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Retinoids and Azelaic Acid to Treat Acne and Hyperpigmentation in Skin of Color

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ABSTRACT

In this review, we examine published data reporting the efficacy of pharmaceutical agents to treat associated postinflammatory hyperpigmentation commonly seen in skin of color. Retinoids and azelaic acid have been widely used to treat acne. Now there are increasing data describing their use in skin of color for the treatment of both acne and the subsequent postinflammatory hyperpigmentation. Historically, some dermatologists have been hesitant to use retinoids in skin of color because of perceived hypersensitivity in this patient population. However, recent data support the use of retinoids and azelaic acid in skin of color as both safe and beneficial.

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INTRODUCTION

Long used in the treatment of acne, retinoids offer dermatologists another option for the treatment of hyperpigmentation. The use of retinoids in hyperpigmentation is supported by an increasing body of literature (Table 1). In the current study, tretinoin, tazarotene, and adapalene (ADA), which have been successfully used to treat acne, are reviewed and their effectiveness in hyperpigmentation is discussed.

Retinoids and Hyperpigmentation

Tazarotene for Postinflammatory Hyperpigmentation

In a blinded, vehicle-controlled trial, 74 acne patients from darker racial ethnic groups (Fitzpatrick skin types IV to VI) were treated with once-daily application of tazarotene 0.1% cream. The primary efficacy variable was the overall disease severity of postinflammatory hyperpigmentation (PIH). Patients also were evaluated for the pigmentary intensity of hyperpigmented lesions, area of hyperpigmented lesions, and degree of hypopigmentation.[1] In addition, the tolerability of the medication was evaluated as measured by erythema, burning, peeling, and dryness. These categories had a grading scale of 0 to 5, based on severity.[1] Results showed clinically significant reductions in overall PIH severity and in the intensity and extent of hyperpigmentation when compared with vehicle within 18 weeks ($P \leq .05$).[1] In addition, throughout the study, dryness, erythema, burning, and peeling were mild in both groups.[1]

Adapalene for Acne in African American Patients

A meta-analysis of 5 randomized trials assessing ADA 0.1% gel evaluated the primary efficacy parameters of total lesion counts (sum of inflammatory and noninflammatory lesions), inflammatory lesion counts, and noninflammatory lesion counts on both Caucasian and African American patients.[2] The primary safety parameters evaluated were erythema, scaling, and dryness. Each of these adverse events was evaluated on a 0 to 3-point grading scale, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe.[2] The meta-analyses were compared using the Cochran–Mantel–Haenszel test. Results showed ADA 0.1% gel significantly reduced a greater number of inflammatory lesions among African American patients with Fitzpatrick skin types IV through VI vs Caucasian patients ($P=.012$).[2] Reductions in total lesion counts were similar in the 2 groups ($P>.3$). In addition, there was significantly less erythema ($P<.001$) and scaling ($P=.026$) in the African American group.[2] Although the incidence of dryness was similar for both groups, fewer of the African American subjects had moderate or severe scores for dryness (7% vs 18% of Caucasian). In summary, based on these studies, ADA may have better efficacy for inflammatory lesions in African Americans than in Caucasians and is a good choice for patients with skin of color.[2]

Adapalene for Postinflammatory Hyperpigmentation

An open-label trial of 44 black South African patients studied the effects of ADA 0.1% gel on acne and PIH. Investigators observed color change over 12 weeks. Other efficacy variables assessed were inflammatory lesion counts, noninflammatory lesion counts, and overall severity scores.[3] The authors noted a reduction in hyperpigmented macules in 66% of patients and a drop in mean total facial lesion count of up to 72%.[3]

Adapalene/Benzoyl Peroxide and Tolerability in Skin of Color

A retrospective meta-analysis combined 3 randomized, double-blind, vehicle-controlled clinical trials using ADA and benzoyl peroxide (BPO) to assess tolerability in skin of color. The study included 909 patients treated over a 12-week period. Patients were evaluated at each visit for erythema, scaling, dryness, and burning, and a score of 0 (none) to 3 (severe) was assigned.[4] For the meta-analysis, comparisons were made

using the Cochran–Mantel–Haenszel test. Results showed that there were no statistically significant differences in dryness, scaling, and burning with the ADA/BPO protocol in subjects with Fitzpatrick skin types I to III compared with subjects with Fitzpatrick skin types IV to VI.[4] The erythema of patients with Fitzpatrick skin types IV to VI was rated as "none" more often than that of patients with Fitzpatrick skin types I to III (P<.001). This could be due to the difficulty in visualizing erythema in patients with darker skin types, particularly Fitzpatrick skin type VI. The analysis established that acne patients with Fitzpatrick skin types IV to VI were not more susceptible to cutaneous irritation from treatment with the ADA/BPO gel when compared with patients with Fitzpatrick skin types I to III.[4]

