Out of the Dark: The Medical Management of Melasma

Neal Bhatia, MD; Joseph Bikowski, MD

Melasma is a relatively common form of largely gender-specific epidermal hyperpigmentation associated with a number of environmental and physiologic risk factors and triggers. In susceptible individuals with a history of melasma, both prevention (with sunblock, because solar radiation is a primary trigger) and treatment are indicated. Hydroquinone (HQ), often used in combination with other agents (eg, tretinoin and topical corticosteroids), is the standard of care for melasma. However, as of late there have been concerns regarding the side effects associated with HQ use. The US Food and Drug Administration has proposed withdrawing HQ products that have not been studied as investigational new drugs. A number of other therapeutic options exist for melasma treatment, including azelaic acid, tretinoin, topical corticosteroids, and chemical peels, used either separately or in various combinations. In a number of clinical trials, azelaic acid has demonstrated results comparable to those seen with HQ.

Melasma, a relatively common form of epidermal and dermal noninflammatory hyperpigmentation, results from a dysfunction of the melanin pigmentary system. Lesions occur when an upregulation of melanin synthesis, increased numbers of melanocytes, or both cause greater deposition of melanin in dermal and epidermal melanosomes.[1-6]

Multiple risk factors and biological/environmental triggers have been implicated in the etiopathogenesis of melasma, including sex, genetics, degree of exposure to solar radiation, pregnancy, use of oral contraceptives, hormonal therapies (eg, estrogen-progesterone treatments), and use of photosensitizing medications.[1,3,5,7-9] Melasma tends to be highly gender specific; hence, approximately 90% of patients are female.[2,3,5,10] Persons with dark skin are also more susceptible, particularly those with Fitzpatrick skin types IV to VI, although patients with all skin types and ethnicities can develop melasma.[1,5,6]

Dr. Bhatia is Associate Clinical Professor, University of Wisconsin, Milwaukee. Dr. Bikowski is Clinical Assistant Professor, Ohio State University, Columbus.

Drs. Bhatia and Bikowski are consultants for Intendis, Inc. Dr. Bhatia also is an investigator for Intendis, Inc.

Melasma clinically presents as symmetric hypermelanoses, with typically light brown or gray-brown macules primarily on sun-exposed skin areas.[1,2,11] Facial melasma tends to manifest in one of 3 patterns: centrofacial, malar, and mandibular; however, melasma lesions may also appear on the forearms. Histologically, the condition may be primarily epidermal, dermal, or mixed, as determined by Wood lamp examination (Wood light accentuates epidermal melasma). Epidermal melasma is characterized by excess melanin deposition in basal, suprabasal, and stratum corneum layers, whereas dermal melasma exhibits melanophages in both the superficial and the deep dermis.[1,2,6,12,13] Data on the incidence and prevalence of melasma are lacking, although a survey of 2000 patients who frequent primarily African American dermatologic practices found that pigmentary disorders were the third most common reason for a visit to a dermatologist.[14] Pawaskar et al[15] have suggested that the occurrence and impact of melasma have been underreported in ethnic populations.

THERAPEUTIC OPTIONS

Melasma has been described as refractory to treatment because there is no cure and the condition tends to recur in susceptible individuals. Therefore, the use of

a strong sunscreen is a therapeutic constant. The processes whereby degradation of the characteristic melasma macules is achieved may require therapies of relatively long duration.[1-3,7,16] Treatment goals are suppression and control of lesions. Parameters of successful treatment include reduction of macular lesions (local degradation of melanosomes, removal of melanin granules); inhibition of melanocyte activity (local inhibition of melanosome formation); downregulation of melanocyte proliferation; improvement in cosmetic effect; shortening time to beneficial treatment effect; and prevention and inhibition of recurrence.[2,3,5,17] The standard medical management of melasma includes broad-spectrum sunscreens typically used for prevention and various depigmenting agents, such as hydroquinone (HQ), tretinoin, azaleic acid, topical corticosteroids, kojic acid, and chemical peels.[1,4,18]

Sunscreens and Camouflage Makeup

Because solar radiation, particularly UVA and UVB, is known to increase the risk of developing melasma or exacerbating existing disease, sunscreen and sun avoidance are essential for both prevention and management.[7,12,19] A broad-spectrum agent, containing both zinc and titanium (which have peaks of absorption in the UVA and UVB ranges, respectively), is recommended. The sunscreen should also have a sun protection factor higher than 45. Patients with melasma or those who are at risk for melasma should be advised to use sunscreen daily, particularly under conditions of exposure.[3,7,19]

