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JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

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*The exact process by which trifarotene ameliorates acne is unknown.

†**PIVOTAL Studies 1 & 2 Design[2]—First large-scale, multicenter, randomized Phase 3 clinical trials evaluating the efficacy and safety of topical therapy vs vehicle in both facial and truncal acne over 12 weeks. Patients:** Screened and randomized to once-daily trifarotene cream 50 µg/g (n=1,214) or vehicle (n=1,206). **Primary endpoints:** 1) absolute change in inflammatory and non-inflammatory lesion counts on the face from baseline to Week 12; 2) Investigator Global Assessment (IGA)[5] success rate on the face. **Secondary endpoints:** 1) absolute change in inflammatory and non-inflammatory lesion counts on the trunk from baseline to Week 12; 2) Physician Global Assessment (PGA)[5] success rate on the trunk. **Success rate:** Percentage of patients achieving IGA face rating of clear (0) or almost clear (1) and PGA trunk rating of clear (0) or almost clear (1) and at least a 2-grade change in IGA or PGA rating from baseline at a particular study visit. **Safety endpoints:** Incidence of adverse events and local tolerability (erythema, scaling, dryness, and stinging/burning).

‡vs 44.8% reduction with vehicle; $P<0.001$ for face and vs 50% reduction with vehicle; $P<0.001$ for trunk.[2]

§The definitions of severity for the 5-point IGA (face) and PGA (trunk) scales were the same: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate) and 4 (severe).[2]

Please see brief summary of full Prescribing Information on the next page.

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IMPORTANT INFORMATION ABOUT

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WHAT IS AKLIEF CREAM?

AKLIEF Cream is a prescription medicine used on the skin (topical) to treat acne vulgaris. Acne vulgaris is a condition in which the skin has blackheads, whiteheads, and pimples.

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AKLIEF Cream is for use in people 9 years of age and older. It is not known if AKLIEF Cream is safe and effective in children younger than 9 years old.

Do not use AKLIEF Cream for a condition for which it was not prescribed. Do not give AKLIEF Cream to other people, even if they have the same symptoms you have. It may harm them.

WHAT SHOULD I TELL MY DOCTOR BEFORE USING AKLIEF CREAM?

Before you use AKLIEF Cream, tell your doctor if you:

- have skin problems, including eczema, cuts or sunburn.
- are pregnant or planning to become pregnant. It is not known if AKLIEF Cream will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AKLIEF Cream passes into your breast milk. Breastfeeding women should use AKLIEF Cream on the smallest area of skin and for the shortest time needed while breastfeeding. Do not apply AKLIEF Cream to the nipple and areola to avoid contact with your baby. Talk to your doctor about the best way to feed your baby if you use AKLIEF Cream.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you use any other medicine for acne.

WHAT SHOULD I AVOID WHILE USING AKLIEF CREAM?

- Minimize exposure to sunlight. You should avoid using sunlamps, tanning beds, and ultraviolet light during treatment with AKLIEF Cream. If you have to be in sunlight or are sensitive to sunlight, use a sunscreen with SPF (sun protection factor) of 15 or more, and wear protective clothing and a wide-brimmed hat to cover the treated areas.
- You should avoid using AKLIEF Cream on skin areas with cuts, abrasions, eczema, or on sunburned skin.
- You should avoid using skin products that may dry or irritate your skin such as medicated or abrasive soaps and cleansers, cosmetics that have strong skin drying effects and products containing high levels of alcohol.
- You should avoid the use of "waxing" as a hair removal method on skin treated with AKLIEF Cream.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF AKLIEF CREAM?

The most common side effects of AKLIEF Cream include: application site (skin) irritation, itching and sunburn.

AKLIEF Cream may cause serious side effects including:

- **Local skin irritation.** Local skin reactions are common with AKLIEF Cream, are most likely to happen during the first four (4) weeks of treatment and may decrease with continued use of AKLIEF Cream. Signs and symptoms of local skin reaction include:
  - o Redness o Dryness o Scaling
  - o Stinging or burning

To help reduce your risk of developing these local skin reactions, when you begin treatment with AKLIEF Cream, you should begin applying a moisturizer on your skin as often as needed.

Tell your doctor if you develop symptoms of a local skin reaction. Your doctor may tell you to use AKLIEF Cream less often, or temporarily, or permanently stop your treatment with AKLIEF Cream.

These are not all of the possible side effects of AKLIEF Cream. For more information, ask your doctor or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088. You may also contact GALDERMA LABORATORIES, L.P. at 1-866-735-4137.

HOW SHOULD I USE AKLIEF CREAM?

- Use AKLIEF Cream exactly as your doctor tells you to use it. Apply a thin layer of AKLIEF Cream over the affected areas one (1) time each day, in the evening.

APPLYING AKLIEF CREAM:

- Wash the area where the cream will be applied and pat dry.
- If you receive a sample tube of AKLIEF Cream, follow your doctor's instructions about how much to apply
- AKLIEF Cream comes in a pump. Press down on (depress) the Pump one (1) time to dispense a small amount of AKLIEF Cream and spread a thin layer over your face (forehead, cheeks, nose, and chin). Avoid contact with your eyes, lips, mouth and the corners of your nose. Press down on the pump two (2) times to dispense enough AKLIEF Cream to apply a thin layer to cover your upper trunk (the area of your upper back that you can reach, shoulders, and chest). One (1) more pump may be used to apply a thin layer of AKLIEF Cream to your middle and lower back, if acne is present.
- When you begin treatment with AKLIEF Cream, you should begin applying a moisturizer on your skin as often as needed.

HOW SHOULD I STORE AKLIEF CREAM?

- Store AKLIEF Cream at room temperature, 68° to 77° F (20° to 25° C).
- Keep AKLIEF Cream away from heat.
- If you received a sample tube of AKLIEF Cream from your doctor, keep the tube tightly closed.

Keep AKLIEF Cream and all medicines out of the reach of children.

WHAT ARE THE INGREDIENTS OF AKLIEF CREAM?

Active ingredient: trifarotene

Inactive ingredients: allantoin, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane, cyclomethicone, 5% ethanol, medium-chain triglycerides, phenoxyethanol, propylene glycol, purified water.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT AKLIEF CREAM?

- Talk to your doctor or pharmacist.
- Visit www.AKLIEF.com or call 1-866-735-4137.

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GALDERMA LABORATORIES, L.P., Fort Worth, Texas 76177 USA
Revised: 9/19

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References: 1. AKLIEF Press Release. Federal Drug Administration approval 2019. **2.** Tan J, Thiboutot D, Popp G, et al. Randomized phase 3 evaluation of trifarotene 50 µg/g cream treatment of moderate facial and truncal acne. *J Am Acad Dermatol.* 2019;80(6):1691-1699. **3.** Fisher GJ, Harvinder ST, Xiao J, et al. Immunological identification and functional quantitation of retinoic acid and retinoid x receptor proteins in human skin. *J Biol Chem.* 1994;269(32):20629-20635. **4.** AKLIEF (trifarotene) Cream 0.005% [Prescribing Information]. Ft Worth, TX: Galderma Laboratories, L.P.; October 2019.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Clinical Relevance of Skin Pain in Atopic Dermatitis

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ABSTRACT

Skin pain is increasingly recognized as an impactful symptom in atopic dermatitis (AD) because of its association with patient discomfort, disease burden, and reduced quality of life. Although the nature of skin pain in AD has not been systematically studied and is therefore not well understood, patients report soreness, discomfort, and tenderness that may reflect peripheral and central pain sensitization. The high prevalence of skin pain suggests that it is not adequately addressed by current therapies for AD and may be undertreated compared with other symptoms. This review discusses the clinical relevance of skin pain with respect to its experience, pathophysiology, relationship with itch, and treatment implications. Recent studies suggest that skin pain presents as a neuropathic symptom independent from itch and the "itch-scratch cycle", and poses a unique burden to patients. Recognition of the significant consequences of skin pain and discomfort should reinforce the need to assess and treat this symptom in patients with moderate-to-severe AD.

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INTRODUCTION

Atopic dermatitis (AD) is a skin disorder characterized by chronic relapsing pruritic eczema resulting from altered skin barrier function and neuroimmune dysregulation.[1] Moderate-to-severe AD can result in functional impairment, sleep disturbance, and anxiety and depressive symptoms.[2,3] While nearly all people with AD suffer from the hallmark symptom of itch,[3-5] skin pain is another sensory symptom of the condition, but one that is less recognized by dermatologists and treatment guidelines. Skin pain in AD has been underappreciated for multiple reasons including: a lack of awareness by patients and clinicians; a lack of a common lexicon for describing skin pain; a view that skin pain is a corollary of physical signs of AD that will improve after treating skin lesions; and the assumption that skin pain and itch cannot be experienced simultaneously.

Until recently, little was known about the frequency of skin pain, its causes, and its impact on the quality of life (QoL) for patients with AD. In this article, we establish the clinical relevance of skin pain in AD by reviewing new evidence of its nature, pathophysiology, prevalence, and consequences. We also detail why this symptom should be considered in AD assessment and treatment.

What is meant by skin pain in AD?

The concept of pain, including skin pain, is complex and multifactorial. How pain is experienced differs among individuals, and what a dermatologist conceptualizes as skin pain may vary widely from the patient's experience of this symptom.

Qualitative studies provide greater patient insight into skin pain. In a natural language processing and centrality analysis, word choice and experiences of patients with AD were examined from an international cross-sectional, open-ended survey.[6] Itch was the most impactful symptom, but pain also led to a significant, distinct burden for patients. Pain was linked to itch in some patients, and to embarrassment and annoyance in others, suggesting both physical and emotional consequences.

Patients with AD use different words to describe their experience of skin pain. Many use neuropathic descriptors, such as "burning", "stinging", "tingling", and "pinprick-like".[7-10] In one study, 36 of 43 (84%) patients with AD reported skin pain, with 67% of them describing it as a "burning sensation" or "soreness or discomfort". Others characterized it as a "stinging sensation" (47%), "sensitivity" (44%), or "stabbing feeling"

(22%).[8] Descriptions of skin pain differed between adults and adolescents—adults reported more burning pain (64% vs 40%) and soreness (71% vs 27%) and adolescents reported more stinging pain (67% vs 25%). Certain skin pain descriptors were associated with milder sensations for some participants; for example, one participant rated "skin soreness" as 1 to 4 on a 10-point scale, but rated "skin pain" as 5 to 10. Similarly, "burning sensation" referred to a painful experience for some participants, whereas others used the term to describe erythema or nonpainful sensations.

These findings establish skin pain as a relevant concept for patients with AD, and suggest that physicians may need to consider skin pain more broadly to be inclusive of qualifiers, such as "soreness", "tenderness", and "discomfort".

What causes skin pain? Isn't it due to itch and scratching?

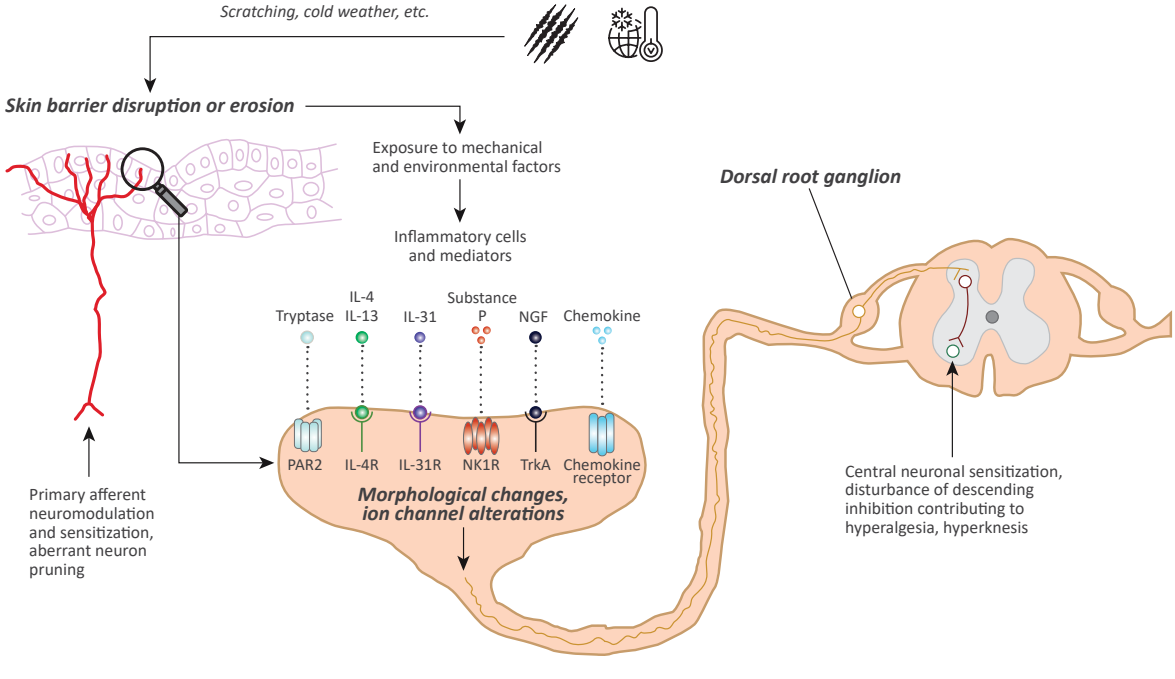
Association with itch

Patients with AD usually associate skin pain with itch.[4,7] In a survey of 103 patients with AD, 61% reported that pain occurred simultaneously with itch, with a nearly four-fold frequency of concomitant pain and itch compared with itch alone.[7] Patients may experience and describe pain and itch similarly using the terms "burning" and "stinging".[10] Itch intensity may also drive the frequency and intensity of skin pain.[4,11,12] The strong link between skin pain and itch may, in part, be explained by overlapping dysregulated neural circuits. Both pain and itch sensations are conveyed by cutaneous C and Aδ nerve fibers.[13-15] Recent imaging data revealed that intraepidermal nerve fibers are decreased in AD, although it is unclear how this neuroanatomical change contributes to itch and pain symptoms.[16,17]

Skin pain can also occur independently of itch. In an internet survey study of 602 adults with AD in the US, 9% of those who reported no or mild itch had moderate or severe pain (3.7% of the overall sample) whereas among those with severe itch, 28% had mild pain (8.1% of overall sample).[12] Scratching behavior appears to be only a small contributor to skin pain. In a clinical practice study of 305 patients with AD, 17% believed their pain was unrelated to scratching, while 72% believed it was only partially related; moreover, many patients experiencing skin pain had no corresponding sign of skin excoriations.[10] These findings are consistent with studies that indicate patients with AD generally have exaggerated responses to pain- and itch-evoking mechanical stimuli in both lesional and non-lesional skin.[13]

AD severity appears to contribute to skin pain independent of itch. In the US survey,[12] patients with mild AD were more likely to attribute their pain only as a result of scratching, whereas patients with severe AD were more likely to report recurrent or constant skin pain. Location of lesions also played a role—more intense pain was reported with facial lesions. Altogether, while itch, scratching, and skin pain are related, the evidence also supports skin pain as a distinct symptom in AD.

FIGURE 1. Possible mechanisms behind skin pain in AD. Neuromodulation in AD may be caused by exposure to mechanical or environmental factors and inflammation within lesional but also non-lesional skin. Since sensory neurons for itch and pain overlap, peripheral sensitization caused by inflammatory mediators (eg, cytokines and chemokines) associated with itch may also increase pain sensitivity. Centrally mediated sensitization at the spinal level may additionally occur in AD (eg, following prolonged afferent pruriceptive barrage).



Mechanisms and pathophysiology of skin pain in AD

Some anatomical areas—the palms, soles of the feet, and the chest—are especially prone to skin pain in AD,[7,11] which may be explained by greater sensory nerve density as well as by their frequent use and exposure. Skin pain can be generated by multiple and overlapping mechanisms that originate within or outside of skin lesions, and some patients may experience multiple types of pain.[13] Broadly, these mechanisms can be divided into mechanical causes, peripheral sensitization, and central sensitization (Figure 1).

Mechanical causes

Recurrent, widespread skin lesions, which are red, swollen, cracked, and weeping, are an obvious source of pain in AD.[7] Skin pain is more frequent in patients with AD who have skin excoriations,[10] since scratching exacerbates pain through additional skin barrier disruption and erosions. Daily activities can aggravate skin pain in certain anatomical areas. The hands are especially vulnerable to damage and fissures from cleaning products and cold weather. Other physical aggravating factors include sources of heat (eg, hot weather, warm water), surface contact (eg, clothing), and perfumes or scented lotions.[7-9] Skin pain has also been linked to dermatitis near the eyelid and perioral areas, and pruritus when sweating.[7,10,12] Patients may limit physical, social, or work-related activities in an effort to avoid sources that aggravate their skin pain. Withdrawal of topical corticosteroids, especially after long-term use, can also cause skin pain, particularly at facial and genital areas where the skin is thinner.[18]

Peripheral sensitization

In AD, primary afferents—C and Aδ fibers—are thought to be peripherally sensitized by exogenous stimuli due to impaired barrier function and by inflammatory mediators. Patients with AD have increased circulatory and dermal concentrations of various proinflammatory cytokines and neurotrophic factors.[19-21] Many of these mediators are released locally in the skin by inflammatory cells, including mast cells and eosinophils,[22] and some, such as nerve growth factor and interleukin 31, can cause morphological changes to neurons and increase sensitivity of peripheral nerves in human and mouse models of pain.[23-25] These changes include rapid alterations in the properties of ion channels expressed in sensory neuron pathways and longer-term transcriptional changes. Several chemokines, such as CXCL10 and CCL17, may also promote inflammation and neurological changes leading to chronic pain and itch in AD.[24]

In addition, barrier impairment from AD itself, scratching, or long-term topical medications (eg, corticosteroids) can expose, modulate, and sensitize epidermal nerve fibers leading to aberrant activation.[26,27] One suggested mechanism is that disruption of the pruning that keeps epidermal nerve endings below the keratinocyte tight junctions may lead to aberrant activation of epidermal nerves and pathological itch.[26] Sensitization of cutaneous nerve fibers can reduce receptor thresholds and enhance chronic pain and itch.[15] In AD, sensitization likely occurs at skin lesions, but may occur more generally given the hyperknesis and hyperalgesia observed extralesionally in many individuals.[13,21]

Central sensitization

In healthy individuals, pain generally inhibits itch through spinal interneurons that receive input from primary afferent nociceptors while inhibiting spinothalamic pruriceptive transmission.[28] In addition, itch sensitivity is usually inhibited in hyperalgesic skin.[28,29] However, individuals with AD show aberrations to these neuronal circuits. Investigations comparing responses to stimuli between healthy and AD skin found patients with AD exhibit considerable pinprick hyperalgesia and sensitization to non-histaminergic itch in both lesional and non-lesional skin.[13]

Altogether, there may be centrally mediated sensitization at the spinal level in AD, which constitutes a maladaptive central processing of itch leading to blunted pain-induced itch suppression.[29] Central pruriceptive disinhibition could contribute to the hyperalgesia observed after prolonged afferent pruriceptive barrage, thus reflecting centralized sensitization from mechanoreceptive signaling.[13,17]

What is the significance of skin pain?

The burden of pain in AD

Chronic skin pain is the second most common symptom of AD after itch.[9] Up to 61% of adults with AD report skin pain, and around 14% report it as severe or very severe, especially among those with moderate-to-severe disease.[3,10,12] More than one-third of patients with AD experience pain at least once per week,[10,12] and 5% report it daily.[12]

Skin pain is strongly linked to emotional distress, often described as an "embarrassment" or "annoyance",[6] and may contribute to anxious and depressive symptoms.[10] It can lead to increased self-consciousness and can limit daily activities such as work or study, socializing, clothing decisions, and pursuit of leisure activities and sports.[3,10,12] Higher disease severity is correlated with the impact of skin pain on QoL, though even mild skin pain can have a negative effect. In one study, persons with AD who had mild pain reported that it affected their self-consciousness (24%), clothing decisions (20%), and overall work or study (16%).[12]

Under-recognition of skin pain in clinical assessments and treatment

The nature of skin pain is subjective and therefore may not be adequately acknowledged or managed by clinicians. Moreover, there is little to no formal guidance or consensus on its assessment and treatment. Skin pain is usually assessed

TABLE 1.

Pain Assessments In Patient-Reported Outcome Measures Used in AD Studies

Measure	Item/question related to pain	Response options/scale	Recall period	Notes	References
Skin Pain NRS	Overall skin pain or soreness	Scale: 1 to 10	Last 24 hours	Developed and validated using patient recommendations; includes pain descriptors	8
Dermatology Life Quality Index	Itch, pain, stinging symptoms	Very much; a lot; a little; not at all	Last 7 days	Combines pain and itch as one item complicating evaluation of pain individually	33
EuroQol Five Dimensions	Pain/discomfort	I have no pain or discomfort; I have slight pain or discomfort; I have moderate pain or discomfort; I have severe pain or discomfort; I have extreme pain or discomfort	None (refers to pain at time of completion)	Not specific to AD or skin pain	34
McGill Pain Questionnaire	20 items of word descriptors and an intensity scale to determine subjective pain experience	Major measures are: (1) the pain rating index; (2) the number of words chosen; (3) the present pain intensity based on a 1–5 intensity scale	None specified	Not specific to AD or skin pain. Good for describing quality and intensity of pain	35
Patient-reported Outcome Measures Information System	Pain behavior (e.g., When I was in pain I squirmed…) and pain interference (eg, How much did pain interfere with your day-to-day activities?)	Pain behavior: had no pain; never; rarely; sometime; often; always Pain interference: not at all; a little bit; somewhat; quite a bit; very much	Last 7 days	Not specific to skin pain, but reliable across different medical conditions. Has not been studied in AD	36

through patient-reported outcomes (PROs). The presence of excoriations can be viewed by clinicians as an indirect measure of skin pain; however, this does not adequately substitute for a direct assessment.[30,31] Skin pain is rarely assessed as a specific or separate symptom in AD (Table 1). In some instances, general pain questionnaires have been used, but these tools often fail to capture nuances specific to skin pain. The Patient-Oriented Eczema Measure is a commonly used PRO; however, this tool was not designed to assess skin pain following consideration that it might be difficult to establish in younger patients.[32]

Since skin pain is a distinct and more prevalent form of pain in AD,[11] it is best quantified using a specific tool. Currently, the Skin Pain Numeric Rating Scale (NRS) is the only PRO measure specifically developed for AD.[8] Based on its psychometric validation work, the tool incorporated patient feedback to expand the question stem to include descriptors such as "soreness" and "discomfort". The NRS also uses a 24-hour recall period, which better captures the day-to-day variations in skin pain experienced by patients with AD. More focus on the patient's perspective through PROs and qualitative data could help clinicians understand the unique burden of AD and guide their decision-making, especially related to pain management.[30] The impact of skin pain relative to the overall burden of a patient's disease may differ according to age, gender, duration, and disease severity. Patients concur that optimal assessment of treatment efficacy must include PROs, and that these should be routinely included in the development of the treatment plan.[37] Multiple qualitative studies show that for most patients, skin pain is one of the worst symptoms, a priority for management, and highly important for assessing treatment efficacy.[8,38]

Existing AD treatment regimens may not optimally alleviate skin pain, which could explain why some patients continue to experience it even if they assess themselves as having controlled disease.[2] This residual pain might be indicative of underlying mechanisms and mediators that are not targeted by AD therapies. It also suggests that skin pain should not be assumed to resolve with lesion improvement. Utilization of pain medication has been found to be higher among patients with AD than in those without AD in the US.[39] In contrast, skin pain was not associated with increased analgesic medication use in a Danish cohort, although this study had fewer patients with severe AD.[40]

Greater understanding of the pathophysiology specifically underlying AD skin pain will help optimize treatments and reduce the burden from this symptom. For example, in patients where pain and itch occur concomitantly, analgesics may relieve cutaneous pain but some (eg, opioids) may worsen itch sensation.[13] In other patients whose pain results predominantly from scratching, anti-inflammatory treatments may indirectly

alleviate pain as itch subsides—as shown in a clinical trial of dupilumab, an AD treatment with antipruritic effects.[41]

Perhaps the most beneficial method for managing AD pain is for clinicians to discuss with their patients the impact of skin pain on the overall disease burden to inform and define individualized treatment plans. This could, for example, inform decisions to move a patient from topical to systemic treatment.[42]

CONCLUSION

Skin pain represents a unique burden for patients with AD, and new studies have revealed that this symptom contributes considerably more than previously known to the overall disease burden. The high prevalence of AD in industrialized countries—2–10% among adults[43,44] and 15–30% among children[1]—suggests millions of individuals suffer recurring AD and thus skin pain.

The new evidence also suggests that skin pain is not adequately assessed or managed by current standards of AD therapy. Skin pain severity should be considered relevant when evaluating treatment efficacy and is therefore important to assess in clinical studies and dermatologic practice. Additional research is needed to characterize the pathophysiology behind skin pain, exploring its associations with other AD signs and symptoms, and evaluating targeted treatments; this will help determine patient needs and therapy goals to support individualized, patient-centered care.

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ORIGINAL ARTICLE

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Rationale for Use of Combination Therapy in Rosacea

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ABSTRACT

Background: Rosacea is a chronic skin condition characterized by primary and secondary manifestations affecting the centrofacial skin. The primary diagnostic phenotypes for rosacea are fixed centrofacial erythema with periodic intensification, and phymatous changes. Major phenotypes, including papules and pustules, flushing, telangiectasia, and ocular manifestations, may occur concomitantly or independently with the diagnostic features. The phenotypes of rosacea patients may evolve between subtypes and may require multiple treatments concurrently to be effectively managed. We report the proceedings of a roundtable discussion among 3 dermatologists experienced in the treatment of rosacea and present examples of rosacea treatment strategies that target multiple rosacea symptoms presenting in individual patients.

Methods: Three hypothetical cases describing patients representative of those commonly seen by practicing dermatologists were developed. A roundtable discussion was held to discuss overall and specific strategies for treating rosacea based on the cases.

Results/Discussion: With few exceptions, the dermatologists recommended combination therapy targeting each manifestation of rosacea for each case. These recommendations are in agreement with the current American Acne and Rosacea Society treatment guidelines for rosacea and are supported by several studies demonstrating beneficial results from combining rosacea treatments.

Conclusions: Rosacea is an evolving condition; care should take into account all clinical signs and symptoms of rosacea that are present in an individual patient, understanding that symptoms may change over time, and utilize combination therapy when applicable to target all rosacea symptoms.

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INTRODUCTION

Rosacea is a chronic, multifactorial condition associated with various phenotypes affecting the centrofacial skin.[1] The primary diagnostic phenotypes for rosacea, as defined by the National Rosacea Society, include fixed centrofacial erythema with periodic intensification, and phymatous changes.[2] Major phenotypes, which may occur concomitantly or independently with the diagnostic features, are papules and pustules, flushing, telangiectasia, and ocular manifestations. Secondary signs and symptoms also may occur with the diagnostic or major phenotypes; these may include burning or stinging sensations, facial edema, and a dry appearance of central facial skin.

The presentations of patients with rosacea often involve different combinations of phenotypes or evolve between phenotypes over time and require treatments with different mechanisms of action to manage their disease.[1,2] Vascular changes resulting in chronic vasodilation are central to the pathophysiology of rosacea, potentially affecting all of the phenotypes[3]; therefore, treatments that control vasodilation may lead to overall disease improvement. Guidelines from the American Acne and Rosacea Society (AARS) recommend a phenotype-centered approach to treatment of all rosacea features that a patient displays at any given time.[4,5]

Three hypothetical cases describing representative patients seen by practicing dermatologists were developed. A teleconference was held among dermatologists experienced in the study and treatment of rosacea (the authors) to discuss treatment strategies for the hypothetical cases. This article reports the roundtable discussion proceedings and provides strategies and recommendations for treating rosacea based on the cases.

RESULTS

Hypothetical Case 1: MJ is a 35-year-old female with Fitzpatrick Skin Type I presenting with diffuse facial erythema that persists between episodes of intense facial flushing that are triggered by hot weather, hot water from a shower/bath, and spicy food. She has papules, pustules, and telangiectasia on her cheeks, and her facial skin appears dry and often is irritated by cosmetics. MJ has tried over-the-counter acne cleansers and, most recently, adapalene, without improvement. Her skin became more inflamed and irritated.

Initial treatment recommendations

We identified this patient's most prominent rosacea manifestations as background redness, telangiectasia, and papules and pustules, and agreed that the patient displayed combination rosacea. Dr. Stein Gold felt that this patient made a common mis-

take in treating her rosacea as acne, which can lead to additional irritation. She suggested treatment with first-line combination therapy, including a topical anti-inflammatory drug (eg, azelaic acid, ivermectin) or an oral subantimicrobial dose of doxycycline plus a topical alpha adrenergic agonist, in order to address all of the patient's symptoms except telangiectasia, for which laser treatment would be needed. Dr. Baldwin suggested use of a topical alpha agonist on the day of the telangiectasia treatment, to decrease the background redness and help the patient visualize the telangiectasias, which may be hard to distinguish from the background erythema. Alternatively, a pulsed-dye laser device could target both background redness and telangiectasias during one appointment. The erythema that was not resolved by the laser could be treated with an alpha agonist. Regardless of topical alpha agonist treatment timing, we stressed that it would be important to educate patients on the purpose of topical alpha agonist treatment, as telangiectasias do not contain vasoactive smooth muscle and would be unaffected by this treatment, and therefore may appear more prominent after its use.

We also suggested advising the patient on her general skin care regimen, which should aim to repair the epidermal barrier.

Follow-up recommendations

We suggested following up with the patient 6 to 8 weeks or earlier after the initial visit to assess goals and address any additional aspects of treatment. Dr. Baldwin would stress to the patient that the treatment goal was to achieve clear skin. She noted that patients often accept good results from initial treatment as "good enough" and do not follow up, even though better results are possible. If the patient is not responding adequately to treatment at the follow-up appointment, a discussion regarding treatment compliance was suggested, as well as regimen simplification if needed.

Overall take-home points

The initial visit for rosacea is not a fast one; it requires taking the patient's history, explaining the diagnosis, asking about triggers, and educating patients about avoiding them. Clinicians should recognize the value of combination treatment strategies and the importance of explaining to patients the rationale for this approach, because patients sometimes select 1 product rather than using all that were prescribed/recommended.

Hypothetical Case 2: LL is a 60-year-old male with Fitzpatrick Skin Type II presenting with rhinophyma and persistent centrofacial erythema. He describes decades of episodic facial flushing after eating spicy food or drinking alcohol. The facial erythema became persistent over the last 5 to 10 years. He is self-conscious at work, as his coworkers frequently comment about his red complexion. LL has seen a dermatologist, who prescribed topical metronidazole. He was very compliant, yet after 6 months of therapy, noted no change.

Initial treatment recommendations

We agreed that rhinophyma, persistent erythema, and flushing were the most prominent rosacea manifestations in this patient. Treatment could begin with combination therapy targeting the rhinophyma and background erythema. If the rhinophyma had reached an end stage, procedural treatment would be appropriate. If the rhinophyma was in an early stage, aggressive treatment should be pursued. We suggested combination treatment with a topical alpha agonist, systemic anti-inflammatory medication (modified-release doxycycline or low-dose isotretinoin), and laser therapy. Although isotretinoin is associated with adverse side effects,[6] Dr. Baldwin commented that isotretinoin treatment for rhinophyma is most commonly recommended in older men; there are fewer concerns in this population than when it is prescribed to women of childbearing potential. Modified-release doxycycline could be effective for erythema and thickening edema; however, isotretinoin and doxycycline should not be used together.

Dr. Baldwin also suggested explaining the importance of follow-up to the overall treatment plan. Based on her experience, patients, particularly men, may be more likely to discontinue treatment if they are unhappy with initial results, even when other treatment options are available.

Follow-up recommendations

After initial treatment with a systemic anti-inflammatory, we would reassess the rhinophyma during follow-up, and evaluate whether an ablative physical modality is needed. The patient would likely need maintenance treatment long-term and an ablative procedure to restore his nose to its original form. Dr. Harper suggested controlling the inflammatory aspect of the rosacea before doing a procedure for the rhinophyma.

After laser treatment, we would monitor the patient at follow-up visits; if rosacea was not well controlled, we could make adjustments to the treatment plan. We expect rosacea to be a fluid condition with transient symptoms (other than rhinophyma).

Overall take-home points

For Dr. Stein Gold, the case emphasized the need for aggressive treatment and close follow-up. Dr. Baldwin thought the case served as a good reminder to clinicians that isotretinoin can be an efficacious rhinophyma treatment. This case provoked discussion of the evidence for an association between rhinophyma and alcohol consumption.[7] Dr. Baldwin pointed out that this concern must be balanced with support for patients to address the stigma of rhinophyma. The question of whether rhinophyma is preventable through early treatment was also raised. Dr. Harper suggested that, while there is currently no supporting evidence, it is plausible that early anti-inflammatory treatments may prevent some consequences of chronic inflammation, such as rhinophymata. We all agree that an important point of this case

is that rosacea is a fluid and evolving condition. It is possible to resolve all of a patient's rosacea symptoms with first-line treatment, but the patient may return with new rosacea symptoms that need different treatment due to the nature of the disease.

Hypothetical Case 3: HB is a 45-year-old female with Fitzpatrick Skin Type IV presenting with papules and pustules, but no comedones. Her nose and cheeks show a red hue and feel overly warm to the touch. She often feels a burning or stinging sensation on her face. She was diagnosed with acne vulgaris, but treatment with benzoyl peroxide and tretinoin was not effective and caused irritation.

Initial treatment recommendations

We agreed that the rosacea manifestations most prominently displayed by this patient were papules and pustules and erythema. Dr. Baldwin suggested asking what symptoms bothered the patient in order to direct treatment. If the patient indicated that the erythema was bothersome, she could begin combination treatment for the papules and pustules and the erythema; if the erythema was not bothersome, the patient could try topical ivermectin monotherapy. A topical alpha agonist might also provide relief from the warm feeling and irritation and could be used intermittently for the patient's warmth symptoms if she was not bothered by the skin redness.

Follow-up recommendations

We agreed that the patient's background redness could be reassessed to determine the need for additional treatment. Complete clearing may not occur by the first follow-up visit, and appropriate expectations should be set. The patient would likely show improvement in papules and pustules if she began with ivermectin monotherapy. Her perilesional erythema should improve, too; however, some background erythema would likely remain, and the patient could decide if the erythema was bothersome enough to warrant topical alpha agonist treatment.

Overall take-home points

Rosacea is often overlooked or misdiagnosed in patients with skin of color; however, these patients can and do get rosacea. Dr. Harper noted that Alexis et al[8] reviewed this topic, and that clinicians need to elicit symptom information from patients and not just treat the signs that are visible to a clinician's eyes. Sample medication use may allow patients to assess the effects of a suggested treatment before committing to filling a prescription.

DISCUSSION

In this roundtable discussion, treatment recommendations for 3 representative, hypothetical cases describing patients with multiple rosacea symptoms were elicited. With few exceptions, combination therapy targeting each rosacea manifestation was advised. This approach agrees with the AARS rosacea treatment guidelines, which recommend selecting therapies to target all aspects of rosacea present in a patient.[4,5] We generally recommended treatment including an anti-inflammatory therapy for patients with papules and pustules, and a topical alpha agonist with or without an energy-based treatment for persistent erythema. Mitigation of chronic vasodilation with an alpha agonist may ultimately lead to less inflammation and overall improvement in rosacea. Because vasodilation is a central component of rosacea, alpha agonist treatment is likely to be beneficial for nearly all rosacea patients.

The AARS guidelines highlight evidence supporting concurrent use of multiple therapies for various rosacea presentations.[4] Topical treatment combinations,[9] and oral and topical treatment combinations,[10-16] have demonstrated excellent results. Adjunctive topical treatments used with energy-based therapies[17-19] have also been studied and show great promise in relieving rosacea symptoms. A summary of the key aspects of studies supporting combination therapy is provided in Table 1. These results, as well as the authors' experiences, support combination therapy in patients with multiple symptoms of rosacea.

CONCLUSION

Rosacea is an evolving condition; care should take into account all clinical signs and symptoms of rosacea that are present in an individual patient, understanding that symptoms may change over time, and utilize therapies with mechanisms of action that address each aspect.

DISCLOSURES

Linda Stein Gold: Advisor (Cassiopeia, Cutanea, EPI Health, Foamix, Galderma, LaRoche-Posay, Ortho-Dermatologics, Sol-Gel, Sun); investigator (Foamix, Galderma, Ortho-Dermatologics, Sol-Gel); speaker (Almirall, Foamix, Galderma, Ortho-Dermatologics).

Hilary Baldwin: Advisor (Almirall, BioPharmX, Dr. Reddy's Laboratories, EPI Health, Foamix, Galderma, Journey, Mayne, Ortho-Dermatologics); investigator (Almirall, BioPharmX, Galderma, Ortho-Dermatologics); speaker (Almirall, Foamix, Galderma, Ortho-Dermatologics).

Julie C. Harper: Advisor (Aclaris, Cassiopeia, Cutanea, EPI Health, Foamix, Galderma, LaRoche-Posay, Ortho-Dermatologics, Sun); consultant (BioPharmX, Dermira); speaker (Aclaris, Almirall, EPI Health, Galderma, LaRoche-Posay, Ortho-Dermatologics).

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TABLE 1.

