrophic, cigarette-paper-like appearance to the overlying skin.

FIGURE 2. Largest, refractory keloid before and after systemic then intralesional dupilumab. (A) At baseline, the largest keloid on the central abdomen exhibited a deep shade of red, firm, and shiny. (B) Following 5 months of systemic dupilumab, the keloid became lighter in color, softer, and smaller in size. (C) After switching to intralesional dupilumab, the patient's scar continued to improve in color, firmness, and height, as shown here 2 months into therapy.



most scars flattening so rapidly that the overlying skin developed a cigarette-paper-like appearance (Figure 1b-c). Though the largest keloid on her central abdomen also improved, significant firmness could still be appreciated (Figure 2a-b).

Given that the largest keloid was now the only primary lesion of concern, the decision was made to switch from systemic to intralesional dupilumab directed into the recalcitrant keloid. Dupilumab 300 mg (2 mL) was injected from the manufacturer's pre-filled syringe into a 3-mL syringe barrel capped with a 30-gauge needle to allow for retrograde, threading injections into the dermis. Improvement was noted after a single intralesional treatment session. After two months of biweekly intralesional injections, the keloid further improved in erythema, firmness, and height (Figure 2c).

A sternal scar from a previous cardiothoracic surgery and lower extremity dermatofibromas also incidentally flattened. The patient did not develop any adverse events and elects to continue treatment.

DISCUSSION

Several in vitro studies suggest that CD4+ T cells particularly involved with the T helper 2 (Th2) pathway play an important role in the progression of scarring, with both IL-4 and IL-13 acting as primary pro-fibrotic mediators.[2] Interestingly, a population-based study identified that the risk of developing keloids is higher in patients with atopic dermatitis, a disease well associated with Th2 dysregulation.[4]

Dupilumab is an IL-4 receptor alpha antagonist that inhibits the expression of both IL-4 and IL-13. It is currently approved for the treatment of atopic dermatitis, asthma, and chronic rhinosinusitis. Recently, a case report was published in which a patient with atopic dermatitis began treatment with systemic dupilumab and noticed coincidental improvement of a keloid that had not responded to multiple intralesional triamcinolone injections.[3]

In hopes of further concentrating dupilumab into the most refractory keloid in our patient, we attempted an intralesional rather than purely systemic approach with dupilumab. Rapid improvement was subsequently appreciated. To our knowledge, this is the first report of this method of delivery for dupilumab in treating keloids. Though further studies are warranted, physicians may want to consider systemic dupilumab for treating hypertrophic scars and keloids that are numerous, large, and/or unresponsive to conventional therapy. Our case suggests that the most recalcitrant keloids may further benefit from intralesional rather than systemic dupilumab.

DISCLOSURES

There are no conflicts of interest relevant to this article. A. H. LaChance is a principal investigator for Pfizer. R. A. Vleugels is a principal investigator for Pfizer and her career has been supported by a Medical Dermatology Career Development Award from the Dermatology Foundation. J. F. Merola is a consultant and/or investigator for Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Celgene, Sanofi-Regeneron, Biogen, Pfizer, and Leo Pharma. If compensation is received it is considered honorarium.

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CASE REPORT

Journal of Drugs in Dermatology

A Massive Case of Cutaneous Diffuse Large B-Cell Lymphoma

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ABSTRACT

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma, and extranodal involvement is seen in approximately 40% of cases. However, cases involving the skin and muscle are rare, and skin manifestations most commonly present as plaques, papules, small nodules, or ulcers. In this report, we discuss a case of a large exophytic mass involving skin, soft tissue, and muscle initially thought to be baso-squamous carcinoma subsequently identified as DLBCL and treated solely with chemotherapy.

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INTRODUCTION

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma.[1] Approximately 40% of cases have extranodal involvement that most commonly occurs in the gastrointestinal tract or head and neck (often presenting as Waldeyer's ring).[1] Cases involving the skin and muscle are rare, and most commonly present as plaques, papules, small nodules, or ulcers.[2] These lesions often have a red or bluish-red hue.[2] Large exophytic masses are more common in other cutaneous malignancies such as basal cell carcinoma, and a much less common manifestation of DLBCL. We report a case of DLBCL presenting as a large exophytic mass that was successfully treated with chemotherapy alone.

CASE REPORT

A 48-year-old man presented with a mass on his left shoulder to the Dermatology clinic. He had noticed a small lesion more than 10 years prior to presentation that started as a "pimple" that would wax and wane in size. It steadily enlarged before accelerating in growth 4 months before evaluation. A physical exam showed an exophytic, necrotic, ulcerated mass with foul-smelling necrotic drainage and enlarged lymph nodes in the left axillary basin (Figure 1). The clinical appearance was initially thought to be a cutaneous malignancy such as baso-squamous carcinoma, and urgent resection of the mass was planned.

However, a biopsy revealed a diffuse infiltrate of large, atypical B cells coursing through a fibrotic dermis (Figure 2A). The cells exhibited irregular nuclei, moderately dispersed chromatin, and distinct nucleoli (Figure 2B). The large B cells were positive for CD20 (Figure 2C), showed a germinal center-like/non-double-expressor (BCL2+/MYC-) immunophenotype, and exhibited a high proliferative index (Figure 2D). FISH showed no evidence of MYC rearrangement, leading to a diagnosis of diffuse large B cell lymphoma, not otherwise specified (DLBCL, NOS). Positron emission tomography showed intensely FDG-avid left shoulder soft tissue mass as well as left axillary and left supraclavicular FDG-avid lymph nodes. He was then referred to Medical Oncology but was lost to follow-up.

FIGURE 1. Left shoulder mass on initial presentation to outpatient dermatology clinic.

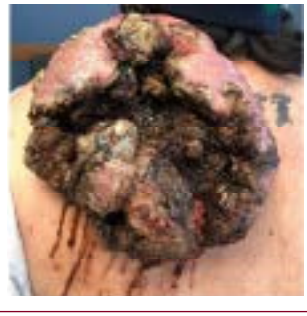


FIGURE 2. Biopsy results of the mass consistent with diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS).

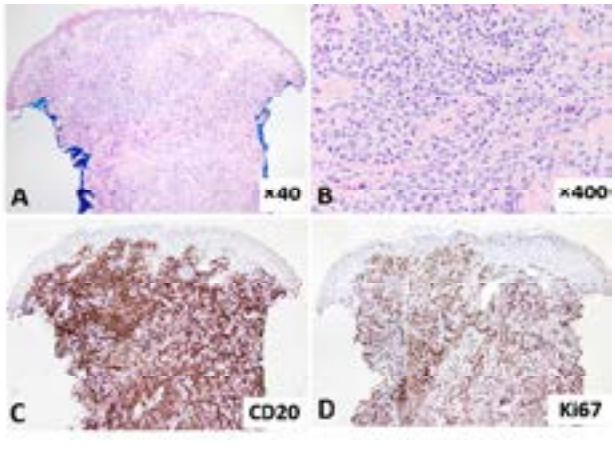


FIGURE 3. Left shoulder mass on presentation to the ICU.

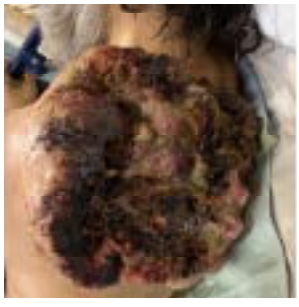


FIGURE 4. Mass on day 7 of cycle 1 of R-CHOP.

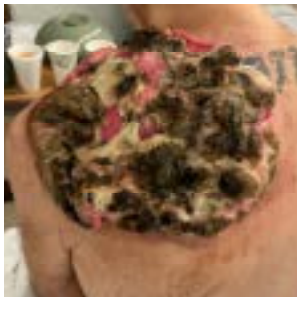
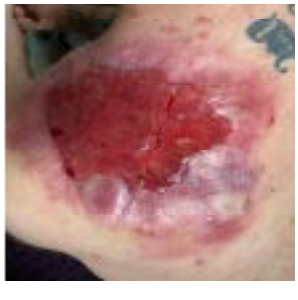


FIGURE 5. Mass 2 months after completing 6 cycles of R-CHOP.



Seven months later, he was admitted to the intensive care unit. The mass was necrotic, fungating, and infested with maggots (Figure 3). Computed tomography showed significant growth of the shoulder mass with worsening subcutaneous and muscular invasion of the left shoulder, re-demonstration of the supraclavicular and axillary lymphadenopathy, and new upper abdominal and retroperitoneal lymphadenopathy. His hemoglobin on admission was 2.9g/dL from chronic blood loss from the mass resulting in hemorrhagic shock. Surgery was consulted for de-bulking of the tumor and removal of the maggots, but the bleeding risk was felt to be too high. Two days after admission and stabilization with multiple packed red blood cell transfusions, he began R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The lesion on day 7 of cycle 1 of R-CHOP is shown in Figure 4. The wound and necrotic sloughing were successfully managed with saline wound wash and Kerlix dampened with Dakin solution. No debridement was required.

He has completed 6 cycles to date and is now in remission. The mass two months after cycle 6 is shown in Figure 5. He is currently undergoing evaluation for a skin graft to complete the wound healing.

DISCUSSION

This patient's presentation of a large cutaneous mass was initially concerning for primary cutaneous malignancy such as a baso-squamous carcinoma. However, biopsy was consistent with DLBCL and imaging revealed involvement of lymph nodes which is consistent with DLBCL, NOS rather than primary cutaneous diffuse large B-cell lymphoma (PCDLBCL) which does not typically have nodal involvement.[3] Aggressive B cell lymphomas can manifest as exophytic skin lesions at first presentation and may mimic carcinoma or other solid tumors. The rapid growth of aggressive lymphoma underscores the need for urgent histologic diagnosis in these cases to guide treatment without delay. Additionally, extranodal involvement of DLBCL is rare and a poor prognostic factor.[4] In fact, only 1.1% of patients with DLBCL have skin involvement and only 4.8% have soft tissue involvement.[4]

DLBCL is typically treated with R-CHOP.[5] Surgery is not a typical management strategy in DLBCL but can be used for palliation. Conversely, surgical resection with wide margins is the treatment of choice for most cutaneous malignancies such as basal cell carcinoma or squamous cell carcinoma. This patient's large cutaneous mass was exquisitely sensitive to chemotherapy alone, and the mass has resolved without any surgical intervention to date. With appropriate chemotherapeutics, even large, exophytic lymphomatous masses can be managed without surgical intervention. Given the potential bleeding complications and risks associated with surgery, this carries direct implications for the management of these patients. DLBCL can present as a large cutaneous mass that resolves with chemotherapy alone and does not require surgical excision or debridement.

DISCLOSURES

The authors have no relevant conflicts to disclose.

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CASE REPORT

Journal of Drugs in Dermatology

A Case Series of Patients With Eczematous Eruptions Following IL-17 Inhibitor Treatment for Psoriasis Vulgaris

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ABSTRACT

Psoriasis vulgaris and eczema are characterized by an imbalance in the Th1 and Th2 immune response and distinct cytokine profiles, where Th1 is more prominent in psoriasis and Th2 is more prominent in eczema. A common treatment for psoriasis is anti-IL-17 therapy, in which inhibition of IL-17 cytokines and the Th1/Th17 immune response may cause a paradoxical shift favoring the Th2 immune response and an eczematous phenotype. Our case series presents three patients who developed a cutaneous eczematous eruption 8-12 weeks following treatment of psoriasis with an IL-17 inhibitor (secukinumab, ixekizumab, or brodalumab) suggesting this phenomenon of shifting cytokine levels away from the phenotype of psoriasis toward the opposing disease.

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INTRODUCTION

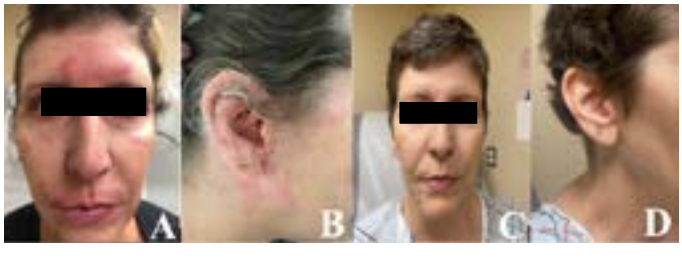
Psoriasis vulgaris is a chronic relapsing inflammatory skin disease characterized by an upregulation of key cytokines involved in immunopathogenesis.[1] Notably, interleukin (IL)-17 is one of several pro-inflammatory cytokines found in lesional skin.[1] Thus, treatments targeting IL-17 have been developed to attenuate the immune response.[1] A specialized group of biologic treatments aimed at inhibiting either IL-17 or the IL-17 receptor have become widely used amongst psoriasis patients with marked improvement.[1] Secukinumab, brodalumab, and ixekizumab are IL-17 inhibitors widely used for the treatment of moderate-to-severe psoriasis vulgaris due to their high safety profile and efficacy based on phase III clinical trial data.[2,3] Additionally, the most common adverse effects reported with this class of biologic treatment are minimal and include injection site reactions, headache, oral and vulvovaginal candidiasis, and nasopharyngitis.[3] Though fairly uncommon in clinical practice, eczema has been a reported reaction following initiation of IL-17 inhibitor treatment in phase III trials.[4] Becoming aware of these adverse events may guide how providers treat and manage these patients.

Herein, we describe a series of three patients who developed eczematous cutaneous eruptions after treatment of psoriasis with an IL-17 inhibitor.

CASE 1

A 46-year-old female with a childhood history of atopic dermatitis (AD) presented to the dermatology clinic with erythematous silvery scaly patches on her scalp and face, and joint pain involving multiple joints. She was diagnosed with psoriasis and psoriatic arthritis. She initially started on secukinumab. Following the loading doses, the patient presented with a new pruritic rash. Physical examination revealed erythematous and eczematous patches and plaques on the scalp, face, ears, anterior neck, and bilateral flexural surfaces of the elbows with superficial fissures and associated burning (Figure 1: A and B). A skin biopsy revealed spongiotic dermatitis, subacute type, and non-specific folliculitis consistent with an eczematous reaction. The decision was made to discontinue the secukinumab and begin a short course of low dose prednisone as a bridge to guselkumab due to her consistent psoriatic lesions. Following the failure of improvement with guselkumab, we started the patient on upadacitinib considering her clinical picture of AD and psoriatic arthritis and she noted a marked improvement in both diseases (Figure 1: C and D).