Data from a number of recent trials indicate that corrective cosmetics and camouflage makeup may also play a role in the management of melasma by improving the patient's quality of life and self-image while he or she is undergoing what may be a protracted course of treatment. Boehncke et al[20] conducted a pilot study in which 20 female patients with a range of facial dermatoses (eg, acne, rosacea, vitiligo) were instructed by a cosmetician in the use of a corrective cosmetic. Patient quality of life was scored at baseline and after 2 weeks of cosmetic use by the Dermatology Life Quality Index survey instrument. Sixteen patients reported improved quality of life. The mean index score (reduced score indicates improved quality of life) decreased from 9.2 at baseline to 5.5 at the end of 2 weeks of makeup use.

A similar outcome was observed in a study of 73 women with severe facial pigmentary disorders (eg, melasma, acne, hypopigmentation, rosacea).[21] These patients received an application of a corrective cosmetic at the initial visit, along with a supply of the product and instructions on its use. Assessments were conducted at baseline and at 2-week, 4-week, and 3-month follow-up visits on 63 patients using the Skindex-16, an evaluative instrument measuring self-reported burden of disease. At the 3-month end point, there was a 30% improvement in mean Skindex-16 score ($P<.001$). The corrective cosmetic was well tolerated.

Hydroquinone

Hydroquinone (1,4-dihydroxybenzene) is a hydroxyphenol; its pharmacodynamic action in the context of melasma appears to involve disruption of melanin synthesis. By inhibiting the action of the tyrosinase enzyme, HQ prevents the enzymatic oxidation of tyrosine to dopa and, thus, the subsequent conversion of dopa to melanin. Other proposed effects of HQ in melasma involve interference with DNA and RNA synthesis, local degradation of melanosomes, and destruction of proliferating melanocytes.[1-3,6,16]

Therapy with HQ at various concentrations (2%, 4%, and 5%) has been described as the gold standard for melasma therapy.[22] Multiple clinical studies have evaluated the efficacy and safety of HQ. In the mid-1960s, Arndt and Fitzpatrick[23] evaluated 2% and 5% HQ therapy for treatment of hypermelanosis, finding no significant difference in efficacy between the 2 strengths and moderate effectiveness in 80% of 56 patients. In a later trial, Fitzpatrick et al[24] used a 2% HQ cream, with beneficial effects reported in 64% of 93 patients. Subsequent trials have confirmed those findings. Sanchez et al[13] reported moderate to marked improvement in 36% of women with melasma treated with a 3% HQ hydroalcoholic solution. A double-blind trial of 2 strengths of HQ (3% and 6%) found that both were significantly more effective than placebo at inducing skin lightening, although the difference in efficacy between the 2 treatment strengths was not significant.[25] In a 16-week, split-face trial that compared 5% ascorbic acid with 4% HQ, best subjective improvement was observed with HQ (93%, good to excellent results with HQ vs 62.5%, good to excellent results with ascorbic acid); however, side effects (eg, irritation) were noted in 11 of 16 patients (68.8%) using HQ versus 1 of 16 patients (6.3%) using ascorbic acid.[26]

Side effects can be a concern with HQ, especially at higher concentrations and particularly because dermatologists may prescribe higher, extemporaneously compounded concentrations of the agent. Side effects associated with HQ include erythema, dermatitis, nail bleaching, postinflammatory hyperpigmentation, hypopigmentation of normal skin, and ochronosis, which has been associated with prolonged use of high concentrations of HQ.[1,27,28]

Combination Therapy: HQ and Other Agents

Hydroquinone has also frequently been used in combination with other agents in the treatment of melasma, particularly topical corticosteroids, tretinoin, and chemical

