THERAPEUTIC INSIGHTS IN MELASMA AND HYPERPIGMENTATION MANAGEMENT

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Statement of Need

Hyperpigmentary disorders including PIH and melasma are more visible in persons with darker skin types but affect all skin types and occur in over 5 million Americans. These conditions may be resistant to treatment and take extended periods of time to resolve. A variety of treatment modalities exist including topical medications, laser therapy, cryotherapy, chemical peels, and use of camouflaging cosmetics. Dermatology providers require advanced knowledge of the signs, differential diagnosis and variants of these disorders, and access to clinical experience with available treatment options including the approved triple combination topical cream. Therefore, gaps exist in the medical knowledge of dermatology providers regarding identification, differential diagnosis, and effective treatment of disorders of hyperpigmentation including PIH and melasma. Providers need expanded understanding of effective use of topical hydroquinone, including appropriate concentrations and length of use as well as advanced understanding of the features, benefits, and safety profiles of available topical treatment options for melasma including combination therapy with hydroquinone, retinoids, and corticosteroids. Dermatology providers will have access to the latest evidence-based data as well as expert insights from leading clinicians to accurately diagnose and select effective treatment strategies for patients with these disorders.

Educational Objectives

The overall information and educational goals of this enduring activity are to expand awareness, explore commonly encountered melasma treatment successes and failures, and compare features, benefits, safety, and efficacy profiles of available treatment options for managing melasma and hyperpigmentation.

Upon completion of this continuing education activity participants should be able to:

- Differentiate clinical signs of disorders of hyperpigmentation including melasma and PIH
- Review appropriate use of topical hydroquinone including choice of concentration, length of course, and expected outcomes
- Summarize features, benefits, and safety of melasma treatment options including topical hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% cream

Target Audience

This activity is intended for dermatologists, residents, and fellows in dermatology, and physician assistants, nurse practitioners, and other healthcare providers with an interest in cutaneous diseases and disorders affecting patients of all skin types.

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 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Therapeutic Insights in Melasma and Hyperpigmentation Management

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ABSTRACT

Melasma and postinflammatory hyperpigmentation (PIH) are the most common forms of dyschromia in patients with skin of color. Both are associated with a high psychological burden of disease. To exacerbate this burden, the need for treatment is chronic, and the results are often suboptimal in the eyes of the patient. Successful treatment is therefore contingent upon a correct diagnosis, patient education, and a carefully considered therapeutic approach. The latter is often multimodal in its design, incorporating sun protection, topical and systemic medications, and in some cases, procedural intervention. Although topical hydroquinone is a mainstay of treatment for melasma and PIH, there are alternatives that have emerged as of late that have shown varying degrees of promise, both in terms of safety and efficacy. In this article, we review the epidemiological, clinical, and histologic features of melasma and postinflammatory hyperpigmentation, and discuss important considerations for both established and emerging treatments for these vexingly common and difficult to treat conditions.

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INTRODUCTION

EPIDEMIOLOGY, CLINICAL AND HISTOLOGIC FEATURES, AND QUALITY OF LIFE

Melasma

Melasma is an acquired disorder of hyperpigmentation that most commonly presents as symmetrically distributed brown to gray macules and coalescent reticulated patches that have a predilection for the face (Figure 1a). It can rarely present on the neck, upper chest, upper back, and extensor forearms. Based upon the depth of melanin deposition, melasma can be classified into 4 subtypes—epidermal, dermal, mixed, or indeterminate—which are delineated by Wood's lamp examination. Epidermal melanin is anticipated to accentuate on exam, while dermal melanin does not, though some clinicopathologic studies have demonstrated that this does not always hold true.[1,2] There may also be a vascular contribution to melasma, as an increase in erythema in telangiectasias have been demonstrated in lesional skin.[3]

The prevalence of melasma is not precisely known, and published estimates have varied widely, ranging from around 1–40%.[4,5] Populations in whom a higher prevalence is observed include pregnant women, individuals with darker skin types (namely Fitzpatrick skin types [FST] III – VI who are of Hispanic, Asian, and African descent), and those who receive abundant and intense sun exposure as a function of geography, occupation, or both. Although less common, men are also affected by melasma, with prevalence estimates similarly broad. One study of Indian men found a prevalence as high as 25.8%.[6]

The pathogenesis of melasma is both multifactorial and incompletely understood. In addition to the aforementioned factors observed in higher risk populations, genetics and hormonal influences are believed to contribute to the development of melasma. It is not uncommon for melasma patients to be in a state of estrogen or progesterone excess, or to report having family members who are similarly affected. In recent years, the contributory role that various signaling molecules, growth factors, and reactive oxygen species may be playing in the pathogenesis of melasma has increasingly come to light, though their detailed discussion is beyond the scope of this review.