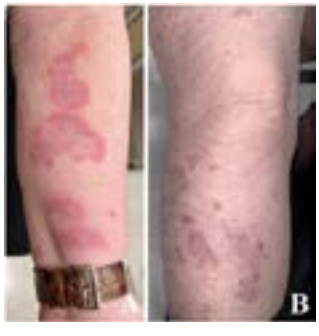
FIGURE 1. Erythematous, pruritic, scaly lesions on the face (A) and the right ear (B), followed by significant improvement of these lesions with upadacitinib (C and D).



CASE 2

A 76-year-old female with a past medical history of asthma presented with psoriasis on her abdomen and upper extremities, and psoriatic arthritis. She has failed multiple agents before including tildrakizumab, methotrexate, psoralen ultraviolet A therapy, and apremalist. The decision was made to start her on brodalumab and she reported worsening of her skin lesions. Physical examination revealed ill-defined annular erythematous scattered plaques with overlying fine scales on her left arm, abdomen, and legs (Figure 2). A skin biopsy of the left arm demonstrated spongiotic dermatitis, a subacute type consistent with an eczematous reaction. Brodalumab was discontinued and she was started on dupilumab and exhibited markedly significant improvement.

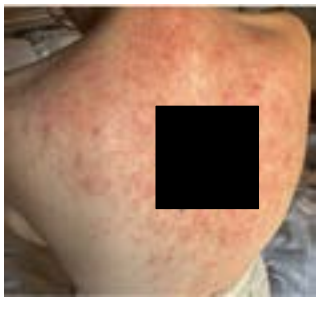
FIGURE 2. Ill-defined annular erythematous scattered plaques with overlying fine scales on the (A) left arm and (B) right leg.



CASE 3

A 45-year-old female with a history of psoriasis on her scalp, thighs, buttocks, and groin was initially treated with risankizumab. However, her psoriatic lesions failed to improve on her buttocks and inguinal folds. She also noticed painful papules and nodules on her right breast, clinically supporting the early stages of hidradenitis suppurativa. Thus, the patient was started on ixekizumab to target the psoriasis and hidradenitis suppurativa. Several weeks following initiation, she developed an erythematous, papular, pustular eruption on the central chest, central abdomen, and upper back (Figure 3). A skin biopsy of the upper and lower back showed spongiotic dermatitis, a subacute type suggestive of an eczematous process. Upon discontinuation of ixekizumab, she later failed adalimumab, apremilast, and guselkumab. She was started on upadacitinib with significant improvement in eczematous symptoms and hidradenitis suppurativa.

FIGURE 3. Erythematous, papular, pustular eruption on the upper back.



DISCUSSION

In this report, we summarized a case series of three patients who exhibited a cutaneous eczematous-like eruption following treatment with an IL-17 inhibitor indicated for psoriasis.

The average duration of the eczematous eruption onset in this series of patients was after completion of the loading dose for each respective biologic, which ranged from 8 to 12 weeks. These abrupt eruptions along with their associated symptoms prompted us to consider switching to different classes of treatments targeting cytokines in the AD immune pathway, including dupilumab and upadacitinib. Dupilumab, which targets IL-4 and IL-13 cytokines, improved eczematous symptoms in one patient case. Whereas upadacitinib, a Janus kinase/signal transducer, and activation of transcription pathway inhibitor approved for both psoriatic arthritis and atopic dermatitis, resolved symptoms in the remaining two patients. The primary histopathological finding on all of the patient's skin biopsies was spongiotic dermatitis, which lies within the group of eczematous diseases and encompasses a broad spectrum of dermatologic disease patterns such as AD, seborrheic dermatitis, and contact dermatitis.[5] Additionally, epidermal acanthosis with parakeratotic foci and microvesculation with perivascular mononuclear infiltrate was seen and consistent with an acute spongiotic dermatitis reaction.

Psoriasis vulgaris and AD are chronic inflammatory skin diseases mediated by T helper (Th) cells and are each caused by an imbalance in the Th1 and Th2 immune response. AD is mainly driven by Th2 cells that secrete IL-4, IL-5, and IL-13.[6] However, psoriasis is predominantly mediated by the Th differentiation toward the Th17 cell line that produces cytokines including IL-17.[7]

The pathogenesis of the eczematous reactions secondary to IL-17 inhibition remains unclear.[8] However, it is known that the Th1 and Th2 pathways exert opposing effects given their distinct immune mechanisms.[9,10] By treating the imbalance of IL-17 cytokines in psoriasis with IL-17 inhibitors, there is a paradoxical shift of cytokines toward the Th2 pathway, favoring the eczematous phenotype of AD exhibited in these patients.[11] The coexistence of psoriasis and eczema is unlikely, however given this concept of shifting from one phenotype to another, the opposing inflammatory pathway predominates.[12]

About 2.2% to 12.2% of patients on IL-17 inhibitor therapies for psoriasis have experienced eczematous eruptions.[12] A systematic review identified secukinumab as the most common causative

biologic for eczematous eruptions followed by ixekizumab.[8] Brodalumab was a less likely cause in this systematic review, and to our knowledge, there has been only one case report in the literature of an eczematous eruption following brodalumab therapy.[8,13] Additionally, a history of atopy including AD, asthma, and allergic rhinoconjunctivitis appears to be a risk factor for developing this phenomenon, as evidenced by 46% of patients who had a history of atopy in a systematic review of AD reported in patients treated with IL-17 inhibitors.[8,14] In our case series, two out of three patients had a history of atopy including AD or asthma.

Eczematous eruptions following IL-17 inhibitor treatment could indicate a paradoxical adverse event in patients, which may cause confusion and difficulty amongst clinicians in management and treatment. Thus, it is important to consider IL-17 inhibitors as a trigger for spongiotic dermatoses that arise in this patient population. Additionally, a personal history of atopy should be accounted for in patients who have a history of psoriasis before initiating treatment, but as shown, this manifestation can be evident in patients with no history of atopy. Further research is necessary to understand this phenomenon to guide management and identify those who may be at risk.

DISCLOSURES

The authors have no conflicts of interest to declare.

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CASE REPORT

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Checkpoint Inhibitor Induced Neurotoxicity in a Case of Metastatic Melanoma

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ABSTRACT

Checkpoint inhibitors (CPIs) are increasingly being used in the treatment of malignant melanoma. While showing promise in metastatic melanoma treatment, CPIs are associated with immune-related adverse events in various organ systems. Among these events, checkpoint inhibitor induced neurotoxicity stands out as a particularly rare yet diagnostically challenging and potentially life-threatening occurrence. We report a unique case of checkpoint inhibitor induced neurotoxicity in a patient with metastatic melanoma directly after beginning treatment with checkpoint inhibitor encorafenib. The patient presented with an unclear clinical course, with features of Guillain-Barré syndrome, myasthenia gravis, and brainstem encephalitis. We followed a recently established management algorithm for checkpoint inhibitor-induced neurotoxicity with positive outcomes. This case report highlights the importance of recognizing checkpoint inhibitor induced neurotoxicity as a potential adverse effect of CPIs when treating metastatic melanoma.

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INTRODUCTION

Metastatic melanoma, the most lethal among primary cutaneous neoplasms, poses significant challenges due to its depth of involvement and potential dissemination to lymph nodes and distant sites.[1] Staging of melanoma is contingent upon these factors, with stage I and II denoting the absence of lymph node involvement or metastasis but differing in terms of their risk of recurrence. In contrast, Stage III melanoma involves regional lymph node metastases, while Stage IV is characterized by distant metastases, both of which are associated with lower survival rates. According to the SEER database, in 2018, individuals diagnosed with stage IV disease in the United States had a 5-year survival rate of 29.8%.[2] Projections indicate a substantial increase in new cases of melanoma by 2030.[3]

One critical genetic determinant in melanoma pathogenesis is the v-raf murine sarcoma viral oncogene homolog B1 (BRAF), an essential component of the RAS-RAF-MEK-ERK mitogen–activated protein kinase (MAPK) cell signaling pathway. BRAF mutations have been identified in a substantial percentage of cutaneous malignant melanoma cases, making them a focal point for targeted therapy.[4]

BRAF inhibitors have demonstrated overall response rates ranging from 37% to 81%.[5] As a result, the recommended first-line regimen for patients with BRAFV600-variant melanoma includes a combination BRAF and MEK inhibitor therapy with either dabrafenib and trametinib, vemurafenib and cobimetinib, or encorafenib and orbinimetinib.[6] While checkpoint inhibitors have revolutionized management of metastatic melanoma, they come with a unique set of challenges. Checkpoint inhibitor induced neurotoxicity is a known adverse effect of checkpoint inhibitors that can be challenging to diagnose due to the varied presentation which may resemble myositis, polyneuropathy, myasthenia gravis, Miller Fisher syndrome, radiculoneuritis, and encephalitis among others.[7,8,9]

This is a rare description of checkpoint inhibitor induced neurotoxicity in the setting of metastatic melanoma. While no prospective studies have defined the optimal management for specific immune-related adverse events, several international guidelines exist.[10] This case serves as a compelling example of the effective application of one such guideline.

CASE PRESENTATION

A 72-year-old male, Fitzpatrick skin type 3, presented to the hospital with right upper extremity weakness and neck pain after initiation of checkpoint inhibitor therapy.

The patient's medical history includes a history of nodular basal cell carcinoma of the right nasal ala, treated with successful

Mohs surgery and pigmented basal cell carcinoma of the left cheek. In 2018, metastatic melanoma originating from an intradermal nevus was diagnosed with a Breslow thickness of 2.2 mm, negative margins for invasive melanoma and melanoma in situ, Clark IV staging, weakly positive BRAFR expression, and 20% PD-L1 positivity. Treatment included wide local excision with a 2 cm margin, sentinel node biopsy, and a year-long regimen of Nivolumab. In 2021, a recurrence was confirmed in the left inguinal lymph node. Treatment with cobimetinib and vemurafenib was initiated and stopped due to sun-related dermal redness. Subsequent binimetinib and encorafenib therapy was discontinued when the patient developed pancreatitis. A trial of Trametinib and Dabrafenib was halted due to fever and rigor from Dabrafenib. Treatment shifted to encorafenib and Trametinib, but encorafenib was stopped due to a rash. A subsequent Pembrolizumab trial was unsuccessful due to intolerance.

In 2023, an MRI conducted for surveillance purposes revealed the presence of a new osseous metastasis at the T12 vertebral body. The patient was treated with oral encorafenib on July 6, 2023. The following day, the patient presented to the hospital endorsing muscle atrophy, right upper extremity weakness and neck pain. The weakness progressed to involve the bilateral lower extremities within 5 days. Physical exam was notable for atrophy in the shoulder muscles, bilateral upper and lower extremity weakness, and bilateral Babinski. No new additional metastases were found in the MRI of the brain or spine. At this time, differential diagnosis included cervical disease versus neuromuscular junction syndrome secondary to encorafenib. We followed a suggested management algorithm for Grade 2 checkpoint inhibitor-induced neurotoxicity which included investigation with labs, Electromyography/nerve conduction study, and a lumbar puncture.[7] Management recommendations were also incorporated into the treatment plan. On July 10, encorafenib was discontinued. The patient subsequently became lethargic in the setting of severe hyponatremia (Na 119) which was addressed. A lumbar puncture demonstrated a protein of 94 mg/dL, glucose of 67 mmol/L, white blood cell count of 14 and red blood cell count of 47 consistent with a cytoalbumino-dissociation . Empiric treatment with a five-day course of intravenous immunoglobulin (0.4 gm/kg daily) was initiated. On July 12, the physical exam was notable for lethargy, inability to abduct the right eye, and areflexia. On July 13, the patient acutely decompensated with worsening of mental status and Cheyne-Stokes respirations, inability to follow commands, and withdrawing minimally in the upper extremities putting him at the verge of intubation. Treatment with high dose steroids (Solumedrol 1 gram IV daily for five days) was initiated. On July 14, the patient demonstrated remarkable improvement. He was alert and oriented to person, place, and time, followed commands, and moved all four extremities spontaneously and on command. On July 15, the patient continued to improve and was able to lift and maintain all four extremities antigravity. The patient made a full recovery within a week.

DISCUSSION

We describe a unique case of checkpoint inhibitor induced neurotoxicity in the setting of metastatic melanoma. Early recognition of checkpoint inhibitor induced neurotoxicity, while difficult due to variable presentations, is essential. This case demonstrates the life-threatening sequelae that may occur despite termination of offending checkpoint inhibitors. Increased awareness of checkpoint inhibitor induced neurotoxicity among dermatologists is essential for early recognition and appropriate management.

While the exact mechanisms underlying checkpoint inhibitor induced neurotoxicity are not fully understood, immune dysregulation and inflammation likely play a role in the development of neurotoxicity. By design, checkpoint inhibitors disrupt the balance between immune activation and regulation, which may lead to an immune response against normal tissues, including the nervous system.[11]

Further research is needed to better understand the mechanisms and optimal management strategies for checkpoint inhibitor induced neurotoxicity. Discontinuing the implicated checkpoint inhibitor and initiating a therapeutic regimen involving a combination of intravenous immunoglobulin and high-dose steroids led to favorable outcomes in this particular case.

CONCLUSION

This case underscores the importance of monitoring and managing immune-related adverse events in patients receiving immune checkpoint inhibitor therapy. While no prospective studies have defined the optimal management for specific immune-related adverse events, guidelines, particularly those supported by case reports like this one, should be considered. Management requires early recognition and should be tailored to presenting symptoms.

DISCLOSURES

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CASE REPORT

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Intralesional Sodium Thiosulfate as Adjuvant Therapy in Severe Calciphylaxis

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ABSTRACT

Calciphylaxis is a rare disease characterized by calcification of the middle layer of small arteries and arterioles, causing secondary cutaneous ischemia. The diagnosis is clinical but may be confirmed by histological examination. The optimal treatment is not exactly known, although there is consensus that a multifactorial approach is required. This report is regarding the case of a female patient with a kidney transplant requiring peritoneal dialysis, in the late postoperative period of partial parathyroidectomy due to severe hyperparathyroidism, with refractory hypocalcemia and severe calciphylaxis, subsequently treated with intralesional sodium thiosulfate due to initial intolerance to intravenous thiosulfate treatment.