peels, such as glycolic acid or ascorbic acid. The combination of HQ, tretinoin, and a topical corticosteroid has been well studied in the literature. Tretinoin promotes connective tissue remodeling in the papillary and reticular dermis and helps minimize dermal inflammation. The addition of a topical corticosteroid to tretinoin helps reduce irritation associated with the retinization of skin, and the addition of tretinoin to a topical corticosteroid may also help prevent the skin atrophy associated with topical corticosteroid usage.[2,5,12] Moreover, tretinoin may promote better penetration of HQ to sites of melasma lesions.[22] In an open-label trial, Kang et al[29] used a formulation of 0.1% tretinoin, 5% HQ, and 1% hydrocortisone in 25 Korean women with recalcitrant melasma. The regimen, because of its potential for side effects, called for twice-weekly applications. At the end of 4 months, 10 of the patients (40%) had more than 50% improvement as determined by the Melasma Area and Severity Index scale, 4 patients (16%) showed an improvement between 30% and 49%, and 6 patients (24%) showed no improvement. Erythema, peeling, and burning were experienced by 18 of the 25 patients, despite the twice-weekly application regimen. The safety and efficacy of 4% HQ, 10% buffered glycolic acid, vitamins C and E, and sunscreen were evaluated versus sunscreen alone in 39 Hispanic women, Fitzpatrick skin types III to V, with bilateral melasma.[30] Each treatment was applied to the entire face twice daily. The study cream produced significantly better results (P<.0001) than did sunscreen alone as measured by decreases in degree of pigmentation. Although irritation was common with the study treatment, 75% of patients using the cream versus 13% of patients using only sunscreen experienced significant decreases in pigmentation at the end of the 12-week study (P<.0001). However, when Hurley et al[31] tested the efficacy of 4% HQ versus the combination of 4% HQ and 20% to 30% glycolic acid peels, no significant differences in skin depigmentation were found between treatments among 21 patients with bilateral epidermal and mixed melasma (P=.75). Both treatments produced significant improvement compared with baseline.

Two large, 8-week, multicenter, randomized, investigator-blinded trials, with 641 adult patients, compared a triple-combination agent of 4% HQ plus 0.05% tretinoin plus 0.01% fluocinolone acetonide with each combination of 2 of those constituents.[32] Combined data from the 2 studies showed that a greater percentage of patients in the triple-combination group (26%) experienced complete clearing of lesions than did patients in all dual-combination groups (5%). Adverse events were common across all treatment combinations. At 8 weeks, 41% of patients in the triple-combination group manifested erythema, 38% experienced desquamation, and

18% reported burning and dryness. In the tretinoin plus HQ group, 44% experienced erythema and 61% reported desquamation. The triple-combination treatment has been tested in approximately 2000 patients with melasma. A summary of the short- and long-term (8 weeks, 6 months, and 12 months) clinical trial data by Torok[33] revealed that the triple-combination agent resulted in clear or almost clear rates of 77% after 8 weeks, increasing to between 78% and 84% clearance at 6 months and between 81% and 94% at 12 months.

HQ CONTROVERSY

Hydroquinone is a myelotoxin (a toxin implicated in the destruction of bone marrow cells) found in many foods. It is also a major metabolite of benzene, a leukemogen (substance associated with development of leukemia).[34,35] It has been associated with nephropathy in animal models, including chronic progressive nephropathy.[36] In several in vitro and in vivo test systems, HQ has been found to be genotoxic, inducing, for example, micronuclei sister chromatid exchanges and chromosomal aberrations.[35] Inhibition of CPP32 protease and upregulation of myelocyte production induced by HQ could have implications for benzene-induced myeloid leukemia.[34]

Within the past few years, regulatory agencies in Europe and Japan, and now the US Food and Drug Administration (FDA), have raised questions concerning the safety of topical HQ. Since January 2001, the inclusion of HQ in cosmetic products has been banned in the European Union (EU), although prescription HQ is still available.[36,37] According to Westerhof and Kooyers,[37] the EU decision was based on mid-term side effects data, including HQ-related development of exogenous ochronosis and leukoderma-en-confetti. A large body of evidence links HQ with carcinogenesis and interference with apoptosis of neoplastic cells. A United States perspective was provided in a recent paper by Draelos,[22] who pointed out that although the association with ochronosis has been known for many years, the association of HQ with carcinogenesis is more recent but remains controversial. There is, however, evidence that HQ may be toxic to melanocytes.[22] On August 29, 2006, the FDA published a proposed rule in the *Federal Register* designed to govern over-the-counter use of skin bleaching drug products.[38] In that document, the FDA noted that a substantial amount of research has been conducted on the skin bleaching ingredient HQ, and a number of reports have appeared in the literature since publication of the Tentative Final Monograph on the FDA's proposed rule on skin bleaching drug products for over-the-counter human use, published in the *Federal Register*, September 3, 1982. As a result, the FDA has evaluated substantial additional new data on the safety of HQ.