Histologically, there is an increase in epidermal and dermal melanin that is generally believed to be unaccompanied by an increase in the number of melanocytes,[1,2] though one case that demonstrated increased epidermal melanocytes that protruded into the dermis has been reported.[7] Melanocytes present in melasma lesions are typically enlarged, and have elongated dendrites to facilitate transfer of increased numbers of melanosomes to neighboring keratinocytes. An increase in mast cells, dermal blood vessels, and solar elastosis may also be present.[1,2]

Melasma can cause significant psychosocial distress and quality of life impairments in those affected. Melasma patients have reported lower levels of self-esteem, decreased freedom, and annoyance at costly treatments, which negatively impact their social life, leisure time, and emotional well-being.[8,9] In some cases, a poor correlation between disease severity and quality of life has been observed, suggesting that the patient may

FIGURE 1A. Melasma before treatment.

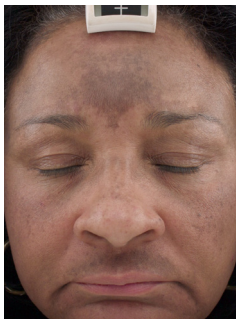
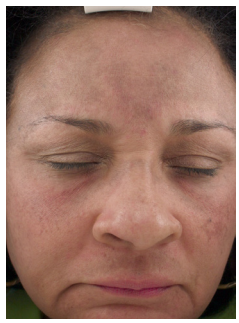


FIGURE 1B. Melasma after treatment with triple combination cream (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%).



perceive their disease to be worse than it has been objectively assessed.[10] Conversely, successful medical management of melasma has been shown to produce feelings of confidence and positive life perceptions in patients.[11]

Postinflammatory Hyperpigmentation

Postinflammatory hyperpigmentation (PIH), like melasma, is an extremely common acquired disorder of hyperpigmentation that follows endogenous cutaneous inflammation or external injury. Lesions can range from light brown to dark grey or black, and are distributed where the original cutaneous insult occurred. The color of the lesion is largely dictated by the depth of the pigmentary alteration, which is a consequence of the Tyndall effect of light scattering.[12] PIH that is primarily epidermal is characterized by increased melanin in keratinocytes, whereas dermal PIH displays increased melanophages in the dermis.

As in the case of melasma, PIH tends to occur more commonly in those with FST III to VI,[13] which is likely related to the degree of constitutive cutaneous pigmentation in affected individuals.[14] These patients also tend to exhibit a greater frequency, duration, and severity of PIH lesions. The prevalence of PIH is difficult to isolate, but can be quite high. One study found the incidence of PIH in acne patients with skin of color (SOC) to be 65.3% among African-Americans, 52.7% among Hispanics, and 47.4% among Asians.[15] A survey of Arab Americans residing in Detroit, MI, found 56.4% of respondents expressing concerns about alterations in their skin tone.[16]

Of note, PIH may have a strong association with melasma. In a study of 400 individuals, post-acne related pigmentation was observed to be six times more likely to occur in melasma patients.[17] As with melasma, PIH has also been found to negatively impact self-perception and social/emotional functioning in those afflicted.[18]

Designing a Therapeutic Strategy

A multimodal approach is required to successfully treat melasma and PIH, though the details of a given approach are contingent upon each individual patient's clinical presentation, general health, financial resources, and levels of compliance and reliability. Daily conscientious photoprotection should be a component of all treatment regimens, and is in most cases accompanied by the use of a topical lightening agent. Hydroquinone (HQ) is the gold standard in topical skin lightening, and when combined with tretinoin and a topical corticosteroid, its efficacy and tolerability are enhanced[19] (Figure 1b). Moreover, a triple combination cream (Tri-Luma®; fluocinolone acetonide 0.01%, HQ 4%, tretinoin 0.05%) is the only topical medication that is FDA approved for the short-term treatment of moderate to severe melasma of the face.[20]

The choice of first-line lightening agent is also dictated by whether a patient is pregnant or breastfeeding. For example, the use of HQ as well as topical retinoids such as tretinoin and adapalene should be avoided in pregnant women due to their pregnancy category C classification, while tazarotene is pregnancy category X. The transcutaneous absorption of HQ is reported to be about 35% with subsequent secretion in breast milk, though the manifestations of potential toxicity are unclear. Nevertheless, chronic use in breastfeeding women is not recommended.[21] Given that melasma will often flare during pregnancy, and likely persist during at least the initial months of breastfeeding, physicians should possess a comprehensive knowledge of topical lightening agents that can be substituted into a patient's treatment plan during these times. There are a number of other topical agents that also work to combat hyperpigmentation via tyrosinase inhibition, antioxidation, or a combination of both (Table 1), that may be incorporated into a patient's lightening regimen as alternatives or adjuncts to HQ or topical retinoids, when circumstances necessitate.