Summary of Key Aspects from Studies Supporting Combination Treatment for Rosacea

Study	Study Design	Study Treatment	Key Efficacy Outcomes
Topical Treatment Combinations			
Gold et al, 2017[9]	Double-blind, randomized, controlled 12-week study in 190 patients with moderate to severe erythema and inflammatory lesions	Topical brimonidine gel 0.33% and topical ivermectin cream 1% QD for 12 weeks; or brimonidine vehicle and ivermectin cream 1% QD for 4 weeks then brimonidine gel 0.33% and ivermectin cream 1% QD for 8 weeks; or brimonidine vehicle and ivermectin vehicle for 12 weeks	The proportion of patients achieving an IGA rating of clear or almost clear was significantly greater in patients receiving combination treatment all 12 weeks vs vehicle (61.2% vs 36.8%; *P*=0.003) and numerically greater in patients receiving combination treatment for 8 weeks vs vehicle (50% vs 36.8%; *P*=0.135)
Topical and Oral Treatment Combinations			
Dahl et al, 1998[10]	Multicenter, 4-month open-label, 6-month double-blind vehicle-controlled study in patients with moderate to severe erythema, inflammatory lesions, and telangiectasia	Oral tetracycline 250 mg QID and topical metronidazole gel BID for 4 months (n=113); then successfully treated patients received 0.75% topical metronidazole gel or vehicle BID for 6 months (n=88)	In the open-label phase, tetracycline and metronidazole treatment cleared all papules and pustules in 59% of patients, resulted in fewer papules and pustules in 92% of patients, and resulted in less erythema in 73% of patients
Del Rosso et al, 2010[11] (reviewed in Bhatia et al[20])	Phase 4, exploratory, multicenter, investigator-blinded, parallel-group 12-week study in 207 patients with moderate papulopustular rosacea and persistent erythema	Topical AzA gel 15% BID plus oral doxycycline 40 mg QD; or metronidazole gel 1% QD plus doxycycline 40 mg QD	For patients who received AzA plus doxycycline vs those who received metronidazole plus doxycycline, 20.8% vs 17.8%, respectively (*P*=NS), experienced ≥75% improvement from baseline in inflammatory lesion count at week 2, and 62.3% vs 52.5%, respectively (*P*=NS), achieved treatment success at week 12, defined as an IGA score of clear or minimal
Del Rosso, 2010[12] (reviewed in Bhatia et al[20])	Phase 4, open-label, multicenter, community-based 12-week study in 224 patients with papulopustular rosacea	Oral doxycycline 40 mg was added to stable topical treatment regimens including medications containing metronidazole, AzA, and/or sodium sulfacetamide 10%–sulfur 5%	At week 12, most patients had clear (38.6%) or near clear (37.1%) IGA scores while none had clear or near clear scores at baseline; the change in IGA scores distribution between baseline and week 12 was statistically significant (*P*=0.0012)
Ertl et al, 1994[13] (reviewed in Bhatia et al[20])	Randomized, double-blind, 32-week study in 22 patients with severe rosacea, defined as significant erythema with multiple papules and/or pustules, or recalcitrant rosacea, defined as disease incompletely controlled by prior therapies	Weeks 1–16: oral isotretinoin 10 mg QD plus topical tretinoin cream 0.025% QD; or oral placebo plus topical tretinoin cream 0.025% QD; or oral isotretinoin 10 mg QD plus topical placebo Weeks 17–32: patients previously taking combination treatment switched to topical tretinoin cream only; those previously taking oral placebo plus tretinoin continued on tretinoin only and those previously receiving isotretinoin plus placebo switched to topical placebo only	All treatment groups demonstrated decreases from baseline to week 32 in mean inflammatory lesion counts (isotretinoin plus tretinoin: 12.3 to 3.2; tretinoin alone: 13.3 to 7.7; isotretinoin alone: 16.9 to 5.0) and mean erythema scores (isotretinoin plus tretinoin: 3.7 to 2.3; tretinoin alone: 3.0 to 2.7; isotretinoin alone: 3.0 to 2.0)
Fowler et al, 2007[14] (reviewed in Bhatia et al[20])	Randomized, multicenter, outpatient, double-blind, placebo-controlled 16-week study in 72 patients with moderate to severe erythema, telangiectasia, IGA score ≥2, 8–40 papules and/or pustules, and ≤2 nodules	Oral doxycycline 40 mg plus topical metronidazole gel 1% QD for 12 weeks; or oral placebo plus topical metronidazole gel 1% QD for 12 weeks. From weeks 13 to 16, patients received oral doxycycline 40 mg QD or placebo only	Patients who received doxycycline plus metronidazole treatment experienced significantly greater decreases from baseline to week 12 in mean inflammatory lesion counts vs patients who received metronidazole plus placebo (–13.86 vs –8.47; *P*=0.002) and significantly greater mean percent change in IGA score (–66.4% vs –48.2%; *P*=0.008)

TABLE 1. (CONTINUED)

Summary of Key Aspects from Studies Supporting Combination Treatment for Rosacea			
Study	**Study Design**	**Study Treatment**	**Key Efficacy Outcomes**
Schaller et al, 2019[15]	Multicenter, randomized, investigator-blinded, parallel-group 12-week comparative study in 273 patients with severe rosacea and inflammatory lesions	Topical ivermectin cream 1% QD and oral doxycycline 40 mg modified-release capsules QD; or topical ivermectin cream 1% QD and placebo	Ivermectin plus doxycycline treatment resulted in a significantly greater reduction in inflammatory lesions from baseline from week 4 through week 12 (percentage reduction at week 12: –80.3 ± 21.7 vs –73.6 ± 30.5; *P*=0.032) and in a significantly higher proportion of patients achieving 100% lesion clearance at week 12 compared with ivermectin monotherapy (17.8% vs 7.2%; *P*=0.006)
Thiboutot et al, 2009[16] (reviewed in Bhatia et al[20])	Two-phase, multicenter study. Phase 1: open-label, nonrandomized, 4- to 12-week study. Phase 2: double-blind, randomized, vehicle-controlled, maintenance 24-week study among patients with moderate to severe papulopustular rosacea who experienced ≥75% reduction in inflammatory lesions in the open-label phase	Open-label phase (n=172): topical AzA gel 15% BID and oral doxycycline 100 mg BID for 4–12 weeks Double-blind phase (n=136): AzA gel 15% or vehicle BID for 24 weeks	By week 12 of the open-label, combination therapy phase, the mean inflammatory lesion count decreased from 19.3 (range, 10–79) at baseline to 3.3 (range, 0–28), and 81.4% of patients had experienced ≥75% reduction in inflammatory lesions
Topical and Energy-based Treatment Combinations			
Deaver Peterson et al, 2019[17]	Open-label 18-week study in 20 women with mild to severe erythema due to erythematotelangiectatic rosacea	Multifunctional 3-in-1 facial cream with vitamins, active herbal ingredients, and sunscreen and mineral sunscreen powder for 18 weeks with 1 full-face IPL treatment at week 12	At week 18, the mean overall investigator redness score was significantly improved (baseline, 3.05 ± 0.97; week 18, 2.05 ± 0.76; *P*<0.01), and all patients agreed or strongly agreed that the treatment regimen improved their baseline redness
Tanghetti et al, 2020[19]	Multicenter, interventional, open-label 56-day study in 46 patients with moderate to severe erythema	Energy-based therapy (potassium titanyl phosphate laser; IPL therapy; pulsed-dye laser Vbeam Perfecta; or pulsed-dye laser Cynergy) on study days 1 and 29 and topical oxymetazoline hydrochloride cream 1% on days 3–27 and days 31–56	On day 56, >90% of patients displayed ≥1-grade improvement in CEA at 6 hours post-treatment and 65% of patients were satisfied with treatment, based on their skin appearance
Hofmann et al, 2017[18]	Case report in a patient with moderate to severe erythema and inflammatory lesions	Potassium-titanyl phosphate laser therapy and topical brimonidine gel 0.33% QD	The patient experienced a visible reduction in facial erythema from baseline

AzA, azelaic acid; BID, twice daily; CEA, Clinician Erythema Assessment; IGA, investigator global assessment; IPL, intense pulsed light; NS, not significant; QD, once daily; QID, four times daily.

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ORIGINAL ARTICLE

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Atopic Dermatitis and the Role of the Skin Microbiome in Choosing Prevention, Treatment, and Maintenance Options

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ABSTRACT

Background: Atopic dermatitis (AD) is a common skin condition characterized by disturbed barrier function, skin inflammation, and cutaneous dysbiosis. Clinically, it manifests as chronic-recurrent xerosis, pruritus, and erythematous lesions. Its pathophysiology is complex, making the selection of appropriate treatment options a task.

Aim: To share insights gained from a literature review and discussions with experts in dermatology on key factors related to the prevention, treatment, and management of AD in relation to the skin microbiome.

Methods: Results from an expert panel were summarized and discussed to provide updated recommendations for the treatment and maintenance of AD.

Results: Evidence supports a strategy for managing inflammatory skin diseases with a selenium-rich post-biotic thermal water and biomass containing moisturizer. The moisturizer helps to restore homeostasis of the skin, re-populate a diverse microbiome, encourage the growth of commensal bacteria, and improve barrier function and symptoms of AD.

Conclusions: Normalization of skin microbiome diversity using a topical moisturizer containing post-biotic aqua and biomass may offer a valuable option for the treatment and maintenance of inflammatory skin diseases. Clinicians should discuss the benefits of this treatment in the context of a full AD management program that covers prevention, active treatment, and maintenance.

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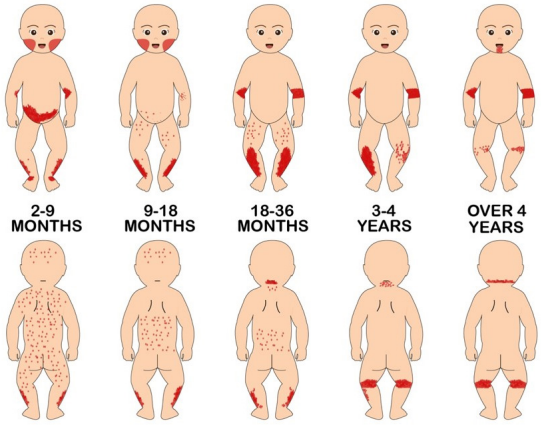
INTRODUCTION

Atopic Dermatitis

Atopic dermatitis (AD) is a common inflammatory skin condition characterized by chronic-recurrent xerosis, pruritus, and erythematous lesions.[1] In industrialized countries, the prevalence of AD has been rising since the 1940s; and it is now one of the most frequent chronic inflammatory skin disorders in the world.[2,3] With a reported prevalence of over 20% in children and up to 8% in adults,[1,4-7] over 92 million people in the United States (U.S.) alone suffer from AD. As there are no objective diagnostic tests for AD,[1] diagnosis is made clinically based on the presence of one or more symptoms, which often include: pruritus, erythema, scaling, xerosis, edema, excoriations, oozing, crusting or lichenification.[2,5] Although AD can affect any area of the body, the typical anatomical locations of flare-ups (defined as acute, clinically significant worsening of the signs and symptoms of AD)[8] depend on age, and patterns change between infancy, childhood, and adulthood.[9] For example, in

FIGURE 1. Common anatomical locations of atopic dermatitis in infancy and childhood, by age range.



infancy, the cheeks are often affected (Figure 1), whereas in adulthood, it preferentially affects the head, neck and flexures eg, antecubital fossae, popliteal fossae.[8,9] AD is associated with substantial disease-related morbidity and disability.[1] Of all skin disorders, AD has the highest disability-adjusted life-years.[10,11] While there are few estimates of the costs of AD, a 2002 study estimated that the direct costs to the payer were USD 3.8 billion, per year.[12]

AD Populations

Children are particularly at risk for developing AD. The onset of AD displays an age-dependent distribution;[6] with symptoms typically appearing between two to six months of age and with 90% of atopic-prone children developing AD by the age of five years.[5] The severity of AD can be classified based on symptomatology, skin lesion characteristics and the size of the affected skin area.[4] Population-based survey data from the U.S. has revealed that the majority (ie, 67%) of childhood AD encompasses a mild disease state, followed by 26% and 7% of moderate and severe disease states, respectively.[4,7,13] There is also evidence to suggest that individual risk factors may predispose specific individuals to AD. Notably, while there is a slight-to-no association between AD and gender,[14,15] there are racial/ethnic disparities, with the severity of AD being higher in African and East Asian populations.[1,16-18] Patients with AD often present with inflammatory diseases, which has led some investigators to believe that systemic immunity may predispose specific individuals.[19] Given the wide variation in prevalence rates worldwide (ie, from 0.9% in India to 24.6% in Columbia), environmental factors are also thought to be involved with the development of AD.[1] While research has investigated many contributing components individually, recent findings indicate that a complex interaction between the environment, host's genetics, skin barrier function, and an immune response are implicated in the development of AD.[2,3]

The Tri-Directional "AD-Skin Barrier-Microbiome Trinity"

AD is a multifactorial disease, with considerable individual variation with regards to the impact and combination of contributing factors.[3] As such, AD has been described as a "heterogenous eczematous disorder".[4] This heterogeneity contributes to the fact that the causes of AD are poorly understood. While its pathogenesis is complex, AD can be characterized by skin barrier dysfunction, aberrant immune response and dysbiosis.[2] As early as the 1990s, investigators have been exploring the hypothesis that a cutaneous barrier abnormality initiates the pathogenesis of AD.[3,20-22] This hypothesis followed the discovery of evidence that suggested a non-immune causative event early in the development of AD. In 2012, Kong and coworkers hypothesized that a decrease in microbial diversity and an increase in the population of staphylococcus precedes the flare of AD (Figure 2). The flared state is characterized by low bacterial diversity, consisting largely of staphylococcus. Only once diversity is increased, and the staphylococcus population normalized does the flare resolve and skin return to its baseline. Since then, the role of barrier function in AD has been investigated in numerous clinical trials.[23-25] Resulting from a disruption in the skin's barrier is an increase in trans-epidermal water loss, and a decrease in skin hydration, a reduction in ceramides, fillagrin, and antimicrobial peptides. Dry and pruritic skin ensues, which prompts scratching, an exacerbation of the barrier dysfunction, and establishment of the itch-scratch cycle. Additionally, barrier dysfunction permits the penetration of external stimuli, such as allergens, toxins, irritants and bacteria which may lead to irritation, inflammation, or infection.[26]

While dysbiosis and barrier disruption are both components of AD, it is unclear which is the chicken and which the egg. Does the disease cause dysbiosis and barrier defect or does the aberrant stratum corneum cause atopic dermatitis? In consideration of these findings, a new concept of the pathogenesis of AD has emerged, which considers the microbiome, barrier function, and AD as an interplaying trinity.

METHODS

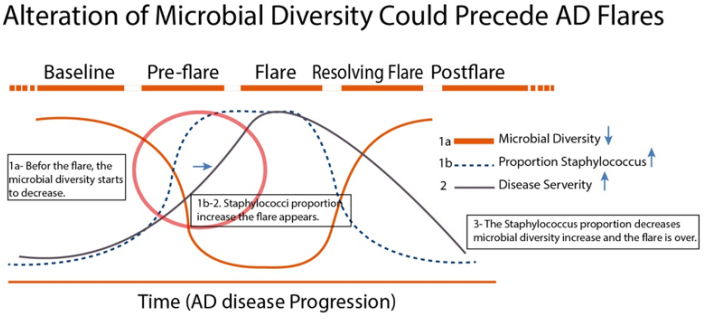
A working group of clinicians, all experienced in managing patient populations with AD, convened for a one-day meeting in New York City on November 2, 2019. To optimize clinical outcomes in AD, the panel reviewed literature surrounding the topic of the skin microbiome in patients with AD and developed and discussed clinical recommendations related to prevention, treatment, and maintenance of AD.

Key Insights

Cutaneous Dysbiosis in AD

Skin microbes play a critical role in maintaining skin health: controlling pathogenic species, priming the immune system, and preventing inflammation and infection. In another bi-

FIGURE 2. The relationship between the skin microbiome and atopic dermatitis. An increase in the proportion of *Staphylococcus aureus* and a reduction in microbial diversity precedes atopic dermatitis exacerbation and the severity of flares-ups. *Figure adapted from Kong et al, 2012.*[34]



directional relationship, dysbiosis leads to barrier dysfunction and barrier dysfunction results in aberrant microbiome.[29] The cutaneous microbiome is an ecosystem that includes a diverse array of microorganisms, including viruses, fungi, mites, and bacteria.[31] The composition of this ecosystem can be altered by many factors, including but not limited to anatomical location,[32] pH, moisture level, and the distribution of hair follicles and sebaceous glands, gender, age, and ethnicity.

A recent review investigated the relationship between the skin microbiota and barrier function and describes how each component can affect the other.[29] Baldwin et al (2017) describe how the skin microbiota can interact with the cutaneous barrier through the release of proteases, lipases, ureases, bactericidal peptides and by quorum sensing and skin nutrition. Conversely, they also describe how the skin barrier interacts with the microbiota through mechanisms such as providing nutrients, controlling the climate, and balancing and regulating bacteria.[29]

In AD and other inflammatory disorders such as psoriasis and acne vulgaris, the importance of maintaining a balanced and diverse microbiota has been demonstrated. In an environment that favors invasive organisms, colonization of pathogenic bacteria may ultimately breakdown the cutaneous barrier. Indeed, over 90% of AD patients have colonization of the pathogenic bacteria *Staphylococcus aureus*, and increasing disease severity has been found to correlate with a reduction in microbial diversity. The temporal shifts in the skin microbiome have long been associated with AD flares. For example, microbial communities at disease sites are dramatically different in AD patients compared to controls.[34] In AD, the proportion of *S. aureus* and commensal *S. epidermidis* are significantly increased during flare-ups; and following therapy, colonies of *Streptococcus, Propionibacterium,* and *Corynebacterium* species are observed.[34] These findings reveal an association between skin microbiome and AD.

Current Topical Treatments for AD

Standard topical therapy in AD includes topical corticosteroids (TCS), calcineurin inhibitors (TCI) and crisaborole, all of which function by inhibition of numerous aspects of the inflammatory response in AD. The use of TCS ultimately reduce the expression of pro-inflammatory genes and effectively reduce inflammation by suppressing the immune reaction mediated by lymphocytes, mast cells, eosinophil, dendritic cells, and macrophages.[9] However, high potency TCS are not suitable for sensitive areas, such as the face, eyelids, genitals, and skin folds; there are local and systemic side effects associated with the extended use of TCS, such as skin atrophy, telangiectasia, striae, dyspigmentation, development of glaucoma, hypothalamic-pituitary-adrenal axis suppression, growth retardation, and Cushing's syndrome.[35,37] Therefore, TCS are not suitable for everyone or in all cases of AD management.

TCIs, such as tacrolimus and pimecrolimus that were approved in 2006, are macrolactams with immunosuppressive characteristics. Like TCS, TCIs decrease the release of pro-inflammatory cytokines. Unlike steroids, they lack many of the unwanted side effects on healthy skin. Also, TCIs have lower transepidermal fluxes, which was thought to increase their safety.[37] However, 5–6 years after release, the FDA issued a black box warning for both drugs regarding the theoretical risk of malignancy. This warning was met with criticism from numerous medical associations regarding the scientific rationale for this decision. Side effects of use are primarily complaints of skin warmth and burning.

Crisaborole ointment (Eucrisa, Pfizer) is a phosphodiesterase type 4 inhibitor with demonstrated efficacy and safety in patients aged two years and older with mild-to-moderate AD.[38] Two multicenter phase III trials demonstrated sustained efficacy when using crisaborole ointment in patients with mild-to-moderate AD, over 28 days.[38] When compared to vehicle, treatment with crisaborole ointment showed reduced pruritus and other signs of AD.[39] Primary side effects of crisaborole are stinging and burning of the skin which generally resolves over time.[39] Furthermore, although TCS and TCIs are effective at reducing the inflammation associated with AD flares, they do not correct abnormalities to the cutaneous barrier, which is a major contributor to the pathogenesis of AD. It is important to remember that although TCS, TCIs and crisaborole are effective at reducing the inflammation associated with AD flares, they do not effectively repair the skin barrier which is a major contributor to the pathogenesis of AD.

The use of quality moisturizers containing occlusives and humectants have been found to improve barrier function, reducing trans-epidermal water loss and improving skin hydration.[35,40] However, partial restoration of the barrier function in AD-affected skin with emollients is not always sufficient as it

does not completely address all aspects of the flawed physiology of the cutaneous barrier. Furthermore, the durability of effect is relatively short lived. As such, they offer only partial and temporary restoration of the skin's barrier function.[36] Utilizing barrier repair creams with physiologic lipids help to address the shortcomings of conventional everyday moisturizers.

Restoring the Diversity of Skin Microbiota in AD Patients

Skin microbes play a critical role in maintaining skin health (eg, suppressing pathogenic species, priming the immune system, preventing inflammation and infection). Microorganisms require water to thrive, and the amount of available water in particular areas partially determines which type of bacteria can inhabit that location. In such a way, water can be viewed as both a culture medium and a prebiotic.[41] Dry environments favor the growth of *S. aureus* and inhibit the growth of beneficial commensal organisms such as coagulase-negative staphylococci.[29] Commensal bacteria thus compete with pathogenic bacteria for the same ecological niche. In unfavorable environmental conditions, (ie, dry skin), this can become problematic as commensal bacterial are an integral part of the healthy innate immune system and provide protection against inflammation and infection.[29] Therefore, maintaining the skin's moist barrier and homeostatic microbiota is necessary to reduce the promotion of pathogenic species and the chronic persistence of AD symptoms.

Through overpopulation of pathogenic organisms comes a loss of the skin's barrier and, subsequently, increased susceptibility to chronic inflammation. This understanding of the critical role of the cutaneous barrier in the pathogenesis of AD has led to recent advances in barrier repair therapies. Many topical treatments have been found to restore the skin's barrier in AD[36,42,43] and some have been found to diversify bacteria preceding the observed improvements in skin barrier function and disease severity.[34] This has led to the hypothesis that the regulation of bacterial populations is necessary to restore skin homeostasis in AD. While emollients can restore barrier function, experts agreed that this is not sufficient to treat AD-affected skin. Instead, they proposed that regulation of bacterial populations to restore homeostasis is required.

The effect of supplementation with probiotics on AD development and severity has been studied in various clinical trials with controversial results.[44-48] Some studies have evaluated the application of prebiotics to "feed" the bacteria, which are part of the healthy epidermis. Following promising preclinical results,[49,50] a treatment formula containing lysates from the Gram-negative bacterium *Vitreoscilla filiformis*, grown in a LRP-Thermal Spring Water (TSW), significantly improved AD severity in a randomized trial.[51]

Post-biotic Aqua Posae Filiformis

The post-biotic Aqua Posae Filiformis (APF), a biomass of *Vitreoscilla filiformis*, a non pathogenic bacteria grown in a medium containing La Roche Posay Themal spring water (LRP-TSW) has been shown to act on the balance of the microfloral balance, without the use of antibiotics.[50] LRP-TSW exhibits both pre- and probiotic properties that enhance the diversity of the skin microbiome.[52] A recent review was undertaken to explore the role of LRP-TSW as a topical pre- and probiotic therapy in improving the diversity of the skin microbiota and reducing dryness and pruritus in inflammatory skin diseases.[52] Investigators concluded that the concentration of minerals (eg, selenium) and nonpathogenic microbes in crude LRP-TSW is thought to explain its therapeutic benefit when used for inflammatory skin diseases at the thermal center of LRP. Clinical studies have shown topical LRP-TSW treatments stimulate the growth of Gram-negative bacteria at the expense of Gram-positive bacteria, which improves skin microbial diversity.[52] This results in an improvement in both non-diseased dry skin and inflammatory skin conditions. These findings support the historical use of thermal spa waters to treat inflammatory disorders. LRP balneotherapy has been shown to effectively treat AD through optimizing microbial diversity to decrease the severity of active lesions.[52]

Recently, it was found that applying an emollient containing LRP-TSW and the biomass of APF (Lipikar Balm AP+, La Roche-Posay Pharmaceutical Laboratories, France), to AD-affected skin was able to return the compositional balance of the microbiome to that of nearby unaffected skin. The composition of this LRP-TSW and APF emollient has been described previously and is summarized in Table 1.[54] In this pivotal study, AD symptoms improved for over 70% of the subjects, with a concurrent increase of bacterial diversity and a decrease in the abundance of Staphylococcus on the affected skin.[54] This trial was significant for confirming the importance of a reduction in the composition of microbial communities in AD flares. For the first time, investigators demonstrated that the topical application of a prebiotic could be used as a therapeutic approach to modulate or balance the immune system and normalize the cutaneous microbiota. Moreover, these results were found to last for at least one month following the discontinuation of the treatment.[55]

DISCUSSION AND CONSENSUS

Guidelines for the topical treatment of AD have not changed significantly over the past ten years with the exception of the introduction of crisaborole.[4,8,34,36] However, treatment of more severe AD has changed dramatically due to the development of agents that target immune responses and inhibit T cells and target Th1, Th2, Th22, phosphodiesterase-4 (PDE4), IL-4, and IL-31.[56] The traditional paradigm of using steroid and antimicrobial strategies to control AD flares is shifting towards a more holistic approach, which encourages optimizing the microbiome through regulatory factors.[30-32] Advisors agreed that the skin microbiota plays a key role in dermatologic health and disease and that skin barrier repair is imperative to AD management.[2,3,21,23] As such,

TABLE 1.

Ingredients of the LRP-TSW Moisturizer[55]		
Component	**Ingredients**	**References**
Emollient A	Shea butter (20%), niaciniamide (4%), mannose	Seite, Zelenkova, Martin (2017)[55]
LRP-TSW	Bicarbonate (387mg/L), calcium (149mg/L), silicate (31.6mg/L), magnesium (4.4mg/L), strontium (0.3mg/L), selenium (0.053mg/L), zinc (<0.005mg/L), copper (<0.005mg/L)	Seite (2013)[53]
Biomass	*Vitreoscilla filiformis*	Seite, Zelenkova, Martin (2017)[55]

they recommend that skincare products targeting AD should be developed with a focus on maintaining the balance of healthy skin microbiome. Overall, board members were in agreement that maintaining microbial homeostasis is a crucial component of AD therapies. Currently, an AD management program that includes reducing pathogenic organisms, optimizing the re-population of the (healthy diversified) microbiome, and restoring the skin barrier is needed. As the microbiome plays a role in the prevention of AD and also in the active phase of the disease,[39,50] a product displaying pre- and post-biotic activity may prove beneficial.

Given the biological properties of LRP-TSW and of the biomass of *Vitreoscilla filiformis*, its use in a LRP-TSW and APF emollient for treating AD warrants consideration as a new strategy for treating inflammatory skin conditions.[52,53] This process combines the beneficial effects of an emollient containing the lysate of nonpathogenic bacteria *Vitreoscilla filiformis*, to target a significant factor in the pathogenesis of AD. LRP-TSW displays anti-free radical, immunomodulatory, anti-inflammatory properties. It also introduces selenium and strontium to reduce the production of inflammatory cytokines.[53] Furthermore, the biomass contained in the LRP-TSW and APF emollient releases lysates that normalize dysbiosis, re-balancing the bacterial content of lesions and nonlesional areas of AD skin.[55] Given these findings, investigators approved of the use of this selenium-rich TSW as an active ingredient in topical, irritant-reducing formulations.[53] Overall, these findings suggest that a new strategy for managing inflammatory skin diseases may be to combine the use of pre- and post-biotics into a moisturizer. Such a treatment may help restore homeostasis of the skin, re-populate the diversity of the microbiome, encourage the growth of commensal bacteria, and improve barrier function and symptoms of AD.

CONCLUSION

Enhancement of skin microbiome richness and diversity with a combination of LRP-TSW and APF in an emollient base may offer a valuable option for the treatment and maintenance of inflammatory skin diseases. Clinicians should discuss the benefits of such a product in the context of a full AD management program that covers prevention, active treatment, and maintenance.

Future Directives

Given that AD progresses through various stages of development, the use of a product that is specially formulated to target a particular phase of the disease may warrant further investigation. For example, future investigations may evaluate a LRP-TSW/APF containing moisturizer during the pre-flare period of AD. The moisturizer is approved for application on children as young as 2 weeks.

DISCLOSURES

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Rhofade® (oxymetazoline HCl) cream, 1%

Not an actual patient.

RHOFADE cream is the #1 prescribed topical treatment for persistent facial erythema associated with rosacea in adults*

See results with RHOFADE cream

At hours 3, 6, 9, and 12 on Day 29 of clinical trials, a ≥2-grade improvement in persistent facial erythema was seen in 12% to 18% of subjects using RHOFADE cream vs 5% to 9% using vehicle. The most common side effects at the application site include: dermatitis, worsening of rosacea pimples, itching, redness, and pain.[1] These are not all the possible side effects of RHOFADE cream. Individual results may vary.

Unretouched photos of clinical trial subject. Individual results may vary.

*Based on Symphony Health PHAST data recording the number of prescriptions written between July 2017 and October 2019.[2]

INDICATION

RHOFADE cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

IMPORTANT SAFETY INFORMATION AND WARNINGS

WARNINGS AND PRECAUTIONS

Potential Impacts on Cardiovascular Disease
Alpha-adrenergic agonists may impact blood pressure. **RHOFADE** cream should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

Potentiation of Vascular Insufficiency
RHOFADE cream should be used with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop.

Risk of Angle Closure Glaucoma
RHOFADE cream may increase the risk of angle closure glaucoma in patients with narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

CONTRAINDICATIONS

There are no contraindications for **RHOFADE** cream.

ADVERSE REACTIONS

The most common adverse reactions ≥1% for **RHOFADE** cream were: application-site dermatitis 2%, worsening inflammatory lesions of rosacea 1%, application-site pruritus 1%, application-site erythema 1%, and application-site pain 1%.

For topical use only. Not for oral, ophthalmic, or intravaginal use.

Please see full Prescribing Information for RHOFADE cream at rhofadehcp.com and Brief Summary attached.

References: 1. RHOFADE® cream full Prescribing Information 2019.
2. Data on file. EPI Health, LLC.

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RHO-JA2-0320

EPIHEALTH
Advancing Dermatology

RHOFADE® (oxymetazoline HCl) cream, 1%

BRIEF SUMMARY—PLEASE SEE THE RHOFADE® CREAM PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

RHOFADE cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

DOSAGE AND ADMINISTRATION

For topical use only. Not for oral, ophthalmic, or intravaginal use.

Prime the RHOFADE cream pump before using for the first time. To do so, with the pump in the upright position, repeatedly depress the actuator until cream is dispensed and then pump three times. Discard the cream from priming actuations. It is only necessary to prime the pump before the first dose.

RHOFADE cream tubes do not require priming.

Apply a pea-sized amount of RHOFADE cream, once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) avoiding the eyes and lips. Wash hands immediately after applying RHOFADE cream.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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Alpha-adrenergic agonists may impact blood pressure. RHOFADE cream should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

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Risk of Angle Closure Glaucoma

RHOFADE cream may increase the risk of angle closure glaucoma in patients with narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 489 subjects with persistent facial erythema associated with rosacea were treated with RHOFADE cream once daily for 4 weeks in 3 controlled clinical trials. An additional 440 subjects with persistent facial erythema associated with rosacea were also treated with RHOFADE cream once daily for up to one year in a long-term (open-label) clinical trial. Adverse reactions that occurred in at least 1% of subjects treated with RHOFADE cream through 4 weeks of treatment are presented in the table below:

Adverse Reactions Reported by ≥ 1% of Subjects Through 4 Weeks of Treatment in Controlled Clinical Trials

Adverse Reaction	Pooled Controlled Clinical Trials	
	RHOFADE Cream (N = 489)	Vehicle (N = 483)
Application-site dermatitis	9 (2%)	0
Worsening inflammatory lesions of rosacea	7 (1%)	1 (< 1%)
Application-site pruritus	5 (1%)	4 (1%)
Application-site erythema	5 (1%)	2 (< 1%)
Application-site pain	4 (1%)	1 (< 1%)

In the long-term (open-label) clinical trial, the rates of adverse reactions over a one-year treatment period were as follows: worsening inflammatory lesions of rosacea (3%), application-site dermatitis (3%), application-site pruritus (2%), application-site pain (2%), and application-site erythema (2%). Subjects with persistent erythema along with inflammatory lesions were allowed to use additional therapy for the inflammatory lesions of rosacea.

DRUG INTERACTIONS

Anti-hypertensives/Cardiac Glycosides

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives and/or cardiac glycosides is advised.

Caution should also be exercised in patients receiving alpha-1 adrenergic receptor antagonists such as in the treatment of cardiovascular disease, benign prostatic hypertrophy, or Raynaud's disease.

Monoamine Oxidase Inhibitors

Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on RHOFADE cream use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. A literature article describing intranasal decongestant use in pregnant women identified a potential association between second-trimester exposure to oxymetazoline (with no decongestant exposure in the first trimester) and renal collecting system anomalies. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 3 times and 73 times, respectively, the exposure associated with the maximum recommended human dose (MRHD). The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Following repeated use of oxymetazoline hydrochloride solution nasal spray for the treatment of nasal congestion at a dose 5 times higher than recommended, one case of fetal distress was reported in a 41-week pregnant patient. The fetal distress resolved hours later, prior to the delivery of the healthy infant. The anticipated exposures for the case are 8- to 18-fold higher than plasma exposures after topical administration of RHOFADE cream.

Human Data

No adequate and well-controlled trials of RHOFADE cream have been conducted in pregnant women. Across all clinical trials of RHOFADE cream, two pregnancies were reported. One pregnancy resulted in the delivery of a healthy child. One pregnancy resulted in a spontaneous abortion, which was considered to be unrelated to the trial medication.

Lactation

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breast milk production, or to establish the level of oxymetazoline present in human breast milk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOFADE cream and any potential adverse effects on the breastfed child from RHOFADE cream or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness of RHOFADE cream have not been established in pediatric patients below the age of 18 years.

Geriatric Use

One hundred and ninety-three subjects aged 65 years and older received treatment with RHOFADE cream (n = 135) or vehicle (n = 58) in clinical trials. No overall differences in safety or effectiveness were observed between subjects ≥ 65 years of age and younger subjects, based on available data. Clinical studies of RHOFADE cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

OVERDOSAGE

RHOFADE cream is not for oral use. If oral ingestion occurs, seek medical advice. Monitor patient closely and administer appropriate supportive measures as necessary. Accidental ingestion of topical solutions (nasal sprays) containing imidazoline derivatives (e.g., oxymetazoline) in children has resulted in serious adverse events requiring hospitalization, including nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma. Keep RHOFADE cream out of reach of children.

EPI HEALTH

Advancing Dermatology

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Patented. U.S. Patent Numbers: U.S. 7,812,049; U.S. 8,420,688; U.S. 8,815,929; U.S. 8,883,838; U.S. 9,974,773; and U.S. 10,335,391.
Made in the U.S.A.

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ORIGINAL ARTICLE

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Impact of Atopic Dermatitis Lesion Location on Quality of Life in Adult Patients in a Real-world Study

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ABSTRACT

Background: Atopic dermatitis (AD) has a negative impact on patients' quality of life (QoL).
Objective: To report the impact of specific AD lesion locations on QoL in adult patients with AD using real-world data.
Methods: The Adelphi US Disease Specific Programme was conducted between January–April 2018. Physicians documented patient demographics/characteristics, AD lesion locations, and body surface area; patients completed questionnaires reporting the impact of lesion locations on QoL.
Results: AD severity was moderate in 51.6% of patients and severe in 6.0%. Lesions were commonly identified in more than one location. All AD lesion locations impacted QoL. Visible areas were most bothersome, including head/neck (68%), hands/fingers (58%), front (30%), upper extremities (22%), and lower extremities (16%), with statistically significant associations for a number of Dermatology Life Quality Index (DLQI) items. Itch, soreness, pain, and stinging are also associated with a number of body areas but in particular with those that are most visible/accessible. Lesions on the head/neck and hands/fingers (58%) demonstrated an increased impact on the anxiety and depression dimension of the EuroQol 5-Dimension tool.
Conclusions: In patients with AD, quality of life was most affected in patients with lesions in visible areas, including head/neck, hands/fingers, and upper extremities, with statistically significant associations for a number of DLQI domains. Physicians should be aware of the burden of AD lesions on QoL and consider having conversations with patients to better understand the impact of these lesions.
Prior presentation: 28th Annual European Academy of Dermatology and Venereology Congress; 9–13 October 2019, Madrid, Spain. Poster number P0233.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease affecting 2%–7% of adults globally.[1-3] While itch has been reported as the hallmark and most burdensome symptom of AD,[4] other symptoms include skin pain and sleep disturbance,[5-8] which have all been shown to negatively impact patients' physical and psychosocial well-being.[9] AD limits lifestyle, activities, and social interactions in 40%–50% of patients and 17% are dissatisfied with life, compared with 11% of adults without AD.[4] Taken together, patients with AD experience significant impairment of quality of life (QoL).

Assessing QoL in AD is important from both patients' and physicians' perspectives in clinical practice and clinical studies,[10] and is ultimately beneficial for tailoring treatment. Recently, there has been an increase in the assessment of QoL and patient-reported outcomes, in addition to disease severity assessments in clinical studies with AD patients.[9] Functional and emotional QoL is reportedly impaired in AD patients and correlates with disease severity.[4,11] Silverberg et al found significantly high Dermatology Life Quality Index (DLQI) scores with increasing severity as assessed by SCORing Atopic Dermatitis (SCORAD) where patients with more severe

AD had high DLQI scores of 24.7 (score 0–30).[4] Higher DLQI scores indicate a large effect on QoL.[12] Danish patients with AD lesions in visible areas such as the face or neck were primarily interested in resolution of symptoms.[13] These aforementioned studies assessed the overall impact of AD on QoL in general, or by disease severity; however, they did not examine the effect of specific locations of AD lesions on QoL. Here, we report the impact of AD lesion location on QoL in adult patients using real-world data.[14-16]

METHODS

Study Design/Patients

This was a point-in-time, observational study for which detailed methodology of the Adelphi US Disease Specific Programme has been reported previously.[14-16] Briefly, this was a United States survey of physicians (N=150) and adult AD patients (N=599) from January to April 2018. Physicians completed a form indicating patient demographics and characteristics and documented AD locations and body surface area of lesion locations. Disease severity was based on subjective assessment and rated independently by patients and their physicians.[17] AD patients were aged 18 years or older, with current or a history of moderate-to-severe AD (as assessed by the physician). Mild patients with a history of moderate-to-severe AD at the time of data collection were included and completed the questionnaires for self-assessment.[17]

Body areas with AD lesions assessed were the head and neck, upper extremities, lower extremities, front, back, face, hands/fingers, feet/toes, and pelvis/genitals. The front included the chest, abdomen, pelvis, and genitals. The face comprised the skin around the eyes and other areas of the face.

Data Collection

Each affected body area was recorded by the physician on the Patient Record Form and patient-reported outcomes were captured by the patient on the Patient Self-completed Questionnaires. Patient-completed forms were linked to completed forms from physicians. The collection of patient data was compliant with the Health Insurance Portability and Accountability Act of 1996[18] and the Health Information Technology for Economic and Clinical Health Act of 2009.[17] The DSP is research involving survey procedures and, as such, does not require ethics committee approval.

Patients provided information covering the location of their most bothersome AD lesion, as well as the effects of their AD on QoL, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each physician could include up to 5 patients. The DLQI assessed how the patient's condition had affected their life over the last week.[12,19] This questionnaire comprises 10 questions, of which each is scored 0–3; with a maximum score of 30. For each question, a score of 0–1 indicated no effect on QoL[12]; the higher the score, the greater the impact of AD on QoL. The 6 sub-scales included in the DLQI include symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment.

The EuroQol 5-Dimension 3 Level (EQ-5D-3L) is a questionnaire that assesses overall health related to quality of life, including the 5 dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[20,21] There are 3 response levels for each question (no problems, some problems, extreme problems). Scores range from less than zero (negative numbers are valued as worse than death) to 1 (which correlates to perfect health).[22] For the EQ-5D-Visual Analog Scale, patients were asked to indicate how good or bad their own health was today on a scale of 0–100, where 0 represents the worst imaginable health state and 100 the best imaginable health state.

The Patient Oriented Eczema Measure (POEM) questionnaire had 7 items with a maximum score of 28 asking patients about their symptoms and skin appearance over the last week.[23] Scores of 0–2 indicated clear or almost clear skin; 3–7, mild; 8–16, moderate; 17–24, severe; 25–28, very severe AD.[23]

In addition to completing these questionnaires, patients were asked two questions:

What one area do you find most bothersome? How bad was your Atopic Dermatitis at the times listed? (Today)

In tandem, physicians completed Patient Record Forms for each patient, recording their responses to the following questions:

Which regions of the patient's body are currently affected by AD symptoms? And what is / was your overall assessment of the severity of AD symptoms in this patient based on your own definition of the terms mild, moderate & severe? (Current level of severity)

STATISTICAL METHODS

Patient-reported outcomes (DLQI, EQ-5D-3L, and POEM) were compared between each body area reported on the Patient Record Form (affected vs not affected) using inverse weighted probability regression adjustment, adjusted for potential confounding factors including age, sex, body mass index (BMI), major concomitant conditions (Charlson comorbidity index), and body surface area of other body areas affected (depending on the body areas focused upon in any given comparison). The inverse probability weighted regression adjustment analysis was first tested to ensure it was balanced (ie, the confounders, after adjustment, did not differ significantly between the 2 groups being compared). The aim was to ensure that for each confounder the standardized difference was no more than 0.1. If the inverse probability weighted regression adjustment did

not achieve this, then interaction terms and squared terms were added iteratively until either balance was achieved or no further improvement could be gained (if no further improvement could be gained but the largest effect size was <0.2, then the inverse probability weighted regression adjustment model was considered to be balanced).

Data were dichotomized by whether a patient had involvement in multiple areas. A Benjamini and Hochberg test (with a false discovery rate of 10%) was performed to adjust for multiple comparisons; p-values ≤0.0334 were considered statistically significant. For the likelihood of an AD lesion location being most bothersome, the proportion of patients with an affected AD lesion who rated it as most bothersome was determined via comparison with the rest of the population with that lesion. Additionally, the inverse probability weighted regression adjustment (with the same confounding factors) was performed on the individual dimensions of the EQ-5D-3L questionnaire for head and neck (vs not head and neck) and hands/fingers (vs not hands/fingers). The 3 levels for each dimension of the EQ-5D-3L were dichotomized by combining the 2 more severe levels. Individual DLQI items were also compared for each of the body areas (affected vs not affected), using ordered logistic regression that included the same confounding factors. For this analysis, $P \leq 0.0252$ was considered statistically significant per the Benjamini and Hochberg test.

RESULTS

Demographics and Clinical Characteristics

One hundred and fifty physicians (70 dermatologists, 60 primary care physicians, and 20 allergists) provided records for 1054 patients, of whom 599 completed a patient questionnaire. Patients had a mean age of 39 (standard deviation [SD] 16.0) years old with a mean BMI of 26.2 (SD 4.6) kg/m^2; 77% were Caucasian (Table 1). A high percentage of patients (up to 60%) had lesions in more than one location (Table 1). Physician-reported severity documented on the patient record form identified 254 (42%) mild, 309 (52%) moderate, and 36 (6.0%) severe patients with AD. Prevalence of lesions in multiple locations were: upper extremities (60%), lower extremities (52%), hands/fingers (37%), front (37%), back (29%), head/neck (28%), skin around the eyes/other areas of the face (20%), feet and toes (19%), and pelvis/genitals (6%) respectively.

TABLE 1.