Toxicology and carcinogenesis studies on orally administered HQ conducted under the support of the National Toxicology Program (NTP) have indicated some evidence of carcinogenicity in male and female rats and in female mice. The FDA's Center for Drug Evaluation and Research Carcinogenicity Assessment Committee has evaluated the design, results, and NTP interpretation of these studies and concurs with the NTP's assessment. The committee determined that additional safety studies are needed, and, to date, those studies have not been submitted to the FDA. Based on the evidence of carcinogenicity in animals, the FDA cannot rule out the potential carcinogenic risk from topically applied HQ in humans. In addition, HQ has been shown to cause disfiguring effects (ochronosis) after use of concentrations as low as 1% to 2%.[38]

The FDA has requested safety studies from suppliers of HQ products. In the absence of such studies, which have yet to be provided, the FDA has proposed withdrawing all over-the-counter 2% HQ products, as well as all prescription-strength HQ products not studied as investigational new drugs.[22]

ALTERNATIVE TREATMENTS FOR MELASMA

Azelaic Acid

Azelaic acid (AzA) is a naturally occurring nontoxic C9 dicarboxylic acid that has demonstrated substantial biologic activity and pharmacodynamic properties. Both in vitro and in vivo studies have confirmed that AzA is a reversible inhibitor of tyrosinase, as well as of other oxidoreductases (enzymes that catalyze electron transfers from reducants to oxidants), such as thioredoxin reductase (an enzyme that reduces thioredoxin, an antioxidant).[1,39-41] Appearing to inhibit mitochondrial respiration and DNA synthesis, AzA is to be highly selective for hyperactive or abnormal melanocytes. In vitro studies of normal cells exposed to therapeutic concentrations of AzA have, in general, exhibited no detectable damage.[39,40,42,43] Demonstrating anti-inflammatory, antimicrobial, and anti-keratinizing activity, AzA also possesses inhibitory effects on reactive oxygen species (ROS).[1,2,4,44] Beneficial results have been shown in a range of hyperpigmentation disorders, including melasma and lentigo maligna, primarily through AzA's antiproliferative effects on hyperactive melanocytes and its inhibition of tyrosinase activity.[1,2,45] The mechanism of action in AzA, particularly its anti-keratinizing activity and inhibitory effects on ROS, may be particularly apposite to melasma treatment given the correlation between melasma and UV exposure and resultant photodamage. It has been hypothesized that cumulative, UV-induced DNA damage and melanogenesis presenting as hyperpigmentation could originate from melanocyte and keratinocyte responses to UV irradiation.[46] These processes could include an upregulation of matrix metalloproteinases and the generation of ROS (eg, free radicals and superoxide dismutase).[47] It is also possible that chronic exposure to UVA and UVB radiation and resultant DNA damage could stimulate melanogenesis, as could other melanin-stimulating hormones produced by intact keratinocytes sending their own signals for melanogenesis. The pharmacodynamics of AzA suggest that it could interrupt many of those processes.[1,2,46]

The efficacy and safety of AzA for the treatment of melasma have been investigated in randomized clinical trials (Table).[48-54] Lowe et al[52] conducted a randomized, double-masked, parallel-group study that compared 20% AzA cream with a vehicle for the treatment of facial hyperpigmentation in darker-skinned patients. Following a 24-week treatment period, those in the AzA cream group displayed significantly greater decreases in pigmentary intensity and significantly greater global improvement ($P=.008$) than did those in the vehicle group. Reports of burning and stinging were slightly but significantly more numerous with AzA than with a vehicle. In a noncomparison study in 39 patients with melasma, 20% AzA cream twice daily for 6 months resulted in a mean reduction of 51.3% in pigmentation as compared with baseline.[49]

A prospective, single-blind, right-left comparison study of 30 Asian Indian patients (25 women and 5 men) evaluated twice-daily applications of 20% AzA cream to one half of the face for 24 weeks versus a potent topical corticosteroid, 0.05% clobetasol propionate cream, applied to the other half of the face for 8 weeks, followed by 16 weeks of 20% AzA cream.[54] A broad-spectrum sunscreen was used on both sides of the face. Results at 4, 8, and 16 weeks, as determined by clinical evaluation, found significantly greater lightening of melasma on the side of the face receiving sequential therapy ($P<.001$). However, by week 24, the differences in therapies (although still significant for sequential therapy, $P=.0052$) had largely disappeared; 96.7% of the side treated with sequential therapy and 90.0% of the sides treated with 20% AzA cream alone showed good to excellent treatment responses. The results suggest that AzA monotherapy offers excellent efficacy when compared with sequential therapies that feature potent topical corticosteroids, but without the potential serious side effects, such as skin atrophy, telangiectasia, and acneform eruptions, and without the recurrence of melasma often observed when topical corticosteroid treatment is stopped.