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INTRODUCTION

Calcific arteriolopathy (CA), also known as calciphylaxis, is a systemic vascular disorder characterized by calcium deposits in the arteriolar tunica media, tunica intima hyperplasia, and endovascular fibrosis, leading to ischemic necrosis of affected tissues.[1]

According to the associated diseases, it is classified as uremic CA (UCA) and non-uremic CA. The former is the most frequent and affects patients with chronic kidney diseases (CKD), especially those on dialysis.[2,3]

Recent studies suggest that the key to the physiopathology of its development is the transformation of the smooth muscle cells of the tunica media of the dermal and hypodermal arterioles into osteoblasts and the imbalance between the factors that promote and inhibit vascular calcification.[3,4] Elevated serum phosphorus leads to a phenotype switch from adipocyte to osteoblast-like cells that favor calcification of the arteriolar tunica media.[5] However, CA physiopathology is complex and multifactorial.[1-4]

Skin involvement is characterized by reticular purpuric maculae, which evolve into necrotic ulcers and/or indurated nodules, which are usually accompanied with severe pain. Although the skin is the most frequently affected organ, it can also involve other organs and systems.[5,6] Differential diagnosis with other diseases is important.[7]

CA is unusual and has a high morbidity and mortality. Patients with CKD have a worse prognosis, with a mortality of 45% to 80% at 12 months versus 25% to 45% in patients without CKD.[6] Patients with central location of lesions, high body mass index, and ulcerated lesions are at increased risk of death caused by sepsis secondary to superinfection of the wounds.[6]

Interdisciplinary treatment and all the factors involved in the development of symptoms must be considered.[6] Treatment should be based on three pillars: local wound management, correction of the different predisposing factors, and the use of agents that inhibit the calcification process.[6]

CASE REPORT

We present a 42-year-old female patient with systemic lupus erythematosus diagnosed at age 20, CKD, and kidney transplant, with subsequent graft loss, on non-automated peritoneal dialysis (PD). She was referred from another institution due to severe hypocalcemia, bone pain and rapidly progressing skin lesions that began in the late postoperative period of partial parathyroidectomy due to severe hyperparathyroidism (intact PTH 3600 pg/dL).

Physical examination showed multiple 10/10 painful erythematous nodules and ulcers of variable sizes, irregular in shape, with erythematous-purpuric edges, a necrotic background, located to the right hypochondriac region and the thighs. (Figure 1) Reticular purpuric maculae were observed

FIGURE 1. A 2.4 inches ulcer, irregularly shaped with erythematous-purpuric borders and necrotic fibrinous background on the right flank.

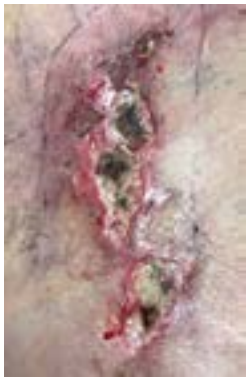
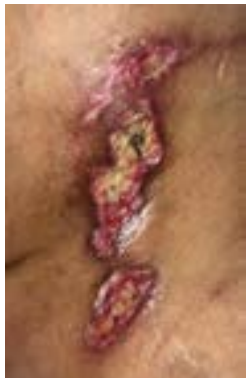


FIGURE 2. One week after intralesional treatment, granulation of the deepest lesions and reduction of the erythematous-purpuric borders were evident.



on the legs, on which there were flaccid blisters and erosions secondary to their deroofing. In the proximal and external region of the left thigh, there was a 6 x 2,5 inches (in), slightly erythematous, indurated, with diffuse edges plaque, on which there were three small ulcerations with a fibrinous background. She also presented amaurosis in the left eye.

The laboratory analysis on admission revealed leukocytes (5370/mm^3) with neutrophilia (77.81%), ionic calcium 0.74 mmol/L (1.00 - 1.35 mmol/L), hypophosphatemia 2.4 mg/dL (2.5 - 4.5 mg/dL), elevated alkaline phosphatase 1170 IU/L (31 - 100 IU/L), AST 81 IU/L (10 - 42 IU/L), ALT 452 IU/L (10 - 40 IU/L), albumin 2.94 g/dL (3.2 - 5.00 g/dL), parathormone 11.1 pg/mL (8.7 - 77.1 pg/mL). Serologies for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, and Epstein Barr virus were negative.

The symptoms were interpreted as post-surgical hypoparathyroidism with suspected calciphylaxis involving the skin, liver, and retina. It was decided to perform a liver and skin biopsy and carry out an ophthalmological evaluation. The skin histopathological analysis showed intimal hyperplasia and concentric calcium deposits at the level of the arterioles tunica media (Von Kossa positive), findings that were consistent with CA. Skin cultures for common and atypical germs were negative. In the liver biopsy, a pattern of hepatocyte necrosis with hemorrhage and sinusoidal dilatation was observed with an absence of parenchymal fibrosis. The ophthalmological evaluation detected loss of vision in the right eye secondary to anterior ischemic optic neuropathy due to a fundus finding of optic disk edema and an absolute blind spot in the entire visual field on optical coherence tomography.

Intravenous (IV) sodium thiosulfate (ST) was initially administered, but it had to be discontinued as the patient developed severe hypocalcemia (5.1 mg/dL (8.5 - 10.5 mg/dL) and 0.74 mmol/L of ionized calcium). Consequently, she received IV calcium plus high calcium peritoneal dialysis bags. Because the IV calcium requirements were high, which involved large volumes unmanageable through PD ultrafiltration, she was switched from PD to hemodialysis (HD). Given the rapid progression of the symptoms, it was decided to start treatment with intralesional ST. Due to severe pain, all procedures were performed under sedation. The three most affected areas (left leg, right external thigh, and right abdomen) were initially infiltrated. In the application technique, a 100 mg/mL ST solution was used. Subcutaneous infiltrations were performed with 0.1 mL per point using a 3 mL syringe with a 30 G needle at 0.2 to 0.4 in from the edge of each ulcer. First, 2 mL of solution was given for each lesion with a distance of 0.4 in between each puncture site. After 72 hours, observing the absence of pathergy or systemic adverse reactions, the procedure continued. Every 72-96 hours, other lesions were added to those previously treated.

Daily wound care was performed with silver sulfadiazine plus lidocaine. Ionic calcium levels were optimized. After 10 days, the intravenously and intradialytic administration of tri-weekly ST, at a dose of 25 g per day, along with 40 mcg of prostaglandins (PGs) per day every 48 hours was started for nine weeks. PGs had to be discontinued after the second administration due to adverse events: ocular ecchymosis, nasal blockage, and facial edema.

After a week of treatment, the appearance of new lesions stopped and the deep ones began to granulate. Within 30 days, most of the skin lesions had re-epithelialized. (Figure 2)

DISCUSSION

Although there are multiple treatments for calciphylaxis, to date there is no approved therapy or drug of choice. Rapid diagnosis, analgesia, wound management for the prevention of infections, elimination of risk factors, improvement of healing, and optimizing the use of drugs are key.[7]

ST is an inorganic salt that has been used intravenously for decades to treat cyanide poisoning. It was later shown to be useful in the treatment of calcium-mediated disorders.[8]

It has antioxidant and vasodilator properties, and dose-dependently, decreases adipocyte calcification and inhibits vascular smooth muscle cell calcification.[5,8] This action would also be favored by an inhibitory action on the formation of calcium phosphate, due to the formation of calcium thiosulfate in urine, which is a salt with a molar solubility of 250 to 100,000 times greater than other urinary calcium salts.[8] ST can be administered intravenously, subcutaneously, or orally.[6-9]

To date, there are no published randomized trials on the use of ST in calciphylaxis. The IV ST is used at a dose of 25 g tri-weekly after dialysis. The most frequent adverse events include metabolic acidosis, volume overload, hypocalcemia, long QT, nausea, and hypotension.[6-9]

The application of intralesional ST was first reported in four patients with stage III-IV CKD in 2013. The dose used was 250 mg/mL, although it was diluted by half with 1% lidocaine in one patient to reduce pain from the punctures. All patients achieved complete re-epithelialization of the wounds.[10]

Intralesional ST can be used in patients who cannot tolerate IV administration due to its adverse events, or in those with small or isolated calciphylaxis lesions.[16] The therapeutic responses were good in published cases in which intralesional ST alone or associated with ST IV were used, although there are no randomized trials.[10]

The only adverse event of intralesional treatment is generally pain at the time of puncture, which makes it necessary to carry out concomitant analgesic treatments, such as dilution with lidocaine, the application of topical lidocaine 1 hour before, or, as in our case, sedoanalgesia. Finally, and very importantly, no pathergy phenomena associated with this technique have been reported to date, nor have we observed so in our patient.[10]

The reported duration of treatment is from weeks to months. The dosing interval ranges from 72 hours to one month in maintenance, and there were cases of further treatment in the event of new lesions.[10,11] In our patient, we performed sessions every 72 to 96 hours.

Intralesional ST is a useful pharmacological therapeutic tool, which can be used alone or associated with IV ST or other systemic treatments, in conjunction with local wound infection prevention care. The choice of route of administration will depend on the number and severity of the lesions, the patient's clinical condition, and their tolerance. The intralesional route can be used when patients cannot tolerate the IV administration due to its adverse events, or when the lesions are few and small.[11] We consider that intralesional ST has a role among the different therapeutic options available for this pathology. The optimal duration of treatment is not determined, although it could be continued until the lesions disappear.[11] Further studies are needed to assess the effect of this new therapeutic modality for calciphylaxis.

DISCLOSURES

The authors have no conflicts of interest to declare.

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CASE REPORT

Journal of Drugs in Dermatology

Multiple Halo Nevi Induced by Intense Sun Exposure

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ABSTRACT

We present the case of a 38-year-old male who reported to our practice with multiple newly developed halos around 26 existing nevi on his trunk. The halo nevi developed after the patient, who lived in the northeast, spent 2 months on a lake in Alabama, with intense heat and sun exposure. This case is remarkable in that it points to ultraviolet exposure as one instigating factor in the development of halo nevi, the development of which is incompletely understood.

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INTRODUCTION

Halo Nevi (HN) or Sutton's nevi, are nevomelanocytic lesions surrounded by a ring of depigmentation. HN typically occur in adolescence and may affect 1% of the population.[1] Sometimes they herald the disappearance of the nevus over time, and this process may take 10 years or longer.[1] They have also been associated with the development of vitiligo and more rarely, with the development of melanoma in adults.[2,3] Usually, HN will occur alone or in limited numbers, but there are rare cases of patients presenting with multiple lesions.[4] We report the case of a 38-year-old male who presented to our practice with multiple newly developed halos around existing melanocytic nevi on his trunk. The halos began after the patient, who lived in the northeast, spent 2 months on a lake in Alabama, with intense heat and sun exposure. The phenomenon of multiple halo nevi developing after intermittent intense sun exposure has been previously reported in an adolescent Japanese male,[4] but not in a Caucasian adult male, making this case rather unique and adding to the evidence that solar radiation is a contributing factor in the development of HN.

Clinical Findings

Our patient is a 38-year-old male who was born with blaschkoid pigmentation of the left lower extremity, extending from his L buttock to his lower leg. He had several common nevi on his trunk and returned to the office for yearly skin examinations. In September 2020, the patient presented after a summer vacation that included intermittent intense sun exposure with the congruent development of 26 HN distributed across his upper and lower back and abdomen. (Figure 1, 2).

FIGURE 1. Halo Nevi on the trunk

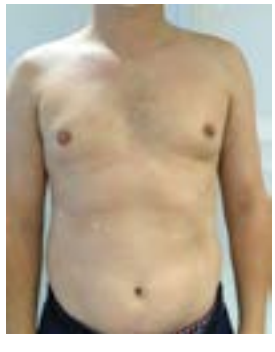
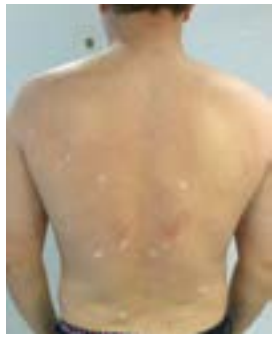


FIGURE 2. Halo Nevi on the back.



A complete skin examination was performed, and no atypical melanocytic lesions were notable. Our patient was advised to limit sun exposure, obtain an ophthalmologic examination, and monitor for new changes in the lesions at regular skin

examinations. At his follow-up visit in January 2021, the HN were still visible and some of the nevi had further regressed leaving depigmented patches.

DISCUSSION

Researchers hypothesize that HN are created by the infiltration of acquired nevi by inflammatory cells, notably T lymphocytes that are CD8+ and Fox p3(+)/CD25+. It is thought that the Foxp3 (+) lymphocytes play a role in trying to decrease the number of cytotoxic CD8+ lymphocytes in the lesion, especially as they are increased in number at the early stages of HN development.[5] The phenomenon of multiple HN has been seen in patients treated with checkpoint inhibitors for metastatic melanoma, eg, pembrolizumab, as reported in 2019, and ipilimumab.[6,7,8] It has also been described in conjunction with medications such as interferon beta, infliximab, imatinib, and tocilizumab.[9] Multiple HN may also be seen in genetic syndromes such as Turner's syndrome, and associated with other autoimmune phenomena including thyroiditis and vitiligo.[2,10]

A 2015 case report discussed the occurrence of 18 halo nevi in a 16-year-old male after a period of intense sunbathing. All nevi were excised and none were found to be abnormal, with immunohistochemistry demonstrating CD8+ T cell infiltration into the nevus. The authors suggest that the response may be the result of photo-koebnerization, or that UV radiation invokes an apoptotic pathway. Like the patient in their study, the halo phenomenon was not observed in every nevus in our patient, and it is unclear why some nevi were affected and others were not.[4]

CONCLUSION

In conclusion, we hope that this case brings attention to a unique opportunity to study the connection between sun exposure and HN development and regression, a correlation that is currently unclear.

DISCLOSURES

The authors do not have any conflicts of interest of any kind to disclose.