Patient Demographics and Characteristics		
Parameter	**Total (N=599)**	
Age, years	38.9 (16.3)	
Female, n (%)	312 (52.1)	
BMI, kg/m2	26.2 (4.6)	
Charlson comorbidity index (major comorbidities)[a]		
Mean (SD)	0.06 (0.35)	
Median (range)	0.0 (0.0–4.0)	
Race/ethnicity, n (%)		
White/Caucasian	463 (77.3)	
Asian[b] or Middle Eastern	44 (7.3)	
Hispanic or Latino	42 (7.0)	
African American	37 (6.2)	
Mixed race	11 (1.8)	
Other	2 (0.3)	
AD severity,[c] n (%)		
Mild	254 (42.4)	
Moderate	309 (51.6)	
Severe	36 (6.0)	
	Single Location	**Multiple Locations**
AD location,[c] n (%)		
Head and neck	32 (5.3)	167 (27.9)
Upper extremities	92 (15.4)	359 (59.9)
Lower extremities	35 (5.8)	310 (51.8)
Front[d]	11 (1.8)	220 (36.7)
Back	1 (0.2)	173 (28.9)
Face[e]	7 (1.2)	119 (19.9)
Hands/fingers	26 (4.3)	222 (37.1)
Feet/toes	5 (0.8)	113 (18.9)
Pelvis/genitals	1 (0.2)	34 (5.7)

Data are mean (SD) unless otherwise stated. AD=atopic dermatitis; BMI=body mass index; SD=standard deviation.
[a]Lower scores=lower concomitant comorbidities
[b]Asian included 'Indian subcontinent', 'Asian other', or 'Chinese'
[c]Physician-rated
[d]Front=chest, abdomen, pelvis, and genitals
[e]Face=skin around the eyes and other areas of the face

Patient-reported Outcomes

Patients with AD included in this analysis of the impact on QoL reported mean (SD) 6.8 (5.6) for DLQI, 0.9 (0.1) for EQ-5D, 81.5 (16.3) for EQ-5D-VAS, and 9.4 (6.9) for POEM (Table 2). AD lesion locations impacted at least one measure of QoL in patients compared to patients who did not have a lesion in that location (Table 2).

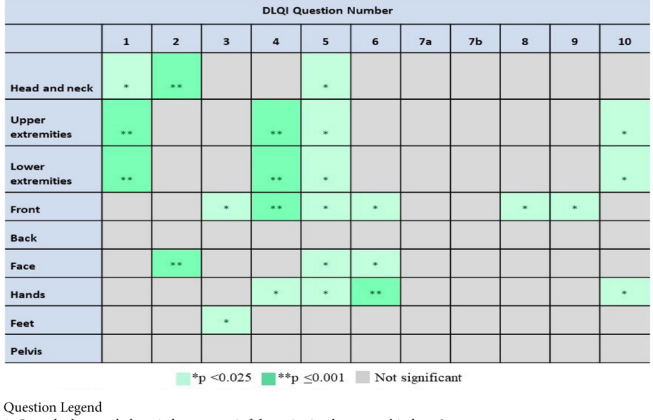
Visible areas most affected with statistically significant associations for a number of the DLQI domains included the head and neck, upper and lower extremities, front, face, and hands (Figure 1). The back and pelvis showed no significant associations with any of the DLQI items (one marginal .0468). The only significant association for feet was for shopping/looking after home or garden (0.004), which would generally involve walking. Personal aspects most likely to be affected by visible lesions include choice of clothing and social/leisure activities. Itch, soreness, pain, and stinging are also associated with a number of body areas but particularly with those that are most visible/accessible.

TABLE 2.

Impact of AD Lesion Location				
	Adjusted mean [difference]			
	DLQI	EQ-5D-3L	EQ-5D VAS	POEM
Overall Baseline, mean (SD)	6.8 (5.6)	0.9 (0.1)	81.5 (16.3)	9.4 (6.9)
Body Area				
Head and neck	7.11 [0.621]	0.892 [-0.02]*	78.6 [-4.2]*	10.9 [2.32]*
Upper extremities	7.05 [0.891]	0.903 [-0.02]*	80.8 [-3.4]*	10.1 [2.55]*
Lower extremities	7.21 [1.16]*	0.895 [-0.02]*	80.2 [-2.8]*	10.0 [1.99]*
Front	7.85 [1.29]*	0.902 [<0.001]	81.0 [0.64]	9.83 [0.63]
Back	7.13 [0.453]	0.891 [-0.03]*	79.6 [-2.9]	10.1 [1.44]
Face	7.79 [1.47]	0.882 [-0.02]	75.9 [-6.1]*	11.7 [2.91]*
Hands/fingers	7.74 [1.24]*	0.894 [-0.02]*	80.4 [-1.9]	11.6 [3.51]*
Feet/toes	8.35 [0.956]	0.857 [-0.05]*	78.8 [-1.0]	11.5 [1.20]
Pelvis/genitals	9.43 [1.21]	0.728 [-0.17]*	68.7 [-12]*	11.9 [1.06]

*p-values ≤0.0334 were considered statistically significant.
Data are p-values based on the inverse probability weighted regression adjustment; [a]Front=chest, abdomen, pelvis, and genitals; [b]Face=skin around the eyes and other areas of the face
AD=atopic dermatitis; DLQI=Dermatology Life Quality Index; EQ-5D-3L=EuroQol 5-Dimensions (3-level) questionnaire; POEM=Patient-Oriented Eczema Measure; VAS=visual analog scale.

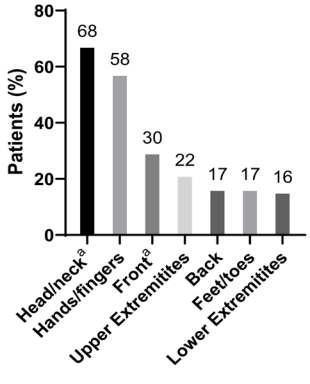
FIGURE 1. Impact of lesions on particular aspects of DLQI by body region.



Question Legend
1. Over the last week, how itchy, sore, painful or stinging has your skin been?
2. Over the last week, how embarrassed or self conscious have you been because of your skin?
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?
4. Over the last week, how much has your skin influenced the clothes you wear?
5. Over the last week, how much has your skin affected any social or leisure activities?
6. Over the last week, how much has your skin made it difficult for you to do any sport?
7a. Over the last week, has your skin prevented you from working or studying?
7b. If 'No' over the last week how much has your skin been a problem at work or studying?
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?
9. Over the last week, how much has your skin caused any sexual difficulties?
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?

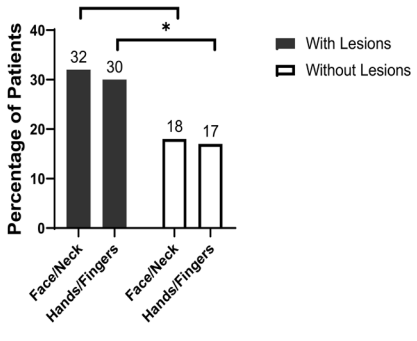
DLQI=Dermatology Life Quality Index.

FIGURE 2. Most bothersome areas in patients with AD.



Only matched patients are included in analysis (ie, patients with data for both Patient Record Form and Patient Self-completed Questionnaires). [a]multiple areas included in term: Front = chest, abdomen, pelvis, and genitals; Head and neck = skin around eyes and other areas of face.

FIGURE 3. Percentage of patients with face/neck and hand/finger lesions who report anxiety and depression as measured by the EQ-5D.



*$p \leq 0.001$. EQ-5D=EuroQol 5-Dimension.

Patients selected the most bothersome lesion location. Of the patients with affected lesions on the head and neck, 68% rated this as most bothersome, and of those with hands/finger lesions, 58% found this most bothersome. Other lesion locations were considered most bothersome to a smaller percentage of patients; front (30%), upper extremities (22%), feet/toes (17%), back (17%), and lower extremities (16%) (Figure 2). Head/neck and hands/fingers had an increased impact on the anxiety and depression dimension of the EQ-5D compared to those without lesions: 32% versus 18%, <0.001; 30% versus 17% <0.001, respectively (Figure 3).

DISCUSSION

The severity of skin inflammation, patient-reported outcomes, and effects of itch, skin pain, and sleep on QoL are important to patients with AD.[5,7] Our data suggest that the specific QoL domains impacted varies depending on specific lesion location. Visible areas, including head and neck, hands/fingers, upper and lower extremities, front, and face were most affected with significant associations for a number of DLQI items. Considering that AD lesions are heterogeneously distributed and that lesion locations affect varying aspects of QoL[24] emphasizes the importance of physicians having conversations with patients about the impact of AD on QoL.

Patients with AD are at an increased risk of comorbid conditions, including depression and anxiety, which often go undiagnosed.[11,24-26] In fact, the risk of anxiety and depression increases with AD severity.[11,24-26] Approximately one in three adults with AD report having depression symptoms and meet diagnostic criteria for major depressive disorder.[26] Our study found that approximately one third (30%) of patients with AD lesions on visible areas such as head/neck and hands/finger reported feeling anxiety and depression on a particular day in the EQ-5D. The hands, fingers, head, and neck are instrumental to everyday activities and social interactions; therefore, it is understandable that patients with chronic AD on visible areas are affected emotionally, experience pain, and feel stigmatised.[13,27] This is consistent with Egeberg et al who report that patients with AD lesions on the face and neck may experience cosmetic concerns.[13] As emotional state is of primary interest for patients with AD,[28] and as the distribution of lesions affects a patient's emotional state, especially those with moderate-to-severe AD, it remains imperative that physicians ask questions to capture the emotional impact of AD lesions on QoL as it relates to treatment response.[24]

Hand AD is one of the most frequently presented conditions in dermatology practice, with symptoms ranging from mild to severe and disabling. Our study found AD lesions on the hands and fingers were the most bothersome among 58% of those who had hand lesions; these patients expressed that their skin had a significant impact on the clothes they wore, as well as their leisure and sport activities and time commitment for treatment. Those with foot lesions reported a significant impact on shopping or gardening, activities that often require walking. Our results are consistent with the literature where patients with AD on their palms or soles, palmoplantar regions,[29] or fingers have an impaired ability to perform day-to-day activities.[30] This is further evidence that, by controlling symptoms, patients' day-to-day activities and QoL could be positively affected.

Goals for managing AD should include symptom control with improved QoL for patients,[10] where social and emotional factors, which have been reported to impact on AD development,[31] are considered in clinical history at routine visits. All AD lesion locations have been shown to impact various QoL domains. These effects varied among location and QoL measure; therefore, it is important that physicians assess QoL in AD patients with a variety of lesion locations. The National Eczema Association encourages strong patient-provider communication, which has been linked to decreased emotional stress and improved adherence to treatment, which in turn improves patients' health outcomes and satisfaction.[32] Understanding patients' perspectives may benefit providers and enhance treatment decisions.[10]

Limitations of our study include the inherent subjectivity of the questionnaire responses. The DLQI and EQ-5D were created to be composite scores; however, information can be gathered by extracting individual domain scores, as performed in this manuscript. In addition, patients' AD severity was categorized according to physician judgement, rather than utilizing a clinical tool. Lastly, depression and anxiety domains in the EQ-5D are self-reported symptoms, not clinically confirmed.

CONCLUSION

In adults with AD, QoL in those with visible lesions located on the head, neck, hands, and fingers was most affected with statistically significant associations for a number of DLQI items. Physicians should be aware of the burden of AD lesions on QoL and consider having conversations with their patients to elicit appropriate information and take action accordingly.

DISCLOSURES

The study was sponsored by Eli Lilly and Company. Peter Lio has served as an investigator for AbbVie, Regeneron/Sanofi-Genzyme, and AOBiome. He has served as an advisor/consultant for AbbVie, AOBiome, Arbonne, Dermavant, Dermira, Eli Lilly, Exeltis, Galderma, IntraDerm, Johnson and Johnson, Kiniksa, L'Oreal, MenloTherapeutics, Micreos, Pfizer, Pierre Fabre, Realm, Regeneron/Sanofi-Genzyme, Theraplex, UCB, and Unilever. He has served as a speaker for L'Oreal, Pfizer, TopMD, and Regeneron/Sanofi-Genzyme. Andreas Wollenberg has received grants, personal fees or nonfinancial support from Abbvie, Almirall, Beiersdorf, Galderma, Hans Karrer, Leo Pharma, Eli

Lilly, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron, and Sanofi-Aventis. Dr. Thyssen has attended advisory boards for Eli-Lilly, Regeneron, Pfizer, LEO Pharma, Abbvie and Sanofi-Genzyme, received speaker honorarium from LEO Pharma, Abbvie, Regeneron, and Sanofi-Genzyme, and received research grants from Regeneron and Sanofi-Genzyme. Jonathan Silverberg is a consultant and/or advisory board member for Anapysbio, Arena, Asana, Boehringer-Ingelheim, Celgene, Dermavant, Dermira, DS Biopharma, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo, Luna, Menlo, Pfizer, Regeneron, Sanofi-Genzyme. He is a speaker for Regeneron and Sanofi-Genzyme. Carle Paul has received grants and has been a consultant for Allmiral, Amgen, Abbvie, Boehringer, Celgene, Eli Lilly, Novartis, Janssen, Sandoz, Pfizer, Leo Pharma, Merck, and UCB pharma; he has been investigator or consultant for Astellas, Pierre Fabre, Regeneron, Sanofi and a consultant for Neuroderm. Evangeline Pierce, Maria Jose Rueda, Amy DeLozier, and Jorge Alfonso Ross Terres are employees and minor shareholders of Eli Lilly and Company. Peter Anderson, James Piercy and Gary Milligan are employees of Adelphi Real World.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Development and Evaluation of an Atopic Dermatitis Care Plan for Providers

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ABSTRACT

Background/Significance of problem: Atopic Dermatitis (AD) is a common, chronic, inflammatory dermatosis and skin disease that follows a relapsing pattern and requires a dynamic stepwise approach to management. Providers feel comfortable treating chronic disease states with a guided tool or care plan in many chronic diseases. Care plans used in many chronic diseases such as asthma, diabetes, and COPD have demonstrated effectiveness in disease and healthcare provider management.There is an unmet need for a universal AD care plan for providers.

Clinical question/project purpose: A universal AD care plan was developed to improve AD disease management and patient outcomes. Post-implementation of providers' perceptions was assessed for how the AD universal care plan affected their ability to provide patient education.

Search of literature/best evidence: Review of literature includes: *CINAHL, ProQuest Health, PubMed, Fusion,* and *UpToDate* databases from 2008-2018. Search terms included: Atopic Dermatitis, Eczema, care plans, care plan use in chronic disease.

Clinical appraisal of literature/best evidence: Analysis of the evidence supported the need for AD education, which then supported the need for a universal AD care plan for providers.

Integration into practice: "Your Eczema Care Plan" was used by thirty-five healthcare providers to improve patient outcomes in a similar manner as other evidence-based care plans.

Evaluation of evidenced-based practice: Post-implementation of providers' perceptions were evaluated on how the AD care plan tool affected their ability to provide patient education. Results suggest patient education, disease management, and QOL are all improved when utilizing "Your Eczema Action Plan."

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INTRODUCTION

Atopic Dermatitis (AD) is a common, chronic, inflammatory dermatosis and skin disease that follows a relapsing pattern and requires a dynamic and stepwise approach to management.[1,2] AD is often associated with an elevated serum immunoglobulin (IgE), familial or personal history of type 1 allergies associated with anaphylaxis, asthma, and allergic rhinitis.[3-6] Some consider AD as the start of the "atopic march", which is defined as the development of AD in infancy and subsequently allergic rhinitis and asthma later in childhood.[7,5-6] According to Lyons et al,[6] "education of the underlying and primary defects, as well as provision of a comprehensive skin care plan, are essential in management of disease flares and disease maintenance in AD" (p.161). Care plan use in many chronic diseases such as asthma, diabetes, arthritis, and COPD have demonstrated effectiveness in disease management.[8,1,5,9,10-12] An AD care plan is a guided tool to assist providers in educating patients on AD.

Co-Morbidities, Incidence and Financial Impact of AD

According to a study by Roduit et al[4] early phenotypes among children with AD (before age two) identified a correlation of food allergies and asthma by the age of six. AD most commonly affects children more often than adults. Onset is most common between three to six months of age. Approximately 60% of children develop AD by their first year of life, while 90% develop AD by five years. Twenty five percent of children younger than 14 years of age are affected compared to two to three percent of adults.[3,13,5] Childhood AD prevalence by race is 20.2% African American, 13% Asian, 12.1% White, 10% Hispanic, and 13% Native American.[14,15] The annual financial impact of AD according to the National Eczema Association [NEA][14] for treating AD was $314 million.[14]

AD is caused by a complex cascade of physiological and non-physiological mechanisms that involve environmental, genetic,

action plans on self-care asthma improvement by decreasing asthma exacerbations. Based on updated treatment guidelines, practitioners should facilitate education and communication between affected patients and their families. The effects of patient education on AD outcomes have not been formally tested. Therefore, there is uncertainty how to best support self-management of eczema research outcomes.[9] There is a gap in literature to support the need for AD education, including the need for a universal AD care plan for providers. This project includes the implementation of AD universal care plan for providers. Providers can utilize the AD universal care plan to improve patient adherence and disease outcomes.

Improving Patient Outcomes

There is an unmet need for a universal AD care plan for healthcare providers.[1,9,10,5] According to Saunder et al,[1] the use of written action plans has considerably improved the patient outcomes in other chronic diseases. There has been a policy shift recently in the U.K. towards self-management in long term conditions.[9] Saunder et al[1] performed a systematic review of the literature to evaluate the written eczema action plans (EAP) in AD. The literature review according to Saunder et al (2016)[1] identified two trials as eligible, highlighting the need for further research on a written EAP to manage AD. According to Ridd et al (2017),9 an international AD study on EAP recommends self-management early in AD to lead to improvement in quality of life. Because of the absence of a well- controlled study designs on how to promote self-management of AD, future studies are needed.9 Action plans are utilized with evidence in other chronic disease states.[10,8,1,9,5,11] The literature suggests studies on self-management in other chronic diseases in adults and children as another lacuna on the need for the project. There is a significant unmet need for a consistent care plan for providers in treating children and adults with AD.[3,10,13,16,6,1,9]

By developing an AD universal care plan, we will provide AD education for providers to utilize in educating patients. As the literature suggests in other chronic disease states, Eczema Action Plans (EAP's) improve patient outcomes in AD.[9,1,10,5,8,11] Providing and implementing an AD universal care plan for adults and children will help decrease disease severity and increase quality of life associated with AD.[9,1,10,5]

There is an unmet need for a universal atopic dermatitis (AD) care plan for providers. AD is a chronic disease. Providers feel comfortable treating chronic disease states with a guided tool or care plan in many chronic diseases.[6] Care plans used in many chronic diseases such as asthma, diabetes, arthritis, and COPD have demonstrated effectiveness in disease self-management.[8,1,5,9-12]The goal of the project was to help providers feel more comfortable in treating and educating AD patients using an AD universal care plan. The purpose of the project was to develop an AD universal care plan for providers to change current behavior by providing a treatment approach and a universal patient educational tool. Post- implementation of providers' perceptions was assessed on how the AD universal care plan tool affected patient outcomes.

Development of the Care Plan

The Care Plan was developed based on a literature review and care plans obtained in the NEA, academic settings, private practices and the National Institute of Allergy and Infectious Diseases, National Institute of Health [NIAID: NIH] in collaboration with the Medical Outcome Specialists (MOS)Team at Pfizer Headquarters within the pharmaceutical industry. The project included the implementation of an AD universal care plan for providers. The Field Medical Directors (FMD/MSL)/ Medical Science Liaisons in a pharmaceutical industry will distribute the AD care plans to the providers throughout the United States. Providers utilized the AD universal care plan to improve patient adherence and outcomes and change current behavior and practice by providing an AD universal patient educational tool.

The course of the project involved the project planner to assist in the development of the AD care plan and review the care plan with the Field Medical Director (FMD) team to distribute the plan to the providers: Dermatologists, Nurse Practitioners (NPs), and Physician Assistants (PAs) across North America. The sixteen FMD colleagues of the project planner, from the North American Medical Affairs Inflammation and Immunology department, and Project partner assisted in distributing the care plans. A survey was developed for providers through Survey Monkey™ to obtain opinions of the effectiveness of the AD care plan. Post-implementation of providers' perceptions was assessed on how the AD care plan affected patient education, self-management, and outcomes. The Field Medical Colleagues, Dermatologists, NPs and PAs, will be educated in their role of the project and project outcomes. The goal was to develop an AD universal care plan to change current practice by providing a care plan including a patient educational tool.

The setting included the east and west coasts of the United States (U.S.). Providers were selected with the assistance of Dr. Michael Gold, the SCALE dermatology conference in Nashville, TN, and a few of the Dermatology Field Medical Director's (FMD) as current experts in Atopic Dermatitis (AD). The providers received the standardized care plan for AD, including the patient education handout. Post-implementation of providers' perceptions was assessed regarding how the AD universal care plan affected patient education and outcomes.

Participants

Participants included direct care providers: Dermatologists, NP's, and PA's throughout the United States. These providers were given the AD universal care plan and sent a post-survey. A goal of 30–50 providers were identified with assistance from

and immunologic factors leading to a skin barrier dysfunction and immune dysregulation.[3,16-19] The prevalence of AD includes 31.6 million 10.1% of people in the United States with some form of AD. The prevalence of AD has been increasing.[5] 96 million (13 %) of children under the age of eighteen and 18 million (7.2%) of adults are affected.[14] AD impacts children and their families along with their caregivers. Symptoms include disrupted sleep with nearly 30% of children reporting concerns five or more nights per week.[14] Parents are also affected with loss of sleep leading to daytime sleepiness, poor work performance, and exhaustion.[14,3] AD is similar to many chronic diseases and impacts children and adolescents' psychological health and quality of life.

Nearly one in five children face being bullied due to AD.[14] Research suggest that children with AD often experience periods of isolation from their peers due to their condition.[14] Co-Morbidities include asthma (50%) and allergic rhinitis (75%). Patients are categorized with mild, moderate, or severe AD. Ninety percent of patients with AD present with mild to moderate disease.[20,3] Skin conditions, including AD, were the fourth nonfatal condition in 2010 leading to years lost due to disability.[21] Patients and caregivers seeking treatment for AD lost $128 million in wages.[14,21]

Diagnosis of AD

AD is diagnosed by histological features, distribution of skin lesions, and morphology.[3] The earliest diagnostic and recognized criteria for AD was developed in 1980 from Hanifin and Rajka. This criteria for AD diagnosis require three of four major criteria, and three of twenty-three minor criteria are met.[3] The latest diagnostic guidelines for AD were published in 2014 by the American Academy of Dermatology (AAD).[3] The essential features in the clinical diagnosis of AD include: pruritus, eczema (acute, subacute, and chronic), with a typical morphology and age-specific patterns which include a chronic and relapsing history. The important clinical features of AD include early age of atopy with a personal or family history of IgE reactivity and xerosis. The associated features in the AAD guidelines include atypical vascular response, keratosis pilaris/pityriasis alba/ hyperlinear palms, ichthyosis, and ocular/periorbital changes, along with other regional findings such as perifollicular accentuation, lichenification, and prurigo lesions. Pruritus is a hallmark of AD and the burden of the disease that impacts patients and families the most.[3]

AD Treatment

Eichenfield et al[3] discuss the recommendations for pharmacological and non-pharmacologic interventions for the treatment of AD. Treatment recommendations are based on levels of evidence. According to the recommendations by the American Academy of Dermatology, moisturizers are a cornerstone of AD therapy and should be included in management plans, maintenance, treatment, and prevention.[6,22] At the time of the last updated guidelines in 2014, treatment options included: topical corticosteroids, topical calcineurin inhibitors, antimicrobials/antiseptics, and antihistamines as the standard management options.[23,19,24]

Current Evidence in AD Treatment

There are newer treatment options available including topical, oral, and injectable medication options.[3,23-24,19] Crisaborole is a topical non-steroidal PDE4 inhibitor for mild to moderate atopic dermatitis in patients 2 years of age and older. Dupilumab is an injectable treatment, an IL-4 and IL-13 inhibitor for moderate to severe patients ages 12 years of age and older. These two medications represent the first two Federal Drug Administration [FDA] therapies in over 15 years.[23-24] According to Saporito and Cohen[19] Apremilast, an oral phosphodiesterase-4(PDE4) inhibitor was FDA approved in 2014 for moderate-to-severe psoriasis. Studies have been performed for use of an oral PDE4 inhibitor in moderate–to-severe AD.[19] Most chronic disease guidelines are updated every five years. A current AD universal care plan, in addition to updated guidelines in AD for providers, should be considered.[17,1,16]

Benefit of Treatment Guidelines

Providers feel comfortable treating chronic disease states with a guided tool or care plan in many chronic diseases.[6] Care plan use in many chronic diseases such as asthma, diabetes, arthritis, and COPD have demonstrated effectiveness in disease management.[8,1,5,9-12] The goal of the project is to help providers feel more comfortable in treating patients with AD using an AD universal care plan.

Patient Education

Similar to many chronic disease states, education on disease self-management is a key component in treating AD. Disease self-management care plans have been proposed as an important strategy in the burden of chronic disease.[9] The relevant literature noted in Ridd et al,[9] describes the definition of interventions to promote self-management for patients/ caregivers. Patient education supports people in management from an emotional, physical and social impact. It involves patient/caregivers in decision making, motivating people to self-manage, and helps monitor symptoms, and know when to take appropriate action.[9,1,10]

The Importance of Education for Providers and Patients

Since AD includes complex pathogenesis and combination of environmental, barrier repair, and immune dysregulation factors, effective patient management and caregiver education regarding disease management is an important component of treatment.[16,3,10,1,9,6] Written action plans in chronic diseases play an important role in education and providing tools to assist providers in disease management with a step-wise approach.[1] Lakupoch et al[12] report the effectiveness of using written asthma

FIGURE 1. Geographic location: State or U.S. territory

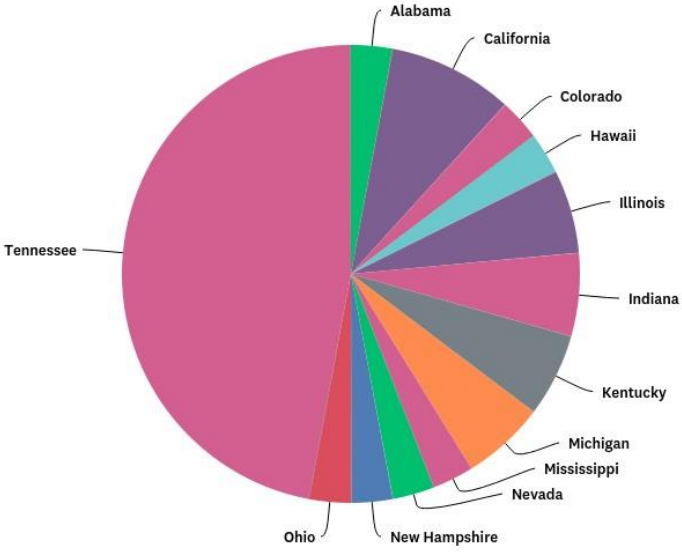
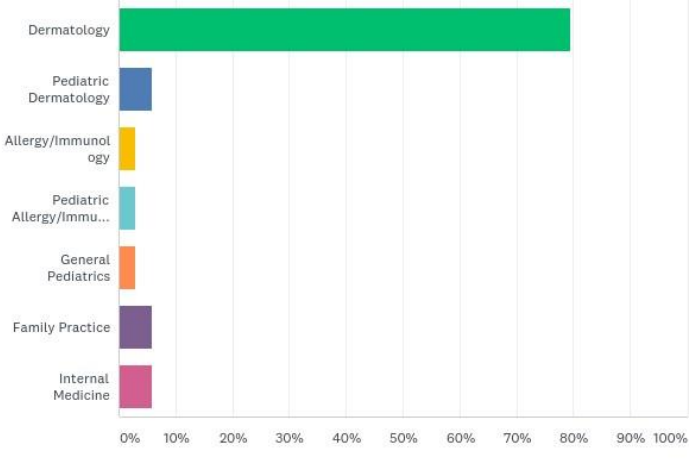


FIGURE 2. *What is your specialty?*



Dr. Michael Gold, and a few of the FMD's from the Inflammation and Immunology Department. The Dermatology Field Medical team across the United States had access to the direct care providers whom were key leaders in the field of dermatology. The project planner, in collaboration with the Practice Partner, Dr. Michael Gold developed a questionnaire to determine the effectiveness of the AD care plan. Institutional Review Board approval was obtained from the sponsoring agencies prior to implementation.

RESULTS

The evaluation of "Your Eczema Action Plan" included thirty-five survey responses from key opinion leaders in dermatology included (physicians, nurse practitioners, and physician assistants) that treat patients with AD across the United States met the project goal of 30–50 responses. The survey evaluated the providers' perceived perceptions of their use of "Your Eczema Action Care Plan" and its value to patient management.

Demographics

Forty-Six percent of the responses included Medical Doctors, 3% were Doctors of Osteopathy, 23% were Nurse Practitioner's, and 29% were Physician Assistant's. The geographic locations of survey responses in the U.S. included: Alabama, California; Colorado, Hawaii, Illinois, Indiana, Kentucky, Michigan, Mississippi, Nevada, New Hampshire, Ohio, Tennessee (Figure 1).

The years of practice ranged from 1–40 years. The average years of practice were seventeen. The specialty of providers in the survey responses included Dermatology =79%, Pediatric Dermatology= 6%, Allergy Immunology=3%, Pediatric Allergy=3%, General Pediatrics=3%, Family Practice=6%, Internal Medicine=6%, Aesthetics and Emergency Medicine were also included in other categories. Figure 2 provides a summary of response data on specialty of practice. The majority of providers, 63% responded they had used AD care plans in the past (Figure 2).

DISCUSSION

Results suggest 97% of the providers agree that the care plan improves patient education. The survey responses included how often the providers utilized the "Your Eczema Action Plan." The results identified twenty-three providers utilized the survey with every patient, 46% utilized the care plan with select patients, and 9 % rarely utilize the care plans.

Data Analysis Report

The results suggest providers used the care plan for appropriate AD patients in approximately 60% of patients. The data suggests that the number of providers that plan to continue utilizing "Your Eczema Action Plan" in practice include 97% of the providers who responded (Figure 3).

FIGURE 3. *Would you plan to continue using "Your Eczema Action Plan" in your practice?*

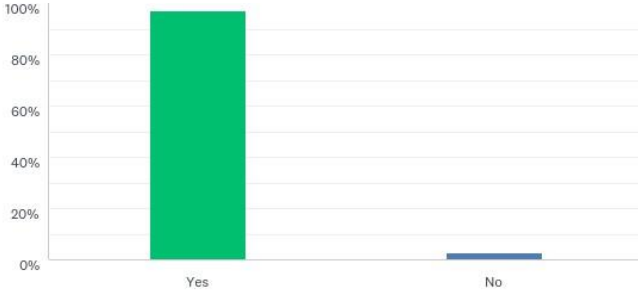
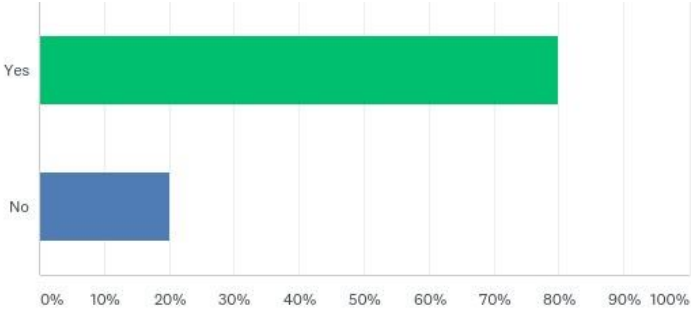


FIGURE 4. *Would you find it helpful to have something like this Eczema Action Plan implemented into your EMR system if it were possible?*



83% of the providers felt they were more comfortable in treating and educating patients with AD, using an Eczema Action Plan. The results also indicated 71% agreed that the AD care plan "Your Eczema Action Plan" decreased the amount of time needed to explain AD therapeutic regimens.

The survey responses indicated the care plan reduced the amount of time needed to deliver the equivalent amount of information to the patient from 10 minutes or greater 7%, 5-9 minutes at 27%, 2–5 minutes at 37%, and less than 2 minutes at 17%.

The data indicated 80% of the providers would find it helpful to have an Eczema Action Plan implemented into their current EMR system (Figure 4). In summary, the descriptive data indicates 85% of the survey providers feel utilizing "Your Eczema" action plan, improves patient adherence. Only 9% did not feel the AD care plan improves adherence and reduces their teaching time. Results indicated the providers felt an AD Universal Care Plan such as "Your Eczema Action Plan" if available to all providers in the U.S, would improve disease management (Figure 5).

Survey results also demonstrate that after utilizing "Your Eczema Action Plan", that Quality of Life (QOL) is improved (see Figure 6). This data emphasizes that providers' perceptions demonstrate the effectiveness of care plans in disease self-management (Figure 6).

Impact of Results

The findings from the post-test demonstrate the importance of care plan utilization in disease management in dermatology. Even though the response rate was limited, the objective was met to help providers feel more comfortable in treating and educating AD patients using an AD care plan. The results suggest that providers' perceptions demonstrate patient education, disease management, and QOL are all improved when utilizing the patient education handout "Your Eczema Action Plan." The importance of the impact in treating AD patients in dermatology is supported by the descriptive data obtained from 35 healthcare providers.

RECOMMENDATIONS

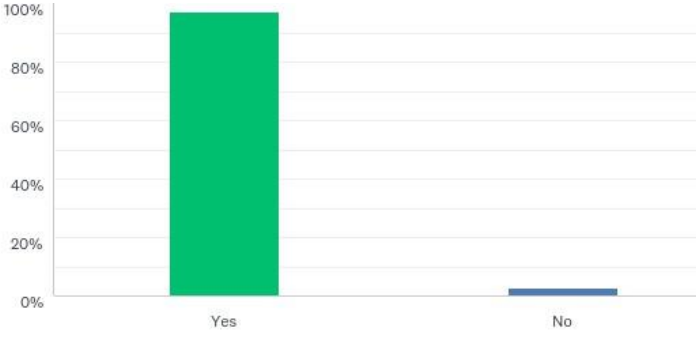
The recommendations for practice based on the outcomes of the Development and Evaluation of an AD Care Plan include the importance of care plan utilization in AD patients. The recommendations for healthcare systems based on project outcomes includes the importance of utilizing care plans in nursing and medical practice for all AD patients.

The project outcomes emphasize that providers' perceptions demonstrate the effectiveness of care plans in disease self-management such as AD. The AD Universal Care Plan such as "Your Eczema Action Plan" if available to all providers in the U.S, would improve disease management, improve quality of life in AD patients, and improve efficiency of healthcare providers delivering education.

CONCLUSION

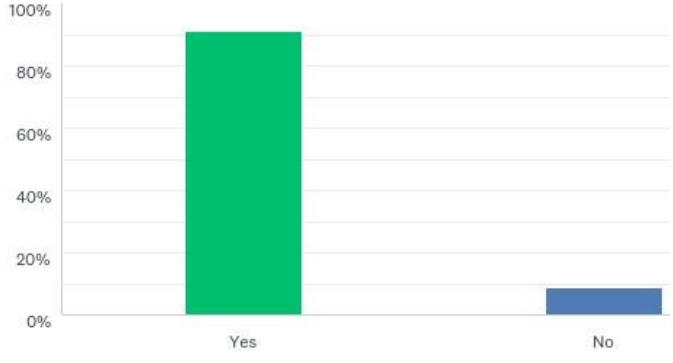
There is an unmet need for a universal atopic dermatitis (AD) care plan for providers. AD is a chronic disease. Providers feel comfortable treating chronic disease states with a guided tool or care plan in many chronic diseases.[6] Care plans used in many chronic diseases such as asthma, diabetes, arthritis, and COPD have demonstrated effectiveness in disease self-management.[1,5,8-12] The Development and Evaluation of "Your Eczema Action Plan" project demonstrates the importance of care plan utilization in AD disease management in dermatology. Results support 97.14% of providers perceive an AD Universal Care Plan such as "Your Eczema Action Plan" improve disease management (see Figure 5). The objective of the study was met to help providers feel more comfortable in treating and educating AD patients using an AD universal care plan.

FIGURE 5. *Do you feel an Atopic Dermatitis Universal Care Plan such as "Your Eczema Action Plan" if available to all providers in the U.S. treating AD, would improve disease management?*



ANSWER CHOICES	RESPONSES	
Yes	97.14%	34
No	2.86%	1
TOTAL		35

FIGURE 6. *Do you feel after utilizing "Your Eczema Action Plan", that Quality of Life is improved in patients?*



ANSWER CHOICES	RESPONSES	
Yes	91.18%	31
No	8.82%	3
TOTAL		34

DISCLOSURES

The authors declare that there are no conflicts of interest regarding the publication of this article.

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ORIGINAL ARTICLE

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Topical Agents Currently in Phase II or Phase III Trials for Atopic Dermatitis

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ABSTRACT

Mild to moderate atopic dermatitis (AD) occurs frequently in children and adults and is usually managed through the use of pharmacologic treatments, such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs), and good skin care practices. As chronic TCS or TCI can lead to the development of adverse effects, there is a need for safe, alternative treatments for patients with resistant AD. A systemic literature review was performed to examine the safety and efficacy of topical agents currently in phase II and phase III clinical trials for AD. Our team searched the databases, PubMed, Google Scholar, and ClinicalTrials.gov, on March 2020 for studies pertaining to the use of topical agents in AD. Key words included each drug (tapinarof, crisaborole, ARQ-151 cream, ruxolitinib) or "topical agents" combined with "atopic dermatitis." Articles published within the last 5 years were included as references. References within retrieved articles were also reviewed to identify potentially missed studies. A total of 24 articles were included in this review. Tapinarof, crisaborole, and ruxolitinib lead to statistically significant improvements in multiple disease severity scores. ARQ-151 cream achieved statistical significance in secondary endpoints, including vIGA-AD and EASI-75, but not in the primary endpoint of the study. All topical agents were well-tolerated by study participants. The findings demonstrate that tapinarof, crisaborole, ARQ-151 cream, and ruxolitinib are safe, effective treatment options for patients with mild to moderate AD.

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INTRODUCTION

Atopic dermatitis (AD) is a pruritic, inflammatory skin disease that affects approximately 5–30% of children and 2–10% of adults.[1-3] The pathogenesis of AD involves a complex interplay of skin barrier defects, dysregulation of the innate immune response, defects in the adaptive immune response, Th2 immune polarization, and an altered skin microbiome.[2] In most cases, AD is successfully managed through elimination of exacerbating factors, good skin care practices, and topical therapies.[3,4] Long term use of topical corticosteroids (TCS), which are considered to be first-line treatment for AD flares, carries the risks of skin atrophy, local skin reactions (telangiectasia, striae and purpura, focal hypertrichosis, hypopigmentation, perioral dermatitis), percutaneous absorption, and rebound flares with discontinued use.[3-5] Topical calcineurin inhibitors (TCIs), the second-line treatment for AD, comes with a FDA Black Box Warning based on the theoretical risk of lymphoma or cutaneous cancer from systemic calcineurin inhibitors in animal studies and transplant patients.[4,5] Therefore, there is a need for alternative safe, long-term treatments for patients with resistant AD in whom chronic TCS or TCI use may lead to development of adverse effects.

In recent years, a better understanding of the underlying pathologic mechanisms in AD has led to the development of novel, targeted therapies. In 2020, the FDA approved the use of Eucrisa™ (crisaborole) for topical treatment of mild-to-moderate AD in patients 3 months of age and older. Novel topical therapies— tapinarof, ARQ-151 cream, and ruxolitinib— are promising treatments options currently in investigation for AD. The purpose of this review is to discuss these four agents in depth and the current evidence behind their use.