In a number of clinical trials, AzA has been compared with HQ. Verallo-Rowell et al[50] randomized 155 patients to twice-daily 20% AzA cream or 2% HQ for 24 weeks. A broad-spectrum sunscreen was used by both groups. Completion rates were comparable for both groups. Sixty-five patients (41.9%) using

Results of Studies Involving Hydroquinone and Azelaic Acid

Study (Year)	Design	Regimen 1	Regimen 2	Duration	Results
Piquero-Martín et al[48] (1988)	Double-blind RCT	20% AzA cream	4% HQ cream	24 wk	Equal efficacy of lesion size and pigmentation reduction
Rigoni et al[49] (1989)	Open-label, no comparator	20% AzA cream	No comparator	6 mo	51% mean reduction in pigmentation from baseline
Verallo-Rowell et al[50] (1989)	Double-blind RCT	20% AzA cream	2% HQ cream	24 wk	74% AzA patients achieved good or excellent results vs 19% HQ patients
Baliña and Graupe[51] (1991)	Double-blind RCT	20% AzA cream	4% HQ cream	24 wk	65% AzA patients achieved good or excellent results vs 73% of HQ patients (no statistical difference)
Lowe et al[52] (1998)	Double-blind RCT	20% AzA cream	Vehicle	24 wk	Statistically significantly greater improvement with AzA ($P=.008$)
Kakita and Lowe[53] (1998)	Double-blind RCT	20% AzA cream + 15%/20% glycolic acid lotion	4% HQ cream + glycolic acid lotion	24 wk	>25% improvement for both treatment groups
Sarkar et al[54] (2002)	Single-blind, right/left comparison	20% AzA cream	0.05% clobetasol propionate cream for 8 wk followed by 20% AZA cream for 16 wk	24 wk	Initially superior results with sequential therapy. At wk 24, treatment differences largely disappeared. Good to excellent results achieved in 97% of sequential therapy and 90% of AzA therapy showed good to excellent responses

Abbreviations: RCT, randomized-controlled trial; AzA, azelaic acid; HQ, hydroquinone.

AzA cream and 67 patients (43.2%) in the 2% HQ group completed the study. In the AzA cream group, 48 patients (73.8%) had a favorable therapeutic response at 24 weeks: 37 patients (77%) had good overall improvement and 11 patients (22.9%) had excellent results. In the HQ group, 34 patients (50.7%) achieved a favorable response: 12 patients (35.2%) achieved good results and 1 patient (2.9%) achieved excellent results. In the HQ group, 20 patients (29.9%) were considered treatment failures ($P<.001$). Only 2 patients (3.1%) were treatment failures in the AzA cream group.

Baliña and Graupe[51] compared 20% AzA cream with 4% HQ in a multicenter, randomized, controlled, double-blind trial involving 329 nonpregnant, nonnursing women (n=164 in the AzA cream group, n=165 in the HQ group). The patients were treated for 24 weeks. At study end point (week 24) 79 patients (48.4%) in the 20% AzA cream cohort had achieved good or excellent overall results compared with 87 patients (52.7%) in the 4% HQ cohort. Initial lesion size was reduced by more

Figure 1. Patient with melasma on the upper jaw and check.

Figure 2. Patient with melasma before (A) and after treatment with azelaic acid gel twice daily for 12 weeks (B).

than 50% in 72 of the AzA cream patients (43.9%) and 80 of the HQ patients (48.4%). The difference was not statistically significant. The 9 treatment failures (5.4%) in the AzA group contrasted with 10 (6.0%) in the HQ group. The investigators suggested that given the overall parity in efficacy, the nontoxic properties of AzA cream might be advantageous compared with HQ, particularly in view of prolonged treatment times and recurrence rates associated with melasma. Unlike HQ, AzA cream has not been associated with the development of ochronosis and appears to have no residual depigmentary effect on normal adjacent skin.[44] Similar efficacy and safety results were obtained by Piquero-Martín et al[48] in a 24-week comparative trial of 60 women on oral contraceptives with melasma who were treated twice daily with 20% AzA cream and 4% HQ.

In addition, AzA cream has also been used effectively in combination with other antimelasma treatments. Kakita and Lowe[53] conducted a 24-week trial in 65 darker-skinned patients in which 20% AzA cream plus glycolic acid (either 15% or 20%) was compared with 4% HQ. Glycolic acid appears to have activity in melasma by the removal of melanin rather than through inhibition of melanocytes or melanogenesis.[2] At study end point, results were comparable across both treatment groups, with a mean improvement of more than 25% in lesion size reduction and pigmentary intensity improvement.