Tazarotene vs Adapalene for Postinflammatory Hyperpigmentation

In a blinded, controlled trial, 180 patients (68 Caucasian, 52 African American, 22 Asian, 27 Hispanic, and 11 other) were treated with either tazarotene 0.1% cream or ADA 0.3% gel and subsequently evaluated for improvement in acne and PIH. The specific severity scales used were total reduction in lesion counts, percentage of patients achieving a 50% lesion count reduction, overall disease severity, and Investigator's Global Assessment (IGA) score.[5] Results showed both tazarotene 0.1% cream and ADA 0.3% gel were effective for acne. However, 20% of patients (5/25) with skin of color achieved complete resolution of PIH at week 16 in the tazarotene 0.1% cream group, and 7% (2/29) in the ADA 0.3% gel group. Tazarotene 0.1% cream was thus shown to be more effective than ADA 0.3% gel in reducing PIH.[5] Subjects experienced more erythema, peeling, dryness, and burning with tazarotene compared with ADA.[5]

Tretinoin for Dyschromia

In a 40-week, blinded, vehicle-controlled trial, 68 African American subjects with hyperpigmentation due to acne, folliculitis, eczema, and shaving irritation were treated with either topical tretinoin 0.1% cream or vehicle applied to face and arms.[6] Investigators assessed both the hyperpigmented skin as well as the normal skin. The designated lesions of PIH and normal skin were assessed with a colorimeter (Chroma Meter CR-200; Minolta Camera, Osaka, Japan) before treatment and after 12, 24, and 40 weeks of therapy.[6] The reduction in hyperpigmentation observed at 4 weeks with tretinoin vs at 24 weeks with vehicle was statistically significant.[6] Assessing the normal skin, no significant lightening was observed clinically; however, mild skin lightening could be observed via colorimetry.[6]

Benzoyl Peroxide/Clindamycin Plus Retinoid

In a community-based trial comparing 3 different topical therapeutic regimens, one subset analysis looked at pigmentary changes with acne cases in skin of color. All patients received combination clindamycin 1%/BPO 5% topical gel containing glycerin and dimethicone. Subjects were randomized to receive this combination therapy in addition to either a tretinoin microsphere gel at concentrations of either 0.04% or 0.1%, or ADA gel 0.1%. Hyperpigmentation was assessed using a subjective 5-point scale, where 0 = absent, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. Hyperpigmentation in those subjects receiving the clindamycin/BPO topical gel in combination with tretinoin gel 0.04% trended toward better resolution when compared with the ADA gel.[7]

Clindamycin and Retinoid for Acne in Darker-Skinned Patients

To assess efficacy and the safety of a topical gel containing clindamycin 1.2% and tretinoin 0.025% in acne and acne-induced PIH in darker-skinned patients, researchers undertook a randomized, double-blind, placebo-controlled study of 33 patients with Fitzpatrick skin types IV to VI.[8] Efficacy was measured using the evaluator's global acne severity scale, lesion counts, PIH severity scales (from 0 = normal to 8 = severe), and patient's global assessment scale. Safety and tolerability were assessed using adverse event reports and a safety assessment scale.[8]

After 12 weeks of therapy, the mean inflammatory lesion count was 11.9 in clindamycin/tretinoin-treated patients compared with the baseline count of 17.4. In the placebo group, the mean inflammatory lesion count went from 17.7 to 13.6 (P=.05).[8] All patients had baseline PIH severity scale scores ≥2, and a substantial proportion had scores of 3 or 4 in the clindamycin/tretinoin gel (70%) and placebo groups (69%).[8] The improvement in mean PIH score from baseline to week 12 was greater for clindamycin/tretinoin gel vs placebo (–1.2 vs –0.9), and this small improvement was consistent throughout the trial. The number of patients with ≥2-point improvements in PIH scores was similar between the clindamycin/tretinoin gel group and the placebo group (33%).[8] The results of this pilot study suggest clindamycin phosphate 1.2%/tretinoin 0.025% topical gel is safe and effective option for treating mild to moderate acne and PIH in patients with skin of color.[8]

"Based on this review of literature, retinoids and azelaic acid offer excellent treatment options for acne patients with skin of color."

Azelaic Acid

Azelaic acid (AzA) is a dicarboxylic acid from *Pityrosporum ovale* that inhibits tyrosinase and has cytotoxic and antiproliferative effects. A 15% gel and 20% cream are commercially available. Studies have found this agent useful in treating hyperpigmentation with acne.[9] A 16-week, baseline-controlled study of patients with Fitzpatrick skin types IV to VI evaluated the efficacy of topical AzA gel 15% applied twice daily (n=20). Assessments at baseline and each visit included IGA of acne on

TABLE 1.