Several systemic agents have gained attention in recent years for their potential skin lightening ability, including tranexamic acid, polypodium leucotomos extract, and glutathione, though a reliable assessment of their safety and efficacy is limited by a dearth of large scale double-blind randomized placebo-controlled trials. Still, it may be reasonable to add some of these

TABLE 1.

Non-Hydroquinone-Based Topical Lightening Agents Reported to be Efficacious in the Treatment of Melasma and Post-inflammatory Hyperpigmentation

Treatment	Source	Mechanism of action	Indication	Protocol	Duration	Remarks
Ascorbic acid (Vitamin C)	Various foods	Tyrosinase inhibition Antioxidant	Melasma	5% ascorbic acid vs 4% HQ[78]	16 weeks	Better subjective response with HQ, but no significant difference in melanin index.
Arbutin	Bearberry plant (*Arctostaphylos spp*, Bergenia crassifolia)	Tyrosinase inhibition, melanosome maturation inhibition	Epidermal melasma	3% arbutin, 4% nicotinamide, 1% bisabolol, 0.05% retinaldehyde daily[79]	60 days	Significant reduction in MASI score.
Azelaic acid (AA)	Pityrosporum ovale yeast	Tyrosinase inhibition	Melasma, PIH	20% AA BID vs placebo[81]	24 weeks	Improvement in subjective scale, melanin index, over placebo.
			PIH	15% AA BID[80]	15 weeks	Improvement in 4 weeks, complete clearance in 31% at 16 weeks.
Green tea	*Camellia sinensis*	Tyrosinase inhibition Antioxidant	Melasma	2% extract TID vs placebo[82]	12 weeks	Significant improvement in mean lesion count and IGA over placebo.
Emblica	Gooseberry *(Emblica officinalis)*	Tyrosinase inhibition	Mild-mod facial dyschromia	emblica, kojic acid, glycolic acid (*Conc. not specified) vs 4% HQ[83]	12 weeks	Significant improvements in hyperpigmentation with both topicals. Similar efficacy with both topicals.
Flutamide	Synthetic	Binds androgen receptor, blocks action of testosterone	Melasma	1% flutamide vs 4% HQ daily[84]	16 weeks	Significant reductions in MASI for both groups, with flutamide demonstrating superiority. No significant difference in melanin indices between both groups.
Kojic acid	Fungi *(Aspergillus oryzae, Penicillium spp, Acetobacter spp)*	Tyrosinase inhibition (copper chelation)	Mild-mod facial dyschromia	emblica, kojic acid, glycolic acid (*Conc. not specified) vs 4% HQ[83]	12 weeks	Significant improvements in hyperpigmentation with both topicals. Similar efficacy with both topicals.
			Melasma	0.75% kojic acid, 2.5% ascorbic acid vs 4% HQ[85]	12 weeks	Significant improvements in both groups, HQ demonstrating superiority.
Licorice	Legume root *(Glycyrrhiza glabra)*	Tyrosinase inhibition	Melasma	20% liquiritin BID vs placebo[86]	4 weeks	70% with excellent response compared to controls. Improvement in melasma rated by 5-point scale.
Mequinol	Synthetic	Tyrosinase inhibition	Melasma	2% mequinol, tretinoin 0.01% daily[87]	12 weeks	Melasma resolved in 80% of subjects at 12 weeks. 20% reported moderate improvement.

