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# Topical Retinoids for Pigmented Skin

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## ABSTRACT

Topical retinoids are an important class of drugs for treating several dermatoses occurring more frequently in patients with pigmented skin, such as melasma, post-inflammatory hyperpigmentation, pseudofolliculits barbae and keloids. They also play a role in managing acne, psoriasis, photoaging, cutaneous T-cell lymphoma, Kaposi sarcoma and disorder of hyperkeratosis in this demographic as well. In general, topical retinoids are well tolerated in pigmented skins. There is little evidence to suggest that patients with darker skin are at increased risk of irritation. However, retinoid dermatitis can induce post-inflammatory hyperpigmentation and attempts should be made to reduce its occurrence by modifying treatment regimens in patients with pigmented skins.

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## INTRODUCTION

The evolving demographic landscape of the United States necessitates that dermatologists become knowledgeable of the various nuances implicit in pigmented skins when choosing a dermatologic medication. Topical retinoids have been an important class of drugs since their inception nearly three decades ago. With varied success, they have been used to treat numerous dermatoses including acne vulgaris, psoriasis, photoaging, Kaposi sarcoma, cutaneous T-cell lymphoma and disorders of hyperkeratosis.[1] Retinoid responsive conditions more common in pigmented skins include melasma, post-inflammatory hyperpigmentation, keloids and pseudofolliculitis barbae.

Retinoids exhibit their biological effects via activation of two different families of nuclear retinoid receptors termed the retinoic acid receptors and the retinoid X receptors.[2] Each retinoic acid receptor comprises three different receptor subtypes (alpha, beta and gamma) which are encoded by distinct genes.[3] Once bound to the nuclear receptor, the drug-nuclear receptor complex binds to retinoic acid response elements, which are enhancing elements responsible for gene transcription.[3] The pharmacologic effect of each retinoid is mediated in part by the specific subset of receptors to which it binds.

According to data from the U.S Census Bureau, the non-Hispanic white population will decrease from 69 percent in 2000 to 50 percent by the year 2050. Simultaneously, rapid growth is expected to continue in the Asian/Pacific Islander and Latino segments.[4] These numbers illustrate a dramatic shift in patient demographics that will occur in years to come. The intent of this article is to review the use of topical retinoids in pigmented skins and develop a set of general guidelines based on the literature and our personal experience.

### Clinical Indications

*Post-Inflammatory Hyperpigmentation (PIH)*

The two most common dermatologic diagnoses among black patients have been reported to be acne and dyschromias.[5,6] Likewise, dyschromias rank as the fourth most common diagnosis in Hispanics.[7] Retinoids are useful in the treatment of hyperpigmentation because they reduce epidermal melanin by blocking the transcription of tyrosinase, induce desquamation, disperse keratinocyte pigment granules and enhance epidermal cell turnover via epidermopoiesis.[7,8]

The efficacy of hydroquinone, the gold standard treatment for hyperpigmentation, is improved by adding a topical retinoid. When used in conjunction with a topical steroid and hydroquinone, tretinoin has been shown to contribute to epidermal absorption of hydroquinone and prevents corticosteroid-induced epidermal atrophy.[9]

Post-inflammatory hyperpigmentation is an acquired disorder characterized by excess deposition of melanin in the epidermis, dermis, or both occurring secondary to cutaneous inflammation or injury. Although the exact mechanism of PIH remains unclear, it is postulated that inflammatory cells release cytokines and other mediators which are capable of stimulating melanocytes and increasing melanin synthesis.[10]

There have been several trials that have investigated the use of topical retinoids in the treatment of PIH in pigmented skins. One such trial involving 54 black subjects with PIH compared the efficacy of tretinoin 0.1% cream applied daily to a vehicle control. After 40 weeks, colorimetry determined a 40 percent lightening of lesions occurring in the tretinoin group versus 18 percent lightening with vehicle. In addition, there was a 23

percent reduction in epidermal melanin content in skin lesions of the tretinoin group compared to three percent with vehicle. Fifty percent of the subjects treated with tretinoin reported moderate-to-severe erythema and desquamation.[11] This trial is one of the best in terms of documentation, photography and inclusion of varying severity of PIH.