MATERIALS AND METHODS

Tapinarof

Tapinarof (GSK2894512 cream, WBI-1001, or Benvitimod™) is a therapeutic aryl hydrocarbon receptor (AHr) modulating agent under investigation for the treatment of AD and plaque psoriasis.[6] Tapinarof's pharmacologic effect is primarily mediated through agonism of AHr, a cytosolic ligand-activated receptor that affects Th2 cytokine and epidermal barrier gene expression in human keratinocytes.[7] AHr regulates innate and adaptive immune responses in the skin and is critical in the development and maintenance of the skin barriers, especially in response to noxious stimuli.[7] In addition to anti-inflammatory properties, tapinarof also exhibits antioxidant properties through the activation of nuclear (erythroid-derived 2)-like 2 pathway.[7,8]

In a double blind, placebo-controlled, randomized phase IIa trial, the safety and efficacy of twice daily (BID) 0.5% tapinarof cream

and 1.0% tapinarof cream was assessed in participants over the course of 4 weeks. Eligible participants had 1–10% of their body surface area (BSA) affected by AD (excluding the face, groin, scalp, and genital regions), an Eczema Area and Severity Index (EASI) score of <12, and an IGA score of 2 or 3.[9] After 4 weeks of treatment, both 0.5% and 1.0% tapinarof creams demonstrated significant reductions in EASI (59.3% and 54.9%, respectively, compared with 7.1% for vehicle; *P*=.03), Scoring Atopic Dermatitis (SCORAD) (56.2% and 50.1%, respectively, compared with 18.4% for vehicle; *P*=.04), IGA (38.9% and 45.8%, respectively, compared with 5.6% for vehicle; *P*=.003), pruritus scores (74.0% and 56.0%, respectively, compared with 30.2% for vehicle; *P*=.04), and affected BSA (64.4% and 57.7%, respectively, compared with 10.8% for vehicle; *P*=.03).[9] In addition, 50% of subjects in both treatment arms achieved an IGA score of 0 (clear) or 1 (almost clear) by week 4 compared to 8.3% for the vehicle arm.[9] At both 0.5% and 1.0% concentrations, tapinarof cream was well-tolerated. Transient skin reactions (papules, pruritus) were mild, and incidence was similar between tapinarof and vehicle groups. There were no serious adverse events (AEs) and no treatment discontinuations resulting from AEs.[9]

In a double-blind, vehicle-controlled, randomized phase IIb trial, the safety and efficacy of tapinarof was assessed in patients aged 12–65 years, with BSA involvement between 5%–35%, and an Investigator's Global Assessment (IGA) score of 3 or higher at baseline.[10] The primary endpoints of the study included an IGA score of clear or almost clear (0 or 1) and a minimum 2-grade improvement (treatment success) at week 12. Important secondary endpoints included a 75% or greater improvement in EASI score and reduction of numeric rating scale (NRS) score for itch from baseline. At week 12, the rates of treatment success with tapinarof cream were 53% (1% concentration BID), 46% (1% concentration once daily (QD), 37% (0.5% concentration BID), and 34% (0.5% concentration QD) compared to 24% (vehicle BID), and 28% (vehicle QD) in the vehicle control.[10] Treatment success was maintained for 4 weeks after the end of tapinarof treatment. Although the rate of treatment emergent adverse events (TEAEs) was higher with tapinarof (56%) than with the vehicle (41%), the events were mild to moderate in severity.[10]

PDE4 Inhibitors: Crisaborole and ARQ-151 Cream

Crisaborole (Eucrisa™) and ARQ-151 cream (roflumilast cream) are small molecule inhibitors of phosphodiesterase 4 (PDE-4), a cyclic adenosine monophosphate (cAMP) degrading enzyme that modulates inflammation and epithelial integrity.[11] PDE-4, expressed in the leukocytes of AD patients, is associated with higher expression of proinflammatory mediators and decreased expression of anti-inflammatory mediator, IL-10, through hydrolyzation of cAMP.[3,12] PDE-4 inhibitors suppress both Th2 and Th1 cytokines and therefore, have an anti-inflammatory effect in both the Th2 dominated acute phase and Th1 dominated chronic phase of AD.[13]

Crisaborole

In two randomized, vehicle-controlled, double-blind phase III studies (AD-301 and AD-302), the safety and efficacy of crisaborole BID application was assessed in patients ≥2 years of age with an Investigator's Static Global Assessment (ISGA) score of 2 (mild) or 3 (moderate) and >5% BSA involvement (excluding scalp). The mean age of patients in the crisaborole ointment treatment groups was 12 and 12.6 in both studies.[14] The primary endpoint of the study was the percentage of patients who achieved an ISGA score 0 (clear) or 1 (almost clear) with a >2-grade improvement from baseline by day 29. Key secondary endpoints included the proportion of patients with an ISGA score of 0 or 1 at day 29, time to success in ISGA score, and reduction in pruritus severity and signs of AD.[14] By day 29, more crisaborole-treated patients achieved ISGA score success (IGA score of 0 or 1 and >2-grade improvement) than vehicle-treated patients in both studies (AD-301: 32.8% vs 25.4%, *P*= .038; AD-302: 31.4% vs 18.0%, *P*<.001).[14,15] Crisaborole-treated patients achieved success in ISGA score earlier than vehicle-treated patients (*P*<.001).[14,15] More crisaborole-treated patients also achieved ISGA scores of clear 0 or 1 by day 29 than vehicle-treated patients (AD-301: 51.7% vs 40.6%, *P*= .005; AD-302: 48.5% vs 29.7%, *P*<.001).[14,15] Pooled data between the two studies demonstrated that more crisaborole-treated patients achieved improvements in pruritus compared to vehicle-treated patients (pooled data, days 8, 15, 22: *P*<.001; day 29: *P*=.002), with improvements seen earlier in crisaborole-treated patients than vehicle-treated patients (1.37 vs 1.70 days, *P*=.001).[14,15] Pooled data also demonstrated that a greater proportion of crisaborole-treated patients than vehicle-treated patients experienced improvements in disease severity, as measured by reduction in sign and symptoms such as erythema, exudation, excoriation, induration/papulation, and lichenification (*P*<0.002).[14,15] A secondary analysis of both phase III studies by Yosipovitch et al confirmed that significantly more patients experienced early improvement in pruritus with crisaborole than with the vehicle (56.6% vs 39.5%; *P*<0.001).[15,16]

Crisaborole was well-tolerated, as the majority of TEAEs were mild to moderate in severity, and most were considered unrelated to treatment. Treatment-related AEs with crisaborole included application-site pain (burning or stinging), which occurred in 4.4% of crisaborole-treated patients compared to 1.2% of vehicle-treated patients.[14,15] The rates of study discontinuation due to AEs were identical between crisaborole and vehicle treatment groups.[14,15] The long-term safety of crisaborole was confirmed in a multicenter, open-label, 48-week safety study (AD-303) with patients who completed AD-301 and AD-302 phase III studies without experiencing crisaborole treatment-related AEs or serious AEs.[15,17] Over 48 weeks, only 10.3% of patients experienced treatment-related AEs. Of these, the majority of AEs were considered mild (51.2%) or moderate (44.6%) in severity.[15,17] The most common AEs reported were atopic

dermatitis (3.1%), application-site pain (2.3%), and application-site infection (1.2%).[15,17] There was no change in the frequency of AEs throughout the study. Rescue therapy with a TCS or TCI was required in 22.2% of patients, with the majority (79%) resuming crisaborole after the end of rescue therapy.[15,17]

In a multicenter, open-label, single-arm, phase IV study (CrisADe CARE 1), the safety, effectiveness, and pharmacokinetics (PK) of crisaborole BID application was assessed in infants aged 3 to <24 months with an ISGA score of 2 (mild) or 3 (moderate) and BSA involvement of ≥5% for 28 days. A subgroup with clinical diagnoses of moderate AD and BSA involvement of >35% (excluding the scalp) participated in PK assessments.[18] The primary endpoints of the study were the number of patients with TEAEs, severe AEs, and with clinically significant changes from baseline in height, weight, vital signs, electrocardiogram, and clinical laboratory parameters. TEAEs were reported by 64.2% of patients, 98.9% of which were rated as mild or moderate in severity.[18] TEAEs were considered treatment-related for 16.1% of patients, and the most frequently reported were application-site pain (3.6%), application-site discomfort (2.9%), and erythema (2.9%).[18] In addition, no safety concerns were identified in clinical laboratory findings of weight, height, electrocardiograms, or vital signs.[18] In terms of efficacy, 30.2% of patients achieved ISGA success (ISGA score of 0 (clear) or 1 (almost clear) with ≥ 2-grade improvement from baseline) by day 29.[18] Similarly, 47% of patients achieved an ISGA score of 0 (clear) or 1 (almost clear) by day 29.[18] These findings are consistent with rates reported for crisaborole-treated patients aged ≥2 years in pivotal phase III studies. Additionally, improvements in EASI score (by 57.5%) and Patient-Oriented Eczema Measure total score (by 8.5%) were observed by day 29.[18] PK analyses demonstrated that crisaborole exposure among infants in this study was comparable with that in patients aged ≥2 years in previous phase III studies.[18]

ARQ-151 Cream

In a double-blind, vehicle-controlled, proof-of-concept phase II study, the safety and efficacy of ARQ-151 cream was assessed in patients aged >12 years with mild to moderate AD involving 1.5%–35% of BSA. Patients were randomized to receive 0.15% ARQ-151 cream, 0.05% ARQ-151 cream, or vehicle QD for 4 weeks.[19] After 4 weeks of once-daily treatment, neither treatment arm achieved statistical significance in the study's primary endpoint, the mean reduction in EASI total score, compared to the vehicle arm.[19] On the secondary endpoint, the mean percent change from baseline in EASI Total Score, 0.15% ARQ-151 cream demonstrated a statistically significant improvement compared to the vehicle (72.3% vs 55.8%, *P*=0.049). Both treatment arms also achieved treatment efficacy as measured by EASI-75 (0.15% ARQ-151 cream: 59.1% vs vehicle: 31.1%, *P*=0.009 and ARQ-151 0.05%: 52.3% vs vehicle: 31.1%, *P*=0.045).[19] ARQ-151 0.15% cream also demonstrated a statistically significant improvement compared to the vehicle in the percentage of patients achieving an assessment of clear or almost clear (52.3% vs 31.1%, *P*=0.040) in the Validated Investigator Global Assessment–Atopic Dermatitis (vIGA-AD).[19] Both doses of ARQ-151 cream were well-tolerated. The incidence of TEAEs and application site reactions were low (<5%) and similar between active treatment arms and the vehicle arm. TEAEs were mild to moderate in severity and there was only one serious AE, which was unrelated to treatment.[19]

Ruxolitinib

Ruxolitinib (RUX) is a second-generation selective inhibitor of Janus kinase (JAK)1 and JAK2, intracellular signal transducers and activators of transcription-signaling events that regulate the expression of type 2 cytokines— IL-4, IL-5, IL-13, IL-22, IL-23, IL-31—associated with AD.[20,21] JAK inhibition has been shown to alleviate chronic itch directed from neuronal responses by type 2 cytokine signaling.[21,22] JAK inhibition also improves skin barrier function through the regulation of filaggrin, an essential skin barrier protein.[21,23] Furthermore, JAK inhibition represents an opportunity to target the diverse pathogenic pathways involved in AD.

In two randomized, vehicle-controlled phase III studies, the safety and efficacy of ruxolitinib cream was assessed in adolescent and adult patients (age ≥12 years) diagnosed with AD for at least two years, an IGA score of 2 to 3, and BSA involvement of 3-20% (excluding the scalp). Patients in both studies were randomized to receive one of following treatments for 8 weeks: 0.75% ruxolitinib cream BID, 1.5% ruxolitinib cream BID, or non-medicated cream (vehicle).[24] The primary endpoint of both TRuE-AD1 and TRuE-AD2 was the proportion of participants achieving an Investigator's Global Assessment Treatment Success (IGA-TS), defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline, by week 8. Secondary endpoints in both trials included the proportion of participants who achieved a ≥75% improvement in Eczema Area and Severity Index (EASI-75) score and the proportion of participants with a ≥ 4-point improvement in Itch Numerical Rating Scale (NRS4) score by week 8.[24] In TRuE-AD1, 50.0% of patients treated with 0.75% ruxolitinib cream and 53.8% of patients treated with 1.5% ruxolitinib cream achieved IGA-TS, compared to 15.1% of patients in the vehicle control (*P*<0.0001 and *P*<0.0001, respectively).[24] In addition, 56.0% of patients treated with 0.75% ruxolitinib cream and 62.1% of patients treated with 1.5% ruxolitinib cream achieved EASI-75, compared to 24.6% of patients in the vehicle control (*P*<0.0001 and *P*<0.0001, respectively).[24] In TRuE-AD2, 39.0% of patients treated with 0.75% ruxolitinib cream and 51.3% of patients treated with 1.5% ruxolitinib cream achieved IGA-TS, compared to 7.6% of patients in the vehicle control (*P*< 0.0001 and *P*<0.0001, respectively).[24] In addition, 51.5% of patients treated with 0.75% ruxolitinib cream and 61.8% of

patients treated with 1.5% ruxolitinib cream achieved EASI-75, compared to 14.4% of patients in the vehicle control ($P< 0.0001$ and $P<0.0001$, respectively).[24] In both studies, a statistically-significant difference in itch reduction, as measured by the NRS4, was observed for both treatment groups (0.75% and 1.5% ruxolitinib cream) compared to the vehicle control.[24] The overall rate of TEAEs for both studies was comparable between both treatment (0.75% and 1.5% ruxolitinib cream) and vehicle control groups (29.4%, 26.3%, and 33.6%, respectively). The rate of serious AEs was 0.8% and 0.6% for 0.75% and 1.5% ruxolitinib creams, respectively, and 0.8% for the vehicle control.[24] Long-term safety is currently being evaluated for both studies, as part of a 44-week extension period.

CONCLUSION

AD is a chronic, relapsing immune-mediated disease driven by a number of genetic, immunologic, and environmental factors. There is a need for safe, long-term topical treatments for difficult-to-treat, mild to moderate AD. The latest available treatment options either approved by the FDA for AD— Eucrisa™ (crisaborole)— or currently investigated for AD— tapinarof, ARQ-151 cream, and ruxolitinib— are effective, well-tolerated treatment options for mild to moderate AD in children and adults.

DISCLOSURES

Dr. Wu is or has been an investigator, consultant, or speaker for AbbVie, Almirall, Amgen, Arcutis, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Dr. Reddy's Laboratories, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Regeneron, Sanofi Genzyme, Sun Pharmaceutical, UCB, Valeant Pharmaceuticals North America LLC.

Ms. Uppal, Mr. Kearns, and Ms. Chat have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Outcome Disparities Among Men and Women With COVID-19: An Analysis of the New York City Population Cohort

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ABSTRACT

Background: Growing evidence suggests a possible sex disparity in COVID-19 disease related outcomes.

Objective: To explore the sex disparity in COVID-19 cases and outcomes using New York City (NYC) population level data.

Setting: NYC surveillance data from February 29 to June 12, 2020.

Participants: Individuals tested for COVID-19 in metropolitan NYC.

Outcome Measurements and Statistical Analysis: Outcomes of interest included rates of COVID-19 case positivity, hospitalization and death. Relative risks and case fatality rates were computed for all outcomes based on sex and were stratified by age groups.

Results and Limitations: 911,310 individuals were included, of whom 434,273 (47.65%) were male and 477,037 (52.35%) were female. Men represented the majority of positive cases (n=106,275, 51.36%), a majority of hospitalizations (n=29,847, 56.44%), and a majority of deaths (n=13,054, 59.23%). Following population level adjustments for age and sex, testing rates of men and women were equivalent. The majority of positive cases and hospitalizations occurred in men for all age groups except age >75 years, and death was more likely in men of all age groups. Men were at a statistically significant greater relative risk of case positivity, hospitalization, and death across all age groups except those <18 years of age. The most significant difference for case positivity was observed in the 65–74 age group (RR 1.22, 95% CI 1.19–1.24), for hospitalization in the 45–65 age group (RR 1.85, 95% 1.80–1.90), and for death in the 18–44 age group (RR 3.30, 95% CI 2.82–3.87). Case fatality rates were greater for men in all age-matched comparisons to women. Limitations include the use of an evolving surveillance data set and absence of further demographic characteristics such as ethnographic data.

Conclusion: Men have higher rates of COVID-19 positivity, hospitalization, and death despite greater testing of women; this trend remains after stratification by age.

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INTRODUCTION

COVID-19 is caused by a coronavirus first identified after an outbreak of atypical pneumonia in Wuhan, China in December 2019. On January 7, 2020 the World Health Organization (WHO) officially recognized this novel virus as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).[1] The spread of COVID-19 has been rapid; by March 11, 2020 the WHO declared COVID-19 a pandemic.[1] By July 2020, worldwide cases surpassed 12 million, with more than 550,000 deaths. In the United States, total cases exceed 3 million with more than 130,000 deaths.[2]

Early in the pandemic, researchers searched for predictors of viral infection and disease severity. This work suggested that increased age, ethnicity, and certain comorbidities were likely related to adverse outcomes.[3] Evidence of a sex disparity also became apparent.[4] Worldwide, differential outcomes for men were observed to varying degrees.[5] To date, no consensus on this observation exists, nor are there any definitive explanations for a possible sex discrepancy.

Currently, New York State leads the United States in both COVID-19 cases and deaths; NYC was specifically deemed a COVID-19 epicenter. We analyzed the NYC citywide dataset to further explore the sex disparity related to COVID-19. We report sex and age stratified data on testing rates together with COVID-19 related outcomes including positive cases, hospitalizations and deaths in almost one million individuals.

MATERIALS AND METHODS

Study Population

Data on COVID-19 test results were collected by NYC using syndromic and reportable disease surveillance strategies from February 29 (first confirmed case March 1, 2020) to June 12, 2020. After IRB approval, the NYC Department of Health and Mental Hygiene (NYCDOHMH) provided COVID-19 sex-specific age-matched data that included total number of tests, cases, hospitalizations, and deaths. Separately, data on the presence of unspecified comorbid conditions were collected through May 16, 2020 but were only available by gender and were not age-matched.[6] Only individuals with first-time viral tests were included, and those with unknown sex or age data were excluded.

Exposure and Covariates

Exposure of interest was self-reported sex (male or female only; transgender and gender-nonconforming were excluded). Data were stratified into age categories (0–17, 18–44, 45–64, 65–74, and 75+ years) per the NYCDOHMH based on trend similarity within each subgroup.

Outcomes

Outcomes of interest were COVID-19 case positivity, hospitalization rate and death rate. Cases included any New York City resident tested and/or treated in NYC and were defined based on positive nasopharyngeal swabs for SARS-CoV-2. Hospitalizations included reports from hospitals, hospital system and Regional Health Information Organizations, and additional sources were used when data were incomplete. Deaths were a combination of confirmed (NYC resident with positive COVID-19 test) and probable (NYC resident, or pending residency, with no known positive COVID-19 test but death certificate lists COVID-19 or an equivalent as cause of death) and were obtained from the Health Department's surveillance database.

Statistical Analysis

Case positivity, hospitalization and death rates were tabulated utilizing total tests as the denominator and were sex- and age-stratified. Rates per 100,000 individuals in NYC were further computed using 2018 United States Census Bureau data [7]. Relative risks (RR) of positive cases, hospitalization and death were calculated and stratified by age and sex. Relative risks for comorbidities were only calculated by gender. Sensitivity analyses were completed for hospitalization and death utilizing positive cases as the denominator. Case fatality rates (CFR) were calculated as percentages using deaths (probable and confirmed) as a proportion of the total number of positive cases. Missing data were not included, and therefore only complete case analysis was performed. Statistical significance was evaluated at an alpha of 0.05 and model estimates are presented with 95% confidence intervals. All analyses were performed using Stata v14.

RESULTS

A total of 914,541 first-time tests were provided, and after excluding those with unknown age, sex or outcome data, 911,310 (99.6%) individuals were analyzed. Sex and/or age were not reported in <0.5% of tests, cases, hospitalizations or death. Of the 911,310 tested individuals, 434,273 (47.65%) were male and 477,037 (52.35%) were female (Table 1). Overall negative testing rates were greater in women (53.44%) compared to men (46.56%). Test positive rates were 24.47% in men versus 21.10% in women (22.71% overall). The majority of cases, hospitalizations and deaths occurred in men; 51.36% (n=106,275), 56.44% (n=29,847), and 59.23% (n=13,054), respectively.

When stratified by age (Figures 1 and 2, Table 1), in all categories except those aged 0-17, the majority of tests were completed in women. With respect to cases, the majority occurred in men (except those >75 years), with the most significant sex difference observed in the 65–74 age group. Hospitalizations demonstrated a similar pattern with the greatest difference observed in the 45–64 age cohort (62.63%, n=11,189). The likelihood of COVID-19 death, in every age category, was higher in men, with the greatest differences in 18–44 and 45–64 age groups (74.35%, n=600 and 69.01%, n=3365, respectively).

Using gender-stratified population level data (per 100,000), overall rates of testing were almost identical in men and women, and all three outcomes of interest were greater in men (Table 1). Further stratification by age revealed that every age category displayed greater rates of case positivity, hospitalization and death for men compared to women.

The relative risk of case positivity, hospitalization and death was significantly higher in men when compared to women (RR 1.59, 95%CI 1.55–1.64 for death, Table 1). This difference persisted after age-stratification (Table 1). The greatest difference in case positivity was observed in men aged 65–74 years (RR 1.22, 95%CI 1.19–1.24). The greatest difference in hospitalization was observed in men aged 45–64 years (RR 1.85, 95% 1.80–1.90), while the greatest differences in death were in men aged 18–44 years and 45–64 (RR 3.30, 95% CI 2.82–3.87, and RR 2.46, 95%CI 2.31–2.61, respectively). For all remaining age-stratified categories, except for those aged 0-17, and for each outcome, men demonstrated a statistically significant increased risk compared to the age-matched group of women.

Hospitalizations and deaths due to COVID-19 in men and women were also compared to the total number of positive tests as opposed to the total number of tests (Table 2). Similarly, almost all age-matched comparisons demonstrated greater risks for men compared to women.

Analysis of comorbidity data (Table 3) revealed 78.5% of men who endorsed a comorbidity in comparison to 80.1% of women.

TABLE 1.

Total Number of Individuals With COVID-19 Tests, Rates per 100,000 Individuals, and Relative Risk of Outcomes of Male vs Female Sex Stratified by Age in NYC Until June 12, 2020

	Male		Female			
	(n, %)	Per 100,000	(n, %)	Per 100,000	Relative Risk	95% CI
Total Testing (n=911,310)						
0–17	24,154 (5.56%)	2713	20,508 (4.30%)	2394	–	–
18–44	177,978 (40.98%)	10923	202,790 (42.51%)	11721	–	–
45–64	149,224 (34.36%)	15317	164,617 (34.51%)	15194	–	–
65–74	49,063 (11.30%)	15788	49,413 (10.36%)	12518	–	–
75+	33,854 (7.80%)	16795	39,709 (8.32%)	11820	–	–
Overall	**434,273**	**10840**	**477,037**	**10860**	**–**	**–**
Tests Negative (n=704,394)						
0–17	21,033 (6.41%)	2363	17,895 (4.75%)	2089	–	–
18–44	139,015 (42.38%)	8532	165,748 (44.04%)	9580	–	–
45–64	110,540 (33.70%)	11346	128,053 (34.02%)	11819	–	–
65–74	35,066 (10.69%)	11284	37,817 (10.05%)	9580	–	–
75+	22,344 (6.81%)	11085	26,883 (7.14%)	8002	–	–
Overall	**327,998**	**8187**	**376,396**	**8569**	**–**	**–**
Cases (n=206,916)						
0–17	3,121 (2.94%)	351	2,613 (2.60%)	305	1.01	0.97–1.06
18–44	38,963 (36.66%)	2391	37,042 (36.81%)	2141	1.20	1.18–2.14
45–64	38,684 (36.40%)	3971	36,564 (36.33%)	3375	1.17	1.15–1.18
65–74	13,997 (13.17%)	4504	11,596 (11.52%)	2938	1.22	1.19–1.24
75+	11,510 (10.83%)	5710	12,826 (12.74%)	3818	1.05	1.03–1.07
Overall	**106,275**	**2653**	**100,641**	**2291**	**1.16**	**1.15–1.17**
Hospitalizations (n=52,883)						
0–17	282 (0.94%)	32	230 (1.00%)	27	1.04	0.88–1.23
18–44	4,334 (14.52%)	266	4,051 (17.59%)	234	1.22	1.17–1.27
45–64	11,189 (37.49%)	1148	6,675 (28.98%)	616	1.85	1.80–1.90
65–74	6,914 (23.16%)	2225	4,779 (20.75%)	1211	1.46	1.41–1.51
75+	7,128 (23.88%)	3536	7,301 (31.69%)	2173	1.15	1.11–1.18
Overall	**29,847**	**745**	**23,036**	**524**	**1.42**	**1.40–1.44**
Deaths (Confirmed and Probable) (n=22,038)						
0–17	9 (0.07%)	1	5 (0.06%)	1	1.53	0.51–4.56
18–44	600 (4.60%)	37	207 (2.30%)	12	3.30	2.82–3.87
45–64	3,365 (25.78%)	345	1,511 (16.82%)	139	2.46	2.31–2.61
65–74	3,469 (26.57%)	1116	1,874 (20.86%)	475	1.86	1.76–1.97
75+	5,611 (42.98%)	2784	5,387 (59.96%)	1604	1.22	1.18–1.26
Overall	**13,054**	**326**	**8,984**	**205**	**1.59**	**1.55–1.64**

FIGURE 1A. Total testing of COVID-19 in NYC by age and sex.

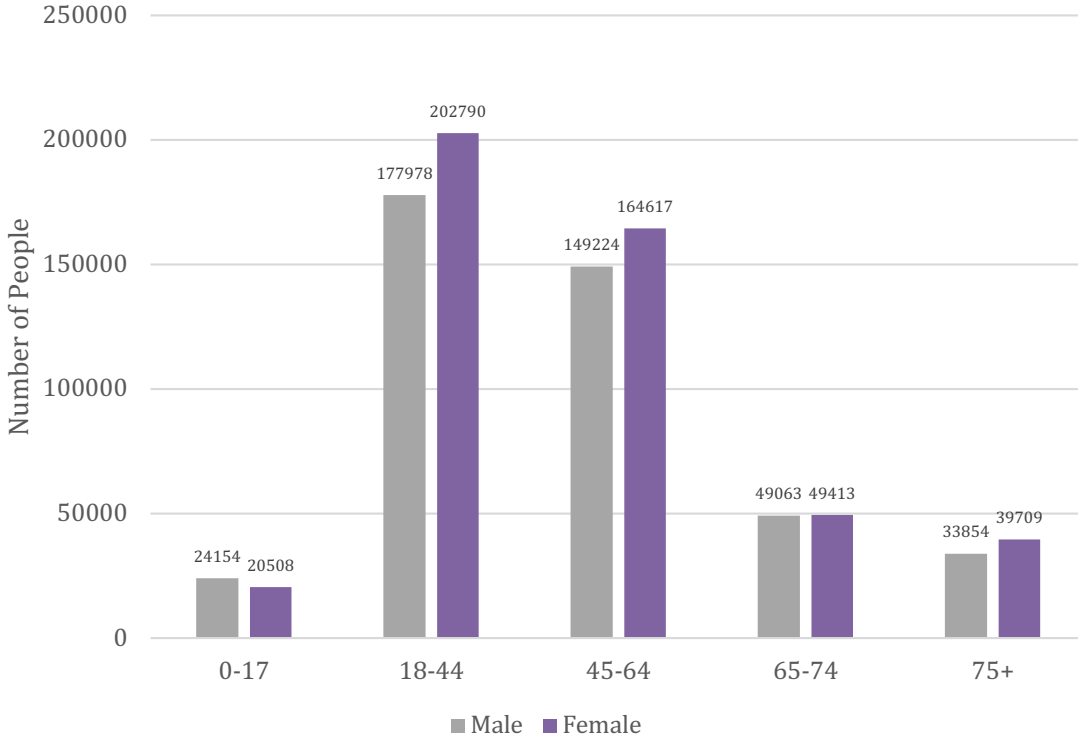

FIGURE 1B. Total cases of COVID-19 in NYC by age and sex.

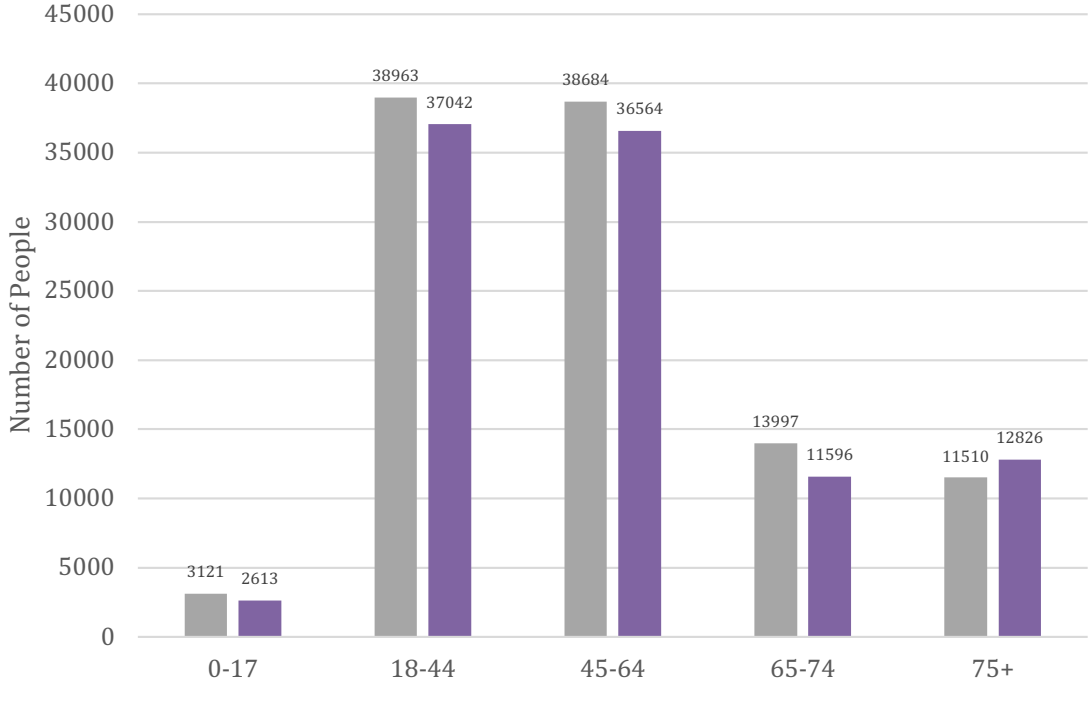

FIGURE 2A. Total hospitalizations of COVID-19 in NYC by age and sex.

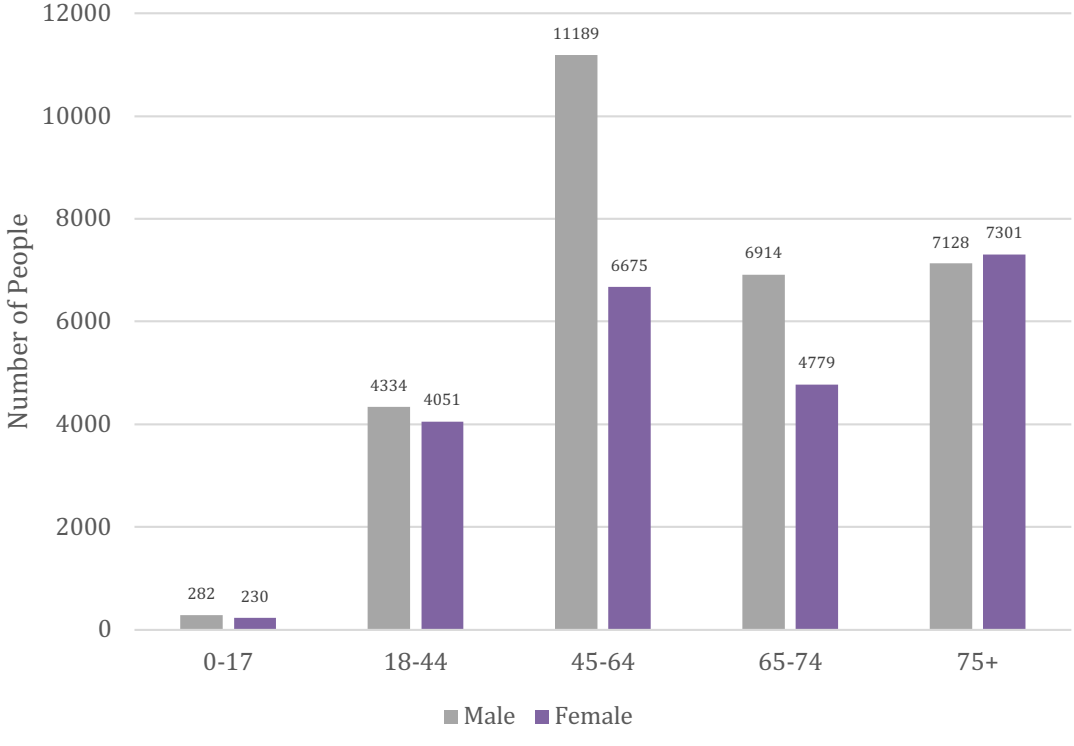

FIGURE 2B. Total deaths of COVID-19 in NYC by age and sex.

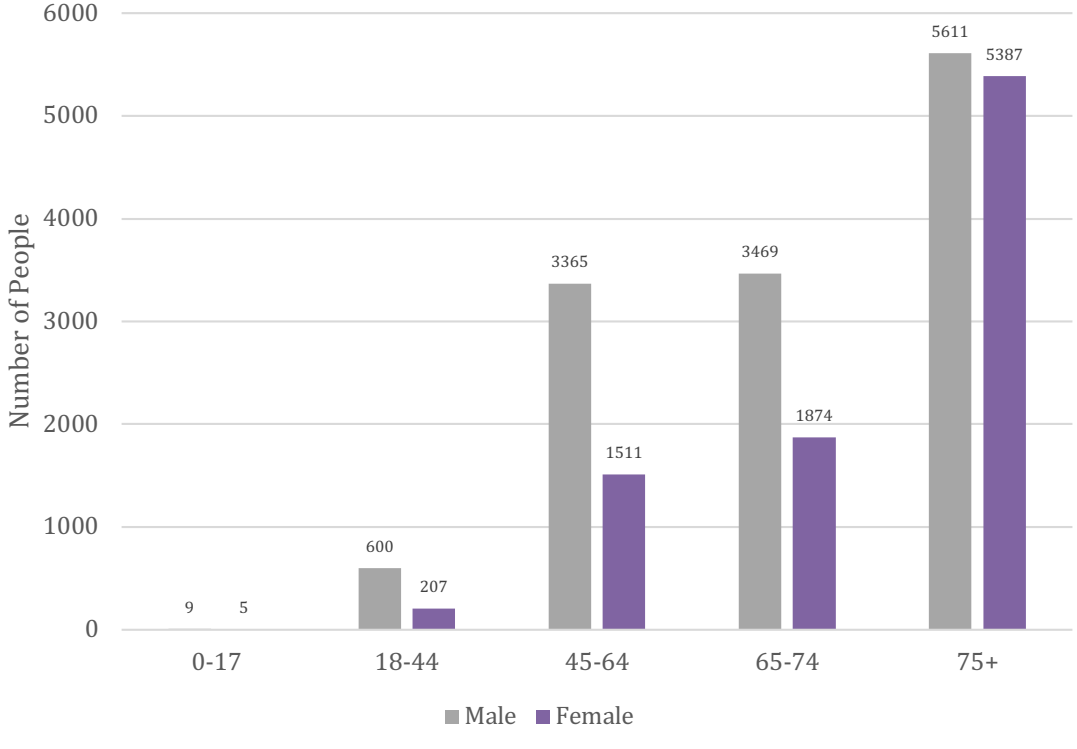

TABLE 2.

Relative Risks of COVID Outcomes of Male vs Female Sex Stratified by Age Groups Assessing Positive Cases Only in NYC Until June 12, 2020

	Hospitalizations		Death	
Age	Relative Risk	95% CI	Relative Risk	Per 100,000
0–17	1.03	0.87–1.21	1.51	0.51–4.49
18–44	1.02	0.97–1.06	2.76	2.35–3.23
45–64	1.58	1.54–1.63	2.10	1.98–2.32
65–74	1.20	1.17–1.23	1.53	1.46–1.61
75+	1.09	1.07–1.11	1.16	1.13–1.19
Overall	**1.23**	**1.21–1.24**	**1.37**	**1.34–1.41**

TABLE 3.

Rates and Relative Risk of Comorbidities in COVID-19 Related Deaths of Male vs Female

	Male (n, %) (n=9,634)	Female (n, %) (n=6,223)	Relative Risk	95% CI
Deaths as of May 16, 2020 (15,857)*	--	--	--	--
Underlying Conditions**	7,563 (78.50%)	4,985 (80.11%)	0.99	(0.99–0.99)
No Underlying Conditions	85 (0.88%)	11 (0.18%)	–	–
Unknown	1,986 (20.62%)	1,227 (19.71%)	–	–
Overall	**9,634**	**8,223**	**--**	**--**

*Sex data missing for n=3
**At least one of: diabetes, lung disease, cancer, immunodeficiency, heart disease, hypertension, asthma, kidney disease, gastrointestinal/liver disease, and obesity.

Data were missing for almost 20% of each gender group. The relative risk of having a comorbidity was 0.99 (95%CI 0.99–0.99) when comparing men and women dying from COVID-19.

The case fatality rate for the entire cohort was 10.6% (Table 4). Men had a greater CFR overall compared to women (12.28% vs 8.93%). In every age category, men had higher CFRs compared to age-matched female counterparts with the most significant difference in the 65–74 age category (24.78% in men versus 16.16% in women).

DISCUSSION

The COVID-19 pandemic has had an immeasurable impact, affecting healthcare systems, the global economy, and society as a whole. Exploration of trends within the existing COVID-19 data may guide directions for further study and novel treatment development. Our analysis demonstrates that despite higher absolute rates of testing in women in NYC, men in almost every age group had higher rates of test positivity, hospitalization and death. These findings persist after stratification for age. Our findings represent the largest current COVID-19 series of age matched data from a metropolitan region and elaborate upon trends observed in other countries across the globe.[5]

TABLE 4.

Case-Fatality Rates of COVID-19 in Males and Females in NYC Until June 12, 2020 Stratified by Age

0–17	0.24	0.29	0.19	–
18–44	**1.06**	**1.54**	**0.56**	--
45–64	**6.48**	**8.70**	**4.13**	
65–74	**20.88**	**24.78**	**16.16**	
75+	**45.19**	**48.75**	**42.00**	
Overall	**10.65**	**12.28**	**8.93**	

While our data represent a single metropolitan region (NYC), they mirror data from over 50 countries across six continents. In all but one country (Portugal), rates of death were equivalent or greater in men versus women, with an estimated 60% increased risk of severe illness or death.[5] Interestingly, many European countries report increased rates of female case positivity.[5,8] Larger datasets from other COVID-19 epicenters, Italy and China, demonstrate increased case numbers and poorer outcomes in men, but this may be confounded by comorbidities and lifestyle behaviors.[8]

Men aged 18–44, 45–64, and 65–74 were more likely than age matched women to be hospitalized or die as a result of COVID. This may be attributable to a sex-based physiologic difference in the course of the disease; this may be hormonal and/or non-hormonal, but also may be due to the underlying mechanism of disease. Pathophysiologically, SARS-CoV-2 viral spike proteins bind to the angiotensin converting enzyme-2 (ACE2) receptor, and are primed by acellular serine protease (TMPRSS2), ultimately facilitating entry into cells.[9] Studies demonstrate ACE2 and TMPRSS2 expression throughout the body, including the prostate and testis.[10] ACE2 expression is controlled by the X-chromosome, and therefore X-linked gene inactivation in women may be relevant.[11] ACE2 expression within the testis occurs in both Sertoli and Leydig cells as well as in spermatogonia and spermatids.[10] TMPRSS2 gene fusions (TMPRSS2-ERG) are involved in the development and progression of some prostate cancers.[12] Expression levels of both ACE2 and TMPRSS2 were detected at low levels in the testis, but co-expression was less than <0.1% suggesting that direct entry into testis was unlikely to occur.[13] In contrast, testicular or scrotal discomfort concerning for viral orchitis is reported with COVID-19. This condition was also reported with the original SARS coronavirus.[13,14] There is limited data regarding viral positivity in the testis, and no studies have assessed viral shedding in extra-prostatic secretions.[15,16] Overall, this suggests that ACE2 and TMPRSS2 expression in male specific organs may not provide an adequate explanation for this observed sex disparity.

Younger men in our series displayed a greater magnitude relative risk of death (age 18–44) and hospitalization (age 45–64) suggesting a possible differential disease course secondary to circulating androgen levels. The androgen receptor is a gene promoter of both gene transcription and expression of TMPRSS2.[17] Men with hyper-androgenic states, including male pattern baldness, comprised 71% of a series of COVID-19 hospitalized men.[18] The androgen receptor is composed of various lengths of CAG repeats which confer differential expression levels; this finding in men has been speculated as an explanation of ethnic differences in COVID-19 deaths.[19] Androgen depravation therapy (ADT) may confer a differential response to SARS-CoV-2 infection as evidenced by a large study demonstrating an approximate four-fold decrease in odds of case positivity and disease severity in men on ADT compared to controls.[20] Ongoing randomized trials are exploring the impact of ADT on COVID-19 outcomes including a non-steroidal anti-androgen, bicalutamide and a gonadotropin releasing hormone antagonist, degarelix (ClinicalTrials.gov NCT04374279 and NCT04397718). One study implied that 5-alpha reductase inhibitors, which prevent the conversion of testosterone to dihydrotesterone, might reduce ACE2 levels and thereby blunt viral infectivity, suggesting a potential differential impact of testosterone and dihydrotesterone levels.[21] Similarly, research suggests that spironolactone may have a protective effect with regard to COVID-19 given a weakly anti-androgenic activity as well as some cardio- and reno-protective effects.[22]

Our data suggest that the differences in risk of adverse outcomes diminish as men and women age; men older than 75 had the least magnitude difference in relative risk of hospitalization and death compared to age matched women. With increasing age, levels of testosterone are known to decrease, implying a role for testosterone levels in the outcomes of those infected by COVID-19.[23] Hypogonadism, the clinical state of testosterone deficiency, is associated with numerous comorbidities known to worsen COVID-19 outcomes; these include obesity, type 2 diabetes mellitus, and obstructive sleep apnea.[24] Low testosterone states are associated with elevated levels of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-alpha; this may potentiate the COVID-19 related cytokine storm observed in severe disease states.[24] Other data implicated pro-inflammatory cytokines including IL-8, IL-10, IL-17a, and IL-23 in more severe disease course.[25] It remains to be seen whether these cytokines may be clinically useful in terms of predicting disease outcomes, or may manifest differently in men as opposed to women. Importantly, the largest absolute number of deaths occurs in both men and women of age > 75, arguing against any protective effect of an isolated age-related hormone decline.