TABLE 1. (CONTINUED)

Non-Hydroquinone-Based Topical Lightening Agents Reported to be Efficacious in the Treatment of Melasma and Post-inflammatory Hyperpigmentation						
Treatment	**Source**	**Mechanism of action**	**Indication**	**Protocol**	**Duration**	**Remarks**
Mulberry	Mulberry tree *(Morus alba)*	Antioxidant	Melasma	75% mulberry extract BID vs placebo[88]	8 weeks	Significant improvements in MASI, melanin index, MelasQoL score.
N-acetyl-glucosamine (NAG)	Monomeric unit of chitin	Tyrosinase inhibition	Facial hyperpigmentation	2% NAG, 4% niacinamide vs placebo[89]	10 weeks	Significant improvements in expert visual grading, and various technology-assisted image analysis techniques compared to controls.
Niacinamide	Amide form of vitamin B3	Melanosome transfer inhibition	Melasma	4% niacinamide vs 4% HQ[90]	8 weeks	Good to excellent response in 44% of subjects with niacinamide vs 55% with HQ. No significant differences in melanin index. Niacinamide reduced mast cells, improved solar elastosis on histological analysis of melasma lesions.
			Facial hyperpigmentation	2% NAG, 4% niacinamide vs placebo[89]	10 weeks	Significant improvements in expert visual grading, and various technology-assisted image analysis techniques compared to controls.
Retinoids	Synthetic	Tyrosinase inhibition, melanosome transfer inhibition, increased epidermal turnover	PIH (caused by acne)	0.1% adapalene daily[91]	12 weeks	Significant improvements in degree of hyperpigmentation and lesion counts. n = 65 African American subjects; less then 5% reported moderate or severe skin irritation.
Rucinol	Synthetic	Tyrosinase inhibition	Melasma	0.3% rucinol vs placebo BID[92]	12 weeks	Significantly improved clinical pigmentation score and melanin indices compared to control.
Silymarin	Milk thistle *(Silybum marianum)*	Tyrosinase inhibition, antioxidant	Melasma	0.7% silymarin vs 1.4% silymarin vs 4% HQ[93]	12 weeks	Significantly reduced MASI score in all groups, with no significant differences in response among groups.
4-N-Butylresorcinol (4NBR)	Synthetic resorcinol derivative	Tyrosinase inhibition, antioxidant	Melasma	0.1% 4NBR vs placebo BID[94]	8 weeks	Significant improvement in Mexameter reading compared to control.

HQ = Hydroquinone; MASI = Melasma Area and Severity Index; IGA = Investigator's Global Assessment; MelasQoL = Melasma Quality of Life; BID = twice daily; TID = three times daily; Mild-mod = mild to moderate; PIH = postinflammatory hyperpigmentation

as second- or third-line agents to the treatment plans of highly motivated patients who do not possess any contraindications to therapy, and whose melasma has been refractory to first-line topical therapy alone.

Additional adjunctive therapies include chemical peels, lasers, and intense pulsed light.[22-25] Though these treatments may enhance the results yielded by photoprotection and topical and/or systemic therapy, they should never be used as first-line monotherapy due to the risk of PIH, especially in SOC. Their use requires careful counseling to ensure that patients understand that these physical modalities will at best provide some temporary improvement in the appearance of melasma, and that relapse is possible despite the high financial burden these treatments might carry. It is reasonable to anticipate better outcomes in the treatment of PIH, provided that the initial inflammatory event or cutaneous injury that caused the dyspigmentation has been fully quelled. Only reliable, compliant patients should be selected for these procedures, as pre- and post-treatment regimens require a high degree of adherence in order to prevent adverse effects such as PIH, scarring, and skin infection.

When designing a treatment approach for a given patient, clinicians should remind themselves to consider the differential diagnosis of facial hyperpigmentation (Table 2). Conditions that mimic melasma may require a therapeutic redesign, and may also affect the manner in which a patient is counseled on treatment options, cost, and outcome expectations. All discussions about treatment should first be preceded by a thorough history that inquires about past dermatologic conditions, recent cutaneous exposures, medical comorbidities, and medications (including over the counter supplements and analgesics, or other remedies that may have been purchased from the Internet or when traveling abroad), in order to first rule out other potential causes of non-melasma facial hyperpigmentation.

This review will highlight established and emerging therapies for the medical management of melasma and PIH, with an emphasis on their mechanisms, protocols, and outcomes.

Photoprotection

Consistent, rigorous, daily photoprotection is the foundation of all active and maintenance treatment regimens for melasma and PIH. Ultraviolet (UV) light is known to exacerbate both conditions, while the regular aggressive use of topical sunscreen alone has been conversely demonstrated to improve hyperpigmentation in both pregnant women and non-pregnant SOC patients.[26,27] Patients should be instructed to apply a sunscreen with broad spectrum UV protection with a sun protection factor (SPF) of ≥ 30, as part of their daily morning routine, as well as every two hours throughout the day depending on the nature and location of their activities. Some have advocated for the use of sunscreens with SPF ≥ 70, as they have been shown to add clinical benefits when applied in volumes typically utilized by consumers.[28]

TABLE 2.

