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Treatment of Acne-Induced Macular Hyperpigmentation in Fitzpatrick Skin Types V to VI: A Scoping Review

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ABSTRACT

Acne-induced macular hyperpigmentation (AMH) is a common issue among patients with highly melanated skin, particularly those with Fitzpatrick Skin Types (FST) V - VI, which includes nonwhite patients with 'brown' and 'black' skin types. Despite the significant physical, emotional, and social harm caused by AMH, many clinical trials either fail to report FST data or do not include patients with FST V to VI. This scoping review summarizes current research on AMH treatment for patients with FST V to VI. Our review underscores the need for more data on the efficacy, safety, and tolerability of AMH treatments for patients with FST V to VI. Dermatologists who treat AMH should routinely collect data on patient FST, race, and ethnicity. Clinical trials should enroll more patients with FST V to VI from diverse racial and ethnic backgrounds to generate data that better informs clinical practice. This approach will ensure that treatment strategies are based on data relevant to the patient populations most in need of effective AMH care.

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INTRODUCTION

Acne-induced macular hyperpigmentation (AMH) refers to post-inflammatory hyperpigmentation in acne and is common in patients with highly melanated skin.[1] The Fitzpatrick Skin Type (FST) system categorizes patients based on skin sun-reactivity. FST V-VI includes patients with skin of color, or skin described as 'brown' or 'black.'[2] Phototype distribution varies across racial groups, as 87.3% of Black/African American patients are FST V-VI compared to 29.7% of Hispanic patients.[3] AMH prevalence is higher among patients with skin of color compared to those with FST I- III, and among Black/African American patients (65%) compared to Caucasian patients (25%).[4,5]

Patients with skin of color prioritize AMH clearance as their chief goal.[6] Individuals with AMH are more likely to experience social stigmatization compared to those with clear skin.[7] AMH causes emotional distress for skin of color patients worsened by the chronicity, visibility, and co-occurrence with acne.[8,9] AMH co-occurrence with acne predicts lower quality of life ratings compared to isolated acne.[10] Limited studies investigate AMH treatment outcomes among FST V-VI. We aim to provide a scoping review of the current literature on AMH treatment among patients with FST V-VI.

MATERIALS AND METHODS

We performed a literature review using keywords to search titles and abstracts within PubMed, Embase, and Web of Science (Figure 1). Included studies involve AMH treatment for patients with FST V-VI. We excluded studies if: A) ≤50% of participants were FST V or VI, and B) data was not grouped by FST. We manually reviewed the full texts of the remaining articles to confirm they met the inclusion criteria.

Treatments

Overview

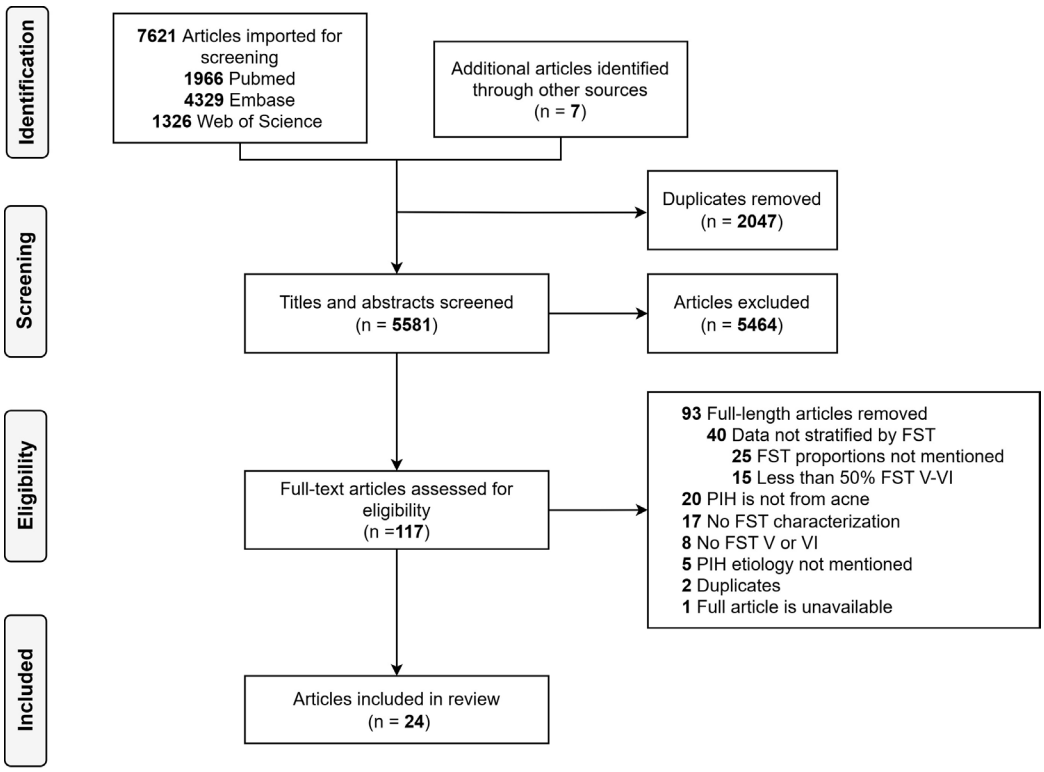
AMH clearance relies on the treatment of underlying dermatoses to prevent recurrent or worsening hyperpigmentation.[1] Early incorporation of anti-hyperpigmentation treatments may improve pigmentary outcomes and patient satisfaction. However, skin susceptibility to ultraviolet radiation (UVR)-induced sun damage may increase on topicals.[11] Clinicians should advise patients to routinely apply sun protection and educate patients on minimizing sun exposure.