It is possible that some of the observed age and sex based differential effect is not due to increased risk in men alone, but instead derives from a protective effect in women <75 as reflected by CFRs in this subgroup. If this effect is hormonally driven, it may become diminished when a women experiences menopause. The rheumatologic and immunologic literature suggests that women may have enhanced immune responses to a wide variety of pathogens, potentially due to the impact of progesterone and estrogens on the immune system (estrogen receptor expression occurs throughout immune system cell types), but also due to altered gene dosage of sex chromosomes.[26] Upon entrance into menopause, women may experience an "immune-senescence" resulting from an immune decline due to reduced hormone levels.[27] Additionally, estrogen is a known driver of ACE2 expression.[28] Nevertheless, an increase in estrogen levels may not alone offset the risk of worsened disease in men; males with obesity have increased circulating estrogen levels due to peripheral aromatization of testosterone to estrogen, yet continue to have worsened outcomes with COVID-19.[29] Prospective trials are underway assessing the impact of administration of female sex hormones including progesterone and estrogen to men hospitalized with COVID-19 (ClinicalTrials.gov NCT04365127 and NCT04359329).

Finally, the observed sex disparity in COVID-19 outcomes may relate to comorbidity differences. The Center for Disease Control lists potential risk factors for worsened outcomes with COVID-19.[30] Many of these comorbidities occur in greater rates amongst men.[31] Men have more severe disease profiles, reduced rates of healthcare utilization, and riskier lifestyle habits.[31] However, when analyzing these data, rates of comorbidities among those dying in NYC were comparable between sexes. Differences in comorbidities between men and women may not provide an adequate explanation for the observed sex disparity in COVID-19 outcomes.

Limitations of our study include the surveillance-based nature of this evolving dataset. Ethnographic data were missing in a large percentage of citywide data, prohibiting inclusion of ethnicity in our analysis. However, given our study size, including population-level adjustments, we can assume our findings are sufficiently powered, generalizable and externally valid. Data on antibody testing may permit more meaningful analysis, but at this time antibody testing remains suboptimal. While specific data on comorbidities in men and women would be ideal, these data were similarly not available given our cohort size and the rapid course of disease in our region. Furthermore, we were unable to temporally stratify our data, introducing possible bias from under sampling of earlier cases as testing was initially limited. This may overemphasize the absolute number of hospitalizations and deaths compared to cases, but is unlikely to be different between sexes. Case fatality rates in our series were calculated utilizing a broad definition of death (probable and confirmed), therefore the true magnitude of this effect is likely overestimated. Data were obtained in aggregate for age grouping and sex, thereby preventing further

in-depth modelling with narrower age categories. Sex was self-reported and no effort was made to query patients regarding transsexualism. Given rates of transsexualism nationwide ranging from 0.39–0.56%, discordance between reported sex and biologic sex is unlikely to impact our results.[32]

CONCLUSION

In the NYC population, men have higher rates of COVID-19 and higher rates of hospitalization and death due to COVID-19. Numerous theories have been postulated to explain these underlying differences, and while studies considering the role of androgens and other sex hormones offer the most robust evidence to date, this relationship is complex and warrants further study.

DISCLOSURES

Authors have no relevant conflicts to report.

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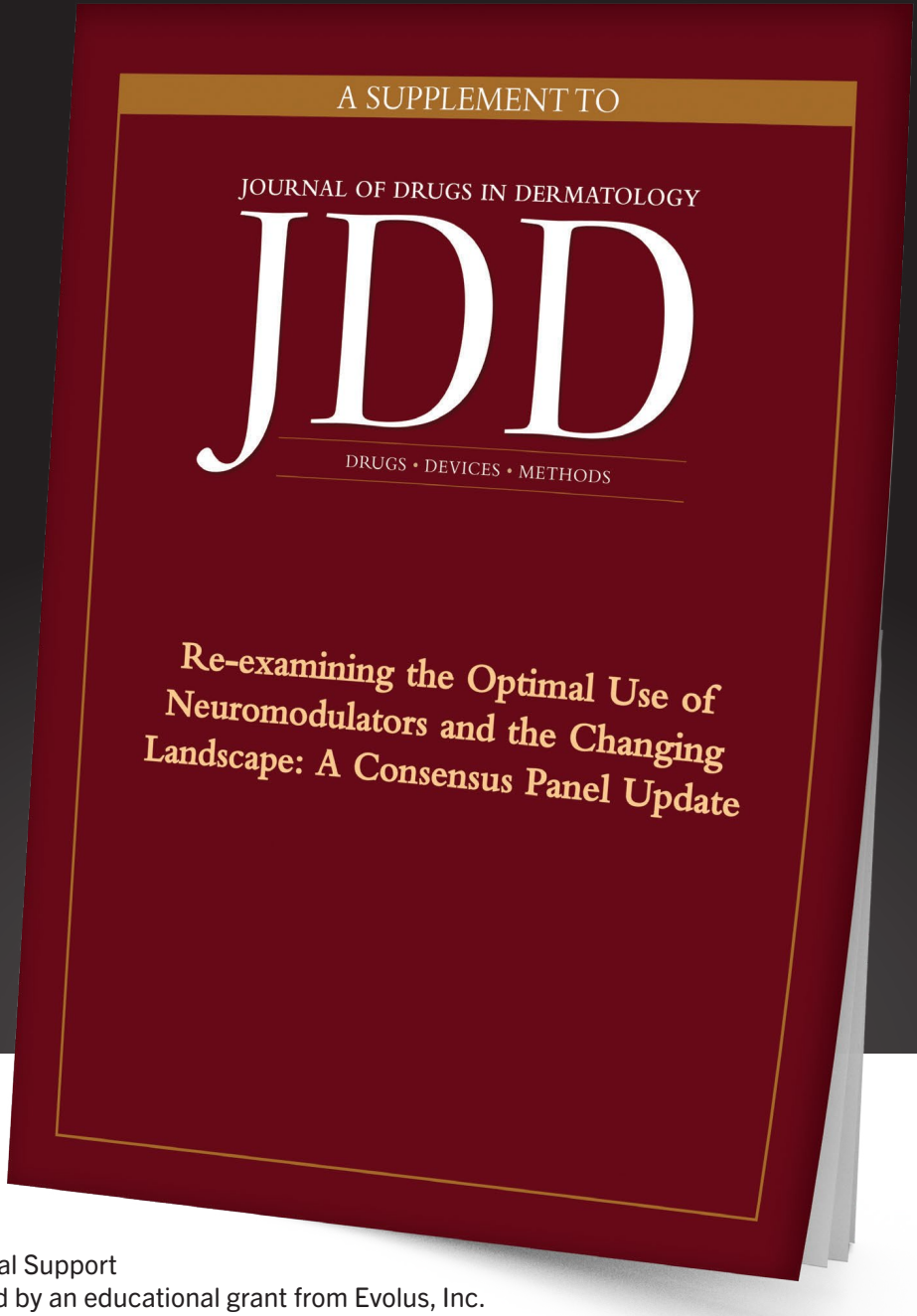

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ORIGINAL ARTICLE

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Hydrogen Peroxide Topical Solution, 45% for Common Warts: Phase 2 Efficacy and Safety Trial Results

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ABSTRACT

Background: No FDA-approved prescription therapies are available for common warts.

Objective: We evaluated a proprietary hydrogen peroxide topical solution, 45% (w/w) (HP45) for treatment of common warts.

Methods: In the phase 2 randomized, double-blind, vehicle-controlled WART-203 trial (NCT03278028), eligible patients aged ≥8 years had 1–6 warts (1 target wart) on the trunk or extremities with a Physician's Wart Assessment™ (PWA) grade ≥2 (range, 0 [clear] to 3 [wart 3–8 mm in diameter or length]). Patients self-administered HP45 or vehicle twice weekly for 8 weeks and were evaluated through 12 weeks posttreatment (week 20). Efficacy assessments included mean change in target wart PWA grade from baseline at week 8 (primary endpoint) and proportions of patients with target wart clearance. Safety assessments included treatment-emergent adverse events (TEAEs) and local skin reactions (LSRs).

Results: A total of 157 patients completed 8 weeks of treatment (HP45, n=79; vehicle, n=78); 151 patients completed the 20-week posttreatment evaluation (HP45, n=75; vehicle, n=76). A significantly greater reduction in mean target wart PWA grade from baseline at week 8 was achieved with HP45 (−0.87) vs vehicle (−0.17; $P<0.0001$) and maintained at week 20 (−1.00 vs −0.39; $P=0.0004$). The proportion of patients with target wart clearance at week 8 was significantly greater with HP45 (25.3%) vs vehicle (2.6%; $P<0.0001$) and remained significantly greater at week 20 (37.3% vs 11.8%; $P=0.0002$). Forty-seven patients reported 76 TEAEs; most were mild or moderate in severity. Most LSRs were mild and resolved by week 20. In pediatric patients (HP45, n=13; vehicle, n=6), greater reductions in mean target wart PWA grade from baseline were observed with HP45 vs vehicle at weeks 8 (−1.0 vs 0) and 20 (−1.2 vs −0.5).

Conclusion: These findings support the efficacy and safety of HP45 for the treatment of common warts in patients ≥8 years of age.

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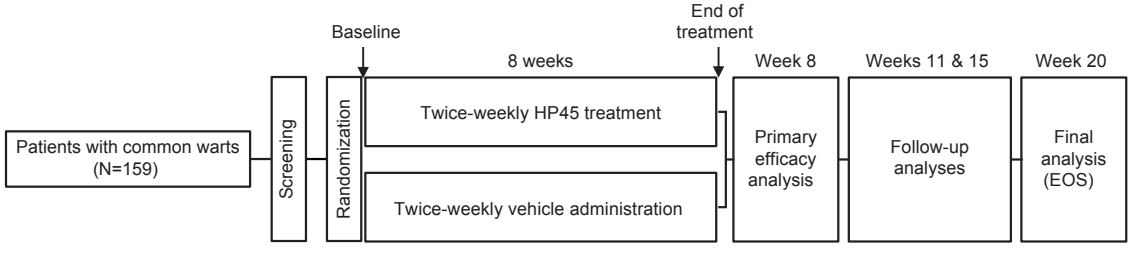
INTRODUCTION

Common warts, also known as verruca vulgaris, are benign skin and mucosal growths caused by human papillomavirus (HPV) infection of keratinocytes.[1] Common warts can occur at virtually any anatomic location, but typically occur on the fingers, hands, and sites prone to trauma (eg, knees, elbows).[2] In immunocompetent individuals, cutaneous warts may spontaneously resolve; however, they often persist for years, may spread to distant anatomic regions by autoinoculation, and may be painful.[1-3] Approximately 10% of the population is affected by warts, and common warts account for 70% of this prevalence.[4,5] Common warts are more prevalent in children, especially adolescents, affecting 10% to 20% of school-aged children, typically those aged 12–16 years.[5]

No specific antiviral therapies are available to treat cutaneous HPV infection, and no US Food and Drug Administration–approved prescription treatment is available for cutaneous common warts. Many therapies provided by health care practitioners involve the off-label use of drugs approved for other indications, the safety and/or efficacy of which is unproven for treating common warts. These therapies employ locally destructive or ablative modalities to treat lesions, and include cryotherapy with liquid nitrogen or another cryogen, electrosurgery, curettage, application of acids (eg, salicylic acid, trichloroacetic acid) or blistering agents, locally cytotoxic therapies, and topical immunotherapy or immunomodulatory agents.[2,6,7] Several of these are available in over-the-counter formulations with lower concentrations than those used in the office setting.[2] While sometimes effective, many are painful and may necessitate anesthesia and/or analgesia. Moreover, some procedures can be complicated by adverse cosmetic outcomes like scarring and infection. No single therapy is consistently

FIGURE 1. Phase 2 WART-203 study design.



EOS, end of study; HP45, hydrogen peroxide topical solution, 45% (w/w).

effective in all cases, and substantial variability exists among practitioners in the methods employed and the outcomes.[2] Over-the-counter formulations of topical salicylic acid and freezing kits are available for home use but are only modestly beneficial.[7]

Hydrogen peroxide (H_2O_2), a compound ubiquitous in the environment, is commonly used at low concentrations (3%–6%) as a topical antiseptic/disinfectant and in wound irrigation. Local application of high supraphysiologic concentrations of H_2O_2 may overwhelm the skin's innate antioxidant defense systems, allowing it to act on lesions through direct oxidation of organic tissues, generation of reactive oxygen species, or local lipid peroxidation, and by generating local concentrations of oxygen that are toxic to abnormal lesional cells.[8]

A proprietary, stabilized, high-concentration H_2O_2 topical solution, 45% (w/w) (HP45), delivered via a proprietary device, is in clinical development for the treatment of common warts.[9] We report the results of a phase 2 clinical trial that investigated outcomes during 8 weeks of HP45 treatment and a 12-week posttreatment period in adults and children with common warts. The objective of this study was to evaluate the efficacy and safety of HP45 compared with vehicle during treatment and during posttreatment follow-up.

METHODS

Study Design

The phase 2 WART-203 trial (NCT03278028) was a randomized, double-blind, vehicle-controlled, multicenter study of twice-weekly topical administration of HP45 vs matching vehicle (a water-clear, colorless solution indistinguishable in physical appearance from HP45) for up to 8 weeks in patients with common warts. At screening, an investigator identified 1 target wart and up to 5 nontarget warts on the trunk or extremities of each patient. During the 8-week treatment phase, all target and nontarget warts continuing to have a grade of ≥1 on the Physician's Wart Assessment™ (PWA; Table 1) were treated twice weekly. The patient self-administered the first of the twice-weekly treatments at the study center under the investigator's supervision and the second of the twice-weekly treatments at home (the guardian administered treatment if the patient was a minor). Patients completed 13 study visits (screening; randomization/first treatment; 7 additional weekly visits; primary efficacy evaluation at week 8; follow-up evaluations at weeks 11 and 15; and an end-of-study evaluation at week 20; Figure 1).

Study Patients

Eligible patients were ≥8 years of age with a clinical diagnosis of common warts, and 1–6 warts (1 designated by the investigator as the target wart) on the trunk or extremities. The target and nontarget warts were ≤3 mm thick and had a longest axis (length or diameter) of 3–8 mm. Each wart was required to be a discrete lesion and could not be clinically atypical, periungual, subungual, genital, anal, mosaic, plantar, flat, or filiform type, or covered with hair that would interfere with treatment or evaluations. Each wart was required to have been present for ≥4 weeks and have a PWA grade of ≥2. Patients were excluded if they were immunocompromised, had a history of human immunodeficiency virus infection, or had received the HPV vaccine within the previous year. Additional exclusion criteria included treatment with specified intralesional, systemic, and topical therapies, or presence of other skin conditions upon enrollment or within a specified time period before study initiation.

Efficacy Assessments

Efficacy endpoints were based on PWA grades (Table 1). At every study visit, the investigator assessed the target and nontarget warts using the PWA; at visits where study medication was administered, the PWA was completed before treatment. Efficacy assessments were conducted in the per-protocol population, defined as all randomized patients who missed no more

TABLE 1.

PWA Scale	
Grade	**Description**
0	Clear: no visible wart; no further treatment indicated
1	Near clear: a visible wart <3 mm in maximal diameter (or length)
2	A visible wart ≥3 mm and <6 mm in maximal diameter (or length)
3	A visible wart ≥6 mm in maximal diameter (or length)

than 3 treatment visits, completed the week 8 and week 20 assessments, and had no major protocol violations.

The primary efficacy endpoint was the mean change in target wart PWA grade from baseline to week 8 in patients who received HP45 vs those who received vehicle. Secondary efficacy analyses during the treatment and posttreatment periods included comparisons between the HP45 and vehicle treatment groups for: the proportion of patients with the target wart cleared (PWA = 0); the proportion of patients with all treated warts cleared; mean per-patient percentages of treated warts cleared; and the number of treated warts cleared.

Safety assessments were performed on the safety population, which included all randomized patients, and included the number and severity of treatment-emergent adverse events (TEAEs), number and severity of local skin reactions (LSRs), vital signs, and clinical laboratory parameters. LSRs associated with irritation at all treated wart sites, including the skin immediately surrounding the warts, were rated at every postscreening visit (study visits 2–13) by the investigator and patient on a 4-point scale of 0 (none), 1 (mild), 2 (moderate), or 3 (severe). LSR signs assessed by the investigator were erythema, edema, erosion, ulceration, vesicles/bullae, excoriations, and scabbing; symptoms reported by patients were stinging/burning and pruritus. At treatment visits, LSRs were assessed both pretreatment and 10 ± 4 or 20 ± 4 minutes after treatment application for patient or investigator assessments, respectively.

Statistical Analyses

The primary efficacy endpoint was evaluated using analysis of covariance with baseline PWA as the covariate. Proportions of patients achieving target wart clearance were analyzed using Fisher's exact test, and proportions of patients with all treated warts cleared and the number of treated warts cleared were evaluated using the Cochran-Mantel-Haenszel test. The mean per-patient percentages of treated warts cleared were evaluated using analysis of variance. No missing data imputation was used. For all efficacy analyses, 2-tailed alpha for statistical significance was 0.05 with no adjustment for multiple comparisons.

For the safety analyses, the proportions of patients with TEAEs was tabulated by treatment and Medical Dictionary for Regulatory Activities System Organ Class. Vital signs and clinically relevant abnormal laboratory results were also tabulated. No inferential testing was performed.

A post hoc analysis evaluated the efficacy and safety in a nonprespecified subset of patients aged ≥8 to <18 years. The same efficacy endpoints and safety assessments were used for this analysis in pediatric patients.

RESULTS

Study Patients

Of 159 patients who were randomized and treated, 157 patients completed 8 weeks of treatment (HP45, n=79; vehicle, n=78) and were included in the per-protocol population for efficacy analyses. A total of 151 patients completed posttreatment evaluations at week 20 (HP45, n=75; vehicle, n=76). Of 20 pediatric patients randomized, 19 completed the study (HP45, n=13; vehicle, n=6; mean age, 12.1 years); 1 patient withdrew consent. These patients were included in the total study analysis as well as a post hoc analysis. Baseline demographics and clinical characteristics of study patients are summarized in Table 2.

Efficacy Analysis

Per-Protocol Population

For the primary efficacy analysis, a significantly greater reduction in mean target wart PWA grade from baseline at week 8 was achieved with HP45 vs vehicle (–0.87 vs –0.17; $P<0.0001$; Figure 2). A significantly greater reduction in PWA grade from baseline for HP45 vs vehicle was observed as early as week 3 (–0.32 vs –0.14; $P=0.04$) and was maintained through week 20 (–1.00 vs –0.39; $P=0.0004$; Figure 3).

The proportion of patients with the target wart cleared at week 8 was significantly greater among patients treated with HP45 vs vehicle (25.3% vs 2.6%; $P<0.0001$), with a significant difference between treatments first observed at week 4 that was maintained through week 20 (Figure 4A). A significantly greater proportion of patients achieved clearance of all treated warts with HP45 vs vehicle at week 8 (19.0% vs 2.6%; $P=0.001$; Figure 4B); a significant difference was observed as early as treatment week 4, and from weeks 6 to 8.

At week 20, the proportion of patients with the target wart cleared was significantly greater with HP45 treatment vs vehicle (37.3% vs 11.8%; $P=0.0002$; Figure 5). The proportion of patients with the target wart graded clear or near clear at week 20 was significantly greater with HP45 treatment vs vehicle (41.3% vs 17.1%, respectively; $P=0.0009$; Figure 5), and represented an increase in the proportion of patients with clearance of the target wart from week 8. Similarly, at week 20, a significantly greater proportion of patients treated with HP45 vs those treated with vehicle maintained all treated warts cleared (33.3% vs 7.9%; $P=0.0002$), and all treated warts graded clear or near clear (40.0% vs 15.8%; $P=0.0019$; Figure 5). The mean per-patient percentage change from baseline in PWA grade for treated warts at week 20 was significantly greater after treatment with HP45 vs vehicle (–43.8% vs –17.7%; $P=0.0002$); similar results were observed for the mean per-patient percentage of treated warts cleared at week 20 for HP45 vs vehicle (39.8% vs 13.3%; $P=0.0001$). The percentages of PWA responders are summarized in Table 3; significant differences were observed for HP45 vs vehicle at week 8,

TABLE 2.

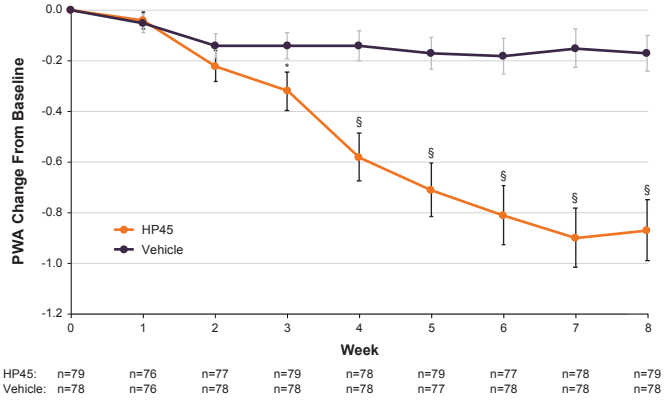
Baseline Demographics and Clinical Characteristics, ITT Population			
Characteristic	**HP45 (n=81)**	**Vehicle (n=78)**	**All Patients (N=159)**
Age, y			
All patients			
Mean (SD)	38.0 (18.1)	41.6 (17.4)	39.7 (17.8)
Range	9–85	9–76	9–85
Pediatric patients			
Mean (SD)	12.5 (2.6)	11.0 (2.5)	12.1 (2.6)
Range	8–17	8–17	8–17
Age group			
<18 y	14 (17.3)	6 (7.7)	20 (12.6)
18–64 y	62 (76.5)	64 (82.1)	126 (79.2)
>64 y	5 (6.2)	8 (10.3)	13 (8.2)
Gender			
Female			
All patients	48 (59.3)	43 (55.1)	91 (57.2)
Pediatric patients	5 (38.5)	2 (33.3)	7 (36.8)
Race			
White			
All patients	78 (96.3)	70 (89.7)	148 (93.1)
Pediatric patients	13 (100)	6 (100)	19 (100)
African American	1 (1.2)	4 (5.1)	5 (3.1)
Native Hawaiian or other Pacific Islander	1 (1.2)	1 (1.3)	2 (1.3)
Asian	1 (1.2)	0	1 (0.6)
Other	0	3 (3.9)	3 (1.9)
Ethnicity			
Hispanic or Latino			
All patients	13 (16.1)	16 (20.5)	29 (18.2)
Pediatric patients	3 (23.1)	2 (33.3)	5 (26.3)
Not Hispanic or Latino			
All patients	65 (80.3)	55 (70.5)	120 (75.5)
Pediatric patients	10 (76.9)	4 (66.7)	14 (73.7)
Not reported	3 (3.7)	7 (9.0)	10 (6.3)
Fitzpatrick Skin Type			
All patients			
I	3 (3.7)	0	3 (1.9)
II	30 (37.0)	28 (35.9)	58 (36.5)
III	26 (32.1)	26 (33.3)	52 (32.7)
IV	16 (19.8)	19 (24.4)	35 (22.0)
V	4 (4.9)	2 (2.6)	6 (3.8)
VI	2 (2.5)	3 (3.9)	5 (3.1)
Pediatric patients			
I	1 (7.7)	0 (0)	1 (5.3)
II	5 (38.5)	1 (16.7)	6 (31.6)
III	4 (30.8)	4 (66.7)	8 (42.1)
IV	3 (23.1)	1 (16.7)	4 (21.1)
V	0 (0)	0 (0)	0 (0)
VI	0 (0)	0 (0)	0 (0)

TABLE 2. (Continued)

Baseline Demographics and Clinical Characteristics, ITT Population			
Characteristic	**HP45 (n=81)**	**Vehicle (n=78)**	**All Patients (N=159)**
PWA grade of 2 or 3, %[a]			
PWA = 2	60.8	60.3	60.5
PWA = 3	39.2	39.7	39.5
No. of treated warts per patient			
Mean	1.89	1.81	1.85
Range	1–6	1–6	1–6

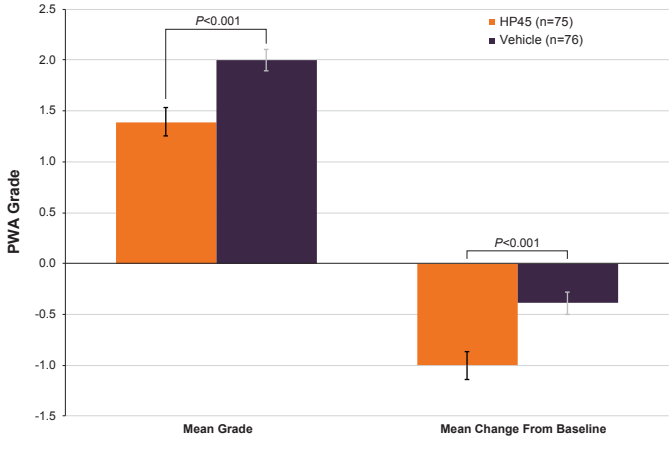
PWA grades are from the per-protocol population (HP45 n=79; vehicle n=78); demographic data for patients <18 years of age are for the per-protocol population at week 8 (HP45, n=13; vehicle, n=6) with percentages based on the number of patients enrolled and treated.
Data reported are n (%) unless otherwise indicated.
HP45, hydrogen peroxide topical solution, 45% (w/w); PWA, Physician's Wart Assessment™.
[a]PWA grade of patient's target wart.

FIGURE 2. Mean change from baseline PWA grade by treatment week (primary efficacy variable), per-protocol population (N=157).



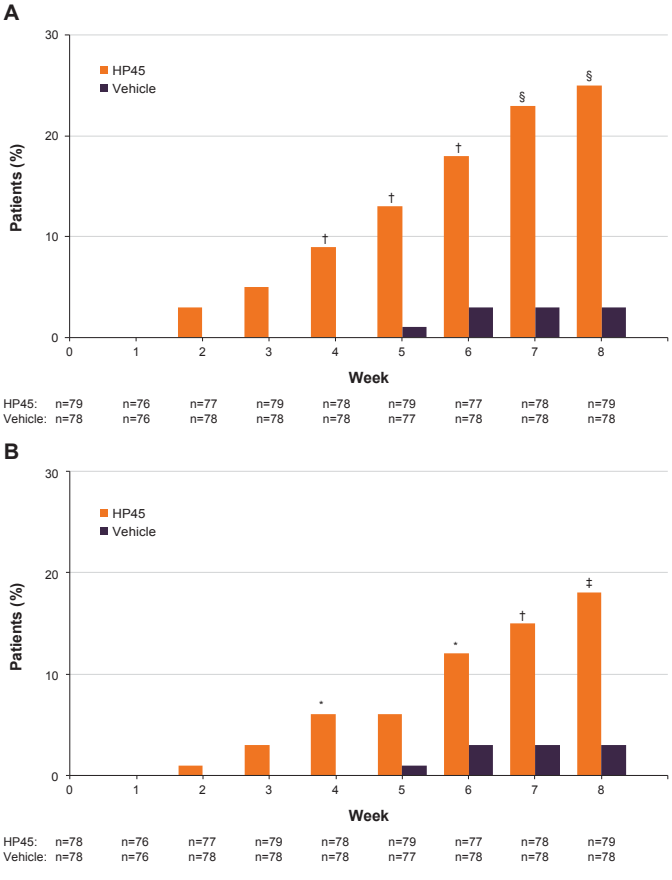
Between-treatment comparisons performed using analysis of covariance with baseline PWA as the covariate.
Error bars indicate standard deviation.
HP45, hydrogen peroxide topical solution, 45% (w/w); PWA, Physician's Wart Assessment™.
*$P<0.05$.
§$P\leq0.0001$.

FIGURE 3. Mean PWA grade and mean change from baseline PWA grade at week 20, per-protocol population (N=151).



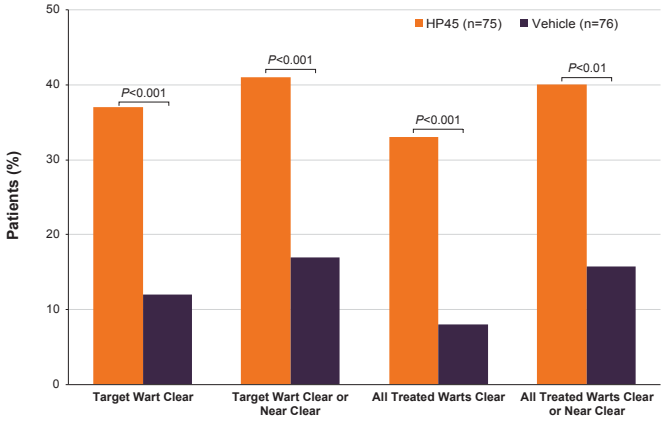
P values were calculated using type 3 tests of fixed effects.
Error bars indicate standard deviation.
HP45, hydrogen peroxide topical solution, 45% (w/w); PWA, Physician's Wart Assessment™.

FIGURE 4. Proportions of patients with (A) target wart clear and (B) all treated warts clear by treatment week, per-protocol population (N=157).



Clear wart defined as PWA = 0.
In A, between-treatment comparisons were performed using the Fisher exact test (left-sided probability ≤ frequency). In B, between-treatment comparisons were performed using the Cochran-Mantel-Haenszel test.
HP45, hydrogen peroxide topical solution, 45% (w/w); PWA, Physician's Wart Assessment™.
*P<0.05. †P<0.01. ‡P≤0.001. §P≤0.0001.

FIGURE 5. Proportions of patients with target warts or all treated warts clear or almost clear at week 20, per-protocol population (N=151).



Clear defined as PWA = 0; near clear defined as PWA = 1.
Between-treatment comparisons for target wart assessments were performed using the Fisher exact test (left-sided probability ≤ frequency), and comparisons for all treated warts were performed using the Cochran-Mantel-Haenszel test.
HP45, hydrogen peroxide topical solution, 45% (w/w).

and were maintained through week 20 (P<0.0001 for both time points).

Pediatric Patients

Numerically greater reductions in mean target wart PWA grade from baseline were observed with HP45 vs vehicle at every assessment, with similar reductions noted at weeks 8 (–1.0 vs 0; P=0.05; Figure 6) and 20 (–1.2 vs –0.5; P=0.24). The proportions of patients who achieved target wart clearance were numerically greater with HP45 vs vehicle at week 8 (38.5% vs 0%; P=0.11) and week 20 (46.2% vs 16.7%; P=0.24). The proportions of patients with the target wart grade of clear or near clear (PWA ≤1) were numerically greater with HP45 vs vehicle at week 8 (46.2% vs 0%; P=0.06) and week 20 (53.9% vs 16.7%; P=0.15). Similar findings were observed for the proportions of patients achieving clearance of all treated warts with HP45 vs vehicle at week 8 (30.8% vs 0%; P=0.29) and week 20 (46.2% vs 0%; P=0.09).

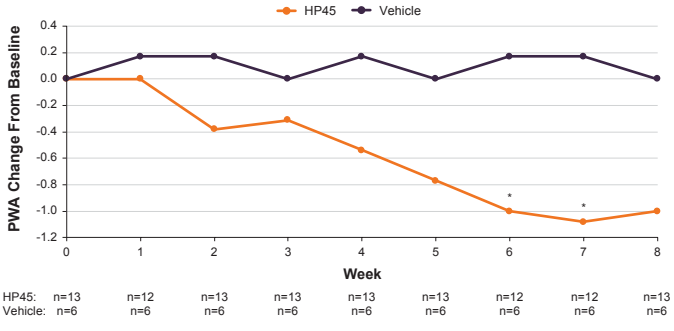
TABLE 3.

PWA Responders (n, %) With All Treated Warts Clear or Near Clear (PWA = 0 or 1) by Treatment and Visit, Per-Protocol Population

Study Week	HP45	Vehicle	*P* Value
1	n=76 1 (1.3)	n=76 1 (1.3)	0.99
2	n=77 7 (9.1)	n=78 5 (6.4)	0.49
3	n=79 7 (8.9)	n=78 4 (5.1)	0.32
4	n=78 22 (28.2)	n=78 6 (7.7)	0.0007
5	n=79 23 (29.1)	n=77 3 (3.9)	<0.0001
6	n=77 27 (35.1)	n=78 6 (7.7)	<0.0001
7	n=78 30 (38.5)	n=78 6 (7.7)	<0.0001
8	n=79 27 (34.2)	n=78 6 (7.7)	<0.0001
11	n=75 28 (37.3)	n=76 7 (9.21)	<0.0001
15	n=75 28 (37.3)	n=74 9 (12.2)	0.0003
20	n=75 30 (40.0)	n=76 12 (15.8)	0.002

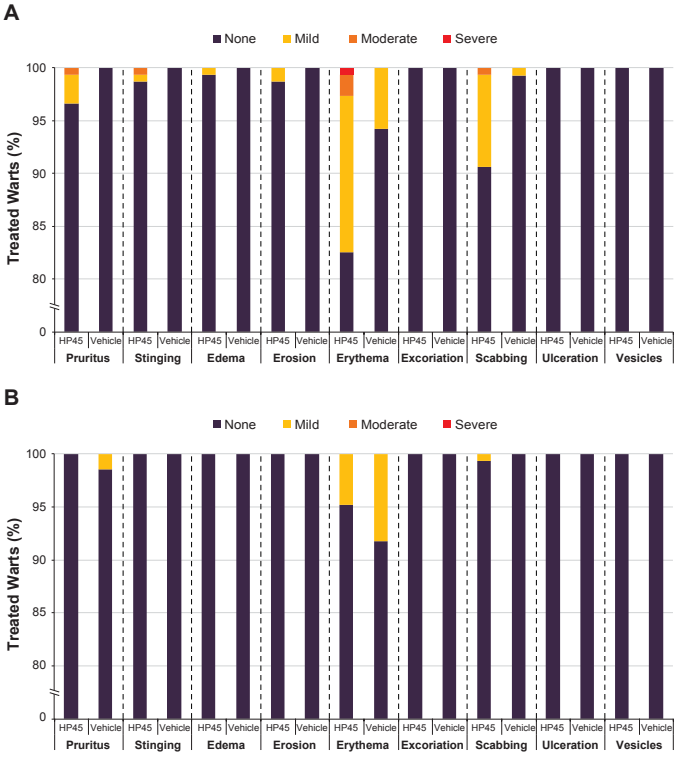
Values for weeks 1–8 are from the per-protocol population; those for weeks 11–20 are from a subset of that population because some patients dropped out of the study after week 8. *P* values for HP45 vs vehicle were calculated using the Cochran-Mantel-Haenszel test.
HP45, hydrogen peroxide topical solution, 45% (w/w); PWA, Physician's Wart Assessment™.

FIGURE 6. Mean change from baseline PWA grade by treatment week (primary efficacy variable), pediatric per-protocol population (N=19).



Between-treatment comparisons performed using analysis of covariance with baseline PWA as the covariate.
HP45, hydrogen peroxide topical solution, 45% (w/w); PWA, Physician's Wart Assessment™.
*P<0.05.

FIGURE 7. Local skin reactions by severity at (A) week 8 and (B) week 20, safety population.



Percentages are based on the total number of treated warts for each treatment group.
Number of treated warts at week 8: HP45, n=149; vehicle, n=138. Number of treated warts at week 20; HP45, n=145; vehicle, n=134.
HP45, hydrogen peroxide topical solution, 45% (w/w).

TABLE 4.

Summary of Adverse Events, n (%)			
	HP45 (n=81)	Vehicle (n=78)	All Patients (N=159)
All TEAEs	44 (54.3)	32 (41.0)	76 (47.8)
Patients with TEAEs	28 (34.6)	19 (24.4)	47 (29.6)
SAEs reported	0	0	0
Patients with an SAE	0	0	0
TEAEs by severity			
Mild	16 (19.8)	15 (19.2)	31 (19.5)
Moderate	12 (14.8)	3 (3.9)	15 (9.4)
Severe	0	1 (1.3)	1 (0.6)
Patients who discontinued due to TEAEs	0	0	0
TEAEs by preferred term			
Nasopharyngitis	5 (6.2)	4 (5.1)	9[a] (5.7)
Upper respiratory tract infection	4 (4.9)	4 (5.1)	8 (5.0)
Viral gastroenteritis	2 (2.5)	1 (1.3)	3[b] (1.9)
Headache	2 (2.5)	1 (1.3)	3 (1.9)
Sinusitis	0	3 (3.9)	3 (1.9)
Constipation	0	2 (2.6)	2 (1.3)
Hypertension	2 (2.5)	0	2 (1.3)
Influenza	2 (2.5)	0	2 (1.3)
Injury	2 (2.5)	0	2 (1.3)
Skin hypopigmentation	2 (2.5)	0	2 (1.3)

TEAEs by preferred MedDRA term are reported for TEAEs that occurred in 2 or more patients in either treatment group.
HP45, hydrogen peroxide topical solution, 45% (w/w); MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]In pediatric patients, 2 TEAEs of nasopharyngitis occurred in the HP45 group, and 1 occurred in the vehicle group.
[b]One TEAE of viral gastroenteritis occurred in a pediatric patient treated with HP45.

Safety Analysis

Safety Population

All 159 randomized patients were evaluated for safety. A total of 47 patients reported 76 TEAEs, all of which were mild or moderate in severity in the HP45 group, and no patient discontinued treatment due to a TEAE (Table 4). Six TEAEs reported by 4 patients treated with HP45 (4.9%) were considered related to treatment (application-site pain, skin pain, skin exfoliation, skin hyperpigmentation, skin hypopigmentation); none were serious or severe. The only treatment-related TEAE experienced by more than 1 patient was skin hypopigmentation (n=2; 2.5%); the events were transient and resolved 14 and 28 days after onset, respectively.

In the LSR assessment at week 8, patients treated with HP45 reported mild and moderate pruritus in 4 (2.7%) warts and 1

(0.7%) wart, respectively, vs none in the vehicle group (Figure 7A). Stinging was reported for 2 warts treated with HP45 (1 mild, 1 moderate) vs none in the vehicle group. Among investigator-reported LSRs, the reaction observed most frequently was erythema (HP45, 17.4%; vehicle, 5.8%) One case of erythema on an HP45-treated wart was reported as severe. At week 20 most LSRs had resolved (Figure 7B), the most frequently observed LSR was erythema (HP45, 4.8%; vehicle, 8.2%), and all were of mild severity. No clinically significant findings were observed in vital signs or laboratory test results.

Pediatric Patients

In the safety analysis of pediatric patients, 3 patients reported 4 TEAEs; none were severe or considered related to study treatment. These included 2 TEAEs of nasopharyngitis and 1 of viral gastroenteritis in the HP45 group, and 1 TEAE of nasopharyngitis in the vehicle group.

In the LSR assessment of pediatric patients at week 8, moderate pruritus was reported for 1 of 28 warts (3.6%) treated with HP45 vs none of 17 treated with vehicle. Moderate stinging/burning was reported for 1 wart treated with HP45 (3.6%) vs none treated with vehicle. Among investigator-reported LSRs at week 8 for pediatric patients, mild erythema was reported for 3 warts (10.7%) in the HP45 group vs 1 wart (5.9%) in the vehicle group. All patient- and investigator-reported LSRs in the HP45 group resolved by week 20.

DISCUSSION

This phase 2 study demonstrated the efficacy and safety of HP45 for the treatment of common warts, with half of the twice-weekly treatments self-administered—or administered by a guardian if the patient was a minor—at home. All primary and secondary efficacy endpoints were met, with significantly greater wart clearance after treatment with HP45 than with vehicle. Effectiveness was established at the end of the treatment period at week 8, and 12 weeks after treatment completion at week 20. The onset of treatment success was observed as early as week 3 or 4 for most outcome measures. The percentage of patients who achieved clearance of the target wart at week 20 (37.3%) with HP45 treatment was greater than that observed at week 8 (25.3%), suggesting a continued effect of HP45 after an 8-week course (16 total applications) of treatment. HP45 was also well tolerated, as the incidences of TEAEs and LSRs were low.