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BRIEF COMMUNICATION

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Unique Usages of Dehydrated Human Amnion Chorion Membrane Allografts in Dermatology

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ABSTRACT

Dehydrated human amnion chorion membrane (dHACM) allografts are synthetic skin substitutes derived from placental tissue. dHACM allografts are used for replacing lost or damaged dermal tissue, as they contain many of the components found within the extracellular matrix that are beneficial in wound healing. Common uses of dHACM allografts include the healing of diabetic and non-diabetic foot and leg ulcers, decubitus ulcers, and wounds following debridement. While these grafts have been proven to be beneficial in other disciplines of medicine, their potential for use in the field of dermatology is emerging.

Current clinical cases and research have shown dHACM allografts to be beneficial in repairing damaged tissue due to dermatologic conditions. They could play a role in the treatment of conditions causing chronic wounds, including dermal scarring or loss, and the repair of fragile skin. Examples of dHACM allograft use in dermatology include cases of pyoderma gangrenosum, Netherton syndrome, and wound healing with Mohs micrographic surgery. This literature review explores the efficacy of using dHACM allografts for the treatment of healing wounds within the field of dermatology.

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INTRODUCTION

Dehydrated human amnion chorion membrane (dHACM) allografts, such as EpiFix and AmnioFix among others, are synthetic skin substitutes derived from placental tissue. Comprised of an epithelial layer and 2 fibrous connective tissue layers, dHACM allografts function to repair lost or damaged dermal tissue. Healthy dermal tissue typically contains the extracellular matrix (ECM), which is made up of collagen, fibroblasts, proteoglycans, elastin, hyaluronic acid, fibronectin, and other components, all of which play a role in wound healing. dHACM allografts, derived from sterilized and dehydrated placental tissue, contain many of the components found in the ECM of the dermis, which makes them beneficial for wound healing.[1]

dHACM allografts are harvested from donors following cesarean section and thoroughly screened for infectious or viral diseases. They are comprised of 3 layers, the amnion, the chorion, and the intermediate layer separating the 2. The amnion, the side typically facing the fetus, is comprised of an epithelial layer with a fibroblast layer that contains types I and III collagen, contributing to the tissue's strength.[2] The amnion also contains other components of the ECM, including laminin and fibronectin, which contribute to the stroma and basement membrane.[2] The intermediate layer separates the amnion from the chorion and contains many nutrients such as glycoproteins. Lastly, the chorion layer, the side that contacts maternal tissue, is comprised of multiple layers that contribute to both the strength of the tissue and have nutrients that promote cell growth.[3] Altogether, the amniotic membrane consists of an epithelial layer and 2 fibrous connective tissue layers that contain important components of the ECM including fibroblast growth factor, platelet-derived growth factor, transforming growth factor-beta 1, and multiple interleukins. These components contribute to the wound healing properties of the human amnion chorion membrane.

dHACM allografts have been shown to improve the healing of tissue of the skin, cornea, ligaments, and periodontal tissue, among others. Common uses of dHACM allografts include the healing of diabetic and non-diabetic foot and leg ulcers, decubitus ulcers, and wounds following debridement. Patients receiving dHACM allografts for chronic leg ulcers due to venous insufficiency or diabetic nervous system degeneration tend to have poor circulation. This lack of blood flow leads to decreased delivery of nutrients required for wound healing, increased scarring of tissue, and increased risk of infection.

Multiple studies have shown that dHACM allografts are superior to standard treatment of chronic wounds, including regular debridement, compression stocking and bandages, and regular dressing changes. One randomized controlled trial evaluating the use of the standard of care with or without dHACM allograft application for diabetic foot ulcers showed that 92% of patients with dHACM allograft application reported fully healed ulcers after 6 weeks, while only 8% of patients who did not receive dHACM allografts reported healing after 6 weeks.[4] Additionally, patients receiving dHACM allografts experienced significantly faster healing time and a 0% recurrence rate with 12 months of follow-up.[4] In addition to decreased time of wound healing, the use of dHACM allografts has been shown to decrease the pain associated with leg ulcers, as dHACM allografts contain anti-inflammatory properties.[5]

Another study comparing the application of dHACM allografts to compression therapy and leg elevation for the treatment of venous stasis ulcers showed significantly greater wound closure for patients receiving dHACM allografts.[6] In this study, 62% of patients receiving dHACM allografts versus 32% of patients treated conservatively with compression stockings experienced 40% wound closure 1 month following the initiation of treatment.[6] In addition to the use of dHACM allografts for skin ulcers, specialties such as ophthalmology have used these allografts for cornea repair, and orthopedic surgery has shown the benefits of using dHACM allografts for the repair of poorly vascularized tissue, such as tendons, ligaments, and cartilage.[6,7] The antimicrobial and anti-inflammatory nature of amniotic tissue has led to decreased scar tissue formation and decreased pain following tissue repair in orthopedic surgery.[7]

Multiple cases reporting the benefit of using dHACM allografts for healing dermatologic conditions exist; however, there is no comprehensive literature addressing the use of dHACM allografts within dermatology. The goal of this paper is to review the literature and state dermatologic conditions that could benefit from the application of dHACM allografts.

MATERIALS AND METHODS

Two reviewers independently searched PubMed and MEDLINE using the terms "dehydrated human amnion chorion membrane allograft" and "dermatology" for published articles and found 7 articles from the years 2015 to 2021, as no articles pertaining to this topic were published prior to 2015. Of the original 7 articles, 2 articles were excluded, as they did not address the use of dHACM allografts for the treatment of specific dermatologic conditions. Five articles were included, and 4 of the 5 are included in Table 1, as they addressed the use of dHACM allografts for the treatment of unique dermatologic conditions. One article was included in this manuscript, but not included in the table, as it addresses the function of dHACM allografts. Additionally, the *JAAD Case Reports* database was searched using the term "dehydrated human amnion chorion membrane allograft," and 3 additional cases, not found on PubMed, addressing dHACM use for healing dermatologic conditions were included. A total of 7 articles pertaining to dHACM allograft use for the treatment of dermatologic conditions are included in Table 1. No articles containing negative results, in which the treatment of dHACM allografts for healing chronic wounds failed, were found. After a search was completed, the 7 articles were analyzed for unique dermatologic conditions successfully treated with dHACM allografts. The main parameters were study design, anatomical location of condition, type of dermatologic condition treated, number of patients treated, and response to treatment.

TABLE 1.

Research Articles Addressing Dermatologic Conditions Successfully Treated With dHACM Allografts

First Author	Year of Publication	Type of Study	Anatomic Location	Condition Treated	# of Patients	Time to Re-epithelialization
Kempton[9]	2018	Case Report	Scalp	Erosive Pustular Dermatosis, superimposed on Lamellar Ichthyosis	1	12 weeks
Lyons[10]	2018	Case Series	Scalp	Full-thickness defects following Mohs micrographic surgery	5	7, 11, and 21 weeks 2 patients still healing at time of reporting
Wisco[11]	2016	Case Series	Lower eyelid	Eyelid defects following Mohs micrographic surgery	3	6.5, 2, and 2.5 weeks
Bacik[12]	2018	Case Report	Lower face and neck	Ulcerated Hemangioma	1	5 weeks
Snyder[13]	2015	Case Report	Leg	Pyoderma Gangrenosum	1	8 weeks
Frigerio[14]	2019	Case Report	Scalp, trunk, extremities	Netherton Syndrome	1	2.6 weeks
Toman[8]	2022	Retrospective Case-Control Study	Face, head, and neck	Defects following Mohs micrographic surgery	143	4.4 weeks

RESULTS

Results of our literature review showed that multiple dermatologic conditions could benefit from the use of dHACM allografts for wound treatment. One retrospective case control study reporting the efficacy of treating skin defects following Mohs micrographic surgery (MMS) found treatment of defects with dHACM allograft led to significantly lower risk of infection (P=0.004), improved scar cosmesis (P<0.0001), lower rates of scar revision (P<0.0001), and less reoperation (P=0.0007) as compared to patients who received repair using autologous tissue.[8] MMS of the scalp, lower eyelids, and other locations on the head and neck also resulted in improved wound healing following dHACM allograft treatment.[10,11] The treatment of full thickness scalp and forehead defects with exposed calvarium in 5 patients following MMS with dHACM allograft repair showed improved healing time, preferable cosmetic results, and decreased pain as compared to healing via secondary intention.[10]

In a case of pyoderma gangrenosum refractory to 3 months of immunosuppression and wound care, the application of dHACM allografts showed promising results with a decrease in wound size by more than half within 2 months, a decrease in pain by half within hours of application, and a complete absence of pain within 4 days.[13] Another favorable result from the application of dHACM allograft was observed among a patient with a 7-year history of erosive pustular dermatosis superimposed on lamella ichthyosis, refractory to antibiotics, antifungals, intralesional corticosteroid, and antihistamines.[9] Within 12 weeks of dHACM allograft application, the lesion had completely healed with no recurrence at five month follow-up.[9] While no comprehensive literature exists, multiple case studies and case series have reported dHACM allografts to be successful in treating wounds caused by erosive pustular dermatosis, pyoderma gangrenosum, ulcerated hemangioma, Netherton syndrome, and defects following MMS. Table 1 includes a comprehensive list of unique dermatologic conditions successfully treated with dHACM allografts.

DISCUSSION

dHACM allografts are beneficial as wound healing adjuncts for both acute and chronic wounds in dermatology. Acute wounds induced via MMS have shown promising results in terms of healing with the application of dHACM allografts. Patients and families report increased ease of post-operative wound care, as dHACM allografts require once weekly dressing changes, while standard wound dressings require daily changes. This advantage is multiplied when it comes to wounds located in difficult to reach or see places such as the head, neck, and back. Additionally, as patients receiving MMS are typically of older age, ease of wound care is particularly important for both patients and their caregivers.

dHACM allografts could also play a role in the treatment of conditions causing chronic wounds, including dermal scarring or loss and the repair of fragile skin. Cases reporting successful treatment of chronic wounds on an infant with Netherton syndrome with subsequent protein and electrolyte loss due to skin fragility, and an infant with a chronically ulcerated hemangioma of the chin and neck refractory to propranolol, suggest the use of dHACM for the treatment of refractory skin conditions due to fragility.[12,14] As early treatment of infantile hemangiomas is vital to stop further progression and reduce the risk of ulceration and infection, dHACM should be considered early in refractory infantile hemangiomas.[12] The success of dHACM allografts in treating refractory pyoderma gangrenosum and erosive pustular dermatosis also demonstrates its ability to aid in the healing of chronic wounds.

While dHACM allografts are effective for the treatment of both dermatologic and non-dermatologic conditions, limitations in regard to the cost of treatment exist. Currently, amniotic membrane grafts remain expensive and range in price from US $2000 to $10 000.[15] In the study by Zelen et al, the average cost of application of allografting was US $2798.[4,16] It has been suggested that further studies are warranted regarding quality of life after treatment to justify use of the expensive biomaterials.[16] However, in the management of diabetic foot ulcers, dHACM usage in a cohort of Medicare patients was cost-effective by reducing major amputations, emergency department visits, inpatient admissions, and readmissions.[17] The cost of dermatologic conditions could potentially decrease with the use of dHACM allografts by avoiding further medical expenses, especially in the setting of chronic or refractory disease.

This article highlights the importance of considering the use of dHACM allografts for the treatment of multiple dermatologic conditions. dHACM allografts have been shown to decrease the time of wound healing, decrease pain involved with wounds, improve the convenience of dressing wounds, decrease the risk of infection, and heal lesions refractory to standardized therapy. Conditions described in this paper as well as other dermatologic conditions causing both acute and chronic wounds could benefit from the use of dHACM allografts in everyday clinical practice.

DISCLOSURES

The authors have no conflicts of interest to declare.

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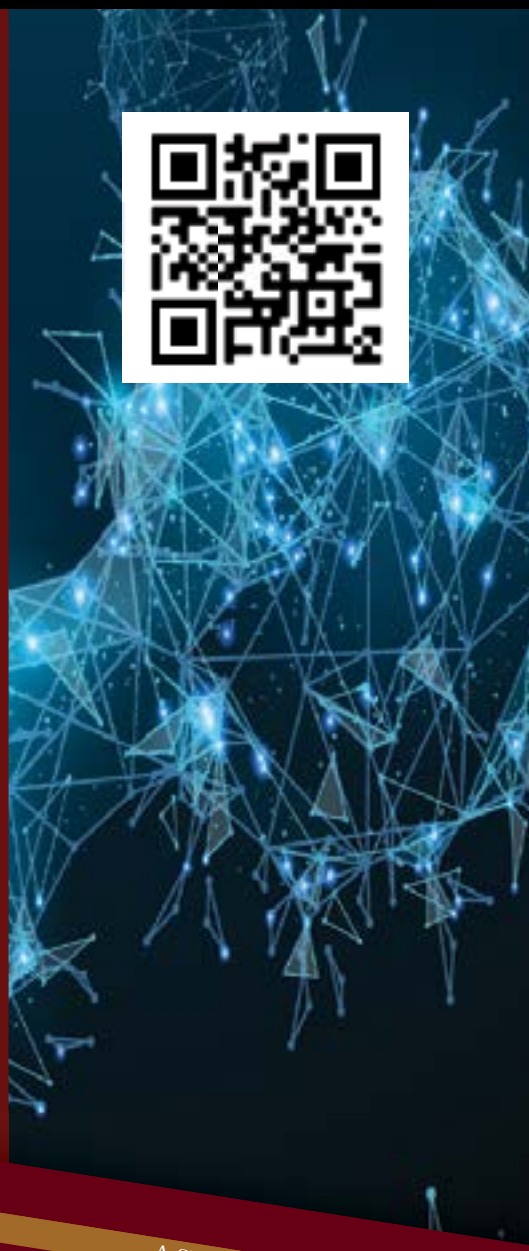
Prurigo Nodularis



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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

A Case Series on the Use of Brentuximab Vedotin for the Treatment of Mycosis Fungoides

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ABSTRACT

Background: Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody that appears to be more effective against CD30-expressing cutaneous T-cell lymphoma (CTCL) compared to current standard-of-care treatments.
Objective: To determine the real-world efficacy and adverse effects of BV use in patients with mycosis fungoides (MF) who were treated with BV at Atrium Health Wake Forest Baptist Medical Center.
Methods: Study staff performed a retrospective chart review of patients diagnosed with MF who were prescribed BV at Atrium Health Wake Forest Baptist Comprehensive Cancer Center
Results: Regardless of their response to BV, all patients in our cohort had higher CD30 positivity on subsequent biopsies compared to their initial skin biopsy.
Conclusions: Improved understanding of appropriate CD30 testing and evaluation will allow for quicker invention of patients with BV responsive CTCL.