Topical Treatments

Topical Retinoids

Retinoids activate retinoic acid receptors and simultaneously treat acne and AMH.[12] Daily tazarotene 0.1% cream treated AMH

FIGURE 1. Article selection methodology for inclusion in scoping review.



Abbreviations: *FST*, Fitzpatrick Skin Type; *PIH*, post-inflammatory hyperpigmentation.

in an 18-week, double-blinded, randomized trial of 74 patients (FST V, N=41; FST VI, N=17). The treatment group experienced significant (P<0.05) decreases in overall hyperpigmentation, pigmentary intensity of individual lesions, and lesion size.[13] Trifarotene 0.005% cream treated concurrent acne and AMH in a randomized trial of 123 patients (FST V, N=32; FST VI, N=13) with improvement in the post-acne vulgaris hyperpigmentation index at week 24 (P<0.01) from baseline.[14]

Lotion formulas may improve retinoid tolerability by minimizing irritation.[15] Daily tazarotene 0.45% lotion was used to treat acne in two, 12-week double-blinded, randomized, vehicle-controlled phase III clinical trials (N=1614), though initial reports did not characterize FST or AMH outcomes.[16] Post-inflammatory hyperpigmentation (PIH) Severity Scale ratings for FST V patients (N=2) decreased from moderate at baseline to mild and normal at the end of the study.[17]

Clindamycin 1.2%/tretinoin 0.025% gel was evaluated for daily AMH treatment in a 12-week, double-blinded trial of patients with FST IV-VI (FST V, N=23; FST VI, N=8).[18,19] Improvement in the mean PIH Severity Score from baseline to end-of-study was greater within the treatment group (-1.2) compared to the vehicle (-0.9), though this result was not statistically significant.[18,19]

Chemical Peels

Chemical peels are exfoliative agents that penetrate the skin, promote desquamation, and remove a specified depth of epidermis or dermis to promote skin regeneration.[20] Patients with FST V-VI should use superficial chemical peels (eg, salicylic or lactic acid) limited to epidermal penetration to minimize the risk of post-peel hyperpigmentation.[20] Salicylic acid (SA) is a lipophilic acid formulated for superficial peeling in concentrations between 20% and 30%.[21] In a 10-week open-label study, bi-monthly SA peels were used to treat AMH in five patients with FST V-VI.[22] A total of five SA peels were administered in the sequence: 20% (2 peels) and 30% (3 peels). Patients applied daily 4% hydroquinone for 2 weeks prior to treatment until study completion. AMH outcomes were determined by independent-investigator assessment of photographs and grading of clinical improvement from baseline. At the study endpoint, significant clinical improvement (>75%) was observed in 80% of patients.[22]