A previous phase 2 randomized clinical trial with 98 patients with common warts demonstrated the superiority of HP45, but not of a 40% H2O2 solution (HP40), compared with vehicle for the clearance of warts (data on file, Aclaris Therapeutics, Inc.). Taken together, the results of this previous study as well as the current study suggest that the 5% increase in H2O2 concentration with HP45 vs HP40, which represents approximately a 12.5% increase in oxidative potential, is critical to the efficacy of HP45 in the treatment of common warts. We theorize that this increased efficacy may be due to increased local destruction of the virally infected tissue, or to achieving a level of local irritancy sufficient to induce a local immune response to the HPV, or a combination of both.

Limited studies have attempted to evaluate the treatment of warts in children. In the systematic review by Kwok et al, only 4 studies of children-only participants were identified. Active treatments included abrasion, duct tape application, relaxation imagery, and dinitrochlorobenzene,[7] and, in studies with both populations, insufficient data were available to conduct subgroup analyses of children vs adults. Results of the post hoc analysis of pediatric patients in the WART-203 trial provide supportive evidence that treatment with HP45 is safe, well tolerated, and efficacious in pediatric patients aged 8 to <18 years with common warts.

Strengths/Weaknesses

It is important to note that subject blinding to treatment in a clinical trial of high-concentration H2O2 may be challenging as the drug is reactive upon skin contact; however, evaluators did not observe treatments, thus ensuring blinding. In the pediatric population, analyses were limited by low patient numbers (<20) as this trial was not powered for subgroup analyses in that population. This limitation likely contributed to the lack of statistical significance vs placebo that was observed in the efficacy analysis of these patients. However, the trend in efficacy is very encouraging and, along with the excellent tolerability, suggests this may be a potentially valuable therapy for pediatric patients.

CONCLUSION

Treatment with HP45 topical solution was well tolerated and resulted in a significantly greater reduction in mean target wart PWA grade as well as a significantly greater proportion of patients achieving target wart clearance vs placebo. Effectiveness was established by the end of the 8-week treatment period and continued through the last follow-up assessment at week 20. Incidences of TEAEs and LSRs were low. This study thus provides supportive evidence for the safety and efficacy of HP45 topical solution in the treatment of common warts. A phase 3 clinical program evaluating the safety and efficacy of HP45 treatment of common warts in patients ≥1 year of age is currently underway.

DISCLOSURES

SKT has conducted clinical studies sponsored by Aclaris Therapeutics; SRS has been an investigator and consultant for Aclaris; MHG has conducted clinical studies sponsored by and is a consultant for Aclaris; KKG is an investigator for Aclaris and has received grants for clinical studies, and has received honoraria as a speaker for Aclaris; JS owns stock in Aclaris Therapeutics; SDS is the former Chief Scientific Officer of Aclaris Therapeutics and may own stock/stock options in that company.

ACKNOWLEDGMENT

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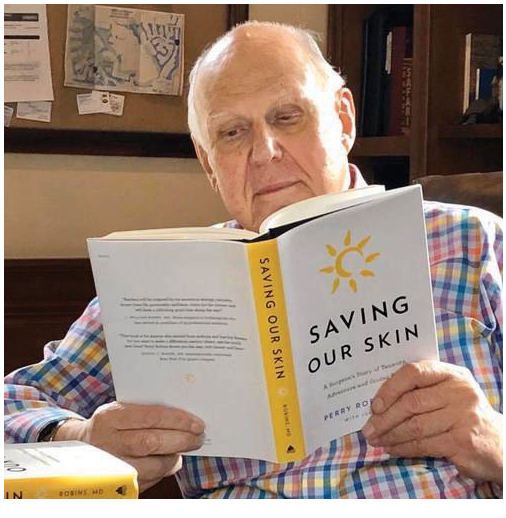

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Prospective Analysis in Patients With HAE Under Prophylaxis With Lanadelumab: A Real-life Experience

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ABSTRACT

Background and Objectives: Patients with the rare disease hereditary angioedema (HAE) suffer from recurrent acute attacks of edema. There is no curative therapy, but the frequency of attacks and quality of life of severely affected patients can be improved by prophylactic therapy. The monoclonal antibody lanadelumab has been approved for routine prophylaxis in patients with HAE since November 2018.

Patients and Methods: In this prospective assessment, a long-term therapy with lanadelumab was initiated in 12 adult patients with HAE. We analyzed their course of disease 6 months after the start of long-term prophylactic therapy using a validated quality-of-life questionnaire and evaluated the frequency and severity of attacks as well as side effects. Furthermore, the therapy with lanadelumab was compared with the previous medication.

Results: To date, our study is the first prospective quality of life analysis in HAE patients under treatment with lanadelumab in real life conditions. Mean attack frequencies were reduced from 6.4 to 0.3 attacks per month and patient in our cohort (P<0.0001). No severe attacks occurred under lanadelumab prophylaxis. In all patients, quality of life increased significantly.

Conclusions: Lanadelumab is an effective but expensive long-term prophylaxis for HAE patients. A favorable side-effect profile has been shown.

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INTRODUCTION

Patients suffering from the bradykinin-induced genetic disease hereditary angioedema (HAE) show recurrent swelling of subcutaneous and submucosal structures. The attacks can affect almost every part of the body and may lead to a life-threatening situation in case of laryngeal edema. In contrast to allergic angioedema, symptoms are non-pruritic. Triggering factors as well as the frequency of attacks and impairment of the patients' quality of life vary greatly between individuals.[1] The prevalence of diagnosed cases of HAE type I and II (caused by a mutation leading to decreased (=type I) or dysfunctional (=type II) C1-Inhibitor (C1 INH)) is approximately 1.5 per 100 000.[2] A third and even rarer type of HAE is known as HAE with normal C1 INH (nC1 INH-HAE). In some of these patients, mutations in the coagulation factor FXII gene, angiopoietin gene, or plasminogen gene are found, but in the majority of cases, the genetic alteration is unknown.[3]

In HAE type I and II, the mutations are located in the SERPING1 gene on chromosome 11, which encodes for C1 INH. According to a recent publication of Ponard et al, 748 different SERPING1 variants have been found until today in HAE patients.[4] It is assumed that no genotype-phenotype relationship exists in HAE.[5] C1 INH is involved in numerous physiological processes, including the complement system, the coagulation, and kinin systems.[6] Physiologically, the protease inhibitor C1 INH has an inhibitory effect on the synthesis of the tissue hormone BK by blocking kallikrein.[7] Kallikrein, on the other hand, cleaves BK from the high-molecular-weight kininogen (HMWK).[8,9] BK, in turn, increases vascular permeability and vasodilatation, thus leading to local edema formation.[10]

For the acute treatment of HAE type I and II attacks, several therapeutic options are available: plasma-derived C1 INH concentrate replaces the missing or dysfunctional complement system regulator and is administered intravenously (Berinert®, Cinryze®). One recombinant human intravenous C1 INH agent is available (Ruconest®) and also licensed for HAE type I and II acute treatment. Icatibant, a specific antagonist of BK 2 receptor (Firazyr®) is the only subcutaneous licensed acute treatment option in the EU in HAE therapy. In the US, ecallantide, an inhibitor of plasma kallikrein (Kalbitor®, sc) is another approved therapy for acute angioedema in HAE patients.[11] Most patients diagnosed with HAE are educated in self-application of their medication, which enables direct and successful treatment of edema in most cases.

If on-demand therapy solely is not sufficient due to a high frequency of attacks, long-term prophylaxis (LTP) should be offered to patients in order to reduce the frequency, duration, and severity of attacks, and to improve their quality of life.[11] The decision when to start LTP must be made individually and should be (re)evaluated by the patient and an HAE specialist during every medical check-up. Until today, there is no explicit indication on when to start or stop LTP.[12] In the German HAE guideline, more than twelve severe HAE attacks per year are required to begin LTP.[13] Besides the frequency of (severe) HAE attacks, the analysis of the patients' health related quality of life (hr-QoL) can be a major indicator for the decision whether to start LTP or to continue on-demand therapy alone. A specific questionnaire for adult patients with HAE type I and II has been developed by a Spanish multi-center research project, referred to as the HAE-QoL.[14]

Regarding the approval of LTP substances, there are differences between the EU and the US. Several trials showed that plasma derived C1 INH (EU: Berinert®, sc; Cinryze®, iv) is an efficient and safe LTP in HAE type I and II patients.[15-17] Attenuated androgens and anti-fibrinolytics are two more potential treatment options for LTP in HAE type I and II – but under heavy discussion due to inadequate efficacy (anti-fibrinolytics) and an unfavorable efficacy/side-effect profile (attenuated androgens). According to the current guideline of Betschel et al, both agents should not be used as first-line prophylaxis in the therapy of patients with HAE type I and II.[11]

Lanadelumab, a fully human monoclonal antibody (Takhzyro®, sc) is approved since 2018 for first line LTP in HAE type I and II patients. It acts by binding plasma kallikrein and inhibiting its proteolytic activity. The recommended starting dose is 300 mg every two weeks. In patients who are constantly attack-free under this treatment, a dose reduction to 300 mg every four weeks may be considered, especially in patients with low weight.[11] The drug can be self-administered by the patient or by a caregiver after appropriate training (Summary of product characteristics, Shire®).

In 2017, a first phase 1b, multicenter, double-blind, placebo-controlled, multiple-ascending-dose trial was published. 37 HAE patients were enrolled and received either lanadelumab or placebo. The lanadelumab group showed fewer attacks and reduced cleavage of HMWK.[18] Further studies with different treatment regimens, longer treatment periods and more patients confirmed the first positive results.[19,20] Under regular prophylaxis with lanadelumab, the overall attack rate and the burden of individual breakthrough HAE attacks could be significantly reduced. The most frequently reported side effects of LTP with lanadelumab are injection site pain and viral infection of the upper respiratory tract.[19] Until today, the longest published treatment period with lanadelumab in HAE type I and II patients is 26 weeks.

Our aim was to analyze the treatment effect on the clinical course and patients' hr-QoL over a period of at least six months in HAE type I and II patients under real-life conditions. This is the first publication beyond the registration studies to evaluate the effect of lanadelumab in HAE adult patients.

PATIENTS AND METHODS

Study Design

The trial was designed as a prospective real-life observational study to evaluate the impact of a LTP with lanadelumab under real life conditions on symptom control and hr-QoL in adult patients with HAE type I and II.

Patients who were insufficiently controlled by an on-demand therapy were enrolled as well as patients with a significant number of breakthrough attacks under previous LTP treatment with another agent.

Treatment effects of on-demand therapy or previous prophylaxis with C1 INH on the one side and LTP with lanadelumab on the other side were compared. Therefore, we analyzed the last six months before the beginning of therapy with lanadelumab for each patient as well as the first six months of prospective LTP with lanadelumab. In patients who underwent LTP with C1 INH prior to treatment with lanadelumab, the preceding six months under on-demand therapy before prophylactic therapy with C1 INH were also considered.

Patients

Patients with HAE type I or II were recruited at the angioedema center of the University Hospital in Ulm. The diagnosis of HAE was based on C1 INH activity levels of less than 50%. All Patients had not been adequately controlled with on-demand therapy (C1 INH concentrates or Icatibant) or had experienced a significant number of breakthrough attacks under the previous LTP with C1 INH replacement.

Criteria for insufficient control were high frequency of attacks despite therapy, insufficient response to symptoms of acute attacks and significant reduction of the hr-QoL. The beginning of LTP with lanadelumab was evaluated and discussed with all patients individually and independently of an enrollment in this study. Patients were informed about possible side effects and therapeutic alternatives. Only patients with a clear indication for the beginning of LTP or a switch of their present LTP who gave consent were included in this prospective real-life analysis.

Study Procedures

Upon beginning the therapy with lanadelumab, the validated specific hr-QoL questionnaire was filled out by all patients. At that time, patients were either on on-demand therapy with C1

INH (Berinert P 20 IE/kg body weight iv) and/or Icatibant (Firazyr 30 mg sc) or on LTP with C1 INH concentrate (Cinryze 1000 U iv, twice weekly) with insufficient treatment success. Furthermore, their HAE diary of the previous six months (a tool that is routinely used and recommended in the therapy control of HAE patients), with details on the frequency and severity of all attacks, was checked by the angioedema specialist and the information collected for later analysis.

Therapy of all patients was subsequently switched to LTP with lanadelumab (Takhzyro 300 mg, sc), which is approved for this indication. For every patient the starting dose was 300 mg sc every two weeks. The first injection was given by the patient himself, under the supervision and instruction of an HAE specialist during an outpatient appointment. Once the treatment schedule was fixed, patients continued with this therapy for six months. Breakthrough attacks were treated with C1 INH (Berinert P 20 IE / kg) and/or Icatibant (Firazyr 30 mg) as required. The overall frequency, location, and severity of attacks were assessed in the patients' HAE diary as described earlier. The location of angioedema was divided into the categories abdominal, cutaneous and upper aerodigestive tract. The severity was categorized into mild, moderate or severe according to the scheme proposed by Caballero 2012[21]: "mild" = discomfort noticed but not leading to disruption of daily activities; "moderate" = sufficient discomfort to reduce or affect normal daily activities; and "severe" = symptoms leading to the inability to work or perform daily activities. The hr-QoL was assessed using the standardized "Angioedema Quality of Life" (AE-QoL, Moxie GmbH, Berlin, Germany) questionnaire before starting therapy with lanadelumab and six months after continuous lanadelumab therapy. In our clinic, the hr-QoL of HAE patients is evaluated at regular intervals and before each change of therapy (according to the current HAE guidelines). Therefore, the hr-QoL-data was also available for patients who had been on on-demand therapy and then on LTP with C1 INH before LTP with lanadelumab.

The specific hr-QoL questionnaire covers the domains functioning, fatigue and mood, fears and shame as well as nutrition. Scores for the single domains as well as the total score were assessed.

Statistical Analysis

The overall frequency of attacks, as well as the individual frequency regarding location, severity, and need for medical intervention, were calculated as number of attacks per month of therapy for the two or three treatment phases respectively. The QoL scores were stated as percentages (0%–100%). Higher values suggest an unfavorable impact due to the disease while values around 0 % indicate perfect well-being. After data were tested for normal distribution using Kolmogorov-Smirnov test, means and standard deviations (SD) were calculated. Differences between treatment phases were calculated using paired-sample t-test. The significance value for p-values was set at ≤ 0.05.

RESULTS

Patients

Four male and eight female patients were included. Their age ranged from 16 to 73 years (mean ± SD, 45.4 ± 18.2 years). All patients suffered from HAE type I. Three patients were on prophylactic therapy with C1 INH concentrate before starting therapy with lanadelumab. Breakthrough attacks were treated in all three of them with Icatibant 30 mg sc. Nine patients had only on-demand therapy with Icatibant 30 mg sc or C1 INH concentrate iv.

Prophylactic Dosing Regimen With Lanadelumab

Prophylactic dosing regimen with lanadelumab was 300 mg sc every two weeks according to the approved therapy recommendation. This dosage was maintained in all patients for at least six months. In some patients who were symptom-free under this regimen, and agreed to the change, the injection interval was afterwards extended to a maximum of every four weeks.

The patients tolerated the treatment very well and no side effects of the treatment were reported except for a slight local reaction with erythema around the injection site and mild pain during the injection.

Attack Frequency

During the preceding six months period with on-demand therapy, 24 attacks were recorded for all patients. The overall attack frequency decreased significantly during the first six months of LTP with lanadelumab. Mean frequencies could be reduced from 6.4 to 0.3 attacks per month and per patient in our cohort

FIGURE 1. Comparison of the mean number of angioedema attacks per month under on-demand treatment and lanadelumab prophylaxis (mean ± SD treatment effect, 6.1 ± 2.2 attacks; *P*<0.0001; n=12).

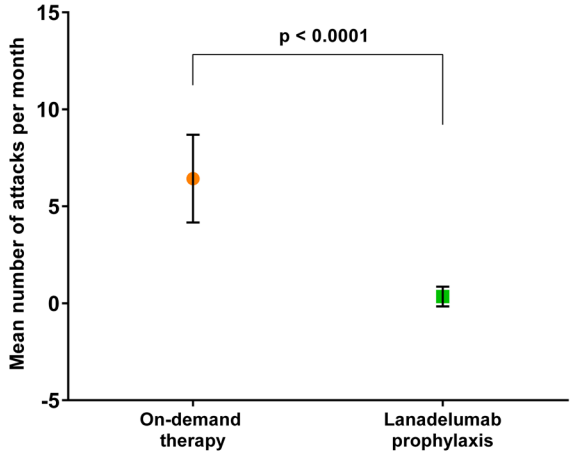


FIGURE 2. Reduction of the mean number of angioedema attacks per month under on-demand treatment and lanadelumab prophylaxis, subdivided by severity of angioedema as rated by the patients (*P*<0.0001 for moderate attacks, *P*=0.0001 for severe attacks; n=12).

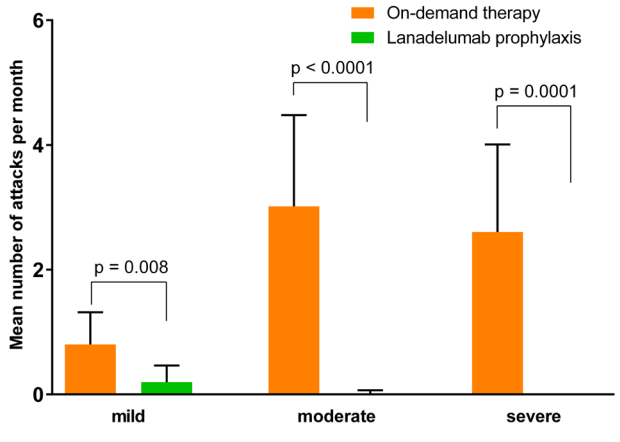


FIGURE 3. Comparison of the mean number of angioedema attacks per month under on-demand treatment and lanadelumab prophylaxis, subdivided by the affected body region (*P*=0.0007 for abdominal attacks, *P*=0.0021 for cutaneous attacks, *P*=0.07 for upper aerodigestive attacks; n=12).

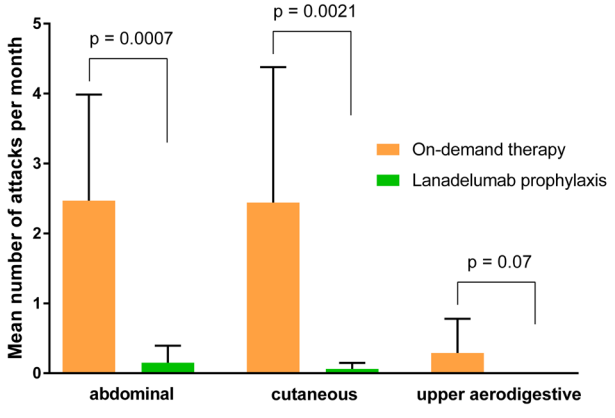


FIGURE 4. The impairment of quality of life under on-demand treatment and lanadelumab prophylaxis in percent (*P*<0.0001; n=12).

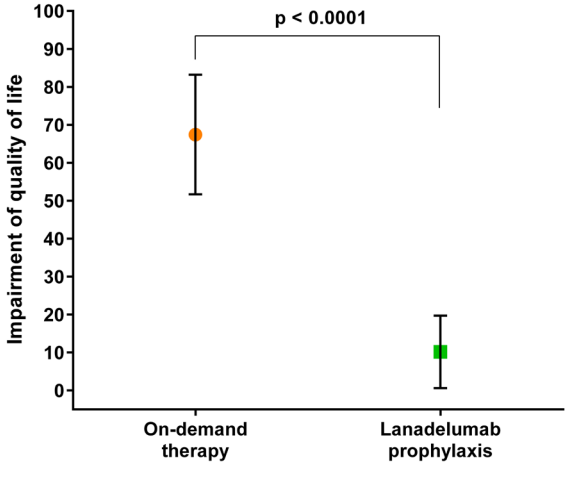
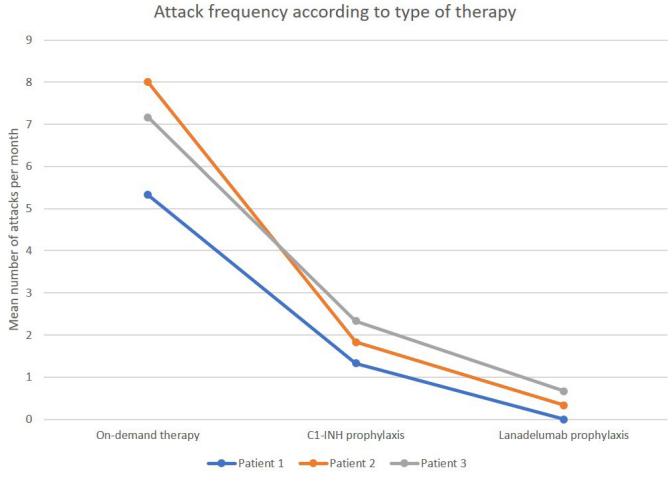


FIGURE 5. The average monthly number of attacks depending on the type of therapy; 3 patients.

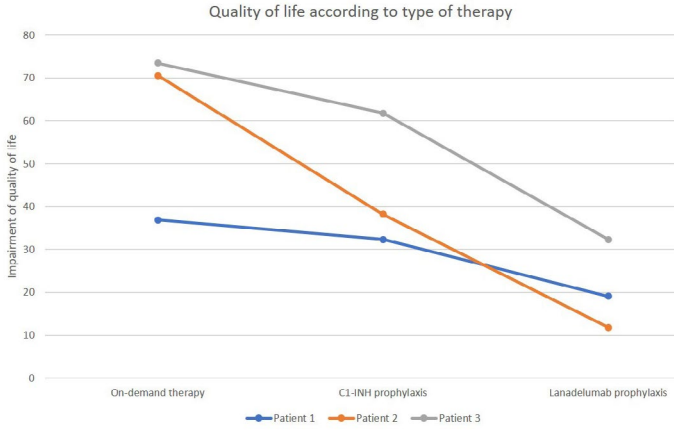


(mean ± SD treatment effect, 6.1 ± 2.2 attacks; *P*<0.0001, Figure 1). The most notable effects were demonstrated for severe and moderate attacks who did not occur at all under therapy with lanadelumab (*P*<0.0001 for moderate attacks, *P*=0.0001 for severe attacks, Figure 2). There was a significant decrease of abdominal (*P*<0.001) and cutaneous edema (*P*=0.002). Edema affecting the upper aerodigestive tract no longer occurred during therapy with lanadelumab (Figure 3), however this result was not statistically significant (*P*=0.07) due to the small overall number of attacks in this anatomical region.

Health-Related Quality of Life

All single domains percentage scores as well as the total score of the angioedema hr-QoL questionnaire decreased six months after initiation of lanadelumab prophylactic treatment in com-

FIGURE 6. The impairment of quality of life in percent depending on the type of therapy; 3 patients.



parison to the on-demand treatment phase. Paired differences were 57,4% (SD, 18,75%) for the total score (Figure 4), 65.2% (SD, 16.9%) for the domain functioning, 49.3% (SD, 37.4 %) for fatigue/mood, 56.0% (SD, 23.7%) for fears/shame and 17.9% (SD, 27.82%) for nutrition. Lower scores indicate an increase in quality of life as the scores reflect the negative impact of the disease. Most notable was the improvement of quality of life in the functioning domain (P<0.0001). The advancements concerning the topic fears/shame, the topic fatigue/mood and the total score were significant as well (P=0.0008, P=0.01 and P=0.0002). Only the improvement in the scores for the nutrition domain did not reach statistical significance (P=0.14).

Patients With C1 INH Prophylaxis Before Lanadelumab Therapy
Three patients received prophylactic therapy with C1 INH concentrate for several years before switching to lanadelumab therapy. In these patients, the average monthly attack rate over a 6-months period was 6.8 (SD 1.1) before the beginning of prophylactic treatment with C1 INH concentrate. It was reduced to 1.8 (SD 0.49) under C1 INH LTP and further to 0.3 (SD 0.3) under prophylactic therapy with lanadelumab (Figure 5). The impairment of the hr-QoL decreased from 60.3 % (SD 16.6) during on-demand therapy to 44.1% (SD 12.7) with C1 INH prophylaxis to 25.7% (SD 6.6) under prophylaxis with lanadelumab (Figure 6).

DISCUSSION

Since their first approval by the FDA in 1986, antibody therapeutics have entered nearly every medical discipline. In 2018, eight of the top ten bestselling drugs worldwide were biologics.[21] Many of the current antibody drugs are in great demand due to their proven efficacy and favorable tolerability profile. Nevertheless, high costs are the other side of the coin and it is therefore crucial to develop a structured selection of patients for which this form of targeted therapy is most beneficial. After the publication of successful registration studies about lanadelumab in the LTP of HAE patients, our trial is the first real-life approach to analyze the effectiveness and especially the influence on HAE patients' hr-QoL.

With a duration of six months LTP with lanadelumab, our study presents results after a comparatively long treatment period. To date, the study with the longest observation period shows data about 26 weeks of treatment (a phase 3, randomized, double-blind, parallel-group, placebo-controlled trial conducted at 41 sites).[19] Furthermore, we were able to compare the clinical course of HAE under lanadelumab therapy with a previous insufficient LTP with C1 INH concentrate in three patients. Concerning this point, it is important to note, that the results should not be interpreted as a counter-argument to LTP with C1 INH concentrate. LTP with C1 INH iv or sc. still represents a first-line treatment option, which has been proven to be highly effective and well tolerated by many HAE patients for many years now.[11,12] Obviously, only patients who were treated insufficiently under the previous LTP were considered for a switch to lanadelumab and therefore included in the present study. In conclusion, we recommend considering lanadelumab as a hopeful therapeutic option for patients who show an insufficient response to LTP with C1 INH concentrate.

In general, the results of our real-life analysis are in line with the registration studies about lanadelumab LTP: In addition to a reduction of the overall HAE attack rate, the number of edema requiring acute therapy, of moderate and severe attacks were reduced in the phase 3 trial published by Banerji et al, which is consistent with our results.[19] These findings show that the mere number of HAE attacks is not sufficient for the decision, which patient may be considered for the relatively expensive treatment with lanadelumab. The severity of the individual attacks should be evaluated carefully as well.

Lanadelumab is not yet approved for children younger than twelve years or for pregnant women. The specific antagonist of BK 2 receptor Icatibant (Firazyr®) is approved for children older than two years of age or with more than 12 kg body weight, but not for pregnant women – and not approved for LTP. For these individuals, only plasma-derived C1 INH is an authorized option for LTP and treatment of acute attacks. As these products hinge on blood donor's availability, this could give rise to supply bottlenecks. Smaller children and pregnant women would not be affected as much by this circumstance, if other patients could refer to synthesized medication such as lanadelumab.

A significant improvement in hr-QoL could be demonstrated in our study, reaching statistical significance in all sub-areas except the topic "nutrition". The quota of HAE patients who were attack-free during the last 16 weeks of a controlled study was 77% in the group receiving 300 mg lanadelumab sc every two weeks, compared to 3% in the placebo group. The results show that an effective LTP allows HAE patients to lead a nearly normal life despite the diagnose of an incurable genetic disease.[19,22] In our study, most notable was the improvement of the quality of life in the functioning domain (P<0.0001). This domain covers the items "impairment of work", "impairment of physical activity", "impairment of spare time activities" and "impairment of social relations".

High costs of therapy as LTP with lanadelumab usually leads to controversies. However, it should be taken into account, that in the case of HAE patients, a high burden of disease does not only lead to direct costs like those for necessary acute treatment. Additionally, chronic comorbidities are frequently diagnosed in patients who suffer under an unfavorable course of disease. For example, anxiety or depression were diagnosed in 35.8% of 1429 HAE patients in a real-world cohort study.[23] Similar results were obtained in a US patient survey of 445 HAE patients:

according to the Hospital Anxiety and Depression Scale, 49.9% and 24.0% of respondents suffered from anxiety and depression, respectively.[24] These diagnoses do not only lead to frequent visits to the doctor but also to a relevant loss of working hours.[25] Concerning the costs of LTP, the patients' body weight may play a further role in the decision making: lanadelumab in obese patients applied every two (if possible every four) weeks can be more cost-effective than LTP with C1 INH iv twice a week adapted to the body weight.

Our study has some limitations: As HAE is an orphan disease, large-scale studies with a high number of patients are unfeasible compared to other diagnoses. In our trial, twelve patients were enrolled, a fact that must be considered when interpreting the results. Nevertheless, a clear improvement of the burden of disease was observed in all of our patients without large variances.

Another limitation is the temporal sequence which could contain a possible bias: The analysis of LTP with lanadelumab was performed prospectively, yet patients' data about previous therapy regimen were collected retrospectively. A third limitation represents the duration of our observation period: six months show a first impression of the therapeutic outcome but are clearly not enough to evaluate long-term effects or long-term side effects of lanadelumab.

DISCLOSURES

JH, ST, and JG received financial support for research projects from Shire/Takheda and financial support for travel expenses to a scientific congress and speakers' fees from Shire/Takheda and CSL Behring GmbH. TKH received financial support for research projects and speakers' fees from Shire/Takheda. MCW and PJS have no competing interest to declare.

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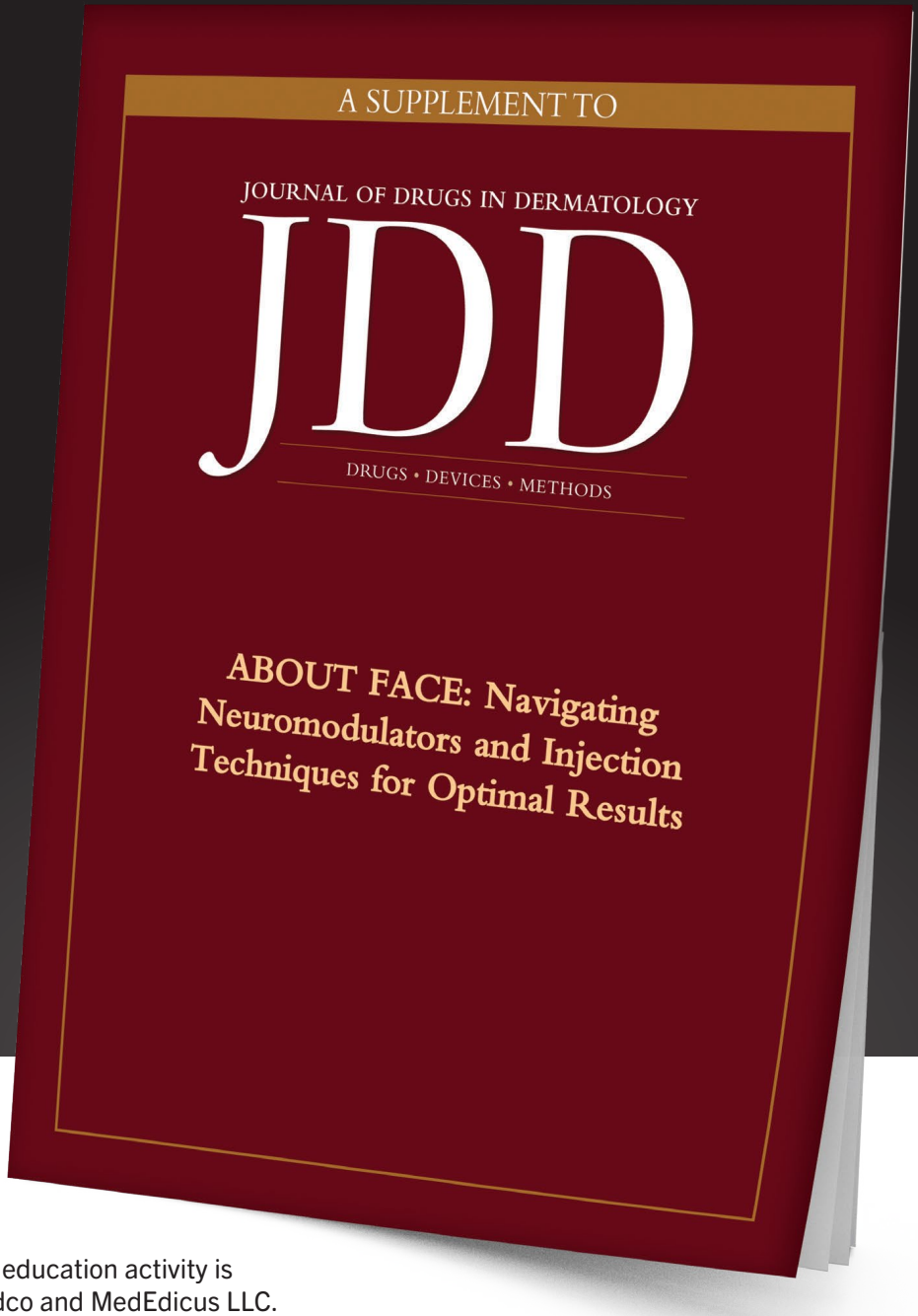

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ORIGINAL ARTICLE

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IncobotulinumtoxinA Demonstrates Safety and Prolonged Duration of Effect in a Dose-Ranging Study for Glabellar Lines

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ABSTRACT

Background: Recently reported clinical data provides evidence that increasing the dose of botulinum toxin A increases the duration of efficacy. A 2-stage Phase 2, randomized, double-blind study investigated the duration of effect and safety of IncobotulinumtoxinA (INCO; Xeomin®, Bocouture®; Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) at doses higher than the approved 20 units (U) for glabellar frown lines (GFL). Primary safety and efficacy endpoints of Stage 1 are reported here.

Methods: 151 subjects with moderate-to-severe GFL were randomized 1:2:2 to receive a single treatment with 20U, 50U, or 75U INCO. The primary efficacy endpoint was median duration of at least 1-point improvement from baseline as assessed by investigator at maximum frown on the Facial Wrinkle Scale.

Results: The median duration of effect was 185 days for the 50U dose group (95% CI:[182, 205]) and 210 days for the 75U dose group (95% CI:[182, 217]). Duration of effect was significantly longer for 75U vs 50U (P=0.0400) and 20U (P=0.0166) despite the study not being powered for confirmatory statistical significance testing between the dose groups. Duration of effect was also longer for 50U vs 20U, however; statistical significance was not reached (P=0.4349). The incidence of treatment-related adverse events was low across all doses (20U:2[6.7%], 50U:6[10.0%] and 75U:8[13.1%]).

Conclusions: These results demonstrate a dose effect of at least 6 months duration with higher doses in the majority of GFL subjects. All doses were well tolerated and safety was consistent with the known safety profile of 20U INCO for GFL.

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INTRODUCTION

IncobotulinumtoxinA (INCO; Xeomin®, Bocouture®; Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) is the only commercially available botulinum toxin A (BoNT/A) preparation free from complexing proteins.[1] INCO is currently approved in worldwide markets and in the United States to treat glabellar frown lines (GFL) at a dose of 20 Units (U) and in the European Union at a dose of 20–30U.

The duration of effect for glabellar lines is approximately 3–4 months in Phase 3 studies investigating the FDA-labeled dose of 20U for INCO, OnabotulinumtoxinA (ONA; Botox®/Vistabel®, Allergan Inc.) and PrabotulinumtoxinA (PRA; Nabota®, Daewong Therapeutics, Korea/ Jeuveau®, Evolus Inc., USA/Nuceiva®, Evolus Inc., Canada, Europe), as well as the FDA-labeled dose of 50U for AbobotulinumtoxinA (ABO; Dysport®/Azzalure®, Ipsen Pharma, Wrexham, UK).[2-4] In the first large, randomized, multicenter, double-blind study to investigate FDA-labeled doses, equivalence between INCO and ONA in the treatment of GFL at the 20U dose in 250 subjects was demonstrated using an investigator-assessed responder rate (≥1-point improvement from baseline on the Facial Wrinkle Scale [FWS] at maximum frown). Similar efficacy profiles were demonstrated at all timepoints (1, 2, 3, and 4 months). Additionally, patient satisfaction was high (>90%) for both treatment groups. In both studies, INCO and ONA were found to be well tolerated.[5] This study supported an earlier head-to-head study demonstrating non-inferiority to ONA in 381 subjects.[6]

In pivotal clinical studies, the duration of effect of 20U INCO for the treatment of GFL was not explored beyond 4 months.[7-9] However, a recent randomized, double-blind, investigator-initiated study showed a strong dose-response relationship with doses of 20, 60, or 100U INCO exhibiting a median duration of effect of 120, 180, and 270 days, respectively. All adverse events (AEs) were mild and consistent with the known safety profile of INCO.[10]

To investigate the duration of effect further for INCO treatment, a prospective, randomized, controlled trial was initiated for the treatment of GFL. This 2-stage study aimed to assess the safety and duration of escalating INCO doses (20U, 50U, 75U in stage 1 and 20U, 100U in stage 2) for up to 360 days. We investigated dose steps of 25 and 30U as these offer practical application to clinical practice and are readily administered from commercially available 50 and 100U vials; 75U was chosen as a suitable intermediate dose. Results for the primary efficacy and safety endpoints from the first stage of this study (dose groups: 20, 50, and 75U) are reported.

SUBJECTS AND METHODS

Study Design

This is a prospective, randomized, double-blind, dose-ranging, Phase 2 clinical study with two stages, conducted across 4 sites in Germany and 5 sites in the USA (ClinicalTrials.gov identification number: NCT03806933; EudraCT identification number 2018-002743-28) as of January 2019. The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice principles. All subjects provided written informed consent prior to beginning any study-related procedures.

In Stage 1, 151 subjects were randomized 1:2:2 to receive GFL treatment with 20, 50, or 75U INCO and followed from treatment until return to baseline severity of GFL wrinkle severity according to the blinded investigator assessment on the FWS at maximum frown. Subjects were required to remain in the study for at least 180±7 days and no longer than 360±7 days, depending on return to baseline.

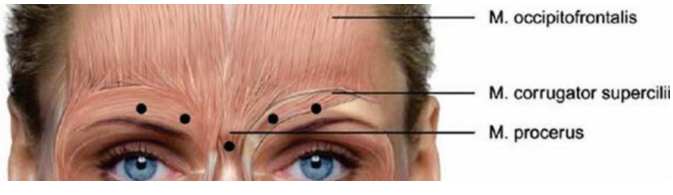
Study Subjects

Male and female subjects (≥18 of age) with moderate (score=2) to severe (score=3) GFL at maximum frown according to both subject and investigator assessment on the 4-point FWS were eligible for this study. Key exclusion criteria included: treatment with BoNT (any serotype) in the facial area ≤12 months before injection; treatment with any facial cosmetic procedure in the glabella area ≤12 months before injection; treatment with any biodegradable filler in the glabella area ≤12 months before injection; any previous insertion of permanent material in the glabella area; and planned cosmetic treatment of the face during the study period.

Study Treatment

Subjects received a single GFL treatment on day 1, with an optional follow-up treatment (20U INCO) for subjects who had completed the main period (MP) of the study. INCO was reconstituted with unpreserved, sterile 0.9% saline solution. The injection volume was constant across all dose groups. Blinded syringes were loaded with a total injection volume of 0.25 mL and administered by the investigator with a 30 or 32G needle in equal aliquots of 0.05 mL into each of 5 injection sites of the procerus and corrugator muscles (Figure 1).

FIGURE 1. Injection scheme. Holding the needle at a 45 degree angle, one injection (0.05 mL) in the procerus muscle at the crossing of two lines connecting the medial part of the eyebrow and the contralateral caruncle; one injection (0.05 mL) on each side of the medial (inner) part of the corrugator muscle, at least 1 cm above the bony orbital rim on an imaginary line drawn vertically from the caruncle; and one injection (0.05 mL) on each side lateral to the previous site in the middle part of the corrugator muscle, at least 1 cm above the bony orbital rim on an imaginary line drawn vertically from the midpupillary line.



Primary Efficacy Endpoint

The primary efficacy endpoint was duration of effect, assessed as the time between treatment and return to baseline severity. Effect was defined as ≥1-point improvement compared to baseline at maximum frown by investigator's live assessment at maximum frown using the FWS, a widely used 4-point standardized photonumeric assessment scale for glabellar line severity (0=no muscle action at all; 1=some even slight muscle action possible; 2=moderately strong muscle action possible; 3=strong muscle action possible that may cause local pallor).

Primary Safety Endpoints

Primary safety endpoints were the occurrence of treatment-emergent AEs (TEAEs), treatment-emergent serious AEs (TESAEs), treatment-emergent AEs of special interest (TEAESIs), related TEAEs, and related TESAEs by dose group as reported by patient and/or investigator. TEAE was defined as an AE emergent with onset or worsening on or after date of the first administration of treatment.