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Another trial studied once daily applied tazarotene 0.1% cream compared to vehicle in 74 subjects of darker racial groups with PIH. After 18 weeks, the treatment group was shown to be significantly more effective than vehicle against PIH, achieving greater reductions in intensity and area of hyperpigmentation. On average, evidence of irritation was no more than trace, and dryness no more than mild, in both groups throughout the study.[12]

The efficacy of clindamycin 1%-benzoyl peroxide (BPO) 5% topical gel in combination with either tretinoin 0.04% microsphere gel or adapalene 0.1% gel in 167 subjects with pigmented skins for the treatment of acne and PIH was investigated in a recent trial. Results showed more rapid and greater resolution of PIH from baseline in subjects receiving clindamycin 1%/BPO 5%/tretinoin 0.04% microsphere gel. It was concluded that this finding may indicate that this lower concentration of tretinoin microspere gel causes less irritation and a decreased capability of producing treatment-induced hyperpigmentation in darker skin types.[13]

The treatment of dermal PIH is more challenging. The histological features of biopsies obtained from 10 Japanese subjects with various types of hyperpigmented skin lesions found that tretinoin gel (0.1%, 0.2% and 0.4%) along with 5% hydroquinone ointment was histologically effective in reducing epidermal, but not dermal melanosis.[14] Accordingly, lesions with primarily dermal hyperpigmentation demonstrated the least amount of clinical improvement.

In summary, formulations of tretinoin, adapalene and tazarotene have all shown efficacy in treating epidermal causes of PIH, with tretinoin 0.004% microsphere gel probably the least irritating in pigmented skins.

*Melasma*

Melasma is an acquired hypermelanosis of unknown etiology characterized by epidermal, dermal, or mixed histological types of hyperpigmentation.[9] While the disease may affect all racial groups, it is most frequently observed in women of darker complexion, especially Latinos and Asians.[15]

A number of studies have explored the efficacy of topical retinoids as monotherapy in treatment of melasma. A trial consisting of 28 black subjects with melasma compared the efficacy and tolerability of tretinoin 0.1% cream daily to vehicle cream. After 40 weeks, the tretinoin group demonstrated a 32 percent improvement in the Melasma Area and Severity Index (MASI) score compared with a 10 percent improvement in the vehicle group. Tretinoin was also found to be superior based on colorimetric and histologic analyses. A mild dermatitis was noted to occur in 67 percent of subjects treated with tretinoin.[16]

Combination therapies, most frequently consisting of hydroquinone, tretinoin and a topical steroid are thought to be superior to monotherapy in the overall management of melasma. Not only does tretinoin facilitate the epidermal penetration of hydroquinone, but the incorporation of a topical corticosteroid helps to reduce the irritative effects of retinoids and hydroquinone.[9] Kligman and Willis reported the original triple combination formula effective in the treatment of melasma, which consisted of 5% hydroquinone, 0.1% tretinoin and 0.1% dexamethasone.[17] Despite its success, the fact that it contained a fluorinated corticosteroid and a high concentration of tretinoin made this formula less favorable.[8]

The first and only triple combination formula to be approved by the Food and Drug Administration (FDA) for the treatment of melasma contains hydroquinone 4%, tretinoin 0.05% and fluocinolone acetonide 0.01%. This medication should not be used for durations longer than eight weeks due to the potential side effects associated with long-term topical corticosteroids, especially when used on the face.[48] The efficacy and safety of this modified triple combination cream for the treatment of melasma was reported in an eight week study of 1,290 subjects with Fitzpatrick skin types I through VI and moderate-to-severe melasma. The mean MASI score in the study population decreased significantly at weeks 4 and 8 compared with baseline across all Fitzpatrick skin types. Based on investigators' global assessments, 75 percent of subjects had moderate to complete resolution after eight weeks of treatment. Twenty-seven percent of subjects experienced at least one adverse effect, mostly due to skin irritation, erythema, or dry skin.[18]

An eight week trial compared once daily applied triple combination cream to twice daily applied hydroquinone 4% cream in 120 Latino subjects with moderate-to-severe melasma. At