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INTRODUCTION

Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody conjugated with monomethyl auristatin E by a protease-cleavable linker.[1] CD30 has a variable association with other cutaneous T-cell malignancies including mycosis fungoides (MF) and sezary syndrome (SS), making it a potential target for therapy.[2] In this study we performed a retrospective chart review of patients with MF who were treated with BV at Atrium Health Wake Forest Baptist Medical Center to determine real-world efficacy and safety of BV use in this patient population.

TABLE 1.

Patient Demographics and Results of Brentuximab Vedotin (BV) Treatment

Patient ID	BV1	BV2	BV3	BV4	BV5	BV6	BV7	BV8
Age	53	71	73	80	30	65	66	71
Ethnicity	Non Hispanic	Non Hispanic	Non Hispanic	Non Hispanic	Non Hispanic	Non Hispanic	Non Hispanic	Non Hispanic
Race	Caucasian	Caucasian	Caucasian	Caucasian	African American	African American	Caucasian	Caucasian
Sex	Female	Male	Male	Female	Female	Female	Male	Male
CD30 positivity on initial skin biopsy	CD30 negative	Clusters of CD30 positive cells	CD30 negative	CD30 negative	CD30 not performed	Rare CD30 positivity	CD30 positive in 5-10% of cells	CD30 not performed
CD30 positivity on subsequent skin biopsies	CD30 positive in 10% of cells	CD30 positive in 70% of cells	CD30 positive in 10-20% of cells	CD30 shows scattered positivity in cells	CD30 positive in 15% of cells	CD30 positive in greater than 90% of cells	CD30 positive in 15-20% of cells	CD30 positive
Response to BV treatment	PR	PR, then progression	Progression	CR	PR	CR	Progression	CR

Key: BV: Brentuximab Vedotin, CR: complete response, PR: partial response

MATERIALS AND METHODS

Study staff performed a retrospective chart review from the medical records of patients diagnosed with MF who were prescribed BV at Atrium Health Wake Forest Baptist Comprehensive Cancer Center.

RESULTS

Of the eight patients identified as receiving at least one dose of BV, 37.5% of patients had an initial skin biopsy that showed CD30 positivity defined as having at least 5% of T cells expressing CD30, 37.5% of patients had initial CD30 negative biopsy but had subsequent skin biopsies that exhibited CD30 positivity, and 25% of patients never had CD30 checked on their biopsy (Table 1).

DISCUSSION

BV appears to be more effective against CD30-expressing CTCL compared to current standard-of-care regimens.[3] Inconsistencies in CD30 detection methods can limit utilization of targeted therapies like BV for CTCL.[3] In our study, objective positive response was observed irrespective of CD30 expression on initial biopsy reports. All patients in our cohort had higher CD30 positivity on subsequent biopsies compared to their initial skin biopsy regardless of BV response (Table 1). One explanation for this finding may be due to a lack of sensitivity to the assay used to detect cell-surface CD30 expression.[4] Improved understanding of appropriate CD30 testing and evaluation will allow more patients with BV responsive CTCL to be identified and treated.[3]

DISCLOSURES

Steven Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Lindsay Strowd has received research funding, grants, or honoraria from Sanofi, Regeneron, Pfizer, Galderma, Lilly, Novartis and Arcutis. Katherine Kelly, Mary Beth Seegars, Rakhee Vaidya, and Leah Edenfield have no conflicts of interest to disclose.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Prior Authorization Timeliness and Success at a Single Center Centralized Pharmacy

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INTRODUCTION

Prior Authorizations (PAs) are a mechanism used by insurance companies to manage coverage of prescribed procedures, services, and medications. Studies have demonstrated that PAs are a burden for providers and reduce access to dermatology medications for patients.[2,3] Specific patient groups such as those with Medicaid may experience significant delays or fail to receive prescribed medications due to delays in the PA process and/or frequent changes in Medicaid formularies. Additionally, patients with complex medical conditions are particularly at risk for delays as specialty medications such as biologics often require a PA.

Previous studies have shown that a centralized pharmacy decreases delays in treatment.[2,5] A centralized pharmacy was shown to decrease the time to PA submission to insurance companies, decrease the time to PA decision to pharmacy, and increase approval rates.4 We retrospectively examined the approval rates and timeliness of PAs at a single academic dermatology center's centralized pharmacy in Pennsylvania between August 2021 to February 2022. PA data including insurance type, medication prescribed, date PA request received by the pharmacy, date PA was submitted by pharmacy, date PA response received by the pharmacy, and PA outcome were analyzed.

We identified 2215 PAs submitted to the centralized pharmacy between August 2021 to February 2022. Of those PAs submitted to insurance companies, 68.3% (n=1512) were 'approved', 18.0% (n=398) were 'denied', 3.4% (n=76) were 'not covered', and 9.0% (n=199) were 'not required'. Systemic dermatology medications represented the majority of the PA requests. Medications with the highest number of PAs included dupilumab (n=462), risankizumab (n=201), Retin-A (n=156), adalimumab (n=132), and guselkumab (n=101). The average time from which a PA request was received from the provider by the pharmacy and a PA was submitted to the insurance company was 0.25 days. The average time from a PA submission to response from the insurance company was 1.59 days. Medicaid patients represented the majority of PA requests (Table 1).

Overall, there was a higher average rate of PA approvals within our centralized specialty pharmacy compared to previous

TABLE 1.

Prior Authorization Characteristics				
Characteristics	Total Number (n)	Approval % (n)	Mean Time of Initial PA request to Pharmacy to when submitted to Insurance Company (Days)	Mean Time of PA submission to insurance company to decision notification (Days)
Total*	2215	1512	0.25	1.59
Top Medications				
Dupilumab	462	327	0.29	1.26
Risankizumab	200	148	0.24	1.46
Retin-A	157	142	0.11	1.46
Adalimumab	131	92	0.32	1.33
Guselkumab	102	78	0.32	1.53
Insurance Type**				
Medicaid	357	278/352	0.22	1.69
Medicare	224	177/221	0.22	0.65
Other	352	254/347	0.39	1.45

*Total reflects all prior authorizations examined; however, not all columns add up to total. Top five medications were selected.
**Insurance types do not add up to the total prior authorization claims as those with reported insurance types were examined.

reports of PA rates prior to a pharmacy intervention (68.2% vs 63.9%).[2] The mean time to PA decision of 1.9 days was also lower compared to two other studies without a centralized pharmacy.[2,4] In conclusion, this study suggests that a centralized pharmacy involvement in the PA process can be beneficial for increasing patient access to medications by streamlining the process through a centralized pharmacy.

This study was limited to data from August 2021 to February 2022 as the department has only been tracking PA data for a limited amount of time. Additionally, our pharmacy utilizes one system to manage and track PAs and a separate system to process prescriptions – therefore, we could not analyze time from initial PA to when a patient fills their prescription. There is a possibility that more data regarding amount of time spent per PA request and specific costs related to each can provide additional insight into how a centralized pharmacy such as this reduces the administrative burden and costs of the PA process.

DISCLOSURES

Dr Susan Taylor's advisory board, consultant, and/or investigator relationships: AbbVie, Arcutis Biotherapeutics, Beiersdorf, Concert Pharmaceuticals, Croma-Pharma, Eli Lilly, GloGetter, Johnson & Johnson, L'Oreal, Pfizer, Piction, Scientis US, and Vichy.

Dr Nicholas Mollanazar advisory board, consultant, and/or investigator relationships: Boehringer Ingelheim, Janssen, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi, Trevi Therapeutics, Menlo Therapeutics Inc, Galderma.

The remaining authors have no conflicts of interest to declare.

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Mpox "Monkeypox" Virus: The Importance of Inclusive Imagery to Prevent Disease Stigma

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ABSTRACT

Since the initial coverage of the monkeypox virus, there has been debate among physicians over how to responsibly communicate public health information without harming historically marginalized communities. On November 28, 2022, the World Health Organization (WHO) announced its plan to rename monkeypox "mpox" following growing concern regarding the stigmatizing nature of the disease's original name. We believe providers, and especially dermatologists, have an opportunity to further shape conversations about the virus to mitigate the same stigmas that were perpetuated by media coverage surrounding the HIV epidemic and contributed to the rise of anti-LGBTQ and HIV+ violence. Specifically, dermatologists have an opportunity to engage in conversations about the psychosocial impact of visible skin disease, advocating for healthcare equity by using both inclusive imagery and non-discriminatory language.

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INTRODUCTION

On November 28, 2022, the World Health Organization (WHO) announced its plan to rename monkeypox "mpox" following growing concern regarding the stigmatizing nature of the disease's original name.[1] The announcement occurred just 4 months after the same organization declared mpox a global emergency due to rapidly rising cases in non-endemic countries, especially among men who have sex with men (MSM). Since initial coverage of the virus, there has been debate among physicians over how to responsibly communicate public health information without harming historically marginalized communities. Given the cutaneous manifestations of this infection and their potential impact on disease perception, dermatologists have the opportunity to shape these conversations.

Stigmatization is a well-described phenomenon in dermatology, in part due to fear of contagion that often results from the visibility of cutaneous manifestations. This may be particularly problematic in the case of mpox, which like other historic viral outbreaks, such as Human Immunodeficiency Virus (HIV), already carries stigma given its association with close contact among MSM. In fact, in studies of individuals living with HIV, those with visible signs of disease, such as lipodystrophy, experienced more psychological distress, lower self-esteem, decreased quality of life, and less social support than those who could conceal their HIV status.[1] Most concerning, there is evidence that infectious disease stigma creates barriers in testing, treatment administration, and contact tracing.[2]

The renaming of mpox suggests experts are aware of the dangers of stigmatizing language. As dermatologists, we would also like to draw attention to the impact of imagery. Though the underrepresentation of skin of color (SOC) images in educational resources has been well described in the literature, the potential impact of overrepresenting SOC in depictions of transmissible diseases has been less explored. Agencies such as the Foreign Press Association, Africa (FPAA) have criticized Western media outlets which depict mpox infection exclusively in patients of African descent, arguing that these photographs "assign calamity to the African race and privilege or immunity to other races."[3] We believe providers have an opportunity to mitigate the same stigmas that were perpetuated by media coverage surrounding the HIV epidemic and contributed to the rise of anti-LGBTQ and HIV+ violence. In doing so, providers should follow the recommendations of the Center for Disease Control (CDC) and be mindful to "include pictures of people [with mpox] from diverse backgrounds and racial/ethnic groups."[4] Inclusive imagery, in addition to the non-discriminatory language supported by the WHO, must be utilized.

Finally, providers should be aware of social media's role in propagating misinformation. Individuals seeking health information online may interact with imagery that is inaccurate or unrepresentative of mpox epidemiology. By creating their public content, dermatologists can help shape public communication so that it is accurate, inclusive, and compassionate.

With the recent renaming of mpox, dermatologists have an opportunity to engage in conversations about the psychosocial impact of visible skin disease. In doing so, they can advocate for healthcare equity, using language *and* imagery that prevents further marginalization of communities that experience stigma and poorer healthcare outcomes.

DISCLOSURES

Dr. Lo Sicco has been an investigator for Regen Lab and is an investigator and consultant for Pfizer. Dr. Adotama is a consultant for Argenx and Janssen. Dr. Gutierrez, Dr. Klein, and Christina Oh have no conflicts to disclose.

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Journal of Drugs in Dermatology

Pruritus in Lupus Patients

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Dear Editor,

I have read with interest the article by Yahya and Gideon (Characterizing Pruritus in Autoimmune Connective Tissue Diseases. *J Drugs Dermatol.* 2019;18:995-998) on pruritus in patients with autoimmune connective tissue diseases.[1] In this study, the authors did a chart review of all patients seen in the Rheumatology-Dermatology clinic at Massachusetts General Hospital, and itch was present in 61% of systemic lupus erythematosus patients (SLE), paralleled the course of inflammatory skin manifestations in 45% of them. However, as the authors comment, pruritus itself is just a symptom, and understanding the pattern of pruritus in each disease may help to identify different etiologies and give different treatments. Therefore, I think is relevant to consider the possibility that the treatment received by the autoimmune patients could induce itching, but the authors do not refer to the pruritus caused by antimalarial drugs (AD). AD are a widely used drug, either in patients with SLE or other autoimmune connective tissue diseases, to improve the cutaneous, musculoskeletal, and mild constitutional symptoms of the patients. We described several years ago, an aquagenic type of pruritus in six of 104 lupus patients, treated with hydroxychloroquine or chloroquine.[2] We studied 105 patients with at least four of the criteria of the American Rheumatism Association classification for the diagnosis of SLE and 31 with CLE. Of the 136 patients, 104 were given AD treatment, of which 29 received chloroquine at a usual dose of 250 mg/day, eighteen were treated with hydroxychloroquine, 200 mg/day, and fifty and seven both, but never in combination. One of the six patients with pruritus had CLE and five had SLE. The patients had an aquagenic or post wetness type of generalized pruritus, which started approximately between 1 and 3 weeks after initiating AD therapy and developed mainly after a hot shower, appearing within minutes after water contact, lasting at a high intensity for approximately 10 minutes, and remaining at a low intensity for several hours, without visible skin changes. It was necessary to stop definitively AD therapy in 2 patients and temporarily in another two.

Because of the great importance of AD in patients with lupus, both for the control of various clinical manifestations, and to avoid greater accumulated damage during the evolution,[3] I think it is very important to know this possible adverse effect.

DISCLOSURES

The author has no conflicts of interest to declare.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Perceptions of United States Dermatology Resident Program Directors Regarding Oral Mucosal Dermatology Training

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INTRODUCTION

The examination of mucosal surfaces is a crucial portion of a complete dermatologic examination,[1] and may provide invaluable clues for the diagnosis of mucocutaneous or systemic disease. The frequency of mucosal examinations, however, varies widely among dermatologists and such surfaces are among the least often examined during a clinical encounter.[2,3] Hypotheses for these observations ranges from patient preference, patient perceived discomfort during evaluation, a low prevalence of malignancy, expectation that other specialists examine these areas, differences in training, and lack of formal training and experience in the evaluation of oral mucosae. To our knowledge, only one study exists evaluating knowledge, training, and practice patterns among dermatologists when evaluating and treating oral mucosae.[4] Among the parameters queried, 54 of 88 (61%) practicing dermatologists in the United Kingdom responded that their training in oral medicine was inadequate for the scope of their clinical practice.[4] This study attempts to evaluate the scope of residency training and provide foundational data regarding the current state of education regarding oral mucosal dermatology in the United States (US).