Differential Diagnosis of Melasma Involving the Face and Neck
Postinflammatory hyperpigmentation
Acanthosis nigricans
Erythema dyschromicum perstans
Chrysiasis
Argyria
Pigmented contact dermatitis
Lichen planus pigmentosus
Solar lentigines
Dermal melanocytosis
Macular amyloidosis
Hydrocarbon-induced toxic melanoderma
Exogenous ochronosis
Medications
Minocycline
Anti-malarials
Amiodarone
Clofazamine
Diltiazem
Antipsychotics (phenothiazines)
Anticonvulsants (phenytoin)
Heavy metals
Argyria (silver)
Chrysiasis (gold)

Visible light (400–700nm) has been shown to induce pronounced and sustained pigmentation in FST IV–VI, and may exacerbate melasma.[29,30] It has more recently been found that OPN3, a G-protein coupled receptor that serves as a visible blue light sensor on melanocytes, promotes melanogenesis through its involvement in a signaling cascade that begins with visible light exposure, and culminates in the increased expression of tyrosinase and dopachrome tautomerase.[31] While physical blocking sunscreens that contain nonmicronized titanium dioxide and zinc oxide confer protection against both UV and visible light, the white to gray sheen they often create on SOC is cosmetically unacceptable to many individuals. Iron oxide is capable of acting as a UV-visible light filter, while providing better cosmesis for SOC. UV-visible light sunscreens containing iron oxide have been shown in various studies to improve Melasma Activity and Severity Index (MASI) scores.[32,33]

Patients should be counseled on multiple photoprotective measures, given their innate value as therapeutic adjuncts, and the challenge to compliance that frequent topical sunscreen application presents. These measures include avoiding di-

rect sun exposure during the late morning to early afternoon hours, seeking shade when possible, wearing photoprotective clothing and accessories, and considering the installation of UV-protective films on window/windshield glass.

Systemic Agents

Tranexamic Acid

Tranexamic acid (TA) is a synthetic derivative of the amino acid lysine, and is perhaps the most widely studied systemic agent for the treatment of melasma. The use of TA for melasma is off-label. TA has historically been employed as a hemostatic agent to treat conditions characterized by aberrant fibrinolysis, such as hemophilia and menorrhagia, at doses of around 3,000 g daily.[34] There is no consensus for the optimal oral dosing of TA for melasma, though it typically ranges from 500–750 mg daily,[35-37] which is around one-sixth of how it is dosed for its other indications. TA is thought to inhibit the UV-induced conversion of plasminogen to plasmin in keratinocytes, thereby causing a reduction in arachidonic acid and prostaglandins, which in turn decreases tyrosinase activity.[38] TA has been shown to decrease angiogenesis and mast cells,[34] thereby possibly functioning to counteract the vascular contribution to melasma's pathogenesis. Due to structural similarities with tyrosinase, TA has also been postulated to competitively antagonize the enzyme, further impeding melanogenesis.[39]

A large retrospective study comprised of 561 Asian patients in Singapore who received oral TA 250 mg twice daily for melasma reported improvements in 89.7%, with a response usually seen within 2 months of treatment initiation. Additional noteworthy findings from this study included a relapse rate of 27.2% following cessation of therapy, and a superior response to treatment in those without a family history of melasma.[36] Other studies have reported relapse rates as high as 72%, occurring within 2 months treatment cessation.[40] A more recent US based prospective study comparing TA 250 mg twice daily with placebo showed a 49% reduction in the MASI score of the TA group versus an 18% reduction for the placebo group.[41] One study that incorporated histologic evaluation of lesional and perilesional skin of patients treated with oral TA 125 mg twice daily in conjunction with topical 2% niacinamide for 8 weeks found significant decreases in melanin indices that were accompanied by a marked reduction in epidermal pigmentation, mast cell counts, and number of dermal blood vessels, the latter of which was thought to be attributable to the antiangiogenic effects of TA.[35]

Concern about potential thromboembolic events (TE) may limit a clinician's willingness to treat melasma patients with oral TA, but these events are in reality exceedingly rare. In the aforementioned retrospective study out of Singapore (n=561), 1 patient developed a deep vein thrombosis and was later found to have familial protein S deficiency.[36] In a meta-analysis comprised of 667 patients spanning 11 studies, no TEs were reported, though it should be noted that only 5 of the 11 studies examined the use oral TA in melasma patients.[34] It is likelier for oral TA-associated side effects to be of a more mild, transient, and mundane variety, namely gastrointestinal upset, menstrual irregularities, and headache, at doses used to treat melasma.[34,41,42]