A comprehensive appraisal of clinical trial data comparing 20% AzA cream with HQ suggests AzA cream has superior efficacy to that of 2% HQ and equivalent efficacy to that of 4% HQ, along with a superior safety profile.[45] Although 20% AzA cream is available in the United States, the 15% gel formulation should result in even greater efficacy. Skin absorption studies indicate that the gel formulation releases more AzA, perhaps as much as 8 times more active ingredient, into the skin than the cream, despite the lower concentration.[55]

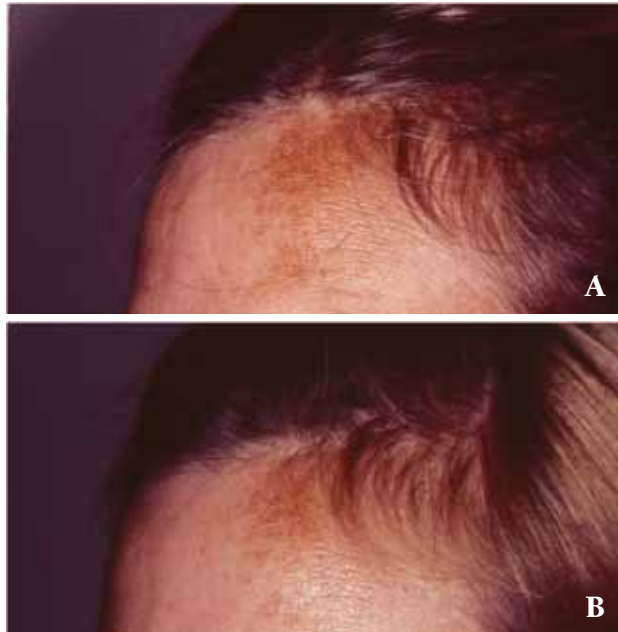Because of its positive safety profile and excellent efficacy both as monotherapy and in combination with other agents, AzA is being used by some practitioners as a useful alternative treatment for melasma. Clinical experience with individual patients treated with 15% AzA gel has shown good results. The patient in Figures 1 and 2 was treated with 15% AzA gel twice daily over a period of approximately 12 weeks; results demonstrated a 50% reduction in melasma lesions. Accordingly, AzA, either as monotherapy or in combination, may be a useful alternative to current standard treatments for melasma.

Tretinoin

Tretinoin (retinoic acid) is an agent with activity in the regulation of cell differentiation.[55] In the context of melasma treatment, tretinoin appears to interfere with tyrosinase induction and melanocyte differentiation leading to melanogenesis. Depigmentary effects include dispersal of keratinocyte granules, interference with pigment transfer of melanosomes to keratinocytes, and acceleration of epidermal turnover, shortening transit time from the basal layer.[1-3,5,56]

Tretinoin at various strengths (eg, 0.1%, 0.01%, 0.05%) has been reported to be efficacious in melasma and is often a component in combination therapy regimens.[1] Griffiths et al[57] randomized 38 women with melasma to vehicle or 0.1% tretinoin applied once daily for 40 weeks. At study end point, 13 patients (68%) in the tretinoin group were clinically rated as improved or much improved versus 1 patient (5%) in the vehicle groups (P=.0006). However, side effects, including erythema and desquamation, were observed in 88% of the tretinoin patients versus 29% of the vehicle patients. The investigators noted

that although tretinoin produces clinically significant improvement, duration of therapy is long and progress may be slow. In contrast, a cohort of Japanese patients (8 with melasma, 3 with xeroderma pigmentosum) who were treated with 0.1% tretinoin for 6 months did not show significant improvement from baseline.[58] Additionally, skin irritation described by investigators as profound required a reduction in tretinoin strength from an initial concentration of 0.1% to 0.025% in 5 patients.

OTHER THERAPIES

Topical corticosteroids have sometimes been used in the treatment of melasma, particularly when combined with HQ, tretinoin, or both.[33] It has been hypothesized that corticosteroids may affect melanin synthesis by inhibiting prostaglandin and cytokine production in the epidermis. Such a mechanism would suppress biosynthetic and secretory functions of melanocytes, thereby downregulating melanin production but not destroying the melanocytes, resulting in an outcome that could explain the rather short-lived benefit of corticosteroid monotherapy.[2,5] When Kanwar et al[59] treated 10 patients with melasma with 0.05% clobetasol propionate for periods between 3 and 14 months, 7 patients experienced 80% to 90% clearance; however, all cleared patients experienced repigmentation within 2 to 3 weeks subsequent to treatment cessation. Chronic topical corticosteroid use is not encouraged because of the unfavorable side effect profile associated with even diluted concentrations of these agents. Side effects attributable to topical corticosteroids include skin atrophy, telangiectasia, itching, acne and acneform eruptions, erythema, and perioral dermatitis.[5]