A total of 142 dermatology residency training programs were identified via the Accreditation Council for Graduate Medical Education public program search database. An anonymous REDCap cross-sectional survey was distributed to program directors (PDs) of all dermatology residency training programs. This study was exempt by the New York University Langone Health Institutional Review Board. Thirty-two completed surveys (22.5% of all dermatology residencies) were obtained. All geographic regions were represented. Table 1 outlines program characteristics. Table 2 summarizes PDs' opinions of and confidence in residents' abilities regarding oral mucosal dermatology and displays available teaching resources in residency and practice patterns among residents. Scores on the Likert-type scale of "4" or "5" were classified as the PD acknowledging importance in the field of dermatology or affirming confidence in the residents' ability in various settings. To our knowledge, this study is the only of its kind to evaluate US training of dermatologists in oral mucosal disorders. Understanding the current climate of residency training in oral mucosal disorders enables the identification of deficiencies to more thoroughly prepare residents for clinical practice. This study evaluated PDs' confidence in the ability of their residents in several areas. About 34.3% expressed confidence in their resident's ability to recognize normal variants of the oral cavity, diagnose oral mucosal diseases (37.6%), and perform procedures on the oral mucosa (40.6%). Furthermore, only 63.3% of PDs reported that their residents routinely examine the oral mucosa as part of the total body skin examination. Inconsistent oral mucosal evaluation as part of the physical examination during resident training may be a contributing factor to the reported

TABLE 1.

Characteristics of Programs Surveyed, n (%)	
Practice Setting	
Primarily Rural	2 (6.7)
Primarily Suburban	7 (21.0)
Primarily Urban	17 (53.3)
Mixed	6 (19.0)
Location in the United States	
Western	2 (6.2)
Rocky Mountain	3 (9.4)
Midwest	6 (18.8)
South Central	2 (6.2)
South East	6 (18.8)
Northeast	13 (40.6)
Number of residents in program	
8 or less	7 (22.0)
9 to 18	16 (50.0)
19 or more	9 (38.0)
Didactic time to oral mucosal dermatology (hours)	
0	2 (6.3)
1 to 5	23 (71.8)
6 or more	7 (21.9)

TABLE 2.

Program Directors' Opinions of and Confidence in Residents' Abilities Regarding Oral Mucosal Dermatology, n (%)	
How important do you believe a strong knowledge of oral mucosal diseases is within dermatology? (1 = not very important to 5 = very important)	
1	1 (3.1)
2	1 (3.1)
3	9 (28.1)
4	12 (37.6)
5	9 (28.1)
How confident do you believe your dermatology residents are in recognizing normal variants of the oral cavity? (1 = not very confident to 5 = very confident)	
1	2 (6.3)
2	3 (9.4)
3	16 (50.0)
4	9 (28.0)
5	2 (6.3)
How confident do you believe your dermatology residents are in diagnosing oral mucosal disease? (1 = not very confident to 5 = very confident)	
1	1 (3.1)
2	2 (6.3)
3	16 (50.0)
4	11 (31.3)
5	2 (6.3)
How confident do you believe your dermatology residents are in performing oral mucosal procedures (ie biopsies and suturing)? (1 = not very confident to 5 = very confident)	
1	4 (12.5)
2	6 (18.8)
3	9 (28.1)
4	10 (31.2)
5	3 (9.4)
Resources available in dermatology residencies and current practices regarding oral mucosal dermatology, n (%)	
Does your institution have an affiliated dental school?	
Yes	9 (28.1)
No	23 (71.9)
Does your program have a faculty member with an interest in oral mucosal diseases (excluding immunobullous diseases)?	
Yes	6 (18.8)
No	26 (81.2)
Does your program have an oral pathologist that is accessible to department members?	
Yes	16 (50.0)
No	16 (50.0)
Does your program have a specialty clinic focusing solely on oral mucosal diseases?	
Yes	1 (3.1)
No	31 (96.9)
Do your dermatology residents routinely examine oral mucosa as part of the total body skin examination?	
Yes	21 (65.6)
No	11 (34.4)

low confidence of PDs in their residents' abilities. In this light, emphasis on the examination of the mouth during training may bolster trainees' familiarity with both normal anatomy and pathology.

Few programs had faculty with interest in oral mucosal dermatology and only one program had a specialty clinic focusing on evaluation of the oral mucosa. However, roughly a third of programs have an affiliated dental school, and about half have an oral pathologist accessible to residents. When dermatology faculty may not be available, collaboration with dental training programs may fill training gaps.

Based on these findings, dermatology resident training in oral disorders is overall lacking. Our study does have significant limitations. A low sample size and response bias among responding programs limit the generalizability of our conclusions. However, our responses are concordant with those of the only other study evaluating oral medicine education among practicing dermatologists.[4]

DISCLOSURES

The authors report no conflict of interest. This article is exempt from IRB approval.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Modified Tzanck Smear to Evaluate For Herpes Simplex Virus

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To the Editor:

Tzanck smear has been historically used by dermatologists to diagnose cutaneous dermatoses including vesiculobullous and granulomatous diseases. A simple, rapid, and cost-effective tool used at the bedside, the Tzanck smear is commonly performed as an adjunct to the physical examination with experienced practitioners consistently achieving a sensitivity and specificity of over 80% and 90% respectively.[1,2] In certain circumstances, however, the resources necessary to perform a Tzanck smear may be limited. Clinicians working in such environments, thus, may benefit from understanding and working with modified diagnostic techniques. We highlight the use of a modified Tzanck smear to diagnose Herpes Simplex Virus (HSV) in a 54-year-old male with a past medical history of childhood varicella and previous vaccinations with Zostavax and Shingrix. The patient noted a new spot on the lower back present for a few days associated with a burning sensation. A physical exam revealed a 15 mm x 6 mm erythematous patch with five overlying 1-2 mm vesicular pustules on the mid-lower back (Figure 1). The lesion was suspicious for a herpetic etiology (Figure 2) and thus a modified Tzanck smear was performed using a sterile number 15 scalpel blade to unroof the vesicle, scrape the base, and smear onto a clean glass slide. Tap water was then placed on the sample and the tip of the Viscot® pre-surgical mini skin marker was dipped into the edge of the water to provide a staining medium. The sample was subsequently cover slipped and examined under a light microscope at 40X power. Multinucleate giant cells were visualized using the above mentioned modified Tzanck smear and led to the identification and diagnosis of HSV (Figure 3). The patient was placed on Valtrex 500 mg PO TID x 7 days for treatment.

FIGURE 1. 15 mm x 6 mm erythematous patch on mid-lower back.

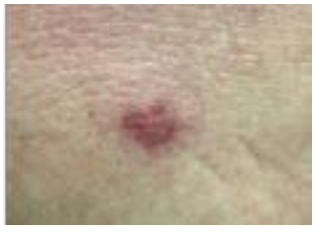
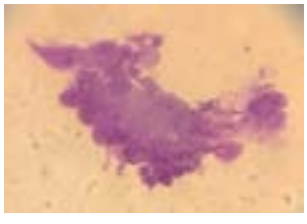


FIGURE 2. View of erythematous patch on mid-lower back via dermatoscope.

Our case represents an opportunity to review the applications and techniques of the Tzanck smear in current practice. Solomon et al first described the utility and effectiveness for detecting HSV using Tzanck preparation as compared to viral isolation.[3] Further use of Tzanck smear has expanded to include diagnostic applications for a variety of dermatological conditions including herpetic infections, pemphigus vulgaris, bullous pemphigoid, and basal cell carcinoma. Currently, use of bedside Tzanck has been largely replaced by other non-invasive diagnostic modalities such as Dermatoscopy. But Tzanck preparations are still clinically applicable as Durdu et al have noted similar diagnostic accuracy of pigmented skin lesions when compared to Dermatoscopy.[4] Typically, a Tzanck smear is performed by using a sterile number 10 or 15 scalpel blade to unroof a vesicle and scrape the base, and smear it onto a clean glass slide. The sample is fixed to the slide with gentle heat, air drying, or by using a methanol-containing fixation solution. The slide is then stained with either Giemsa, methylene blue, or Wright's stain, and examined under the microscope for multinucleate giant cells. In contrast, our modified Tzanck smear was performed as previously described using the tip of the marker to stain our sample. Air drying was also used instead of methanol fixation. In summary, we believe adapting to available resources was critical to our diagnosis as not every setting will be conducive to standard medical practice. In resource limited environments, practitioners should be willing to utilize a variety of novel approaches to arrive at the appropriate diagnoses.

FIGURE 3. Light microscopy using oil immersion lens (100x magnification) showing multinucleate giant cells after modified Tzanck smear technique.



Thus, clinicians can use this modified technique to diagnose their patients with HSV or other similar vesiculobullous and granulomatous lesions in non-conventional settings; as Tzanck smear is a quick cost-effective procedure with relatively high diagnostic sensitivity and specificity.

DISCLOSURES

The authors have no conflicts of interest to declare.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Analysis of Online Communities' Needs Among Psoriasis Patients on Social Media

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To the Editor:

Understanding the patient experience is essential in patient-centered clinical practice. Psoriasis, from mild to moderate, is about improving the quality of life. To create better patient experiences, we need to clearly understand what is important from the patient's perspective. Information from social media is a valuable, unfiltered resource of the thoughts and concerns of patients. Analyzing this data can be an important step in developing meaningful physician-patient relationships. To evaluate this approach, we analyzed Instagram (IG) posts under the tag "psoriasis community" for patient needs.

An Instagram account was created for this study. The tag "psoriasis community" was searched on July 2, 2020, which identified 10,500 publicly available posts. The top 100 posts were analyzed to assess the content. Exclusion criteria included all non-English posts. In total, 79 posts were included in the final analysis. Posts were assessed for primary content and authorship.

Of all the posts, 63.3% were from patients, 21.5% were from companies/products selling treatments, and only 1.3% of the top posts were from healthcare providers/organizations (Figure 1). The content of posts were organized into five categories: advertisements, psoriasis awareness/stigma reduction, personal journey, and inspirational material (Figure 2). 44.3% of posts focused on sharing images of psoriatic plaques to reduce the stigma surrounding psoriasis. 26.6% of posts were longer-form captions of patients sharing their journey with psoriasis, challenges they faced, and advice to other patients. 7.6% of posts featured inspirational messages for patients suffering from psoriasis. There was a total of 1403 comments on the 79 posts analyzed, indicating significant engagement from others.

Further analysis was completed to determine the content of 21 posts that shared information, experiences, or advice. 85.7% of the posts discussed challenges patients have faced, such as stress increasing their flares. 52.3% of the posts discussed the

FIGURE 1. Breakdown of Authorship of "Psoriasis Community" Posts on Instagram. Pictured is the breakdown of authorship of the top 100 posts with the tag, "psoriasis community."

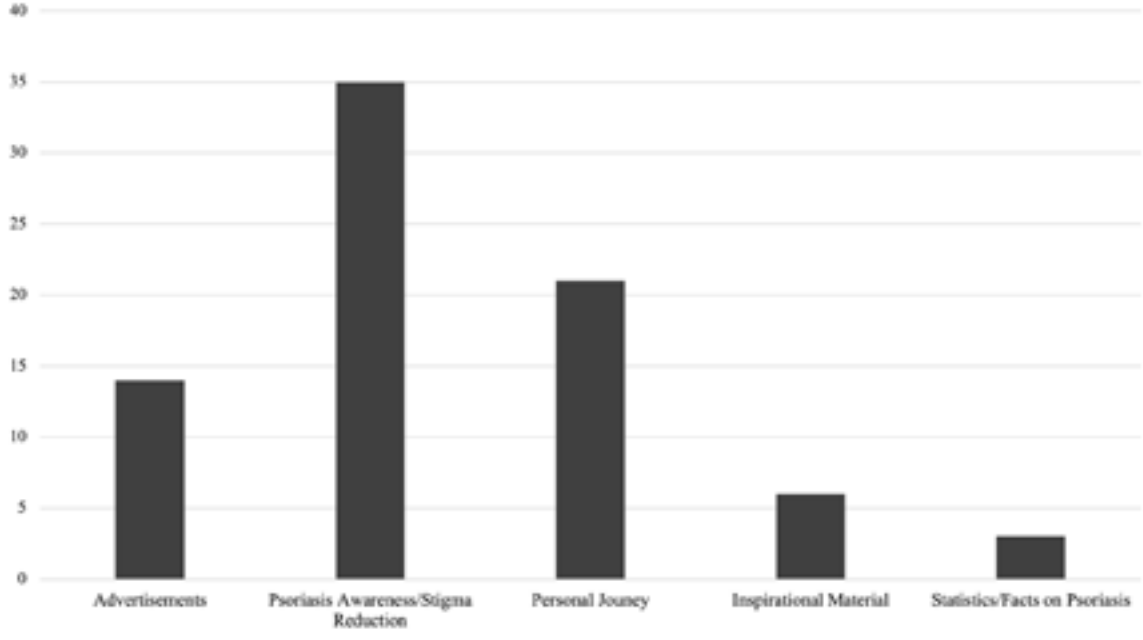
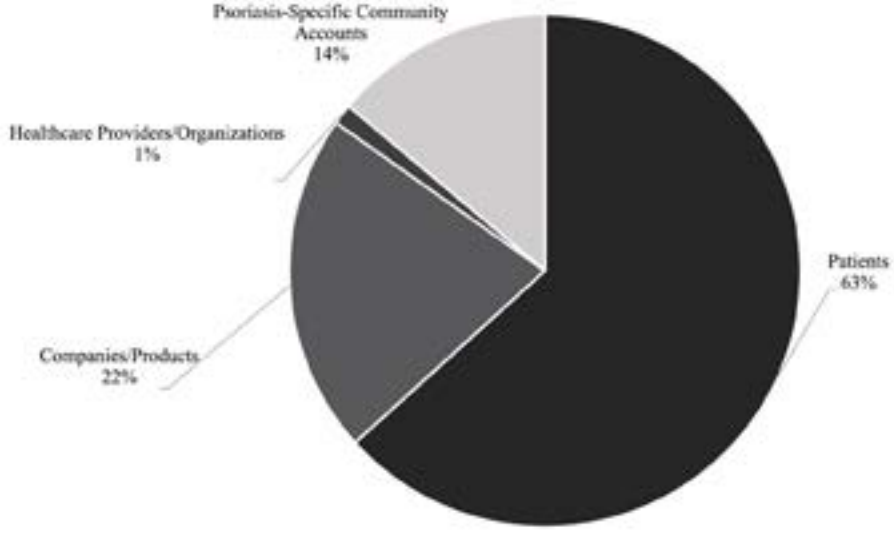


FIGURE 2. Breakdown of the content of "psoriasis community" posts on Instagram. Pictured is the content breakdown of the top 100 posts with the tag "psoriasis community."Pictured is the breakdown of authorship of the top 100 posts with the tag. "psoriasis community."



psychosocial impact psoriasis has had on their self-esteem. 47.6% of the posts shared advice to others with psoriasis, such as improving self-confidence.