Statistical Analysis

Statistical analyses were performed using SAS® version 9.4 (Cary, NC, USA). Efficacy analyses were conducted on the full analysis set (FAS; all subjects who received study treatment and have a baseline and at least one post-baseline value of any efficacy variable). Duration of effect was described by Kaplan-Meier curves per group and the respective medians of times with associated 2-sided 95% confidence interval (CI). A Cox

proportional hazard regression model was applied with factors dose group, study site, and baseline investigator-assessed FWS score at maximum frown. For safety endpoints, descriptive analyses were conducted for the safety evaluation set (SES; all subjects who received study treatment).

Determination of Sample Size

To detect AEs at least once per group with an incidence rate of 3% with a probability of approximately 80%, a sample size of 53 subjects per group was necessary. Assuming an exponential distribution, a median duration of effect of 3 months and a censoring rate of 5%, a minimum of 55 subjects per group, were needed to obtain a precision of 1.1 months with 80% probability and a precision of 1.5 months with 90% probability. In total, approximately 60 subjects per dose group (20U: 30 subjects in both Stage 1 and 2) were deemed necessary.

RESULTS

Participants

In Stage 1, a total of 161 subjects were screened at 4 sites in Germany and 5 sites in the US, with 151 subjects randomized to receive either 20U (N=30), 50U (N=60) or 75U (N=61) INCO (Figure 2). Six subjects discontinued prior to day 180; all 151 randomized subjects were included in the SES and the FAS according to the intention-to-treat principle. Subject demographics and baseline severity of the GFL were similar for all dose groups. The majority of subjects (N=128, 84.8%) had a baseline score of severe (Table 1).

Primary Efficacy Analysis

The median duration of effect was 185 days for the 50U dose group (95% CI:[182, 205]) and 210 days for the 75U dose group (95% CI:[182, 217]). The Kaplan-Meier plot (Figure 3) reveals a dose effect that was most pronounced between day 120 and day 210. Nearly 100% of subjects had not returned to baseline severity within the first 120 days. From day 210 onward, an increasing number of subjects from all three dose groups returned to baseline. For the 20U dose group, the median duration of effect was 177 days (95% CI: [126, 188] in this first cohort (second 20U cohort to be reported in Stage 2) and nearly 100% of subjects had not returned to baseline severity within the first 90 days. Hazard ratios (HRs) from a Cox proportional hazard regression performed over the entire 360-day follow-up period reached statistical significance for 2 out of 3 pairwise comparisons of dose groups despite the study not being powered for confirmatory statistical significance testing between the groups. HRs indicated significant differences in duration of effect: HR=0.67 (95%-CI: [0.46, 0.98]); *P*=0.0400) for 75U vs 50U and HR= 0.56 (95%-CI: [0.34, 0.90]; *P*=0.0166) for 75U vs 20U. A longer duration of effect for 50U vs. 20U was also observed; however, the HR did not reach statistical significance for this comparison (HR=0.83; 95%-CI: [0.51; 1.34]; *P*=0.4394), likely due to the smaller number of subjects randomized to the 20U group in Stage 1 (30 vs 60 subjects) than to the higher dose groups.

FIGURE 2. Subject disposition [main period (MP) Stage 1].

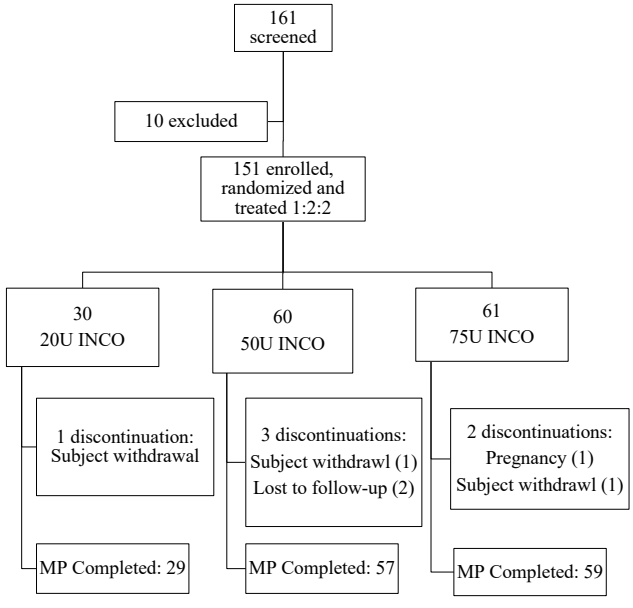
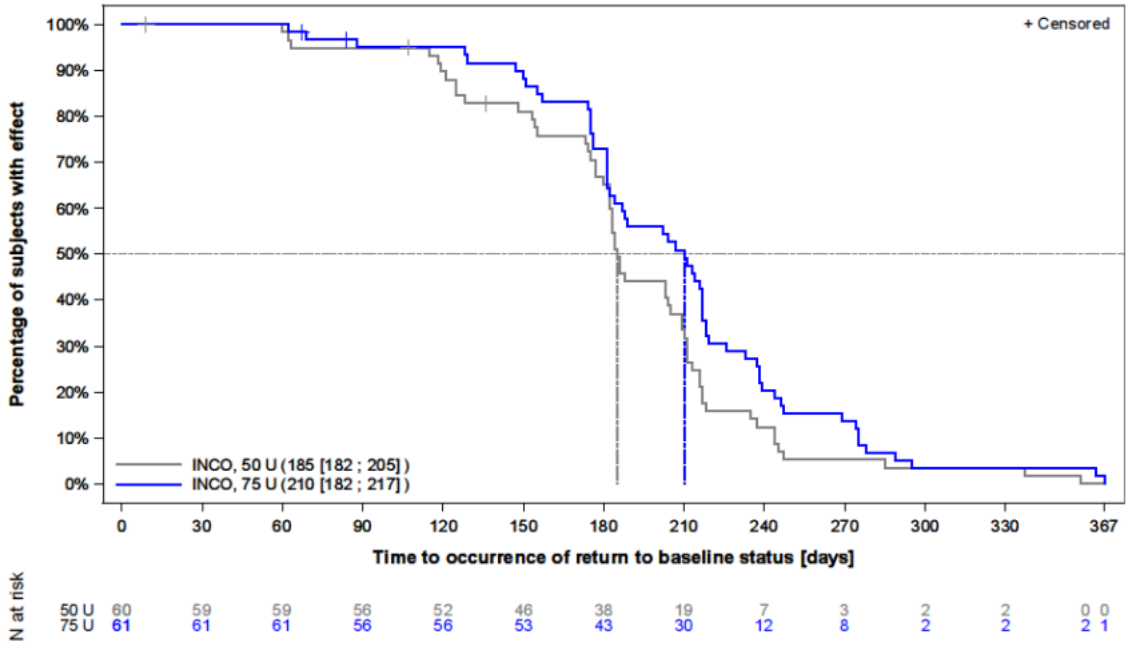


TABLE 1.

Baseline Characteristics (SES/FAS)				
	INCO 20U (N=30)	INCO 50U (N=60)	INCO 75U (N=61)	Total (N=151)
Sex (n [%])				
Male	3 (10.0)	9 (15.0)	7 (11.5)	19 (12.6)
Female	27 (90.0)	51 (85.0)	54 (88.5)	132 (87.4)
Age (years)				
n	30	60	61	151
Mean (SD)	52.3 (11.68)	46.9 (10.27)	49.2 (13.75)	48.9 (12.14)
Median	52.0	45.5	49.0	48.0
Min, max	25, 74	27, 76	22, 74	22, 76
Race (n [%])				
White	28 (93.3)	59 (98.3)	59 (96.7)	146 (96.7)
Black or African American	2 (6.7)	0	1 (1.6)	3 (2.0)
Asian	0	1 (1.7)	1 (1.6)	3 (2.0)
American Indian or Alaska Native	1 (0.3)	1 (1.7)	1 (1.6)	3 (2.0)
Baseline FWS[1] (n [%])				
Moderate (2)	5 (16.7)	9 (15.0)	9 (14.8)	23 (15.2)
Severe (3)	25 (83.3)	51 (85.0)	52 (85.2)	128 (84.8)

[1]Baseline FWS for GFL at maximum frown determined by treating investigator at the baseline visit.
FWS, Facial Wrinkle Scale (2=moderate; moderately strong muscle action possible to 3=severe; strong muscle action possible which may cause local pallor); SD, standard deviation

FIGURE 3. Investigator-assessed duration of effect for 50 and 75U dose groups.



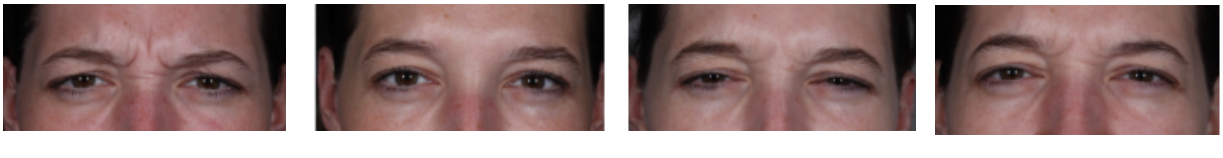
Effect defined by ≥1-point improvement to baseline severity at maximum frown on the FWS. Kaplan-Meier plot, FAS. Final results for 50U (N=60) and 75U (N=61) groups. Numbers in legend denote median time to occurence and 95 % confidence interval.
*Each step of the curve depicts time to return to baseline severity of 1 or more individual subjects (steeper steps indicate more subjects from the respective dose group returned to baseline on that specific day).
+=time of censoring, ie, when time to return to baseline severity could not be observed, eg, in case of subjects dropping out from the study before returning to baseline severity.
N at risk=subjects who are still having an effect.

FIGURE 4. Subjects treated with (a) 50U and (b) 75U of INCO.

(A)

Visit:	Baseline	Day 30	Day 120	Day 180
FWS:	3=Severe	0=None	0=None	1=Mild

(B)



Visit:	Baseline	Day 120	Day 180	Day 210
FWS:	3=Severe	0=None	1=Mild	2=Moderate

TABLE 2.

Incidence of Treatment-Emergent Adverse Events by Dose Group over the entire Main Period of up to 360 days (SES)

	INCO 20U (N=30)	INCO 50U (N=60)	INCO 75U (N=61)	Total (N=151)
	n (%)	n (%)	n (%)	n (%)
Subjects with ≥ 1 TEAE	10 (33.3)	23 (38.3)	26 (42.6)	59 (39.1)
Subjects with ≥ 1 TEAE related to treatment	2 (6.7)	6 (10.0)	8 (13.1)	16 (10.6)
Subjects with ≥ 1 serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)

Primary Safety Analyses

The incidence of TEAEs over the entire MP of up to 360 days was 10 (33.3%) for the INCO 20U group (N=30), 23 (38.3%) for the 50U group (N=60), 26 (42.6%) for the 75U group (N=61), and 59 (39.1%) in total (n=151). No serious TEAEs occurred (Table 2). One TEAE, a pregnancy, led to premature discontinuation of the study. The outcome was a healthy baby.

The incidence of treatment-related TEAEs was 2 (6.7%), 6 (10.0%) and 8 (13.1%) for the 20, 50 and 75U groups, respectively, and 16 (10.6%) in total (n=151). All treatment-related TEAEs were transient and mild to moderate in severity. In the entire SES, incidence of >1% was reported for only 4 Preferred Terms (MedDRA version 22.1): nodule (2[1.3%]), hypoaesthesia (2[1.3%]), headache (6[4.0%]), and eyelid ptosis (2[1.3%]). Over all three dose groups, only 3 subjects (2.0%) reported TEAESIs: eyelid ptosis (2[1.3%]; both related to treatment) and constipation (1[0.7%]; unrelated to treatment). The incidence rates of related TEAEs and of TEAESIs on Preferred Term level are very low and thus not reported by dose group to avoid unblinding of investigators prior to completion of Stage 2.

DISCUSSION

Efficacy

The results of this study demonstrate a dose effect of at least 6 months duration with higher doses for the majority of GFL subjects as assessed by ≥1-point improvement to baseline severity at maximum frown on the FWS. Of note is the high proportion of subjects in this study with GFL rated "severe" at baseline (83–85% of subjects in all dose groups), indicating that such long duration can be achieved with INCO, even for difficult-to-treat patients with severe GFL. In similar studies investigating duration of effect for other neuromodulators, only 35%–41% of subjects per active treatment group had severe GFL at baseline.[12-14]

Preclinical studies demonstrate higher doses result in a longer duration of effect because more BoNT binds to motor endplates, allowing more light chain molecules can reach the cytosol of the neuron.[15] The degradation of more light chain molecules takes a longer time, consequently, the duration is prolonged.[16] Clinical studies with other commercially available neuromodulators have also demonstrated longer duration of effect with increasing dose in the treatment of GFL as described in Table 3. It is important to note that dosing should be based on the clinical data for each product. In an open-label, investigator-initiated study, 30 subjects treated with 120U ABO exhibited a median duration of response of 150 days (21.4 weeks; 95% CI: 120, 180) compared to the 85 days (12.1 weeks) reported in pivotal studies for 50U ABO.[14] A recent pharmacology (Phase 1b) study investigating duration for 40, 60, and 80U vs 20U ONA determined a median duration of response of 19.7 weeks (137.9 days; 95% CI: 16.1, 20.3) for the 20U group and 24 weeks (168 days; 95% CI: 20.1, 24.4) for the 40U group.[17] Duration of response for investigational drug DAXI was explored for the 20, 40, and 60U doses compared to 20U ONA and placebo in a Phase 2 dose-ranging study.[18] A statistically significant difference in median duration of response was observed for 40U DAXI vs 20U ONA, but not for 20U DAXI vs 20U ONA in this Phase 2 trial. Two subsequent Phase 3 studies investigated duration of response for the 40U dose vs placebo and confirmed the Phase 2 median of 24 weeks (168 days).[19]

TABLE 3.

Median Duration of Effect in the Treatment of GFL With Higher Doses.[1]

	INCO		ABO	ONA	DAXI		
	50U	75U	120U	40U	40U	40U	40U
N	60	61	30	50	39	201	204
Study Type	Ph 2	Ph 2	IIS	Ph 1b	Ph 2	Ph 3	Ph 3
Median (95% CI) duration of effect, days	185 (182–205)	210 (182–217)	150† (120–180)	168 (140.7–170.8)	165.2* (137.2–172.9)	168.7* (168–175)	168.7* (168–172.2)

[1]Median duration of ≥1-point improvement from baseline. †Return to baseline severity of Grade 2 or 3. Assessments by investigator at maximum frown on a 4-point scale (INCO, ONA:Facial Wrinkle Scale; ABO:Glabellar Line Severity Score; DAXI:IGA-FWS. Median (95% CI) was based on Kaplan–Meier method.
*[17,32]reported duration of effect in weeks.
CI, confidence interval; Ph, Phase; IIS, Investigator-Initiated Study. Direct study comparisons cannot be made, as studies differ in several aspects.

While a dose effect was demonstrated in our study, the amount of diluent/injection volume may also play a role when it comes to duration of effect. The combination of higher doses and low injection volumes resulted in a high degree of efficacy with sustained duration of effect while maintaining a favorable safety profile. Sustained efficacy beyond 4 months for the 20U dose group is notable for the majority of subjects in this first cohort of 30 subjects. Previous INCO studies have demonstrated efficacy up to 4 months for the majority of patients; however, these previous studies did not extend beyond day 120 or utilize a time to event study design to investigate longer duration.[5,6,9,20]

Safety

The results of this Phase 2, dose-ranging study demonstrate INCO doses of 50U and 75U are safe, well tolerated, and safety is consistent with the known safety profile of the 20U dose for GFL. Notably, the incidence of eyelid ptosis (N=2) in the total SES (N=151) was 1.3%, and no other TEAESIs related to treatment occurred. This favorable safety profile was not unexpected given a previous dose-escalation study in which patients with spasticity received 3 consecutive injection cycles of 400U, 600U, and 600–800U INCO, respectively, without emergence of new TEAESIs.[21]

INCO has demonstrated an excellent safety profile across all large, well-controlled clinical studies, as determined by a pooled safety analysis of 13 studies evaluating more than 6,000 INCO treatments in 2,547 aesthetic patients.[22] Furthermore, INCO is the only BoNT/A with no subjects in clinical studies who have developed neutralizing antibodies and demonstrated a secondary lack of treatment response as outlined in recent updates to the INCO prescribing information.[1] A recent pharmacovigilance analysis of the US FDA AE reporting system database assessed a total of 23,789 BoNT/A cases reported for therapeutic and aesthetic patients. The rate of AEs that involved decreased effect when on treatment for at least 1 year was 0% for INCO compared to other BoNT/As. Causal relationships cannot be established from pharmacovigilance analyses; however, an association was identified in this analysis of one of the largest BoNT/A safety data sets.[23]

By utilizing the only state-of-the-art manufacturing process that employs a 2-step chromatographic purification process to extract from the complexing proteins and leave just the active 150kDa molecule, INCO provides the lowest protein load available compared to other BoNT/A formulations.[1,24-29] INCO contains 0.44ng 150kDa neurotoxin per 100U (0.088 ng/20U dose) and has a high specific activity of 227U/ng, consistent with no denaturing of the BoNT complex during the INCO chromatographic purification process.[24-29] In contrast, ONA, ABO, and PRA all contain complexing proteins and/or denatured BoNT protein that may initiate an immune response, leading to production of neutralizing antibodies that can be associated with decreased effect over time or treatment non-response.[24,31] Investigational drug DaxibotulinumtoxinA (DAXI; RT002, Revance Therapeutics Inc.) contains a virally-derived protein transduction domain (PTD), as part of an added excipient and stabilizer (RTP004). While PTDs have shown promise in pre-clinical efforts for transporting cargo across the cellular membrane, many PTDs have demonstrated immunogenic potential.[29] In line with these findings, DAXI was shown to induce detectable antibody titers to RTP004 within 3 months of use in 30% of tested monkeys, but no long-term immunogenicity data in humans is available at this time.[30,33]

Limitations of our study include low sample size (n=30) in the 20U group for Stage 1, that results in limited power for statistical comparisons to the higher doses. Strengths of our study include a robust observation period of 360 days and high subject retention. Additional strengths include enrollment of males (12.6%), and >80% of subjects with GFL rated "severe" at baseline and across each dose group indicating that even difficult-to-treat patients can achieve long duration with INCO.

CONCLUSION

The results of this study demonstrate a dose effect of at least 6 months duration with higher doses in the majority of GFL subjects. Remarkably, this prolonged duration of effect with INCO was achieved even for difficult-to-treat patients with severe GFL. All doses were well tolerated, and safety was consistent with the known safety profile of 20U INCO for GFL.

DISCLOSURES

All authors except Drs. Roll and Klein have been consultants and/or investigators for Merz Pharmaceuticals GmbH and Merz North America, Inc. Dr. Roll, Lead Medical Expert, and Dr. Klein, Senior Biostatistician, are employees of Merz Pharmaceuticals GmbH. This study and publication were sponsored by Merz Pharmaceuticals GmbH.

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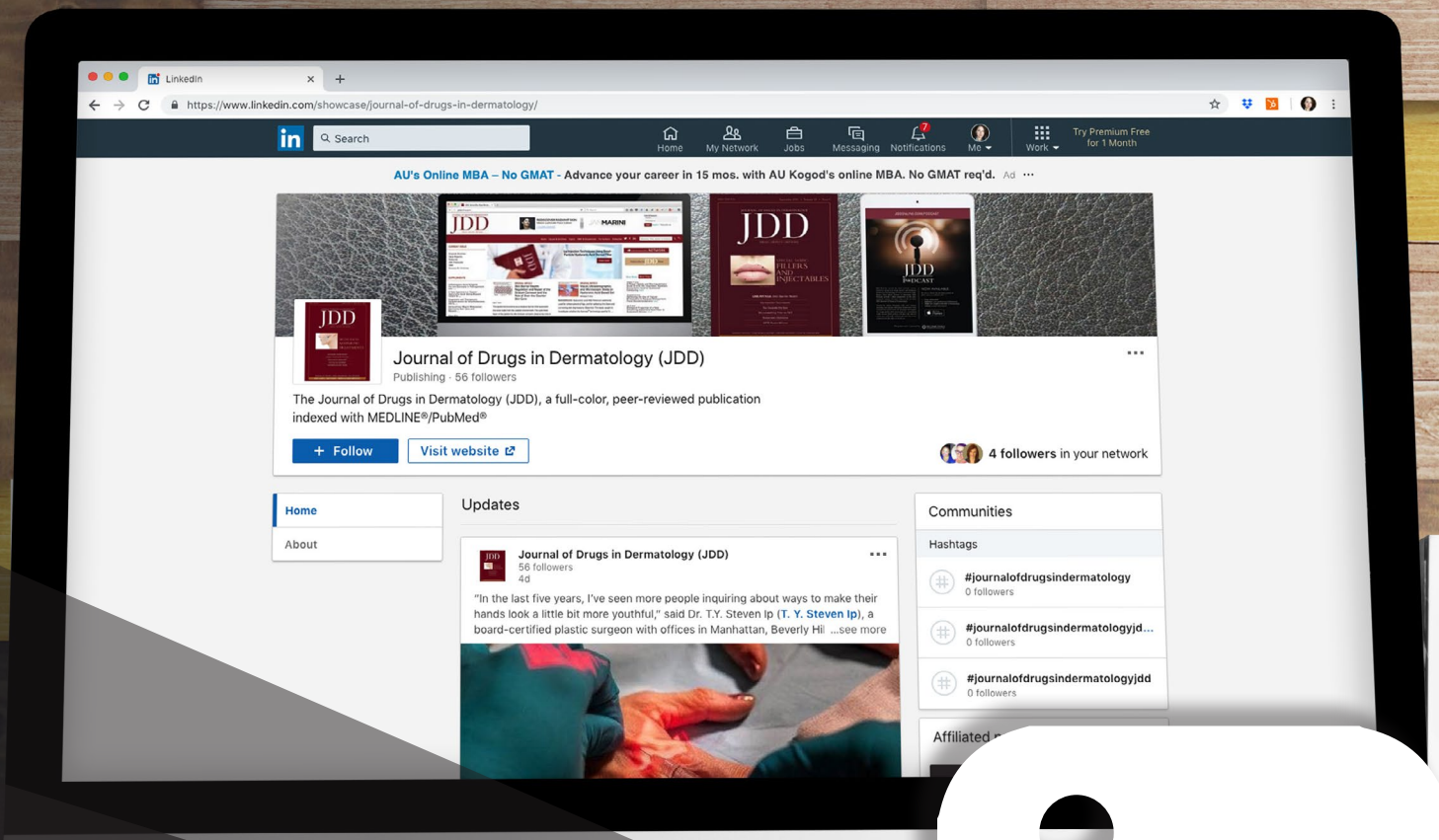

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ORIGINAL ARTICLE

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Hyaluronidase in Dermatology: Uses Beyond Hyaluronic Acid Fillers

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ABSTRACT

Hyaluronidase is mostly widely recognized for its off-label use in correction of complications of hyaluronic acid fillers. However, its utility in other aspects of dermatology is less widely acknowledged. We describe the varied uses of hyaluronidase in dermatology and the underlying evidence base for its dermatological indications. This includes its uses in enhancing drug delivery (for local anesthesia, keloid and hypertrophic scars, and for Kaposi's sarcoma), in the treatment of disorders associated with mucin deposition (myxedema, scleroderma, scleredema, and cutis verticis gyrata) and its potential uses in surgery (as a pre-operative adjuvant in dermatofibrosarcoma protuberans, for periorbital edema, and for hematomas). In select circumstances, hyaluronidase might be more efficacious than more established treatments with fewer adverse effects. We propose hyaluronidase as the latest addition to our global dermatological armamentarium and implore dermatologists to consider its use to enhance their practice.

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BACKGROUND

Hyaluronidase is an enzyme used in ophthalmic surgery and dermatology. Its use is well-established and is the standard approach in dissolving Hyaluronic acid (HA) fillers (off-label) both in overcorrection and vascular emergencies.[1] More recently, its uses in dermatology have expanded to include medical and surgical applications.[2,3]

HA, produced by fibroblasts, is a key component of the extracellular matrix (ECM).[2] Hyaluronidase hydrolyzes HA, reducing ECM viscosity, facilitating dispersal of injected substances and increasing bioavailability leading to its use in aiding the diffusion of local anesthetic injections.[2,4]

Hyaluronidase is used in dermatological conditions in which excessive or abnormal ECM is implicated, such as mucin deposition disorders (resulting in increased glycosaminoglycans) and scars, and where dissolution of physiological HA may be advantageous. We present the wide usage of hyaluronidase in dermatology beyond its cosmetic uses.

Hyaluronidase as an Enzyme

Hyaluronidase is a soluble enzyme, available endogenously in six variants (HYAL1,2,3,4, PH-20, and HYALP1)[5] and exogenously as bovine (Hylase® Dessau, Riemser Pharma GmbH, Greifswald, Germany), ovine (Vitrase®, Bausch & Lomb, Rochester, NY, USA), or human recombinant (Hylenex® Halozyme Therapeutics, San Diego, CA, USA) preparations. Its dosing is expressed in international units (IU) and the dose per preparation depends on the manufacture brand. Its main mechanism of action is degradation of HA through hydrolysis with resultant ECM alteration. Hyaluronidase is licensed by the FDA for increasing absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography.[6] In the European Union, hyaluronidase is licensed for adjunctive subcutaneous drug administration, for increasing LA coverage area, for promoting contrast medium reabsorption in urology, and for promoting reabsorption of subcutaneous hematomas.[2,7-8] Across the world, its most recognized use off-label is for dissolving injected HA or filler-related vascular complications.[8]

Most side-effects are minor and transient and consist of post-injection pruritus, bruising, and swelling.[9] The risk of anaphylaxis is reportedly increased in those with wasp allergies.[8] Two case reports of shock[1] with co-administration of chemotherapy[10] and one report of anaphylaxis[11] have been observed.[8]

Allergy to bee or wasp stings might be associated with an increased risk of allergic reaction to hyaluronidase due to cross-reactivity.[1] A pre-treatment patch test or skin-prick testing might be considered for ovine and bovine preparations as these formulations contain an antigen that can be allergenic.[12] The risk of allergic reactions increases with higher doses.[8]

TABLE 1.

Uses of Hyaluronidase in Dermatology

Study Authors	Intervention	Outcomes	Side-effects
Clark LE, Mellette JR[4]	Hyaluronidase added (7.2 IU/mL) to LA in 72 patients over a one year	Hyaluronidase decreased loss of surface contour	Mild post-operative bruising
Lewis-Smith P[17]	In eight patients, 1500IU of hyaluronidase was diluted in 10mL of 1% lidocaine and injected into a patient, whilst another part of the same patient's arm was injected with 1% lidocaine monotherapy	Hyaluronidase plus anesthesia treated part experienced immediate effects of the anesthesia and area of anesthesia was increased	Minor injection pain
Ahmed S, Ahmed OA[20]	A mixture of 0.5% Marcaine with 1:200 000 epinephrine and 1% lidocaine with 1:200000 epinephrine mixed with 1500U of hyaluronidase was used	Larger areas were covered by the same amount of anesthetic	None reported
Wohlrab J, Finke R, Franke WG, et al[16]	44 patients were injected subcutaneously with either bovine testicular hyaluronidase (0.5mL or 75IU) or 0.5mL placebo (0.9% sodium chloride). All patients were injected with 0.5mL of 0.5% aqueous lidocaine hydrochloride	The addition of hyaluronidase to lidocaine increased the anesthesia's efficacy and increased area lidocaine acted on.	None reported
Aggarwal A, Ravikumar BC, Vinay KN, et al[23]	Group A treated with intralesional TAC (40mg/mL injected at a depth of 3–7mm), group B treated with intralesional TAC with hyaluronidase (1500IU/ml), group C, intralesional verapamil hydrochloride (2.5mg/mL), group D intralesional radiofrequency (at low to medium power), and group E intralesional radiofrequency with TAC (40mg/mL). Groups A, B, and C treated every three weeks for eight treatments, while groups D and E were treated every six weeks for 4 treatment sessions (n=100)	Resolution of scar was most effective in the TAC (75% clearance), TAC and hyaluronidase group (68.75%) and the intralesional radiofrequency with TAC groups (75%), all with comparable outcomes (P<0.01).	Atrophy, reported in 18.75% of the combination TAC and hyaluronidase group compared with 31.25% of patients treated with TAC alone P<0.001)
Goyal NN, Gold MH[24]	A 1mL combination of 5-fluorouracil (250mg/5mL), TAC (40mg/mL), and hyaluronidase (1500U) was injected into 20 patients suffering from keloids or hypertrophic scars	Flattening of scars and resolution of pain and pruritus were reported effects of the treatment. Patients required an average of three treatments to produce the desired results	Pain, superficial ulceration, and scabbing in three patients which resolved by itself
Eisert L, Nast A[25]	Treatment of recalcitrant keloids using a combination of intralesional cryosurgery, triamcinolone (160mg/4mL), 5-fluorouracil (150mg/3mL), and hyaluronidase (100mg/mL)	Treatment of recalcitrant keloids using a combination of intralesional cryosurgery, triamcinolone (160mg/4mL), 5-fluorouracil (150mg/3mL), and hyaluronidase (100mg/mL)	One of the two patients developed hypopigmentation
Hoesly PM, Tolaymat LM, Sluzevich JC[31]	Intralesional hyaluronidase (150U/mL) weekly for 18 weeks was used on the left foot of two patients suffering from pretibial myxedema with clobetasol cream	The left foot had partial plaque resolution after 24 weeks. Another patient had marked flattening of their plaque and a decrease in pain. The untreated feet showed no improvement	Mild injection pain
Menzinger S, Kaya G[33]	Repeated injections of hyaluronidase (120U) were given for a patient with scalp myxedema	The thickness of the scalp was reduced from 1.97mm to 1.15mm assessed with ultrasound after 138 days of treatment	None reported
Smith K, Menon P, Rolfe A[47]	Intralesional hyaluronidase was injected into five DFSPs three times/week with a dose from 300–350 turbidity-reducing units Mohs micrographic surgery was carried out 2–10 days after the last injection	The margins required for the non-hyaluronidase pre-treated patients were 1.5–2.5cm as a maximum margin. The injections treated with hyaluronidase pre-operatively required margin of 0.5–1.5cm	None reported
Menon P, Smith KJ, Crittenden J[49]	DFSP was treated with four weeks of intralesional hyaluronidase injections (three times/week for four weeks; 450 turbidity reducing units) followed by Mohs micrographic surgery four days later	Decreased margin width for excision and a smaller than expected post-operative wound. At 24 months there was no relapse	None reported
Kiyohara T, Tanimura H[44]	Injections of hyaluronidase solution (80U and 1% lidocaine) were given over a 12-week period, with a total of 18 injections given.	Reduced dermal thickening and reduced thickness in the subcutaneous tissue observed. At 2 years follow–up, this was maintained	None reported
Welborn M, Dallo C, Altmeyer M[46]	Patient CVG treated with 150U of hyaluronidase injections every six weeks for a six treatments	After three treatments, furrows were less noticeable and there was some hair regrowth	None reported
Hilton S, Schrumpf H, Buhren BA[53]	20 patients with eyelid edema were treated with 0.2-0.5mL of hyaluronidase (20IU-75IU)	This regimen resulted in rapid reduction of eyelid edema after one injection	Decrease tear trough augmentation
Han JH, Kim J, Yoon KC[54]	2 patients treated with hyaluronidase 1500IU/2ml following post-traumatic hematoma and fibrosis (three-four injections)	The hematoma and fibrosis rapidly resolved	None reported

Enhancing Local Drug Delivery

Adjunct in local anesthesia

The first report of the synergistic effects of hyaluronidase with local anesthetic was reported in 1951 with procaine.[13] Subsequently, several studies have demonstrated its surgical advantages in ophthalmologic and dermatologic surgery (Table 1).[2,4,14] HA hydrolysis with hyaluronidase increases connective tissue permeability, decreasing HA's viscosity and enabling greater dispersion of injected solutions.[15] Example mixtures reported have included doses between 3–75IU.[8] Diluent volume depends on the treated area and a range of 1–10ml has been reported.[1]

In all reported studies, addition of hyaluronidase led to faster onset of anesthetic effect and a greater anesthetized surface area due to increased dispersion of injected solutions.[4,14,16-20] Additionally, there was decreased surface contour irregularities, which could particularly assist in anatomically sensitive areas prone to distortion, such as the lips and eyelids, which require precise alignment during surgery.[4] A notable limitation of concomitant hyaluronidase use was the shorter duration of anesthesia though this did not seem to impact adversely on most procedures.

Distal nerve blocks

Using hyaluronidase and lidocaine could allow for distal nerve blocks, when regional nerve blocks have not dispersed to a large enough area.

A mixture of 0.5% Marcaine was used with 1:200,000 epinephrine and 1% lidocaine mixed with 1500IU of hyaluronidase (Hyalase®,CP pharmaceuticals), allowing for larger areas to be covered by the same amount of anesthetic, with one injection.[20] Adding hyaluronidase might reduce pain associated with injections by decreasing tissue tension.[20]

Keloid and hypertrophic scars

Keloid scars are characterized by excessive collagen and ECM production with dysregulated expression of hyaluronidase mRNA compared to normal skin.[21] HA has a fundamental part in wound-healing and ECM genesis and its disrupted expression in keloid disease is thought to be related to dysregulated hyaluronidase expression.[22]

A randomized controlled trial[23] (n=100) in keloid and hypertrophic scars involved multiple treatment arms. Addition of hyaluronidase (1500IU/ml) to intralesional injection of triamcinolone (TAC) (40mg/ml) in a recombinant mixture appeared to have a lower side-effect profile (atrophy, depigmentation, telangiectasia, injection pain, ulceration, and infection) than intralesional TAC monotherapy, although had a marginally lower resolution rate of keloid scars at 21 weeks follow-up (69% resolution with combination versus 75% with TAC monotherapy).[23] The main side-effects reported were atrophy, reported in 18.75% of the combination group compared with 31.25% of patients treated with TAC alone (P<0.001).[23]

In a separate study,[24] a 1mL combination of 5-fluorouracil (5-FU) (250mg/5mL), TAC (40mg/mL), and hyaluronidase (1500U) recombinant mixture was injected into 20 patients with keloids or hypertrophic scars. Flattening of scars and resolution of pain and pruritus were reported effects of the treatment. Patients required an average of three treatments to produce flattening of keloids and symptom resolution.[24] Triple therapy enabled the reduction in number of injections with a reduced side-effect profile compared to TAC monotherapy.[24]

Hyaluronidase has been shown to support the penetration of 5-FU and TAC.[25] Two patients had a reduction of their scar size of 80% following treatment with a combination of intralesional cryosurgery, TAC (160mg/4mL), 5-fluorouracil (5-FU) (150mg/3mL), and hyaluronidase (100mg/mL).[25]

Taken together, the addition of hyaluronidase to TAC and 5-FU appears to enhance efficacy of treatment of intralesional therapy with reduced side-effects.

Kaposi's sarcoma

Patients with Kaposi's sarcoma (KS)[26] were treated with intralesional vinblastine following prior treatment with 1% lidocaine with or without intralesional hyaluronidase every three weeks. Both vinblastine with and without intralesional hyaluronidase cleared the KS, although combination treatment with hyaluronidase proved more effective in treating tumor nodules. Relapse was reduced in patients treated with the hyaluronidase addition.[26]

Mucin Deposition Disorders

A major constituent of dermal mucin is glycosaminoglycans with HA being abundant.[27] Hyaluronidase has been used successfully in several cutaneous conditions characterized by increased mucin deposition such as pretibial myxedema, scalp myxedema, scleredema, scleroderma, and cutis verticis gyrata.[27]

Pretibial myxedema

Pretibial myxedema is a rare condition in which glycosaminoglycans accumulate in pretibial skin and is associated with Grave's disease and to a lesser degree Hashimoto's thyroiditis.[28] Normalization of thyroid levels rarely corrects this condition and treatment often proves challenging with topical and intralesional corticosteroids used in addition to systemic therapy.[28]

The rationale for hyaluronidase use in pretibial myxedema relates to hydrolysis of excessive HA and ECM reduction, with reported cases of its use in 1949 and 1950.[29-30]

More recently, intralesional hyaluronidase (150IU/mL) weekly for 18 weeks was used on the left foot of two pretibial myxedema patients.[31] One patient had substantial plaque regression, while a second patient treated with the same regimen had marked flattening of their plaque and a decrease in pain.[31]

Paver reported the successful treatment of pretibial myxedema and cutaneous myxoid cysts following treatment with hyaluronidase (1500IU) and TAC (1mg) combination (n=4).[32]

Localized myxedema (distinct from pretibial) can also occur in Grave's disease.[33] A case report[33] presented a patient with scalp myxedema treated with repeated hyaluronidase injections with a reduction in the scalp thickness confirmed by ultrasound.[33]

Scleroderma

Scleroderma is an autoimmune disorder that can result in sclerosis and cutaneous inflammation leading to impairment of function and quality of life.[34] Excessive fibrosis with increased collagen deposition is the hallmark with increased HA in the ECM.[34] The first report of hyaluronidase used in localized scleroderma (off-label) dates back to 1953.[35] Further uses in scleroderma were in microstomia and radiation-induced morphea all demonstrating a symptomatic improvement and a low side-effect profile.[36-39]

Abbas and colleagues[40] demonstrated the efficacy of hyaluronidase (four injections, 150IU) in improving sclerosis.[40] Their patient suffered from microstomia of the mouth resulting in tongue atrophy and decreased mouth-opening.[40] The patient's sclerotic bands resolved almost completely and the patient could open her mouth more widely.[40]

Scleredema

Scleredema is a rare disorder of connective tissue, characterized by mucin deposition with skin induration.[41] It has been reported to occur after streptococcal infection[42] and in diabetic patients (scleredema diabeticorum).[43-44] Dermal thickening is associated with an increase in glycosaminoglycans and can be recalcitrant and challenging to treat.[41]

Injections of hyaluronidase solution (80U,1% lidocaine) were given over 12-weeks to a diabetic scleredema patient (total of 18 injections) with no reported adverse effects.[44] Reduced dermal thickening and reduced thickness of subcutaneous tissue was observed upon T2-weighted magnetic resonance imaging. Other lesions progressively flattened and became softer and this was maintained at two years follow–up.[44] The authors did not comment upon control of diabetes during this time.[44]

Cutis verticis gyrata

Cutis verticis gyrata (CVG) is a cutaneous fibrotic scalp condition characterized clinically by scalp folds and furrows, which may be malodorous, pruritic, and cause a burning sensation.[45] A biopsy-confirmed case of CVG was successfully treated with 150IU of hyaluronidase injections every six-weeks for a total of six treatments,[46] with less noticeable furrows and some hair regrowth with no reported adverse effects. The authors postulate that hyaluronidase decreased HA in scalp areas with excessive dermal thickening, resulting in decreased skin elasticity and hence, improved cosmetic appearance.[46]

Surgical Uses

Neoadjuvant for dermatofibroscarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is a cutaneous malignancy arising in the dermis that shows increased HA.[47] Adjunctive hyaluronidase prior to surgical excision of DFSP was used in two studies.[47-48] Intralesional hyaluronidase was injected at doses of 300–450 IU, followed by Mohs surgery 2–10 days later.[47] Greater polarizable collagen was seen further from the biopsy scar of hyaluronidase-treated tumors and these cells had decreased CD34 expression. Inflammatory reactions further from the biopsy site were greater in hyaluronidase pre-treated cells.[47] The transmembrane glycoprotein CD34 was used to confirm tumor-free margins, since CD34 is commonly used to identify residual DFSP.[49] The decreased CD34 and increased polarized collagen, not usually found in DFSPs, could support hyaluronidase's role in increasing cell differentiation in spindle cells.[47] Decreased margins following hyaluronidase treatment might be due to increased cellular differentiation, possibly accelerating apoptotic progression.[49]

Larger RCTs and long-term recurrence data are required to assess hyaluronidase's use in adjuvant DFSP treatment.[47] Hyaluronidase poses little risk, and could have significant surgical and cosmetic benefits in DFSP treatment.[47]

Periorbital edema

Chronic periorbital edema is a non-specific sign manifesting as swelling beneath the eyelid skin with possible immunological, dermatological, endocrinological, cardiological, and gastroenterological causes.[50]

Acquired lymphedema is a common post-surgical cancer treatment side-effect shown in several animal studies.[51-52] Animal studies revealed that post-operatively, mice had higher HA accumulation following lymph-node removal.[51] This lymphedema was reduced following hyaluronidase treatment in animal studies and immunohistochemical analysis demonstrated that hyaluronidase could augment lymphangiogenesis in lymphedematous limbs.[51] In a separate study, mice with post-surgical lymphedema were injected with human hyaluronidase sustained-release gel pre and post-surgery.[52] Statistically significant enzyme degradation of HA was found, highlighting that hyaluronidase activity can support dispersal of accumulated post-surgical edema.[52]

Hyaluronidase is commonly used to decrease overcorrection or periorbital edema secondary to HA filler placement, although one study reported the successful decrease in periorbital edema in patients with idiopathic edema, not necessarily treated with HA fillers.[53] The effects of hyaluronidase on the edema is therefore not necessarily linked to previous HA filler placement.[53] This can be particularly beneficial as an adjunct during and post periorbital surgery for tumor excision to decrease the common complication of periorbital edema.[53]

Hematoma

Hyaluronidase is licensed by the European Union for reabsorption of subcutaneous hematomas.[8] Swelling and hematoma post facial contusion are frequently reported post-traumatic sequelae and can leave patients with intolerable cosmetic results.[54] A case report presented a patient with a post-traumatic hematoma successfully treated with three injections of hyaluronidase 1500IU/2ml (given at weekly intervals).[54] All hematomas resolved with no adverse cosmetic effects. A different presentation with post-traumatic facial fibrosis in another patient was successfully treated with four hyaluronidase 1500IU/2ml injections, significantly improving fibrotic dimpling.[54] Hyaluronidase liquified the solidified hematoma allowing for absorption and hematoma dissolution, preventing fibrosis.[54] Hyaluronidase is thought to inhibit fibroblast proliferation, degrading HA and reducing fibrosis.[54] Hyaluronidase could plausibly be of therapeutic benefit in highly symptomatic or functionally impairing post-procedural hematomas in dermatology.