**TABLE 1.**

| Summary of Topical Retinoids Used in Pigmented Skins | | |
|---|---|---|
| **Generic Name** | **FDA-Approved Indication(s)** | **Formulations Available** |
| Tretinoin | Acne vulgaris<br>Fine facial wrinkling<br>Mottled facial hyperpigmentation<br>Tactile facial roughness | 0.01, 0.025, 0.05% gel<br>0.02, 0.025, 0.05. 0.1% cream<br>0.05% sol<br>0.04, 0.1% gel (microsphere) |
| Adapalene | Acne vulgaris | 0.1% cream<br>0.1, 0.3% gel<br>0.1% lotion |
| Tazarotene | Acne vulgaris<br>Plaque psoriasis | 0.1% cream<br>0.05, 0.1% gel |
| Bexarotene | CTCL (Stage 1A/B) | 1% gel |
| Alitretinoin | Kaposi sarcoma | 0.1% gel |

weeks 4, 6 and 8, the triple combination cream was significantly more effective than hydroquinone cream alone, while both groups had a similar incidence of irritation.[19] Another trial of 247 East and Southeast Asians with moderate-to-severe melasma compared, once again, triple combination cream applied once daily to hydroquinone 4% cream applied twice daily. After eight weeks of treatment, 64 percent of the subjects receiving triple combination therapy had a melasma global severity score of "none" or "mild" compared with 39 percent in the hydroquinone group. Although treatment-related adverse events occurred more frequently in the triple combination group (48%) compared with the hydroquinone group (14%), most of these were mild in intensity.[20] In subjects with Fitzpatrick skin types I to IV, triple combination has also been shown to be more effective than various combinations of dual therapy for the treatment of melasma.[21]

Chemical peels are occasionally used to improve melasma in lighter-skinned individuals; however, these agents should be used with caution in darker-skinned patients as they have a greater tendency to induce pigmentary changes.[15] A trial of 50 East Indian subjects found that hydroquinone is superior to tretinoin as a priming agent in maintaining the results achieved with peels and in decreasing the incidence of post-peel reactive hyperpigmentation.[22]

Based on the literature and our personal experience, topical retinoids are best used in the setting of combination therapy with topical steroids and hydroquinone for the short-term treatment of melasma and are generally well tolerated across a wide range of racial groups.

*Acne Vulgaris*

Retinoids prevent the formation of microcomedones and eradicate existing comedones by increasing the production of loose, non-coherent horny cells in the follicular orifice.[23] Furthermore, these agents possess direct anti-inflammatory and anti-fibroblastic properties, which make them effective inhibitors of the key pathogenic pathways responsible for PIH and keloids.[24] As sequelae of acne, PIH and keloidal scarring are more likely to occur in darker-skinned patients.[24] Despite the clinical presentation of acne being generally milder in patients with darker skin types, it is characterized by marked inflammation histologically.[25] This may explain why PIH associated with acne is more common in pigmented skins.

Several studies have looked at the role of topical retinoids in treating acne in pigmented skins. An eight week trial of topical tretinoin 0.025% cream in 27 black subjects with acne found a significant reduction in papules, pustules and hyperpigmented macules occurring in 83 percent of subjects treated with tretinoin in comparison to only 13 percent receiving vehicle alone. Many of the subjects in this study experienced irritation; however, the severity was classified as minimal.[1] This was not a randomized controlled study; that is a weakness of this trial.

A 12-week study of topical adapalene 0.1% gel applied daily was conducted in 65 African black subjects with mild-to-moderate acne. Adapalene was shown to be effective against both inflammatory and non-inflammatory lesions. Furthermore, approximately two-thirds of subjects were rated as having less post-inflammatory hyperpigmentation after 12 weeks. Less than five percent of subjects reported moderate or severe skin irritation at any time during the study. Interestingly, the incidence of moderate-to-severe skin oiliness decreased from 66 percent at baseline to complete absence in all subjects after 12 weeks of treatment.[26] This was also not a randomized placebo controlled study, which poses a weakness.

A meta-analysis of five randomized U.S. and European studies on adapalene was conducted to further assess the safety and efficacy of adapalene in black versus Caucasian subjects with

acne. In black subjects, adapalene exhibited efficacy in the reduction of inflammatory lesions and better tolerability, as seen by a decreased frequency of erythema and scaling, compared to Caucasians. [27]

Adapalene gel 0.1% has also been proven efficacious and well tolerated in the treatment of acne in Asian populations. The efficacy and safety of adapalene gel 0.1% versus the corresponding gel vehicle for a period of 12 weeks has been evaluated in 200 Japanese subjects. The median percent reduction of total acne lesion counts at endpoint was significantly greater in the adapalene gel 0.1% group (63.2%) versus the vehicle group (36.9%). Adapalene was well tolerated in these subjects and the adverse events, most commonly dry skin, were classified as transient and mild-to-moderate in severity.[28] Similarly, an eight-week study of adapalene 0.1% gel versus tretinoin 0.025% gel in 150 Chinese subjects with mild-to-moderate acne vulgaris determined that adapalene 0.1% gel was equally effective as tretinoin 0.025% gel for acne lesions, with a more favorable tolerability profile.[29] This trial is particularly noteworthy because it offers a rare direct comparison between topical retinoids for acne in pigmented skins.