Chemical peels, such as glycolic acid and kojic acid, have also been used to treat hyperpigmentation disorders, particularly in those with lighter skin; the use of chemical peels in darker-skinned patients has been associated with depigmentation and hypopigmentation of normal adjacent skin.[1] The efficacy of glycolic acid (an α-hydroxy acid) may be mediated by a number of mechanisms, such as stratum corneum thinning, melanin dispersal in the basal layer of the epidermis, and enhancement of epidermolysis.[16] In several trials, the addition of glycolic acid to other treatments (eg, HQ, AzA, tretinoin) has demonstrated slightly but usually not significantly better results found with the other agents used as monotherapy.[60,61] Kojic acid, or 5-hydroxy-2-(hydroxymethyl)-4-pyrone, has also demonstrated efficacy in the treatment of melasma and other hyperpigmentary disorders. Kojic acid appears to work by inhibiting production of free tyrosinase.[4,62] A split-face trial (n=40) comparing the addition of 2% kojic acid gel to 10% glycolic acid and 2% HQ versus the same formulation without the kojic acid gel found a melasma clearance rate of 60% for the

kojic acid gel combination versus 47.5% for the other therapy.[63] However, kojic acid has also been associated with a relatively high incidence of contact dermatitis.[64,65]

Licorice extracts such as isoliquiritigenin (a chalcone) and glabrene are known to inhibit tyrosinase; they may also disperse melanin and have antioxidant/anti-inflammatory properties.[66,67] However, clinical trial data on the use of these agents in the treatment of melasma are scarce because licorice extract is expensive and the concentrations used in most products are low.[68] A stable derivative of glucosamine, N-acetylglucosamine, has recently been proposed as a treatment for melasma. In a topical formulation, N-acetylglucosamine appears to inhibit tyrosinase and to have anti-inflammatory and chondroprotective properties. In several small studies, a 2% N-acetylglucosamine formulation demonstrated some benefit in the reduction of melasma lesions. A 10-week study in 50 Japanese women that compared N-acetylglucosamine with placebo found a significantly better (P=.089) appearance of facial hyperpigmentation for the active treatment as measured by computer image analysis.[69] A study of 35 white women compared a 4% niacinamide formulation with a combination of 4% niacinamide and 2% N-acetylglucosamine.[69] Both active treatments were also compared with vehicle. The combination was superior to vehicle as measured by both computer image analysis (P=.0017) and grader-blinded assessment (P=.008). The combination was superior to 4% niacinamide as measured by computer image analysis (P=.043).

CONCLUSION

Melasma is a relatively common form of hyperpigmentation. It may be triggered by such risk factors as solar radiation, genetic predisposition, pregnancy, and use of oral contraceptives or hormonal therapies. Women are most commonly affected; hence, approximately 90% of melasma patients are female. Melasma has been described as refractory to treatment. There is no cure and the condition tends to recur; therefore, precautions need to be taken. Among these precautions is the use of sunscreen to reduce exposure to solar radiation.

The standard therapy for melasma is HQ, either as monotherapy or, more often, in combination with other agents such as topical corticosteroids and tretinoin; however, concerns have arisen about side effects. The agent has long been known to promote erythema, dermatitis, and ochronosis in some patients. More recently, a possible association between HQ and carcinogenesis had been proposed. The EU has banned the inclusion of HQ in cosmetic products, although prescription HQ is still available. The FDA has raised similar concerns and has proposed withdrawing HQ products for which safety studies have not been completed.

Other therapies have been used to treat melasma, including AzA, tretinoin, topical corticosteroids, kojic acid, and chemical peels. In head-to-head clinical trials with HQ, AzA has demonstrated superior (vs 2% HQ) or equivalent (vs 4% HQ) efficacy results with a superior side effect and safety profile. Accordingly, AzA gel, either as monotherapy or in combination with other agents, may be considered a useful alternative to HQ where the potential side effects of the latter treatment are a concern.