Patients who have experienced TEs with oral TA tend to not only be taking it at higher doses indicated for the management of hemorrhagic conditions, they also usually have one or more risk factors that predispose them to hypercoagulability, including prior history of TEs (including deep vein thrombosis, pulmonary embolism, arterial thrombosis, and cerebrovascular accidents), hormonal therapy, medication interactions, malignancy, surgery, and prolonged immobility.[37] All melasma patients being considered for oral TA should be screened for other potential contraindications to therapy, which in addition to the aforementioned may also include renal dysfunction, cardiovascular disease, respiratory disease, smoking, and anticoagulant therapy.[36,43] Oral TA is pregnancy category B, and is used in pregnant women with bleeding disorders such as von Willebrand disease.[44] However, given the hypercoagulability induced by pregnancy, and the various treatment options that are available in the post-partum period, a clinician must carefully consider their own comfort level with managing oral TA in a pregnant patient who requests it for the treatment of melasma.

Topical formulations of TA have demonstrated varying degrees of efficacy in the treatment of melasma, though not necessarily superiority when compared with HQ. Two studies have found topical 5% TA to be as effective as HQ 3-4% cream in reducing MASI scores, while causing less erythema and irritation.[45,46] A clinicohistologic study of lesional and perilesional skin in 23 Korean patients with mild melasma who were treated with 2% TA for 12 weeks exhibited significant improvements in MASI scores, as well as decreased epidermal melanin content, fewer CD-31 positive dermal vessels, and a notable decrease in the expression of vascular endothelial growth factor.[47] These histologic findings echo results from previous studies that describe the antiangiogenic histologic changes TA is capable of inducing in the skin of melasma patients.

Microneedling and microinjections have also been successfully utilized to facilitate intradermal TA delivery, with microneedling found by some to deliver superior results, possibly as a consequence of deeper and more uniform drug delivery.[48] There is one reported case of intradermal tranexamic acid administration that resulted in paradoxical hyperpigmentation at the treatment site, which was attributed to drug metabolite-protein-iron complexes akin to those observed in type II minocycline hyperpigmentation.[49]

Polypodium Leucotomos

Polypodium leucotomos (PL) is a tropical fern that hails from Central and South America. Its extract has been shown to possess antioxidative and immunomodulatory effects that are capable of counteracting mechanisms of hyperpigmentation.[50] While generally regarded as safe and well tolerated, studies on its efficacy have yielded mixed results. Used alone or in conjunction with broad spectrum sunscreen and hydroquinone 4% daily, PL extract at a dose of 240 mg BID has been found to improve the appearance of melasma.[51,52] When evaluated as an adjunct to topical sunscreen in the treatment of melasma in Hispanic women, however, oral PL at a dose of 240 mg TID was not found to be significantly better at 12 weeks than topical sunscreen alone, though both treatment arms yielded improvements in the appearance of melasma.[53]

Glutathione

Glutathione (GSH) is a tripeptide composed of the amino acids L-cysteine, glutamate, and glycine, and is recognized as a potent antioxidant. GSH is thought to decrease melanogenesis by several mechanisms, including chelating copper ions to inactivate tyrosinase, antioxidant effects that decrease tyrosinase activity, and shifting the production of eumelanin to pheomelanin.[54,55]

There is one randomized double-blind placebo controlled study of 60 healthy Thai medical student volunteers who were administered 500 mg GSH in 2 divided doses for 4 weeks that yielded a statistically significant reduction in melanin indices at two of 6 sites compared to placebo.[56] A second open-label, single-arm pilot study administered a 500 mg GSH lozenge to the buccal mucosa of 30 Filipino women once daily for 8 weeks. All subjects showed a statistically significant decrease in melanin indices from baseline at both sun-exposed and sun-protected sites, though by the authors' own admission these results were clinically only mild to moderate.[54] Tolerability of oral GSH was excellent in both studies. A randomized, double-blind, split-face study of 30 healthy Filipino women who for 10 weeks received 2% GSH lotion and placebo also found a statistically significant reduction in the melanin index of the GSH-treated side compared to placebo.[57] As was the case with oral preparations, the topical was well tolerated. It is of import to note, however, that these studies share a common thread of small sample sizes comprised of healthy patients, short study periods, and short follow up, which limit meaningful assessment of long term safety, efficacy, and generalizability.