This study provides an analysis of the information shared among the psoriasis community on Instagram. The majority of the material shared focused on patients posting pictures of their psoriatic plaques to reduce the stigma and promote awareness surrounding the disease. This demonstrates the significant psycho-social burden patients face regarding the condition and their desire to reduce the stigmatization they feel. In the longer-captioned posts, this becomes ever clearer with patients outlining the significant morbidity they faced throughout their lives.The majority of the posts indicated issues patients had with self-confidence, anxiety, and self-acceptance. Dermatologists should further inquire about the psycho-social burden patients face, such as the impact psoriasis has had on existing and new relationships. For patients who express significant challenges, screening patients for depression or anxiety should be considered. Furthermore, public information campaigns from the American Academy of Dermatology or the National Psoriasis Foundation should include the de-stigmatization of psoriasis and information on the specific topic areas identified here. Dermatologists may also consider weighing treatment recommendations based not just on PASI but on the visibility of lesions and how the patient has been impacted.

DISCLOSURES

The authors have no conflicts of interest to declare.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Tocilizumab Treatment in COVID-19 Patients: Comparing Cutaneous Disease and Adverse Drug Effects

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ABSTRACT

Actemra (tocilizumab) received emergency use authorization for the treatment of coronavirus disease 2019 (COVID-19) in June 2021. Literature has linked numerous cutaneous adverse effects to tocilizumab. In this current survey, investigators reviewed and compared these adverse effects to the common cutaneous manifestations of COVID-19. While similarities in patient presentation exist, important distinctions are made to aid dermatologists in their clinical diagnosis.

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INTRODUCTION

Over 40 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for coronavirus disease 2019 (COVID-19), have been reported in the United States (US).[1] Pulsipher et al.[2] previously compared the cutaneous manifestations of COVID-19 and adverse effects of remdesivir, an antiviral drug approved by the US Food and Drug Administration (FDA) for SARS-CoV-2. This present survey of Actemra (tocilizumab), a recombinant humanized interleukin 6 (IL-6) receptor antagonist, aims to distinguish COVID-19 disease manifestations from adverse drug reactions.[3]

Tocilizumab, FDA-approved for rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, and cytokine release syndrome, received emergency use authorization for hospitalized COVID-19 patients requiring oxygen, mechanical ventilation, or extracorporeal membrane oxygenation.[4] Tocilizumab may lower risk of mortality, hospital length of stay, and mechanical ventilation requirements.[5]

Cutaneous changes from COVID-19 and tocilizumab are reported in the literature and summarized in Table 1. Tocilizumab adverse reactions include serious skin infections (i.e., cellulitis and necrotizing fasciitis) and cutaneous eruptions.[6–8] Maculopapular rash and urticarial lesions characterize the prominent cutaneous manifestations of COVID-19.[9,10]

TABLE 1.

Summary of Cutaneous Manifestations Observed in COVID-19 Compared to Adverse Drug Reactions from Tocilizumab Treatment Based on Current Peer-Reviewed Literature

Cutaneous Manifestations	
COVID-19 Morphology	**Tocilizumab Adverse Reactions**
Maculopapular eruptions[9]	Cellulitis[7]
Pseudo-chilblain lesions[9]	Necrotizing fasciitis[6,7]
Urticaria[9]	Urticaria[7]
Polymorphic diffuse or localized monomorphic vesicles[9]	Cutaneous sarcoidosis[7]
Acral vesicular-pustulous lesions[7]	Maculopapular eruptions[7,8]
Livedo[9]	Pustulous lesions[7,8]
Petechiae[10]	Skin ulcer[8]
Erythema multiforme[9]	Psoriasiform eruptions[8]

A cross-sectional study of tocilizumab treatment for COVID-19 reports associated morbilliform (10% of n=80) and other maculopapular (2.8% of n=36) eruptions.[11] Prospective cohort analysis (n=51) similarly found a nonspecific cutaneous

rash necessitating drug discontinuation in one patient.[12] Furthermore, development of a pruritic generalized cutaneous toxic erythematous rash with eosinophilia (similar to DRESS syndrome) was also reported in a SARS-CoV-2 patient receiving tocilizumab treatment.[13]

As cutaneous manifestations of COVID-19 and adverse dermatologic reactions of tocilizumab overlap, distinguishing disease and drug effects is imperative. Sharing and reporting cutaneous findings will be an important role of dermatologists as we deepen our understanding of novel SARS-CoV-2 manifestations. As cases of SARS-CoV-2 continue to rise, increased use of tocilizumab will require greater attention to potential cutaneous toxicity.

DISCLOSURES

Dr Dellavalle is Editor in Chief of Journal of Medical Internet Research Dermatology, a Joint Coordinating Editor for *Cochrane Skin*, a dermatology section editor for *UpToDate*, a Social Media Editor for the *Journal of the American Academy of Dermatology (JAAD)*, and a Podcast Editor for the *Journal of Investigative Dermatology (JID)*. He is a coordinating editor representative on *Cochrane* Council.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Home Is Where the Match Is: Mentorship and Dermatology Residency Match Trends Before and During the COVID-19 Pandemic

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To the Editor,

Dermatology is one of the most competitive residencies for matching amongst medical school applicants. A strong connection with a residency program through research or clinical rotations may distinguish between similarly qualified applicants. Our previous study of research-mentor relationships among matched dermatology applicants corroborated the importance of program connections.[1] However, the 2020-2021 residency match cycle was uniquely affected by the COVID-19 pandemic, which prevented applicants from fostering connections with faculty at outside institutions. Our study objectives were to evaluate research-mentor relationships among matched dermatology applicants in the 2020-2021 pandemic match cycle with comparisons to pre-pandemic match cycles.

We searched for publicly available 2021 residency match lists from all U.S. allopathic medical schools. We found the names of 118 matched dermatology applicants from 34 medical school match lists (Table 1). The senior authors of applicants' PubMed-indexed articles published before September 15, 2020 were also identified. The senior author who published with an applicant most often was considered the research-mentor. Mentor and home program connections appeared to play a significant role, with 31.3% of successful dermatology applicants matching at their mentors' institutions, and 30.5% matching at their home programs where their mentors also practiced (Table 2).

We previously evaluated research-mentor relationships among matched dermatology applicants in the top 25 dermatology residencies from 2016-2018 ranked by Doximity Residency Navigator, which combines physician feedback with objective data.[2] We found that 26.2% of successful applicants matched at their mentors' institutions, and 10.3% matched at their home programs where their mentors also practiced.[1] While the subset of matched applicants in our current study differs from that of our previous study, mentor and home program connections appeared to be equally or more important for matching in the 2020-2021 pandemic cycle compared to pre-pandemic match cycles. In a survey-based study of 44 applicants to a dermatology residency program from 2013-2015, all under-represented minorities (URMs) and the majority of matched non-URMs reported having a mentor. Therefore, mentorship likely confers a strong benefit for matching, as faculty provide networking opportunities that build on applicants' social capital while sharing knowledge and experience.[3]

Similarly, Abdelwahab et al. investigated the impact of the COVID-19 pandemic on the proportion of dermatology residency applicants matching into their home programs during the 2021 match.[4] The authors reported that there were statistically significant greater odds of matching at least 1 home applicant in the 2021 vs 2017-2019 cycles (odds ratio=2.3; P=0.02). Home matching occurred more frequently with programs having more spots than the national median (4) and less often with programs having <4 spots (P=0.00001). The authors hypothesized that during the pandemic, with virtual rotations and interviews the norm, programs and outside applicants had difficulty connecting, resulting in applicants and their home programs ranking each other relatively higher.

Abdelwahab et al's findings may be at least partially explained by our study demonstrating that a significant proportion of matched applicants worked with mentors at their home programs. Together, these studies demonstrate that limited exposure of programs to outside applicants and mentor relationships at home programs likely impacted match outcomes during the pandemic. Dermatology applicants without home programs, who have limited mentorship opportunities, are significantly disadvantaged. Novel solutions, such as formal mentorship programs and their promotion through social media,[5] can help make the residency application process more equitable for applicants.

TABLE 1.

Allopathic Medical Schools With Publicly Available Match Lists Containing Applicant Names From 2020-2021 Match Cycle

Allopathic medical schools	Number of matched dermatology applicants	Number of applicants matched at mentors' institutions
Brown University	1	1
Cleveland Clinic	3	2
Eastern Virginia Medical School	0	0
George Washington University	1	0
University of California Los Angeles	10	4
Loyola University	1	0
Mayo Clinic	3	1
Northwestern University	2	1
Thomas Jefferson University	4	2
Southern Illinois University	1	0
Texas Tech University	4	1
University of Alabama	3	1
University of Colorado	3	2
University of Illinois	7	2
University of Iowa	4	4
University of Kansas	0	0
University of Michigan	5	1
University of Minnesota	4	2
University of Mississippi	2	0
University of Nebraska	3	0
University of North Carolina	3	1
University of Oklahoma	2	0
University of Pennsylvania	6	1
University of South Florida	2	0
University of Texas Houston	6	1
University of Texas Medical Branch	2	0
University of Texas Southwestern	9	4
University of Texas Austin Dell	0	0
University of Vermont	2	0
Vanderbilt University	5	1
Virginia Commonwealth University	5	0
Wake Forest University	4	2
Wayne State University	9	2*
Wright State University	2	1

*One applicant matched at mentor's institution which was not their home program. All other applicants who matched at mentors' institutions also matched at their home programs.

TABLE 2.

Dermatology Residency Applicant Match Outcomes 2020-21 and Mentor Locations	
Match Outcomes	**Proportion**
Matched in same program as mentor	31.36% (37/118)
Matched in both home program and mentor program	30.51% (36/118)
Matched in same region as mentor	46.61% (55/118)

DISCLOSURES

The authors have no conflicts of interest to declare.

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Journal of Drugs in Dermatology

14-Gauge Coaxial Bone Needle Leads to Superior Results When Injecting Calcinosis Cutis

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Dear Editor,

Calcinosis cutis can occur idiopathically or be associated with injury, metabolic disease, and different rheumatologic diseases such as scleroderma and dermatomyositis. Calcinosis cutis is often treatment-resistant and leads to decreased quality of life and pain. Medical therapies, such as bisphosphonates, warfarin, tetracyclines, calcium channel blockers, colchicine, laser therapy and surgery, lithotripsy, and even stem cell transplantation have been used with varying success.[1] Lesions of calcinosis cutis can persist even when systemic disease is adequately controlled leaving the patient with a painful reminder of their underlying disease.

Injections of sodium thiosulfate (STS) 250 mg/ml have been effective in treating calcinosis cutis in a handful of case series.[2,3,4] The authors have noted that side effects of intralesional sodium thiosulfate are minimal but include pain, ulceration, and local soft tissue infection. Densely mineralized deposits can be nearly impenetrable with a standard needle. A standard needle can fail to adequately infiltrate STS to a calcified lesion and lead to blunted or even broken needles resulting in treatment failure, increased pain experienced by the patient, or retained needle fragments.

We describe a technique that uses a 14-gauge hollow coaxial bone biopsy set (Figures 1 and 2). This needle is traditionally utilized for osseous lesional biopsies but can be used to drill into the calcium using a stylet (Figure 3). The penetration cannula and stylet are drilled into the calcium nodule with a twisting motion, following cutaneous lidocaine injection, or general anesthesia. Upon achieving appropriate depth, the threaded stylet is removed and replaced with a syringe of STS for injection through the cannula (Figure 4). We have found that this is an effective delivery technique that has led to increased treatment efficacy and reduced pain for the patient.

FIGURE 1 AND 2. Bonopty 14-gauge Bone Penetration Kit.

FIGURE 3. Drilling 14-gauge hollow needle into deposit of calcinosis cutis.

FIGURE 4. Injecting sodium thiosulfate into the hollow portion of the needle directly into the core of the calcium deposit.

One of our patients with calcinosis cutis secondary to dermatomyositis has experienced injections with a standard 27-gauge needle and with the 14-gauge coaxial needle. She experienced greater improvements with the coaxial needle and greater softening of the calcium lesions. After three rounds of injections spaced one week apart, she noted decreased pain and size of the lesions.

Limitations to this data are a sufficient way to quantify the extend of calcium lesions as they are often deep and confluent which makes measuring them difficult. In the future ultrasonography or radiography could be used to further evaluate a response.[5] Head-to-head studies comparing sodium thiosulfate injections using both techniques are required.

STS administration into calcinosis cutis is complicated by nodule firmness leading to insufficient STS infiltration. By utilizing a 14-gauge coaxial bone marrow biopsy introducer needle, we can maximize the drug delivery into these lesions, enhance safety, and improve outcomes for our patients. We suggest that the delivery technique of this novel therapy be modified to benefit our patients and maximize results.