Lactic acid (LA) is an alpha-hydroxy acid used for superficial chemical peeling.[23] Bi-monthly LA peels were used to treat acne scarring in a 12-week open-label study of seven patients (FST V, N=5).[24] A total of four peels were administered with the first peel at half concentration strength (46%) and the subsequent three peels at full concentration strength (92%). Efficacy

assessments were performed monthly for three months after the final peel. Although AMH was not the study's primary focus, pre-and post-treatment assessment of pigmentation was completed during physician-led clinical assessment of patients and clinical photographs. At the study endpoint, investigators subjectively noted lightened scars and "definite improvement" in pigmentation.[24]

Niacinamide

Niacinamide is a physiologically active niacin derivative that decreases pigmentation by inhibiting the melanosome transfer to keratinocytes.[25] Twice-daily application of a dermocosmetic cream consisting of salicylic acid, lipohydroxy acid, and niacinamide with daily tinted sunscreen was used to treat AMH in 43 patients (FST V, N=22; FST VI, N=8) over 8-weeks.[26] Investigators rated AMH using the global PIH severity and hyperpigmentation intensity score. Significant reductions (P<0.0001) in the number of AMH lesions were observed at the study endpoint.[26]

Tyrosinase Inhibitors

Tyrosinase is a multi-copper enzyme central to melanin biosynthesis and skin pigmentation.[27] Azelaic acid is a dicarboxylic acid with anti-tyrosinase activity isolated from the fungi *Pityrosporum ovale*.[28] Twice-daily azelaic acid 15% gel was evaluated for AMH treatment during a 16-week open-label study of 20 patients (FST V, N=4; FST VI, N=16).[29] Investigators evaluated AMH with the Investigator's Global Assessment of Acne (IGA) for PIH. Significant improvements (P<0.05) in AMH severity and distribution from baseline were noted at week 4. Complete AMH clearance was observed for 31% of participants at week 16.[29]

Bakuchiol is a tyrosinase inhibitor with anti-pigmentation properties used to reduce visible signs of photoaging.[30] Twice-daily 0.5% bakuchiol cream was used to treat AMH in a 12-week open-label study of 13 patients with acne (FST V-VI, N=8).[31] Investigators determined the monthly progression of AMH by calculating the proportion of each patient's face containing AMH. The Evaluator Global Severity Score rated AMH severity. Overall differences in monthly AMH scores were not statistically significant. The decrease in AMH scores for participants with baseline AMH severity ≥2 was significant (P=0.03) during week 8, though at week 12 this difference was no longer significant (P=0.08).[31]

Thiamidol is a selective inhibitor of human tyrosinase present in over-the-counter products used to reduce pigmentation.[32] Twice-daily thiamidol was used to treat AMH in a 12-week, single-blinded, vehicle-controlled study of 77 FST V patients. Baseline hyperpigmentation was clinically graded by a dermatologist, while monthly AMH outcomes were determined by patient-reported ratings of hyperpigmentation visibility compared to surrounding skin. After 12 weeks, the treatment group showed significant (P=0.047) improvement in AMH compared with the vehicle.[33] Thiamidol was used to treat AMH in a second 12-week open-label study of 32 participants (FST V, N=24; FST VI, N=5). Participants applied 3 thiamidol-containing products daily: serum and cream with a sun protection factor (SPF) 30 in the morning, and night cream in the evening. Dermatologists graded skin evenness and improvement in overall skin condition, while patients rated their facial skin condition at monthly follow ups. Clinical photography and Mexameter measurements were obtained at follow-ups. A significant (P<0.001) decrease in lesional melanin index scores from baseline was observed in the treatment group. Perilesional melanin index scores remained consistent throughout treatment. The treatment group reported significantly (P<0.001) improved facial skin ratings at follow-up compared to baseline ratings.[33]