There is a dearth of safety data to support the use of intravenous glutathione (IV-GSH) for skin lightening that is incongruent with both increasing consumer demand, and the ease with which it is obtained at various IV "bars," "spas," and "lounges," that in some cases may not have any highly trained medical personnel in their employ. By avoiding first pass metabolism to which oral GSH is subjected, IV-GSH is said to provide more rapid and superior skin lightening results.[54] The use of IV-GSH as a skin lightening agent has been both highly publicized in the media,[58] and widely cautioned against by both the US Food and Drug Administration (FDA)[59,60] and the Philippine Dermatological Society,[61] who share concerns about adverse events, both real and potential. Adverse reactions associated with the use of IV-GSH can range from mild headaches and rashes to anaphylaxis, acute renal failure, Stevens Johnson syndrome, and toxic epidermal necrolysis.[54,61,62] During the past two years, the FDA has issued separate warnings regarding the presence of potential endotoxins in a glutathione-L-reduced powder from a distributer in Alabama,[59] and the sale of unregulated GSH for home intravenous and intramuscular injection by a New Jersey company named Flawless Beauty LLC.[60]

Topical Agents

Cysteamine

Cysteamine is an amino thiol that is endogenously derived from coenzyme A degradation.[63] The exact mechanism of cysteamine's action as a skin lightening agent is incompletely understood. At low concentrations, cysteamine facilitates the intracellular synthesis of glutathione (the antimelanogenic properties of which were described in the preceding section), and is itself a direct scavenger of hydroxy radicals.[63] Early studies conducted on black goldfish revealed cysteamine to be a more potent depigmenting agent than HQ.[64,65]

Two recent studies in Tehran have found cysteamine 5% cream to produce statistically significant decreases in MASI scores and melanin indices when employed as a treatment for epiderma melasma.[66,67] In each randomized, double-blind, placebo controlled study, patients received either placebo or cysteamine 5% once daily for 4 months. Both studies were designed similarly, with only minor differences in the number of patients enrolled and devices used to measure melanin indices. Mansouri et al[66] (n=50) measured melanin indices solely with the Mexameter® skin colorimeter, whereas Farshi et al[67] (n=40) measured melanin indices with both the Mexameter® and Dermacatch® skin colorimeters. One recent case report described a 44-year old woman who was transitioned to cysteamine cream after experiencing steroid atrophy secondary to the chronic daily use of Kligman's formula (5% HQ, 1% dexamethasone, 0.05% retinoic acid) for recalcitrant melasma.[68] Cysteamine cream was applied for 15 minutes nightly, and after 4 months obtained striking improvements in hyper- and hypopigmentation, erythema, and telangiectasias, as well as significant improvements in MASI score and melanin index. Her result was sustained with twice weekly application of cysteamine cream for maintenance, which she continued for 3 years without adverse effects or lesion recurrence.

Methimazole

Methimazole (MMI) is best known for its role as an oral antithyroid agent. It first gained attention as a topical lightening agent after it produced cutaneous depigmentation in brown guinea pigs.[69] Its antimelanogenic effects are derived from potent melanocyte peroxidase inhibition, which disrupts several steps of the melanogenesis pathway.[69-71] It has also been shown to inhibit tyrosinase activity in mushrooms via copper ion chelation, though it is not clear whether this effect is reproduced in humans.[72]

There are several studies that have been devoted specially to comparing the skin lightening ability of 5% MMI with various concentrations of HQ, with varied results. In a double-blind randomized controlled trial involving 50 Iranian patients with melasma, 4% HQ was compared with 5% MMI once daily for 8 weeks.[73] 4% HQ exhibited a higher reduction in MASI coupled with higher satisfaction scores from patients and physicians at 8 weeks, but was associated with increased relapse 4 weeks after stopping therapy. A second double-blinded randomized controlled trial compared response and safety of 5% MMI to 2% HQ in the once daily treatment of 58 Iranian women with melasma.[74] Although the subjects subjectively assessed their outcomes to be the same at 8 weeks, MASI and VisioFace ΔE scores attained by 5% MMI were significantly lower than 2% HQ. 5% MMI had no effect on serum TSH levels. In a case series of two women who had each failed 2 months of therapy with 4% HQ, switching to daily 5% MMI for 8 weeks improved their melasma, though how this outcome was quantified was not specified. Neither subject experienced an alteration in serum TSH.[75] Seeking to determine the pharmacokinetics of 5% MMI on facial skin, another study found MMI to be undetectable in serum 15 minutes to 24 hours following a single topical application to the face.[71] This was extended to 6-weeks of daily topical application, at which point no significant changes in serum TSH, free thyroxine, or free triiodothyronine levels could be detected. Topical MMI preparations were well tolerated in all of the aforementioned studies.