DISCLOSURES

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LETTERS TO THE EDITOR

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The Persistence of Nystatin Use for Dermatophyte Infections

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ABSTRACT

Background: Despite the limited use of nystatin for tinea infections, physicians may continue to use it.
Methods: We assessed the National Ambulatory Medical Care Survey for all to determine the extent of topical nystatin use in tinea infections.
Results: Topical nystatin was used at 4.3% (2.1, 6.0) of all tinea visits. It was not used at visits with dermatologists and was most common among Family Medicine physicians (*P*=.02).
Discussion: Physicians are continuing to use nystatin for the treatment of tinea infections. Dermatologists have discontinued this treatment regimen, whereas other specialties have an opportunity to further improve their knowledge in this regard.

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INTRODUCTION

Topical nystatin is limited in its use for the treatment of tinea infections[1] especially because of its relatively poor minimal inhibitory concentration and minimal fungicidal concentration compared to other topical antifungals.[2] As there are more effective alternatives, any continued use of this medication is an area for quality improvement.[3] In this study, we analyzed the National Ambulatory Medical Care Survey (NAMCS) from 2007 to 2016 to determine the extent of topical nystatin use in tinea infections.

MATERIALS AND METHODS

We analyzed the NAMCS, an annual survey of physicians in the ambulatory setting. Physicians in the survey document visits in a random week of the year. For each visit, they record the physicians' diagnosis, patient demographics, and medications used. To adjust for probabilities of selection and nonresponses, each visit is given an inflation factor called the patient visit weight. This variable allows for the estimation of nationally representative values from observed visits.[4,5]

We analyzed the NAMCS from 2007 to 2016, the most recent years currently available. We assessed the NAMCS for all visits where international classification of disease ninth edition (ICD-9) and ICD-10 codes 110.0, 110.1, 110.3, 110.4 and 110.5 and ICD-10 codes B35.0, B35.1, B35.4, B35.4 and B35.6 were a primary through quinary diagnosis. The analysis was performed with the survey procedures of SAS University Edition (SAS Institute Inc., Cary, NC, USA).

RESULTS

There were 1,014 observed visits for tinea which represents 29.6 (95% confidence interval 27.5, 31.7) million infections. There were 12.3 (10.8, 13.9) million female patients which was 41.5% (36.3, 46.7) of the total. The mean age was 41.7 (40.2, 43.3).

Topical nystatin was used at 526 (224, 827) thousand visits which was 4.3% (2.1, 6.0) of all tinea visits. Nystatin was 5.2% (2.2, 8.1) of topical antifungals and 4.6% (2.0, 7.3) of all antifungals used for tinea. There was no change in use over time (*P*=.8, [odds ratio 1.0 (.85, 1.3)].

There were no observations of nystatin use for tinea at visits with dermatologists. Nystatin was used most commonly by Family Medicine physicians (*P*=.002) at 18.3% (7.0, 29.6) of visits. Despite this, nystatin was only used at 1.0% (0.4, 1.6) of all visits for tinea with Family Medicine physicians.

DISCUSSION

Physicians are continuing to use nystatin for the treatment of tinea infections at a small fraction of visits.[1] The small sample size of visits is a limitation of this study and prevents further analysis. Regardless, as the 95% confidence intervals for medications do not intersect zero, we are confident that there is still an appreciable use of nystatin.

As nystatin has proved ineffective for tinea for several decades,[6] the continued prescription of this medication for dermatophytosis likely represents an educational gap. Some specialties, such as

dermatology likely have already incorporated this knowledge into practice, whereas others such as family medicine may have an opportunity to further improve their knowledge regarding the most efficacious treatments of dermatophytosis.

DISCLOSURES

Dr Fleischer is a consultant for Boerhringer-Ingelheim, Dermavant, Incyte, Qurient, SCM Lifescience, and Syneos. He is an investigator for Galderma, Menlo, and Trevi. He has no other potential conflicts including Honoraria, Speakers bureau, Stock ownership or options, Expert testimony, Grants, Patents filed, received, pending, or in preparation, Royalties, or Donation of medical equipment. Suraj Muddasani and Gabrielle Peck have no conflicts of interest.

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LETTERS TO THE EDITOR

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Topical Moisturizer Meaningfully Reduces Disease Severity in Atopic Patients With Xerosis

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ABSTRACT

Background: Repairing the epidermal barrier is critically important in atopic dermatitis (AD), but the effect of moisturizer on quality of life (QOL) is not well characterized.
Objective: To assess whether the use of a moisturizer improves QOL in atopic patients with xerosis.
Methods: Thirty-five (35) adults with xerosis and AD received a moisturizer designed for AD to apply daily for three months. Adherence was assessed with electronic monitors. Quality of life (QOL) was assessed with the Dermatology Life Quality Index (DLQI) at baseline and follow-up.
Results: Mean adherence to the moisturizer was 46%. Dryness improved from 1.9 at baseline to 1.4 at follow-up (P=0.02). DLQI improved from 3.3 at baseline to 1.5 at 3 months (P=0.005). The "feeling self-conscious or embarrassed due to their skin condition" DLQI item improved from 0.79 at baseline to 0.14 at 3 months (P=0.0009).
Conclusion: Moisturizers are the foundation of AD treatment. Even non-medicated topical emollients can improve QOL in patients with AD.

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INTRODUCTION

Repairing the epidermal barrier is critically important in the treatment of atopic dermatitis (AD) and the associated skin dryness (xerosis).[1] While frequently recommended, the effectiveness of moisturizer treatment in AD is not well characterized.[2] We assessed whether the use of a moisturizer designed for atopic dermatitis improves objective and subjective disease severity in atopic patients with xerosis.

MATERIALS AND METHODS

Thirty-five (35) adult subjects with a diagnosis of xerosis in the context of current or historic AD were recruited from the Department of Dermatology clinics at Atrium Wake Forest Baptist Medical Center. Six patients were excluded due to loss of follow-up. Patients received Cetaphil Pro Eczema moisturizer (Galderma, Ft Worth, TX) equipped with an electronic monitor to measure adherence and were instructed to apply the moisturizer once daily for three months. The use of electronic monitoring was not disclosed until the final visit. Patients were not permitted to apply any other topical moisturizers or prescription treatments during the study period except for daily sunscreen. Xerosis severity was assessed with the Overall Skin Dryness Severity (ODS) score at baseline and follow-up visits. Effect on QOL was assessed with the total and individual Dermatology Life Quality Index (DLQI) scores at baseline and follow-up. At follow-up, the data from the electronic adherence monitors were downloaded. Data were analyzed using the SAS Software 9.4 Differences in group comparisons by mean score were analyzed with a Student's t-test.

RESULTS

Patient demographics included 57% female and 42% male, an average age of 64, and 96 % Caucasian. Mean adherence to the moisturizer was 46%. After three months of using the moisturizer, dryness improved from 1.9 at baseline to 1.4 at follow-up (P=0.02). DLQI improved from 3.3 at baseline to 1.5 at 3 months (P= 0.005). The "feeling self-conscious or embarrassed due to their skin condition" DLQI item improved from 0.79 at baseline to 0.14 at 3 months (P=0.0009).

DISCUSSION

Xerosis is a common symptom associated with AD that may negatively impact QOL with discomfort, pruritus, and the undesirable appearance of skin.[3] Both disease severity and overall QOL improved with the use of a daily moisturizer alone,

even though adherence to the moisturizer was limited. Patients specifically reported positive effects on their self-image as they felt less "self-conscious and embarrassed due to their skin condition." These changes were present regardless of patient adherence. A moisturizer designed for AD improves the disease severity of atopic patients with xerosis and does so clinically meaningfully as evidenced by improvements in QOL and patient self-confidence.

DISCLOSURES

Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance, Medical, Sun Pharma, Suncare Research, Informa, UpToDate, and National Psoriasis Foundation. He is the founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Katherine Kelly, Madison Cook, Rohan Singh, Patrick Perche, Esther Balogh, and Irma Richardson have no conflicts of interest to disclose.

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FEATURED CONTENT

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NEWS, VIEWS, & REVIEWS

Not So Vanilla: What Dermatologists Should Know About Vanilloid Receptors

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INTRODUCTION

The transient receptor potential (TRP) channel superfamily consists of several variably selective cation channels expressed throughout the human body.[1] These channels are activated through various mechanisms and primarily function as sensory receptors, mediating pain sensations, temperature, vision, pressure, osmolality, olfaction, and more.[2] The six members of the vanilloid subfamily of TRP channels (TRPV1-6) are named for the vanilloid compound capsaicin originally found to activate the first TRPV channel (vanilloid receptor 1/TRPV1). However, they are now known to be activated by many exogenous and endogenous ligands. TRPV1, TRPV3, and TRPV4 are expressed in several tissues including the skin, leading to myriad cutaneous functions.[3] Dermatologists benefit from understanding how TRPVs contribute to the neurogenic inflammation that underlies many dermatologic diseases and emerging therapeutics that leverage this connection.

Transient Receptor Potential Vanilloid subfamily

The skin is a major somatosensory organ. Afferent nerve endings throughout the epidermis and dermis detect various stimuli, transducing this information into electrical activity that the central nervous system (CNS) may interpret and respond to. TRPV in the skin are found on sensory nerve fibers as well as keratinocytes, mast cells, dendritic cells, sebaceous cells, dermal endothelial cells, hair follicles, and eccrine glands.[4] Tissue expression and cutaneous functions of TRPV1-4 are summarized in the Table.

Neurogenic Inflammation

Cutaneous neurogenic inflammation is created through the bidirectional interaction of keratinocytes and skin-residing immune cells with nerve endings and their secreted neuropeptide mediators.[5] TRPV1 and TRP ankyrin 1 (TRPA1) appear to be predominant TRP channels involved in neurogenic inflammation.[5] Activation of TRPV1 and TRPA1 located on sensory neurons leads to increased intracellular calcium and the subsequent release of the neuropeptides, namely substance P (SP) and calcitonin gene-related peptide (CGRP); these neuropeptides, in turn, promote mast cell degranulation, vasodilation, and infiltration of neutrophils and T lymphocytes.[6] Moreover, the release of neuropeptides following activation of TRPV1 and TRPA1 modulate proinflammatory gene expression and induce keratinocytes to produce interleukin (IL)-1-alpha, IL-6, and IL-8.[6] TRPV1 is a central integrator of sensation induced by pruritogenic stimuli;[7] however, although not part of the vanilloid subfamily, it has been suggested that TRPA1 is required for itch transduction and skin barrier defects found in chronic pruritus.[8] Notably, TRPV1 channels may become hypersensitive in the setting of proinflammatory or proalgesic mediators such as extracellular protons, neurotrophins, or bradykinin, thus mediating hyperalgesia.[9,10]

Neurogenic inflammation underlies many inflammatory skin diseases, including rosacea, atopic dermatitis (AD), and sensitive skin.

Table 1. Summary of TRPV1/2/3/4 Cutaneous Tissue Expression and Their Biologic Functions[1,23]

Channel	Expression	Functions	Agonists
TRPV1	Cutaneous sensory nerve fibers, mast cells, epidermal keratinocytes, dermal endothelium, hair follicles, differentiated sebaceous glands, eccrine glands	Thermosensation (noxious heat); nociception; autonomic thermoregulation	heat > 43 °C; vanilloids/capsaicin; protons, endocannabinoids; pain
TRPV2	Cutaneous sensory neurons; immune cells (macrophages, mast cells, natural killer cells, dendritic cells, lymphocytes)	Thermosensation (noxious heat); nociception; inflammatory response	heat > 52 °C; PI3 signaling; delta-9-tetrahydrocannabinol, cannabidiol
TRPV3	Keratinocytes; hair follicles	Thermosensation (moderate heat); nociception; wound healing; skin integrity; hair growth; sebaceous gland function	heat > 31 °C; farnesyl pyrophosphate; camphor
TRPV4	Keratinocytes; endothelium	Thermosensation (moderate heat); nociception; mechano-sensation; vaso-motor control; adherens junction control; modulation of cell migration	heat > 25 °C; extracellular osmolarity change; arachidonic acid metabolites; camphor

TRPV Channels and Dermatologic Disease

Rosacea

Given the various environmental triggers for rosacea, much research has been devoted to elucidating the involvement of TRP channels in rosacea pathophysiology. Across different subtypes of rosacea mast cells were found to colocalize with TRPV2 and TRPV4 and, while mRNA levels of TRPV1, TRPV2, and TRPV3 were found to be elevated in all subtypes, TRPV2, TRPV3 and TRPV4 were found to be differentially expressed.[11] Moreover, TRPV4 plays a significant role in mast cell activation in rosacea.[12]

Atopic Dermatitis

Neuroinflammation is strongly associated with AD. Histologically, AD lesions have increased SP- and CGRP-positive cutaneous sensory nerve fibers and, compared to normal controls, increased contacts between mast cells and nerve fibers are found within both lesional and non-lesional skin.[13] Altogether, these findings support the initiation and maintenance of neurogenic inflammation through mast cell activation and induction of cytokine release by keratinocytes by SP and CGRP. Furthermore, the Type 2 helper T cell (Th2) derived cytokine IL-31 directly activates TRPV1+/TRPA1+ sensory nerves in the skin of AD patients.[14]

Sensitive Skin Syndrome

Sensitive skin syndrome (SSS) is characterized by transient sensory perceptions (burning, tingling, stinging, pain, itching) invoked by otherwise innocuous stimuli. The pathogenesis is not completely understood although it is considered a neuropathic disorder.[15,16] Environmental factors such as temperature change are well-known triggers.[17] Given this information, it is suggested that SSS is a result of sensitization of TRPV1 expressed on cutaneous sensory nerves by the inflammatory neuropeptides endothelin-1 and nerve growth factor, ultimately leading to impaired barrier function and decreased thresholds for sensory nerve receptor activation.[18]

CONCLUSION & EMERGING THERAPEUTICS

Topical formulations containing Asivastrep, Pegcantratinib, and ASN008 compounds targeting TRPV1 are promising avenues for treating chronic pruritus and AD.[19] A phase IIb clinical trial demonstrated that Asivastrep cream has superior effectiveness in reducing inflammation and pruritus than placebo cream, though further evaluation of efficacy and safety in larger-scale phase III trials is necessary.[20] The findings from the PAC-14028 cream trials similarly highlighted significant improvements in AD symptoms, without notable safety concerns.[21] Additionally, applying synthetic peptides targeting TRPV1 for UV-induced skin responses holds promise for addressing inflammation and photoaging.[22] These developments offer alternative therapeutic options for patients seeking non-steroidal medications with a favorable side effect profile.

Disclosure

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