Topical Antibiotics

Combination topical acne therapy contains benzoyl peroxide (BPO) and clindamycin and demonstrates activity against *P. acnes*.[34] Twice-daily clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel was used to treat acne in a 16-week open-label study of 20 patients (FST V, N=9; FST VI, N=11). Clinicians rated AMH severity and distribution monthly using the IGA.[35] Investigators observed significant (P≤0.0003) decreases in AMH severity at 16 weeks and improvements in AMH distribution (P=0.03) at weeks 8,12, and 16. Most participants (75%) experienced an improvement in AMH distribution by ≥1-grade.[35]

Dapsone is an antibacterial topical which treats acne.[36] Dapsone 5% gel was used to treat mild-to-severe acne in a 12-week open-label study of 68 FST IV-VI patients.[37] Investigator assessment of acne revealed a significant (P<0.001) decrease in mean total lesions, inflammatory lesions, and comedo counts from baseline. Although the study was not designed to determine AMH outcomes, investigators reported a subjective decrease in AMH at the study's conclusion compared to subjective baseline observations.[37] Dapsone 7.5% gel was used to treat AMH in 20 FST IV-VI patients. Patient-reported subjective assessments of AMH and health-related quality of life improved after ≥18 treatment weeks.[38]

Galactomyces Ferment Filtrate, Dexpanthenol, and Centella Asiatica

The discovery of naturally occurring depigmentation topicals has expanded the armamentarium of therapies used to treat hyperpigmentation.[39] A combination serum of Galactomyces fermentation filtrate, *C. Asiatica*, and dexpanthenol was used twice daily to treat AMH in an 8-week, double-blinded, placebo-controlled, randomized clinical trial of 51 patients (FST V, N=10).[40] AMH outcomes were evaluated biweekly using chromameter and Mexameter readings. Chromameter analysis generated L* scores indicating color brightness ranging from 0 (black) to 100

(white). FST V patients in the treatment group demonstrated a significantly (P<0.05) higher L* score at weeks 4 and 6 compared to placebo, indicating decreased pigmentation. However, this difference was not statistically significant at week 8. Investigators attributed this result to a physiologic decrease in AMH present in the placebo and treatment groups. The melanin index of FST V participants remained lower than the placebo group at all follow-ups, though this difference was not statistically significant.[40]

Peptides

Short-chain peptides modulate fibroblast activity and increase collagen synthesis.[41] A Pro-Lys-Glu-Lys (PKEK) emulsion was used to treat hyperpigmentation from mild acne and melasma in a 12-week, double-blinded, randomized study of 50 FST V-VI patients.[42] Patients applied 0.5 g of the PKEK emulsion at least once daily. Clinicians rated AMH and melasma each month. Ratings for skin evenness and appearance improved from baseline after 12 weeks of treatment. Clinical photographs revealed improvements in skin evenness (P<0.01) and overall appearance (P<0.05).[42] However, this study did not categorize data by pigmentation etiology (mild acne or melasma) or provide the number of patients with AMH.[42]

Energy-Based Therapies

Photodynamic Therapy

Photodynamic therapy utilizes visible light in combination with photoreactive topical porphyrin precursors which function as oxidizing agents to treat dermatological conditions.[43] The use of monthly 5-aminolevulinic acid (20%) and blue light therapy for treatment-resistant AMH was presented in a case report involving a FST V patient.[44] The patient continued their baseline regimen of topical benzoyl peroxide/clindamycin and tazarotene and began daily topical HQ 4% cream 2 weeks preceding the first photodynamic session. Patient ratings and investigator assessment of clinical photographs were used to determine AMH outcomes. After 2 treatments, the patient reported significant subjective improvement in AMH. Complete acne clearance occurred after 3 treatments and was sustained at one-month follow-up after treatment.[44]

Laser Therapy

Lasers treat various skin conditions by emitting light of a specific wavelength which is absorbed by skin chromophores.[45] Melanosome destruction occurs when melanin absorbs light energy. Lasers emit energy with wavelengths of 630 to 1100 nm which penetrate the skin and treat hyperpigmentation with minimal side effects by targeting melanin instead of oxyhemoglobin.[45]