There is one single-blind split face study that compared daily 5% MMI to 4% kojic acid, both in conjunction with twice daily sunscreen (SPF 30) use, in 45 Turkish patients with melasma.[76] At 12-weeks both topicals obtained equivalent improvements in the MASI score, and melanin indices as measured by Mexameter®. 20% of patients treated with 5% MMI experienced redness, burning, and itching that largely tapered off after the first 2 weeks of treatment. 11% of patients treated with 4% kojic acid reported similar adverse effects, though these persisted longer into therapy.

CONCLUSION

Melasma and PIH are common, difficult to treat disorders that greatly impair quality of life in those affected. With the high prevalence of these conditions, and the changing demographics of our nation, dermatologists should anticipate seeing increasing numbers of SOC patients who present seeking help with their management. To illustrate, the US Census Bureau has estimated that by 2050, individuals with SOC will comprise a majority of Americans.[77] Both conditions require an individualized and multilayered approach to treatment that is built upon consistent photoprotection. When designing a given approach, one must carefully consider who their patient is, and what treatments are feasible and responsible in terms of safety, compliance, outcomes, and affordability.

DISCLOSURE

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1. Baseline thyroid function tests should be obtained before initiation of 5% topical methimazole, and should be repeated every 3–4 months while continuing therapy:
   a. True
   b. False

2. Tranexamic acid is thought to improve the appearance of melasma in which of the following ways?
   a. Decreases the number of dermal blood vessels
   b. Inhibits the UV-induced conversion of plasminogen to plasmin
   c. Prevents melanosome transfer to keratinocytes
   d. Chelates copper to inhibit tyrosinase

3. At doses used to treat melasma, oral tranexamic acid is most commonly associated with which side effects?
   a. Menstrual irregularities
   b. Headaches
   c. Gastrointestinal upset
   d. All of the above

A 26-year old Hispanic woman presents complaining of mottled medium brown symmetrically distributed hyperpigmented patched on her bilateral cheeks and upper lip. She reports that the lesions appeared during the first trimester of her pregnancy, and have darkened since then. She is in her third trimester now, and does not plan to breastfeed. She reports that her sister also developed similar lesions when pregnant. Wood's lamp examination reveals accentuation of only small portions of the lesions that are visible on natural light exam. She is very distressed by the lesions, and has been avoiding her normal social activities due to feeling self-conscious about her appearance. She heard about a local med spa that is offering "skin-lightening injections," and asks whether this would be an effective treatment for her condition.

4. What is a reasonable strategy for managing the patient's melasma during the remainder of her pregnancy?
   a. Recommend conscientious photoprotection with sunscreen and other photoprotective modalities
   b. Start combination 4% hydroquinone, 0.01% fluocinolone acetonide, 0.05% tretinoin cream once daily
   c. Start 15% azelaic acid gel twice daily
   d. Both A and C

5. What is a reasonable strategy for managing the patient's melasma after she delivers her baby?
   a. Continue conscientious photoprotection with sunscreen and other protoprotective modalities
   b. Start combination 4% hydroquinone, 0.01% fluocinolone acetonide, 0.05% tretinoin cream once daily
   c. Continue 15% azelaic acid gel once or twice daily
   d. All of the above

Evaluation Form

THERAPEUTIC INSIGHTS IN MELASMA AND HYPERPIGMENTATION MANAGEMENT

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1. The information presented was timely and will influence how I practice.

1 2 3 4 5

2. The information presented enhanced my current knowledge base

1 2 3 4 5

3. The information presented addressed my most pressing questions

1 2 3 4 5

4. The activity provided new ideas or information I expect to use

1 2 3 4 5

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1 2 3 4 5

6. The activity avoided commercial bias or influence

1 2 3 4 5

Impact of the Activity

1. Name one new strategy you learned as a result of completing this activity:

_____

2. Name one thing you intend to change in your practice as a result of completing this activity:

_____

3. Please provide any additional comments on this activity:

_____

4. Please list any topics you would like to see addressed in future educational activities:

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