Retinoids and Azelaic Acid to Treat Acne and Hyperpigmentation in Skin of Color

Treatment/Condition	Study Population	Efficacy Variables	Results
Tazarotene for PIH[1]	74 patients from darker racial ethnic groups	Overall disease severity of PIH, pigmentary intensity of hyperpigmented lesions, area of hyperpigmented lesions, degree of hypopigmentation, and erythema, burning, peeling, and dryness	Clinically significant reductions in PIH ($P \leq .05$) within 18 weeks
ADA for acne[2]	655 patients (46 African American, 609 white)	Total lesion counts (sum of inflammatory and noninflammatory lesions), inflammatory lesion counts, noninflammatory lesion counts, erythema, scaling, and dryness	Reductions in total lesion counts were similar in the 2 groups ($P > .3$); significantly less erythema ($P < .001$) and scaling ($P = .026$) in the African American group
ADA for PIH[3]	44 black South African patients	Color change over 12 weeks, inflammatory lesion counts, noninflammatory lesion counts, and overall severity scores	Reduction in hyperpigmented macules in 66% of patients and a drop in mean total facial lesion count of up to 72%
ADA/BPO and tolerability in skin of color[4]	909 patients (664 Caucasian, 104 black, 103 Hispanic, 38 other)	Erythema, scaling, dryness, and burning scored from 0 (none) to 3 (severe); comparisons were made using the Cochran–Mantel–Haenszel test	No statistically significant differences in dryness, scaling, and burning in subjects with Fitzpatrick skin types I to III compared with those with skin types IV to VI
Tazarotene vs ADA for PIH[5]	180 patients (68 Caucasian, 52 African American, 22 Asian, 27 Hispanic, 11 other)	Overall reduction in lesion counts, percentage of patients achieving a 50% lesion count reduction, overall disease severity, and IGA	Tazarotene 0.1% cream was more effective than ADA in reducing PIH; however, subjects experienced more erythema, peeling, dryness, and burning with tazarotene compared with ADA
Tretinoin for dyschromia[6]	68 African American patients	The designated lesions of PIH and normal skin were assessed with a colorimeter (Chroma Meter CR-200; Minolta Camera, Osaka, Japan)	A statistically significant reduction in hyperpigmentation was observed at 4 weeks with tretinoin vs at 24 weeks with vehicle
BPO/clindamycin plus retinoid[7]	167 patients with Fitzpatrick skin types IV to VI	Subjective hyperpigmentation scale of 0 to 5	Hyperpigmentation in those subjects receiving the BPO/clindamycin topical gel in combination with tretinoin gel 0.04% trended toward better resolution when compared with the ADA gel
Clindamycin and retinoid for acne[8]	33 patients with Fitzpatrick skin types IV to VI	Evaluator's global acne severity scale, lesion counts, PIH severity scales, patient's global assessment scale, and safety assessment scale	Clindamycin phosphate 1.2%/tretinoin 0.025% topical gel is a safe and effective option for treating mild to moderate acne and PIH in patients with skin of color
AzA for PIH[9]	20 patients with Fitzpatrick skin types IV to VI	IGA of acne on a 6-point scale, total lesion count, inflammatory lesion count, noninflammatory lesion count, and IGA for PIH on a 7-point scale	At week 16, 100% of patients had a 2-point improvement in the IGA for PIH
AzA for hyperpigmentation[10]	52 patients with Fitzpatrick skin types IV to VI	Pigmentary intensity, lesion area, and global assessment of improvement; pigmentaryintensity was measured by chromometer	AzA produced significantly greater decreases in pigmentary intensity than did vehicle, as measured by both an investigator's subjective scale ($P = .021$) and chromometer analysis ($P = .039$)

ADA, adapalene; AzA, azelaic acid; BPO, benzoyl peroxide; Investigator's Global Assessment; PIH, postinflammatory hyperpigmentation.

a 6-point scale, total lesion count, inflammatory lesion count, noninflammatory lesion count, and IGA for PIH on a 7-point scale.[9] At week 16, 92% of patients had a 2-point improvement in the IGA for PIH.[9]

A multicenter, randomized, parallel-group study compared the efficacy, safety, and tolerability of AzA 20% cream to its vehicle for the treatment of facial hyperpigmentation in 52 patients with Fitzpatrick skin types IV to VI.[10] The efficacy variables were pigmentary intensity, lesion area, and global assessment of improvement. Pigmentary intensity was measured by chromometer.[10] Results at 24 weeks showed AzA produced significantly greater decreases in pigmentary intensity than did vehicle, as measured by both an investigator's subjective scale (P=.021) and a chromometer analysis (P=.039).[10] In addition, there was a significantly greater global improvement with AzA than with vehicle at week 24 (P=.008).[10] The investigators concluded that AzA is an effective and well-tolerated treatment for hyperpigmentation in darker-skinned patients.[10]

CONCLUSIONS

PIH is an extremely common and distressing condition in patients with skin of color. A growing body of evidence suggests that retinoids are well tolerated in skin of color. Dermatologists should consider retinoids as first-line therapies to treat acne in this patient population. In addition, AzA is another acne treatment that can offer patients improvement in both acne and hyperpigmentation. Dermatologists should consider either agent when treating acne in patients with skin of color. Some of the limitations of the studies cited include most having small sample sizes, lack of colorimetric assessments in most studies, and variable measures of efficacy used. Based on this review of literature, retinoids and AzA offer excellent treatment options for acne patients with skin of color.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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