Q-Switched Nd:YAG 1064-nm lasers treat acne, acne scarring, and pigmented lesions.[46] An Nd-laser was used to treat 22 patients (FST V, N=14; FST VI, N=2) with atrophic scarring from various causes including acne.[47] A Nd:YAG 1,064-nm laser with sub-millisecond pulse durations was used over 6 months with an average treatment interval of 24.5 days.[47] Ten microdermabrasion treatments were administered throughout the study between scheduled laser treatments. Physician-rated clinical photographs showed a significant (P<0.001) improvement in AMH, scarring, and texture at 9- and 10-months post-treatment. The study was limited by poor clinical image quality which resulted in data exclusion.[47] A 650-Microsecond Nd:YAG 1064-nm laser was used to treat acne and AMH of a FST VI patient within a case study. A total of three laser treatments were administered every 3 to 4 weeks. Investigators assessed clinical photographs using the Roberts Hyperpigmentation Scale, though the ratings were not disclosed.[48,49]

Radiofrequency and Microneedling Therapy

Fractional radiofrequency (F-RF) uses an array of bipolar electrodes to generate radiofrequency energy.[50] This technique is proposed to cause less side effects for patients with melanated skin because skin chromophores do not absorb RF energy.[50] F-RF treated skin texture irregularities (eg, acne scarring) in a 24-week, open-label study of 35 FST VI patients.[51] Patients received a total of three F-RF treatments every 4 weeks. AMH outcomes were assessed at 6 and 12 weeks after the final laser treatment. Although AMH outcomes were not numerically rated, investigator comparison of baseline and endpoint clinical photographs demonstrated subjective improvement in overall skin appearance among patients with AMH and acne scars.[51]

Microneedling is proposed to remodel the skin by stimulating keratinocyte or fibroblast proliferation and migration to scar tissue.[52] Conjunctive therapy uses microneedling and F-RF to treat pigmentary disorders.[52] A 24-week open-label study used an F-RF microneedling device to treat facial acne scars of 19 patients (FST V, N=16).[53] Participants received a total of three F-RF microneedling treatments every 4 weeks. At 12 weeks post-final treatment, dyschromia improved in 47.4% of patients.[53]

Preventative Care and Counseling

Patients with AMH are at risk of recurrence from extended sun exposure and UVR-mediated skin damage while using skin-sensitizing topicals. Clinicians treating patients with AMH should emphasize the importance of sun avoidance, AMH treatment adherence, and daily sunscreen use. Current acne and AMH treatment strategies use combination therapy to address both pathologies. For example, both acne and AMH are targeted with topical azelaic acid and topical retinoids, while AMH is managed with hydroquinone and sun protection. However, limitations in Medicaid coverage of topical retinoids may lead to disparities in affordable care access.[54]

Misconceptions regarding photoprotection also exist among skin of color patients which may hinder AMH clearance due to

deleterious sun exposure.[55,56] In a multinational study of facial aging, a higher proportion of Black participants (69%) reported rarely or never using sunscreen in comparison to Caucasian participants (37%).[57] Although FST V-VI skin has an inherent SPF of 13.4, the photoprotection provided by melanin is incomplete and patients remain susceptible to skin pathologies caused by UVR exposure such as skin cancer and melasma.[58] Long-term daily use of SPF 30 in FST V individuals throughout 12 months was associated with improvement in photoaging and pigmentation.[59] In addition, tinted sunscreens offer additional benefits to FST V-VI patients with AMH, as they also protect against visible light and exist in formulations that match a diversity of melanated skintones.[60]

CONCLUSION

Additional data are crucial to assess the efficacy, safety, and tolerability of AMH treatments in patients with FST V-VI. Many AMH clinical trials either fail to report FST or do not include patients with FST V-VI, despite these individuals suffering significant physical, emotional, and social harm from AMH.[61] Patients with FST V-VI suffer from physical, emotional, and social harm caused by AMH.[9,10] Routine collection of data on FST during acne treatment will improve our understanding of AMH progression and patient perceptions among those with FST V-VI. Investigators should collect racial-ethnic data and avoid using the Fitzpatrick scale as a substitute for race or ethnicity.[62] We recommend that future AMH clinical trials prioritize enrolling cohorts that reflect the racial and ethnic diversity of populations most affected by AMH. Specifically, trials should enroll more patients with FST V-VI across diverse racial and ethnic groups to generate data that better informs clinical practice for these patients.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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