A study of 126 East Indian subjects with acne vulgaris evaluated the efficacy and safety of tazarotene 0.1% gel daily for 14 weeks.[30] A statistically significant reduction was observed at weeks 8 and 12 in the mean number of inflammatory acne lesions (70.5% and 86.1% respectively), non-inflammatory acne lesions (81.5% and 92% respectively), and total acne lesion count (75.6 and 88.8% respectively) from baseline. Although 11.9 percent of subjects experienced side effects during treatment with tazarotene, mostly consisting of itching (4.8%), erythema and dryness (2.4%), and burning (1.6%), these events were graded as mild in nature. Because there was no randomization or vehicle control group in this trial, these results must be interpreted cautiously.

Based on the previously discussed trials and our experience, tazarotene appears to be the most effective though most irritating topical retinoid for treating acne in pigmented skins.[30,31] Adapalene 0.1% gel shows the least potential for irritation while still maintaining efficacy comparable to tretinoin 0.025% gel in treating acne in pigmented skins.

*Psoriasis*

Tazarotene is the only topical retinoid FDA-approved for the treatment of mild-to-moderate plaque psoriasis. It is often used in combination with a mid-to-high potency topical corticosteroid or Vitamin D analog to enhance efficacy and tolerability.[32]

To the best of our knowledge, only one trial has investigated the use of topical retinoids for psoriasis exclusively in pigmented skins. A 12-week study consisting of 36 East Indian psoriatic subjects compared the clinical efficacy of tazarotene 0.1% cream with clobetasol propionate 0.05% cream in the treatment of chronic plaque psoriasis.[33] While tazarotene was found to be less effective in terms of reducing erythema and scaling, it was determined to be more effective in reducing plaque induration. As expected, the main side effect of tazarotene was mainly mild irritation seen in 19.4 percent of subjects, whereas hypopigmentation and skin atrophy was seen in 19.4 percent and 8.3 percent of subjects in the clobetasol group, respectively.

As demonstrated in the previously mentioned trial, the risk of hypopigmentation is relatively common and more noticeable in pigmented skins when using clobetasol. Extra consideration must be given to quickly find an appropriate steroid-sparing regimen, potentially using tazarotene, in treating psoriasis in this patient population.

*Photoaging*

Photoaging in darker skinned individuals often becomes apparent at a much later period in life compared to Caucasians.[7] Topical retinoids are useful in the treatment of photoaging because they partially restore type I pro-collagen formation, which is decreased in photodamaged skin.[34] Retinoids counteract the effects of ultraviolet radiation exposure by compacting the stratum corneum, increasing epidermal thickness, eliminating dysplasia and atypia, promoting angiogenesis, increasing granular layer thickness and reducing melanin content.[35]

There is a paucity of studies looking into the anti-aging properties of retinoids in darker skin types. One particular trial explored the treatment of dyspigmentation, which is the primary manifestation of photoagaing in Far-East Asians. In a 40 week trial consisting of 45 photoaged Chinese and Japanese subjects, once-daily application of 0.1% tretinoin cream significantly lightened hyperpigmented lesions due to photoaging.[36] Hyperpigmented lesions in the tretinoin group were lighter or much lighter in 90 percent of subjects as compared with 33 percent in subjects receiving vehicle cream. Erythema or scaling of at least moderate degree occurred in 91 percent of subjects who received tretinoin and in 17 percent of subjects in the vehicle group. This was accompanied by a statistically significant 41 percent reduction in epidermal pigmentation on histologic analysis of lesions treated with tretinoin. The significance of this trial is based on the determination that using topical tretinoin for dyspigmentation, the primary manifestation of photoaging in pigmented skins, can be effectively diminished similarly to fine wrinkling, the primary manifestation of photoaging in Caucasians.