CONCLUSION

Hyaluronidase has demonstrated significant promise when used outside of its licensed use in numerous dermatological conditions spanning medical, surgical, and cosmetic disciplines. As an adjunct to anesthesia, it has demonstrated the ability to disperse the LA over a larger area in a faster timeframe. It may also reduce tissue distortion caused by LA administration, particularly of perioral and periocular skin, which is of particular utility in dermatologic surgery. Hyaluronidase may play a useful role in keloid and hypertrophic scarring, distributing established therapies more effectively while degrading the aberrant ECM. Its use in the pre-treatment of conditions such as DFSP and as combination therapy in KS may be of further interest to dermatologic surgeons. Conditions with excess mucin deposition and fibrosis such as scleroderma could allow for life-changing results in improving microstomia and fibrotic tissue.

Hyaluronidase appears to be a safe and cost-effective treatment, with few adverse effects. We would like to draw the attention of dermatologists to the increasing uses of hyaluronidase and to consider it in cases resistant to common conventional treatments.

DISCLOSURES

The authors have reported no relevant conflicts of interest.

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CASE REPORT

Journal of Drugs in Dermatology

Successful Management of a Black Male With Psoriasis and Dyspigmentation Treated With Halobetasol Propionate 0.01%/Tazarotene 0.045% Lotion

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ABSTRACT

Skin of color patients with psoriasis face unique challenges related to disease characteristics and treatment. Dyspigmentation, including postinflammatory hypo- and hyperpigmentation, more frequently and severely affects patients with skin of color and remains a challenge in psoriasis management. We present the case of a 58-year-old Black male with moderate psoriasis who was treated for 8 weeks with a fixed combination halobetasol propionate 0.01%/tazarotene 0.045% (HP/TAZ) lotion during a phase 3 study (NCT02462070). HP/TAZ was efficacious in this patient, whose Investigator's Global Assessment score decreased from 3 (moderate) at baseline to 1 (almost clear) within 4 weeks, with maintenance of "almost clear" through week 12 (4 weeks posttreatment). Affected body surface area decreased by 50% and quality of life greatly improved from baseline to week 8. The patient experienced dyspigmentation of the affected skin during the trial; hypopigmentation was primarily experienced from weeks 2–8, with the greatest degree at week 4. By week 12, the affected skin area had returned to normal, with only small regions of hyperpigmentation, primarily around the periphery of the lesion. These results indicate that HP/TAZ may be a treatment option for patients with skin of color, who are disproportionally affected by postinflammatory dyspigmentation.

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INTRODUCTION

Skin of color patients with psoriasis face unique challenges related to disease characteristics and treatment. Distribution and severity of psoriasis may be greater in patients with skin of color.[1,2] Dyspigmentation—including postinflammatory hypo- and hyperpigmentation—also more frequently and severely affects patients with skin of color[3,4] and remains a challenge for dermatologists to manage.[5] Finally, Black and Hispanic/Latino patients have demonstrated worse health-related quality of life (QoL) compared with White patients, as assessed by the Dermatology Life Quality Index (DLQI)[6]; these differences are likely related to several factors, which include varying cultural perceptions of skin disorders and the greater negative impact of dyspigmentation in patients with skin of color.[2,7]

The treatment of psoriasis commonly involves the use of topical corticosteroids, such as the superpotent topical corticosteroid halobetasol propionate (HP).[8,9] Corticosteroids are anti-inflammatory, immunosuppressive, antiproliferative, and vasoconstrictive; however, tachyphylaxis and adverse events following long-term use remain a concern.[8-10] The topical retinoid tazarotene (TAZ) has several mechanisms of action that modulate pathogenic factors of psoriasis—including normalizing markers of differentiation, proliferation, and inflammation—though TAZ used alone may induce cutaneous irritation.[10-13] The combination of HP with TAZ may enhance efficacy in the treatment of psoriasis, reduce side effects of both active drugs, and sustain treatment response.[10,11]

A fixed combination lotion of HP 0.01% and TAZ 0.045% (HP/TAZ; Duobrii,® Ortho Dermatologics, Bridgewater, NJ) was developed utilizing a novel polymeric emulsion technology, which allows for rapid and uniform distribution of HP and TAZ, humectants, and moisturizers on the skin.[10] Phase 3 clinical data have demonstrated efficacy and tolerability of HP/TAZ lotion in patients with moderate-to-severe localized plaque psoriasis.[14,15] Here, we present a case report of a Black male with moderate plaque psoriasis who was successfully treated with once-daily HP/TAZ lotion over 8 weeks, with resolution of skin dyspigmentation by week 12.

TABLE 1.

Efficacy and Tolerability Outcomes						
Outcome	Study Visit					
	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
IGA score[a]	3	2	1	1	1	1
Treatment Success[b]	-	No	Yes	Yes	Yes	Yes
Affected BSA	10%	8%	5%	6%	5%	6%
Signs of Psoriasis (at target lesion)[c]						
Erythema	2	1	1	1	0	1
Plaque Elevation	4	0	1	1	1	1
Scaling	3	1	0	1	1	1
Local Skin Reactions[d]						
Itching	0	0	0	0	0	2
Dryness	2	0	0	0	2	1
Burning/Stinging	0	0	0	0	0	0

Face, scalp, palms, soles, groin, axillae, and intertriginous areas were excluded from assessment if psoriasis was present.
[a]IGA based on a 5-point scale: 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe.
[b]Treatment success defined as a ≥2-grade improvement from baseline in IGA score and a score of 'clear' or 'almost clear' (0 or 1).
[c]Signs of psoriasis based on a 5-point scale: 0=none, 1=minimum, 2=mild, 3=moderate, 4=severe.
[d]Itching (within last 24 hours), dryness, and burning/stinging (within last 24 hours) based on a 4-point scale: 0=none, 1=mild, 2=moderate, 3=severe.
BSA, body surface area; IGA, Investigator's Global Assessment.

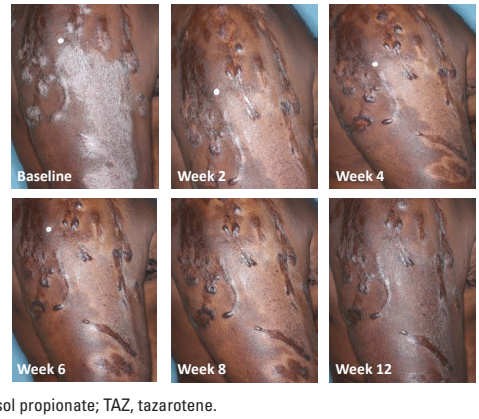
CASE REPORT

The patient was a 58-year-old, non-Hispanic, Black male with moderate psoriasis (Investigator's Global Assessment [IGA]=3) and affected body surface area (BSA) of 10% at baseline (Table 1). The patient was enrolled in a phase 3, randomized, double-blind, vehicle-controlled study that assessed HP/TAZ lotion in participants with moderate-to-severe psoriasis (NCT02462070); detailed methodology and study results have been previously published.[14,15] The patient, randomized to HP/TAZ for 8 weeks with a 4-week posttreatment follow-up, was instructed to apply a thin layer of HP/TAZ lotion once-daily over all affected areas.

The target lesion (Figure 1), located on the upper right arm, was 99 cm^2 in size at baseline; prominent keloid scars were also apparent. The patient also had an additional non-target lesion treated with HP/TAZ during the study (Figure 2). At baseline, both lesions appeared as classic psoriatic elevated plaques covered with white/silvery scales. By week 2 of HP/TAZ treatment, scales had diminished, though affected skin was hypopigmented in the center with hyperpigmentation at the border of the psoriatic plaque resolution. The degree of hypopigmentation appeared to be greatest at week 4, with skin pigmentation nearing normal by week 8. At 4 weeks posttreatment, the affected skin area had returned to normal with small regions of hyperpigmentation, the greatest around the periphery of the affected skin lesion.

The patient achieved treatment success with HP/TAZ lotion, with an improvement to 'almost clear' at week 4 that was maintained posttreatment at week 12 (Table 1). Improvements

FIGURE 1. Target lesion. Patient was treated with HP 0.01%/TAZ 0.045% lotion once daily for 8 weeks, with 4-week posttreatment follow-up at week 12.



HP, halobetasol propionate; TAZ, tazarotene.

FIGURE 2. Additional lesion. Patient was treated with HP 0.01%/TAZ 0.045% lotion once daily for 8 weeks, with 4-week posttreatment follow-up at week 12.

HP, halobetasol propionate; TAZ, tazarotene.

in affected BSA and signs of psoriasis at the target lesion were also observed early following treatment with HP/TAZ lotion and maintained up to 4 weeks posttreatment. The patient had substantial improvements in QoL during the study, with DLQI score decreasing from 9 ("moderate effect" on life) at baseline to 1 ("no effect" on life) at weeks 4 and 8.

No adverse events were reported. Dryness was the only local skin reaction present at baseline (assessed as moderate by the investigator), which subsided at weeks 2–6 and returned to mild dryness by study end (Table 1). No itching was reported during HP/TAZ treatment until posttreatment follow-up, where it was assessed as moderate. The patient did not report burning/stinging at any study visit. Further, there were no instances of skin atrophy, striae, telangiectasias, or folliculitis—other known drug-related skin reactions.

DISCUSSION

Racial and ethnic differences in epidemiology, clinical features, genetic predisposition, and response to treatment of psoriasis are important to address given our increasingly diverse patient population.[7] Here we report the management of psoriasis in a Black male enrolled in a clinical trial who was randomized to treatment with HP 0.01%/TAZ 0.045% lotion once daily for 8 weeks, with a 4-week posttreatment follow-up at week 12.

HP/TAZ was efficacious in this patient, who achieved an IGA score of 1 (almost clear) within 4 weeks and maintained treatment success at weeks 8 and 12. Affected BSA decreased 50% from baseline to week 8. Quality of life was improved in this patient, whose DLQI score by week 8 indicated "no effect" of psoriasis on the patient's QoL, a substantial and clinically meaningful[16] improvement from the "moderate effect" observed at baseline. A clinical feature of this patient was the presence of prominent keloid scars, which are benign fibrous growths resulting from an abnormal connective tissue response.[17] While the cause of the keloids in this patient is not known, the presence of keloids is not unexpected, as there are racial differences in prevalence, with Black individuals forming keloids more often than White individuals.[17]

The patient experienced dyspigmentation of the affected skin during the trial, which is also not unexpected, given that resolution of psoriasis in darker skin is associated with both hypo- and hyper-pigmentation.[18] Dyspigmentation is of particular concern, as it can have significant psychosocial impacts, contribute to greater negative emotions, and even be more bothersome than the psoriasis itself in patients with skin of color.[2,4,7] Hypopigmentation was primarily experienced from weeks 2-8, with the greatest degree at week 4. By week 12 the affected skin area had returned to normal, with only small regions of hyperpigmentation, primarily around the periphery of the lesion. This relatively fast time to resolution is notable given that dyspigmented patches can take between 3 and 12 months to resolve.[2]

Skin color is primarily due to the presence of melanin, a pigment formed by immune cells called melanocytes. Melanin formation, or melanogenesis, is a complex process of melanin synthesis, transport, and release to keratinocytes, which occurs within organelles of melanocytes called melanosomes.[19] The mechanisms and pathogenesis of postinflammatory hypo- and hyperpigmentation in psoriasis are not fully elucidated, though multiple hypotheses have been suggested. Inflammation-associated hypopigmentation may be a result of rapid turnover of keratinocytes during hyperplasia, which can interfere with melanosome transfer.[18] Cutaneous inflammation, through signaling of growth factors and pro-inflammatory cytokines such as IL-17 and TNF-α, can also lead to hypopigmentation through inhibition of melanogenesis,[18,20] with more severe inflammation potentially leading to permanent pigmentary changes through loss or death of melanocytes.[20] Interestingly, it has been observed that while hypopigmentation often accompanies active inflammation, patients are at risk of developing hyperpigmentation once the inflammation has resolved, potentially due to increased numbers and activity of melanocytes.[18,21] This too may be the result of cytokine signaling during inflammation. For example, IL-17 and TNF-α can simultaneously suppress melanogenesis while also stimulating the proliferation of melanocytes; as such, upon resolution of inflammation, the increased number of melanocytes in lesional skin (without concurrent suppression of melanogenesis) will produce excess melanin, leading to postinflammatory hyperpigmentation.[18]

The fixed combination of HP and TAZ used to treat psoriasis in the patient from this case report resulted in psoriasis lesion clearance with self-limited postinflammatory hypopigmentation and low levels of hyperpigmentation observed by week 12. Topical corticosteroids, a mainstay of treatment for psoriasis,[8] are used as first-line therapy for hyperpigmentation when combined with hydroquinone and topical retinoids.[5,22] Corticosteroids are thought to be effective by decreasing cellular metabolism, thereby inhibiting melanin synthesis.[22] Corticosteroids have also been shown to minimize the risk of postinflammatory hyperpigmentation after laser resurfacing.[23] Topical retinoids are effective in treating postinflammatory hyperpigmentation with other agents as described above or as monotherapy.[22] For example, TAZ 0.1% gel and cream have demonstrated efficacy in acne-related postinflammatory hyperpigmentation, significantly improving pigmentation intensity versus vehicle[24,25]; TAZ was also more effective than adapalene 0.3% gel in reducing hyperpigmentation.[25] Tazarotene 0.1% cream is approved as an adjunctive treatment in the mitigation of facial mottled hyper- and hypopigmentation. Retinoids are thought to reduce hyperpigmentation through multiple mechanisms, including:

stimulating keratinocyte turnover (promoting loss of melanin), reducing/inhibiting melanosome transfer to keratinocytes, and interrupting melanin synthesis.[22,26] TAZ has also been shown to downregulate markers of cell proliferation and inflammation such as IL-6,[12,13] which is known to have hypopigmenting effects.[18]

The fixed combination HP 0.01%/TAZ 0.045% lotion used by the patient in this case report has additional efficacy and safety benefits. The new polymeric emulsion technology used to develop HP/TAZ lotion allows for efficient permeation of the active ingredients into the dermal layers, at around half the concentration of traditional topical formulations.[10] Further, HP/TAZ lotion has demonstrated synergistic activity, with efficacy greater than that which would be predicted from the individual active ingredients.[10] The maintenance of therapeutic effect seen in this patient—who sustained disease reduction 4 weeks posttreatment—is likely due to the mechanism of action of TAZ in psoriasis, which restores skin to a quiescent, prelesional status.[27] However, when used alone, TAZ can cause cutaneous irritation; HP alone can also result in AEs that limit long term use. These safety limitations can be minimized when combining HP with TAZ.[10,11] The patient in this case report did not report any adverse events—including any application or irritation events—and local skin reactions were limited. Though the patient was limited to 8-weeks of HP/TAZ treatment as part of the clinical trial design, treatment with HP/TAZ for up to 1 year (maximum 24 weeks of continuous use) in an open-label, long-term study (NCT02462083) has demonstrated a favorable safety profile.[28]

CONCLUSION

In conclusion, this case report in a Black male patient demonstrates that this new formulation of HP 0.01%/TAZ 0.045% lotion was efficacious in the treatment of psoriasis, with treatment success achieved early and maintained 4 weeks posttreatment. Hypopigmentation was evident during resolution of disease, though had completely resolved by week 12 with minimal hyperpigmentation observed. These results indicate that HP/TAZ may be a treatment option for patients with skin of color, who are disproportionally affected by postinflammatory dyspigmentation.

DISCLOSURES

Seemal Desai has served as a research investigator and/or consultant for Skinmedica, Ortho Dermatologics, Galderma, Pfizer, Dermavant, Almirall, Dermira, and Watson.

Andrew F. Alexis has received grant/research support (funds to institution) from Leo, Novartis, Almirall, Bristol-Myers-Squibb, Celgene, Menlo, Galderma, Bausch Health, and Cara; and has served as a consultant/advisory board member for Leo, Novartis, Menlo, Galderma, Pfizer, Sanofi-Regeneron, Dermavant, Unilever, Celgene, Beiersdorf, L'Oreal, BMS, Menlo, Scientis, Bausch Health, UCB, and Foamix.

Abby Jacobson is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company.

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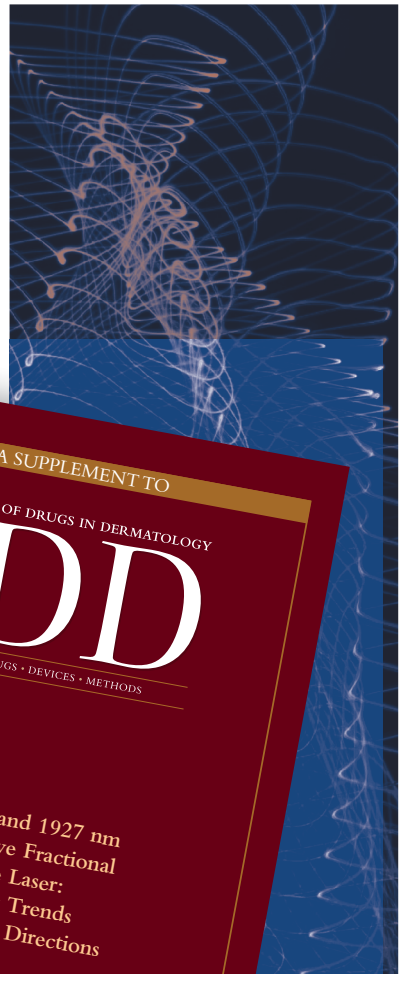

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CASE REPORT Journal of Drugs in Dermatology

Persistent Agminated CD30+ Lymphoproliferative Disorder

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INTRODUCTION

Lymphomatoid papulosis (LyP) is a chronic skin condition, characterized by recurrent eruptions of papules and nodules with or without central necrosis that spontaneously resolve. This condition was originally described by Macaulay in 1968 as a self-healing rhythmical paradoxical eruption that was clinically benign yet histologically malignant.[1] Clinically, it is defined by papules that wax and wane, are generally less than 1cm in diameter, and heal spontaneously after 6–8 weeks with subsequent scarring.[2]

LyP is classified by the World Health Organization (WHO) as a subtype of primary cutaneous CD30+ lymphoproliferative disorders (CD30+LPD), which also includes primary cutaneous anaplastic large cell lymphoma (pcALCL).[3,4] Histopathologically, LyP and pcALCL can show significant similarities, and clinical correlation is often needed to delineate the two, with a common description of LyP lesions being <1cm, while pcALCL is often >2cm. Moreover, a borderline/intermediate phase is often discussed amongst cutaneous lymphoma experts, which is characterized with 1–2cm lesions that can wax and wane or be more persistent. The clinical differential diagnosis can also include pityriasis lichenoides et varioliformis (PLEVA) and pityriasis lichenoides chronica (PLC) that manifest with crops of self-limited necrotic papules and T-cell infiltrates, which can be clonal.[5] These entities are often CD30 negative, although reports of CD30+ PLEVA are known.[5,6] Because of the similarities seen in CD30+ LPDs and PLEVA/PLC, clinicopathologic correlation is often the best way to distinguish between these entities.

Here, we describe the case of a woman who initially presented with a persistent eruption lasting more than two years. Her lesions did not spontaneously resolve but they did respond to topical steroids for a brief period of time. This case represents a histopathologically and clinically atypical lymphoproliferative eruption that is best characterized as a localized CD30+ LPD.

CASE

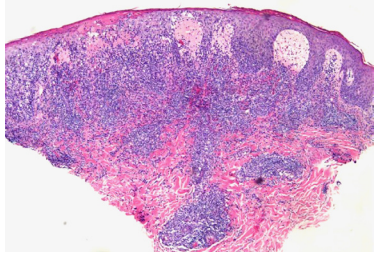
A 38-year-old female presented to a dermatology clinic with concern about an eruption on her right leg for at least two years in duration prior to treatment. She had no significant past medical, surgical or family history, and was taking no medications or over-the-counter supplements. On physical exam, she had a cluster of 5–10 mm pink to red papules in an agminated pattern on her right antero-medial thigh (Figure 1). A punch biopsy was performed and sent for histopathological analysis.

FIGURE 1. Clinical presentation of patient with pink to red papules on her right antero-medial thigh.

Pathology showed a dense, wedge-shaped lymphoid infiltrate with abundant CD3+/CD30+ enlarged atypical T-lymphocytes with significant exocytosis. There was associated papillary dermal edema with admixed reactive lymphocytes and eosinophils (Figure 2A–D).

FIGURE 2. Skin biopsy showing a dense wedge-shaped lymphoid infiltrate with abundant enlarged atypical mononuclear cells with epidermotropism, associated papillary dermal edema, and admixed lymphocytes and eosinophils at 50x (A), 100x (B), and CD30(+) expression at 100x (C).

(A)



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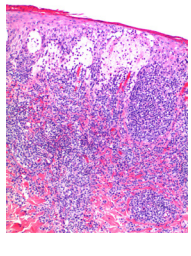

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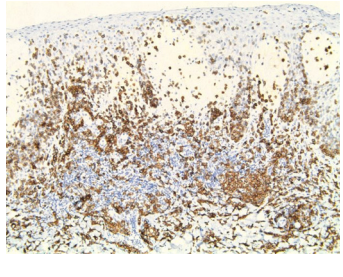

TABLE 1.

Major Histologic Subtypes of LyP Lesions			
LyP Type (frequency)	Predominant Phenotype	Description	Main Differential Diagnosis
A (>80%)[3,7]	CD4+, CD8-	Wedge-shaped infiltrate with scattered or clustered CD30+ tumor cells, intermingled with numerous inflammatory cells, such as small lymphocytes, neutrophils, eosinophils, and histiocytes	C-ALCL, Tumor stage MF, Classic Hodgkin lymphoma
B (<5%)[3,7]	CD4+, CD8-	Epidermotropic infiltrate of small atypical CD30+ or CD30– lymphoid cells with cerebriform nuclei that histologically resembles MF.	Plaque stage MF
C (10%)[3,7]	CD4+, CD8-	Cohesive sheets of CD30+ large atypical lymphoid cells with only a few admixed reactive inflammatory cells.	C-ALCL, Transformed MF (CD30+)
D (<5%)[3,7]	CD4-, CD8+	Epidermotropic infiltrate of small- to medium-sized atypical CD8+ and CD30+ lymphoid cells that histologically resembles primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.	CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
E (<5%)[6,7]	CD4-, CD8+	Consistent dermal angiocentric infiltrates of small and medium-sized to large pleomorphic cells expressing uniformly CD30 and focally CD8 that infiltrate the walls of small to medium-sized dermal, and in some cases subcutaneous, blood vessels	Extranodal NK/T-cell lymphoma

CD20 immunostaining did not highlight a significant B-cell population. Treponema pallidum immunostains and a PAS stain were negative for spirochetes and fungi, respectively. Direct immunofluorescence showed no IgG, IgA, IgM, C3, C5b-9, or fibrinogen deposition. Combining the clinical and histopathological findings, LyP was favored due to the significant positive CD30 staining, although clinically her course was atypical.

The patient was started on twice daily clobetasol propionate 0.05% ointment for four weeks leading to almost total resolution of her lesions. However, four months after the point when the lesions had nearly resolved, after she had stopped the treatment, they reappeared in exactly the same location.

DISCUSSION

Differentiating between the various lymphocytic processes that were diagnostic possibilities in this case has significant therapeutic and prognostic implications. Whereas some of these diseases have a banal course and can self-resolve, others such as primary cutaneous anaplastic large cell lymphoma or recurrent LyP require intervention and clinical workup.

Unlike most cases of LyP, the lesions in this case did not spontaneously wax and wane in more than 24 months. They did improve for approximately four months when treated with clobetasol propionate. However, as mentioned, full resolution was not maintained, and the lesions returned to the same location after discontinuation of treatment.

The clinical course and very focal anatomic presentation of the disease does not neatly place it within the diagnostic criteria for PLEVA/PLC although it has several histologic features of this entity as well, namely a dense lymphocytic lichenoid dermal infiltrate and prominent intraepithelial lymphocytes.
One final, but important, consideration for this atypical lymphoproliferative eruption is pcALCL. LyP and pcALCL share many histopathological features, making them difficult to distinguish under the microscope. Classically, LyP is characterized by recurrent crops of small papules or nodules, whereas in pcALCL, solitary or grouped nodules will grow into ulcerated large tumors or plaques, which are larger than 2cm. While lack of involution is not uncommon in pcALCL, it is rarely reported in LyP. In this case, the patient presented with a cluster of small papules without ulceration similar to those usually found in LyP.

Histopathology of pcALCL can also be similar to LyP, specifically subtype C, with a dense dermal infiltrate of atypical CD30+ T-lymphocytes. However, often, the infiltrate of pcALCL rarely exhibits epidermotropism, and in contrast to our case and the overall density of dermal infiltrate in pcALCL is often much greater. However, clinical correlation is necessary in order to delineate the processes. Regarding the histopathology of LyP, the 2018 World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classification details several histologic subtypes that have been shown to have prognostic implications for lymphoma development.[7] (Table 1) Overall, the pathology of our patient's lesion showed mixed histologic subtype, expressing a dense infiltrate of enlarged CD30+ cells that exhibit significant epidermotropism.

LyP has an excellent prognosis with an estimated five-year survival of almost 100%.[8] Overall, it accounts for about 12% of cutaneous lymphoproliferative disorders, can occur at any age with a mean range of 35–45 years old and a male-to-female ratio of approximately 1:5.[2] Lymphomatoid papulosis can be associated with other lymphoproliferative disorders, with rates ranging from 4% to 20%.[9,10] The most common associated disorders are mycosis fungoides (61%) followed by systemic anaplastic large cell lymphoma (26%), Hodgkin's lymphoma (4%), chronic lymphocytic leukemia (4%), and others (5%).[11]

This report describes a unique case of an atypical lymphoproliferative eruption that did not regress until high potency topical steroids were applied. In light of the overall clinicopathologic presentation, the patient's clinical course most closely aligns with a persistent agminated CD30+ lymphoproliferative disorder, which has been reported mainly in case reports before, though not fully classified by the WHO at this current time.[12] In the prior case reports, as in our case, this process presents with a persistent course, and is often in a single anatomic location located on the trunk and proximal extremities, as opposed to the self-resolving course and more widespread anatomic pattern of LyP or PLEVA/PLC.[12] These patients have a high degree of clinical variability, leading to an alternative diagnosis of localized LyP.[13] When presented with a case such as this, which is less than clear in a variety of criteria, it may be impossible to issue a definitive diagnosis. In those patients, such as this one, it is important to monitor them over time as the clinical presentation may evolve.

DISCLOSURES

Authors have no relevant conflicts to report.

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FEATURED CONTENT

Journal of Drugs in Dermatology

NEWS, VIEWS, & REVIEWS

Is TNF-α Inhibitor-Induced Psoriasiform Dermatitis Always Psoriasiform?

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Tumor necrosis factor-α inhibitors (TNFIs) have significantly improved the quality of life for patients with psoriasis and psoriatic arthritis. Despite their beneficial effects, TNFIs have been reported to cause paradoxical 'psoriasiform' eruptions.[1] Although this nomenclature has become pervasive in the dermatology lexicon, there is a growing body of literature highlighting the protean clinical presentation of this eruption (Figure 1), which could ultimately lead to a delayed diagnosis.[2-5] The diversity of the morphology highlights the importance of identifying key histopathologic characteristics, which to date have not been well-characterized.[2]

Figure 1. Clinical presentation of non-psoriasiform erythrodermic variant of "psoriasiform dermatitis" resulting from a TNF-α inhibitor.

In the current literature, interface dermatitis can be prevalent histologically amongst TNFI-induced 'psoriasiform' lesion biopsies.[3-5] In a case series by Laga and colleagues, four among 16 biopsies for morphologically psoriasiform lesions showed interface/lichenoid dermatitis.[3] Instead of typical psoriasiform hyperplasia with hypogranulosis, confluent parakeratosis, and lymphocytic infiltrate, these biopsies showed epidermal hyperplasia with hypergranulosis, eosinophilic cytoid bodies, orthokeratosis, and band-like lymphocytic infiltrate at the dermoepidermal junction. Additional case series have also reported focal interface/lichenoid dermatitis with predominant CD8+ T-cell infiltrate in the upper dermis.[4,5] Similarly, vacuolar interface dermatitis can be present in TNFI-induced 'psoriasiform' eruptions with vacuolization at the dermoepidermal junction (Figure 2).

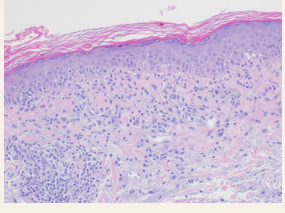

Figure 2. Lymphohistiocytic interface and spongiotic dermatitis with vacuolar changes and nectroic keratinocytes consistent with TNF-α induced 'psoriasiform' eruption".

Importantly, while spongiosis is not a common pathologic feature for psoriasis (more often dependent on biopsy site selection), spongiotic dermatitis is known to be prevalent amongst TNFI-induced 'psoriasiform' eruptions.[2,4,5] Hu and colleagues found that 35% of TNFI-induced 'psoriasiform' biopsies demonstrated spongiotic dermatitis.[2] Similarly, eosinophil-rich perivascular pattern dermatitis may be seen in TNFI-induced 'psoriasiform' eruptions.[3,5,6]

Few studies also observed histopathologic findings of folliculitis on TNFI-induced 'psoriasiform' lesion biopsies.[2,3] Given that some TNFI-induced psoriasiform eruptions may involve the hair follicle, it becomes important to further biopsy areas that do involve hair follicles to verify true psoriasiform dermatitis over folliculitis.

The correlation with histopathologic characteristics and morphology of TNFI-induced eruptions is crucial for diagnosis and differentiation from other cutaneous adverse events of TNFI therapy.[6] However, the broad use of the terms TNFI-induced 'psoriasis' or 'psoriasiform lesions' creates an inconsistency between clinical morphology and histologic findings, which can obscure the true diagnosis and delay proper treatment. For example, some TNFI-induced 'psoriasiform' eruptions will improve with withdrawal of TNFI while other eruptions will worsen even though they fall under the same TNFI-induced 'psoriasiform' category.[2,4,7] Based on the mounting evidence in the literature that TNFI-induced 'psoriasiform' eruptions present with a wide spectrum of overlapping morphology and histopathologic features, the characterization of TNFI-induced lesions should rely more on the histopathologic pattern.[6,7] Therefore, it is certainly warranted to histologically evaluate new cutaneous eruptions of patients on TNFI-based therapy, and the nomenclature should be changed to reflect the unique attributes of this condition.

Disclosure

The authors declare no conflicts of interest.

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ARAZLO™ (tazarotene) lotion, for topical use
Initial U.S. Approval: 1997
This Brief Summary does not include all the information needed to use ARAZLO safely and effectively; please see full Prescribing Information for ARAZLO.

INDICATIONS AND USAGE

ARAZLO™ (tazarotene) lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

CONTRAINDICATIONS

ARAZLO is contraindicated in pregnancy. ARAZLO may cause fetal harm when administered to a pregnant patient *[see Warnings and Precautions, Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Toxicity Based on data from animal reproduction studies, retinoid pharmacology and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Safety in pregnant patients has not been established. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, discontinue ARAZLO as soon as pregnancy is recognized.

Tazarotene elicits malformations and developmental effects associated with retinoids after topical and oral administration to pregnant rats and rabbits during organogenesis. However, limited case reports of pregnancy in females enrolled in clinical trials for ARAZLO have not reported a clear association with tazarotene and major birth defects or miscarriage risk *[see Contraindications, Use in Specific Populations]*.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals. Tazarotene is a teratogenic substance in animals, and it is not known what level of exposure is required for teratogenicity in humans.

Advise pregnant patients of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to ARAZLO therapy. Initiate ARAZLO therapy during a menstrual period. Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO *[see Dosage and Administration, Use in Specific Populations]*.

Skin Irritation Patients using ARAZLO may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ARAZLO, or discontinue use. Therapy can be resumed, or the frequency of application can be increased, as the patient becomes able to tolerate treatment.

Avoid use of concomitant medications and cosmetics that have a strong drying effect. It is recommended to postpone treatment with ARAZLO until the drying effects of these products subside.

Avoid application of ARAZLO to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Because of heightened burning susceptibility, minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ARAZLO. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided. Patients with sunburn should be advised not to use ARAZLO until fully recovered.

ARAZLO should be administered with caution if the patient is taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections:

- Embryofetal toxicity *[see Warnings and Precautions]*
- Photosensitivity and Risk of Sunburn *[see Warnings and Precautions]*

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials, subjects age 9 years and older applied ARAZLO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (66%). Approximately 22% were Hispanic/Latino and 42% were younger than 18 years of age, fourteen of 779 subjects (1.8%) treated with ARAZLO were between 9 years to less than 12 years of age. Adverse reactions reported by ≥1% of subjects treated with ARAZLO and more frequently than subjects treated with vehicle are summarized in Table 1. Most adverse reactions were mild to moderate in severity. Severe adverse reactions represented 1.3% of the subjects treated. Overall, 2.4% (19/779) of subjects discontinued ARAZLO because of local skin reactions.

Table 1: Adverse Reactions Reported by ≥1% of the ARAZLO Group and More Frequently than the Vehicle Group

	Adverse Reactions N (%)	
	ARAZLO Lotion N=779	**Vehicle N=791**
Application site pain[1]	41 (5)	2 (<1)
Application site dryness	30 (4)	1 (<1)
Application site exfoliation	16 (2)	0 (0)
Application site erythema	15 (2)	0 (0)
Application site pruritus	10 (1)	0 (0)

[1]Application site pain defined as application site stinging, burning, or pain

Skin irritation was evaluated by active assessment of erythema, scaling, itching, burning and stinging, with grades for none, mild, moderate, or severe. The maximum severity generally peaked at Week 2 of therapy and decreased thereafter. The percentage of subjects with these signs and symptoms at any post-baseline visit are summarized in Table 2.

Table 2: Incidence of Local Cutaneous Irritation at any Post-Baseline Visit

	ARAZLO Lotion N=774 Mild/Moderate/Severe	**Vehicle Lotion N=789** Mild/Moderate/Severe
Erythema	49%	38%
Scaling	51%	23%
Itching	29%	14%
Burning	30%	6%
Stinging	22%	5%

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with ARAZLO.

Concomitant use with oxidizing agents, as benzoyl peroxide, may cause degradation of tazarotene and may reduce the clinical efficacy of tazarotene.

In a trial of 27 healthy female subjects, between the ages of 20–55 years, receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethinyl estradiol, the concomitant use of tazarotene administered as 1.1 mg orally (mean ± SD C_{max} and $AUC_{0\text{-}24}$ of tazarotenic acid were 28.9 ± 9.4 ng/mL and 120.6 ± 28.5 ng•hr/mL, respectively) did not affect the pharmacokinetics of norethindrone and ethinyl estradiol over a complete cycle.

The impact of tazarotene on the pharmacokinetics of progestin only oral contraceptives (i.e., minipills) has not been evaluated.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary ARAZLO is contraindicated in pregnancy.

There are no available data on ARAZLO use in pregnant patients to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, ARAZLO should be discontinued as soon as pregnancy is recognized.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose equivalent to the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 15 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 1 and 30 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 6 times the MRHD (based on AUC comparison) *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (equivalent to the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (15 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 1 and 30 times, respectively, the MRHD (based on AUC comparison).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (6 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at this dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to the MRHD (based on AUC comparison).

Lactation

Risk Summary There are no data on the presence of tazarotene or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAZLO and any potential adverse effects on the breastfed child from ARAZLO.

Clinical Considerations To minimize potential exposure to the breastfed infant via breast milk, use ARAZLO for the shortest duration possible while breastfeeding. Advise breastfeeding patients not to apply ARAZLO directly to the nipple and areola to prevent direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing Pregnancy testing is recommended for patients of childbearing potential within 2 weeks prior to initiating ARAZLO therapy which should begin during a menstrual period.

Contraception Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO.

Pediatric Use Safety and effectiveness of ARAZLO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years and older based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week clinical trials and an open-label pharmacokinetic study. A total of 300 pediatric subjects aged 9 to less than 17 years received ARAZLO in the clinical studies *[see Clinical Pharmacology and Clinical Studies]*.

The safety and effectiveness of ARAZLO in pediatric patients below the age of 9 years have not been established.

Geriatric Use Clinical trials of ARAZLO did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

OVERDOSAGE

Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, monitor the patient closely and administer appropriate supportive measures, as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest dose was 7 times the MRHD (based on AUC comparison).

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was equivalent to the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose which produced a systemic exposure 6 times the MRHD (based on AUC comparison).

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ARAZLO™
(tazarotene) Lotion, 0.045%

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CRACK THE TAZAROTENE CODE

ARAZLO is the first and only tazarotene lotion, formulated with polymeric emulsion technology, to help deliver the clearance you expect and the tolerability you want[1-3]

- Treatment success* rates were 26% for ARAZLO Lotion vs 13% for vehicle in study 1 and 30% vs 17%, respectively, in study 2 ($P<0.001$ in both studies)[1,4†]
- Most common adverse events (≥1% of patients and greater than vehicle) at application site were pain (5%), dryness (4%), exfoliation (2%), erythema (2%), and pruritus (1%)[1†]

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*Treatment success on the Evaluator's Global Severity Score (EGSS) was defined as at least a 2-grade improvement from baseline and an EGSS score of clear (0) or almost clear (1).[1]

†**Phase 3 study design:** The safety and efficacy of ARAZLO Lotion were assessed in 2 multicenter, randomized, double-blind clinical trials of 1,614 subjects aged 9 years and older with facial acne vulgaris. Subjects had a score of moderate (3) or severe (4) on the EGSS, 20 to 50 inflammatory lesions, 25 to 100 noninflammatory lesions, and 2 or fewer facial nodules.[1]

Indication

ARAZLO™ (tazarotene) Lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

Important Safety Information

ARAZLO Lotion is for topical use only. Not for oral, ophthalmic, or intravaginal use.

Contraindication

ARAZLO Lotion is contraindicated in pregnancy due to the potential harm to the fetus.

Warnings and Precautions

Embryofetal Risk Females of childbearing potential should be warned of the potential risk and should use adequate birth-control measures when ARAZLO Lotion is used. A negative result for pregnancy should be obtained within 2 weeks prior to ARAZLO Lotion therapy, and therapy begun during a menstrual period. If the patient becomes pregnant while using ARAZLO Lotion, treatment should be discontinued.

Skin Irritation Patients using ARAZLO Lotion may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity, adjust or interrupt dosing as needed, increasing or resuming treatment as tolerated. Avoid application of ARAZLO Lotion to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Minimize unprotected exposure to ultraviolet light, including sunlight, sunlamps and tanning beds, during the use of ARAZLO Lotion. Warn patients with high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Instruct patients to use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

ARAZLO Lotion should be administered with caution if the patient is taking drugs known to be photosensitizers (eg, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO Lotion.

Adverse Reactions The most common adverse reactions (in ≥1% of patients and greater than vehicle) were: application site pain, dryness, exfoliation, erythema, and pruritus.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on following page.

References: 1. ARAZLO Lotion [prescribing information]. Bridgewater, NJ. Bausch Health US, LLC. **2.** Tanghetti EA, Kircik LH, Green LJ, et al. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. *J Drugs Dermatol*. 2019;18(6):542-548. **3.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed October 10, 2019. **4.** Data on file.

Ortho Dermatologics

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