*Pseudofolliculitis Barbae (PFB)*

Pseudofolliculitis barbae is a chronic inflammatory disorder that is related to the inherent curvature of the hair follicle in blacks.[37,38] It is rather common, occurring in 83 percent of black army recruits.[37] The utility of topical retinoids may involve reducing the hyperkeratosis that results from cyclic piercing of the follicular epithelium.[39]

The only trial, to the best of our knowledge, to investigate the use of topical retinoids in PFB looked at the combination of tretinoin 0.025% cream at night and hydrocortisone 2.5% cream twice daily for eight weeks in 10 black subjects with mild-to-moderate PFB. Results showed a reduction in the number of papules and hyperpigmented macules in eight out of 10 subjects.[1] This is limited in that this was not a randomized placebo controlled study and had a small number of subjects. In our personal experience, however, topical retinoids are a useful adjunct in treating PFB.

*Keloids*

The incidence of keloids is five to 16 times greater in blacks, Asians and Latinos compared to Caucasians.[24] These overgrowths of scar tissue commonly occur following trauma, surgical incisions, earlobe piercing, and may also develop spontaneously.[1] In the 1980s, researchers observed that retinoids markedly reduced the production of pro-collagen in keloid fibroblast cultures.[40]

There is evidence to suggest that topical retinoids may be useful therapy for the treatment of keloids. A study consisting of 11 subjects treated with tretinoin 0.05% cream for 12 weeks demonstrated a significant decrease in the weight and size of long-standing keloids as compared with baseline measurements.[41] Another study of 28 subjects with hypertrophic scars treated with daily topical 0.05% tretinoin solution not only found a reduction in the size of the lesions, but also a decrease in complaints of pruritus in the majority of subjects.[42] The significance of both the aforementioned trials is marred by their lack of placebo-controlled randomization.

*Cutaneous T-cell Lymphoma and Kaposi Sarcoma*

Topical bexarotene and alitretinoin are FDA-approved for the treatment of refractory stage IA/B CTCL and cutaneous Kaposi sarcoma, respectively. At present, information regarding the efficacy and tolerability of these agents specifically in patients of pigmented skins is limited; however, both are currently used for these specific indications in pigmented skins.

### Practice Guidelines

There is widespread, but largely unproven, belief that people with darker skins are more prone to contact irritation.[43] Based on the previously reviewed studies, there is little evidence to suggest that patients with darker skins are more susceptible to retinoid dermatitis. In fact, the contrary may be true.[44] Often times, there is greater variation with respect to irritant response within a particular group than between groups.[43] Further complicating matters, irritant response may be expressed differently or appear less evident in darker skins.[45] Unfortunately, there is a paucity of quality studies looking specifically at the relationship between skin color and susceptibility to irritation from topical retinoids. Simply asking the patient about their personal history with skin irritation may be a good starting point when initiating topical retinoid therapy.

Selection of the appropriate vehicle, concentration, and dosing frequency of a topical retinoid is critical in minimizing the risk of an irritant reaction to topical retinoids (Table 1). For patients with sensitive, dry skin or those with a prior history of skin reactions, a cream is favored over a gel formulation.[24] In addition, therapy should be initiated at a lower concentration of a retinoid with alternate-day dosing for the first two weeks and increased to once nightly as tolerated.[46] After four to six weeks of treatment with a tolerated lower strength retinoid, the concentration may be increased.[46] To further minimize the irritation and drying effect of topical retinoids, patients should be advised to use a mild cleanser, a non-comedogenic moisturizer with a sun protection factor of 15, as well as discontinue the use of over-the-counter treatments.[47]

## CONCLUSION

Topical retinoids are utilized for a wide variety of dermatologic conditions in patients with pigmented skins. Dermatologists must be mindful of the irritant effects associated with these agents which can potentially lead to PIH in darker skin. A balance must be maintained between early, aggressive therapy with topical retinoids to address the underlying skin disorder and the selection of a tolerable treatment regimen that curtails the risk of retinoid dermatitis with ensuing PIH.[46] Certain guidelines, beginning with proper patient education, should be implemented to minimize the risk of an irritant reaction to topical retinoids in pigmented skins. Further investigation is needed to determine whether a difference in topical retinoid tolerability exists among different racial groups.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

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