REFERENCES

1. Grimes PE. Melasma. Etiologic and therapeutic considerations. *Arch Dermatol*. 1995;131:1453-1457.
2. Gupta AK, Gover MD, Nouri K, et al. The treatment of melasma: a review of clinical trials. *J Am Acad Dermatol*. 2006;55:1048-1065.
3. Lynde CB, Kraft JN, Lynde CW. Topical treatments for melasma and postinflammatory hyperpigmentation. *Skin Therapy Lett*. 2006;11:1-6.
4. Halder RM, Richards GM. Topical agents used in the management of hyperpigmentation. *Skin Therapy Lett*. 2004;9:1-3.
5. Menter A. Rationale for the use of topical corticosteroids in melasma. *J Drugs Dermatol*. 2004;3:169-174.
6. Abramovits W, Gover MD, Gupta AK. Atopiclair nonsteroidal cream. *Skinmed*. 2005;4:369.
7. Grimes PE. An efficacy study of 3 commercially available hydroquinone 4% treatments for melasma. *Cutis*. 2007;80:497-502.
8. Prignano F, Ortonne JP, Buggiani G, et al. Therapeutical approaches in melasma. *Dermatol Clin*. 2007;25:337-342, viii.
9. Nicolaidou E, Antoniou C, Katsambas AD. Origin, clinical presentation, and diagnosis of facial hypermelanoses. *Dermatol Clin*. 2007;25:321-326, viii.
10. Tunzi M, Gray GR. Common skin conditions during pregnancy. *Am Fam Physician*. 2007;75:211-218.
11. Del Rosso JQ. The use of topical azelaic acid for common skin disorders other than inflammatory rosacea. *Cutis*. 2006;77 (suppl 2):22-24.
12. Pathak MA, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in the treatment of melasma. *J Am Acad Dermatol*. 1986;15 (4 pt 2):894-899.
13. Sanchez NP, Pathak MA, Sato S, et al. Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. *J Am Acad Dermatol*. 1981;4:698-710.
14. Halder RM, Grimes PE, McLaurin CI, et al. Incidence of common dermatoses in a predominantly black dermatologic practice. *Cutis*. 1983;32:388, 390.
15. Pawaskar MD, Parikh P, Markowski T, et al. Melasma and its impact on health-related quality of life in Hispanic women. *J Dermatolog Treat*. 2007;18:5-9.
16. Victor FC, Gelber J, Rao B. Melasma: a review. *J Cutan Med Surg*. 2004;8:97-102.
17. Rendon M, Berneburg M, Arellano I, et al. Treatment of melasma. *J Am Acad Dermatol*. 2006;54(5 suppl 2):S272-S281.
18. Bhalla M, Thami GP. Microdermabrasion: reappraisal and brief review of literature. *Dermatol Surg*. 2006;32:809-814.
19. Scheinfeld NS. Melasma. *Skinmed*. 2007;6:35-37.
20. Boehncke WH, Ochsendorf F, Paeslack I, et al. Decorative cosmetics improve the quality of life in patients with disfiguring skin diseases. *Eur J Dermatol*. 2002;12:577-580.
21. Balkrishnan R, McMichael AJ, Hu JY, et al. Corrective cosmetics are effective for women with facial pigmentary disorders. *Cutis*. 2005;75:181-187.
22. Draelos ZD. Skin lightening preparations and the hydroquinone controversy. *Dermatol Ther*. 2007;20:308-313.
23. Arndt KA, Fitzpatrick TB. Topical use of hydroquinone as a depigmenting agent. *JAMA*. 1965;194:965-967.
24. Fitzpatrick TB, Arndt KA, el-Mofty AM, et al. Hydroquinone and psoralens in the therapy of hypermelanosis and vitiligo. *Arch Dermatol*. 1966;93:589-600.
25. Glenn M, Grimes PE, Pitt E, et al. Evaluation of clinical and light microscopic effects of various concentrations of hydroquinone. *Clin Res*. 1993;39:83A.
26. Espinal-Perez LE, Moncada B, Castanedo-Cazares JP. A double-blind randomized trial of 5% ascorbic acid vs. 4% hydroquinone in melasma. *Int J Dermatol*. 2004;43:604-607.
27. Findlay GH, Morrison JG, Simson IW. Exogenous ochronosis and pigmented colloid milium from hydroquinone bleaching creams. *Br J Dermatol*. 1975;93:613-622.
28. Jordaan HF, Van Niekerk DJ. Transepidermal elimination in exogenous ochronosis. A report of two cases. *Am J Dermatopathol*. 1991;13:418-424.
29. Kang WH, Chun SC, Lee S. Intermittent therapy for melasma in Asian patients with combined topical agents (retinoic acid, hydroquinone and hydrocortisone): clinical and histological studies. *J Dermatol*. 1998;25:587-596.
30. Guevara IL, Pandya AG. Safety and efficacy of 4% hydroquinone combined with 10% glycolic acid, antioxidants, and sunscreen in the treatment of melasma. *Int J Dermatol*. 2003;42:966-972.
31. Hurley ME, Guevara IL, Gonzales RM, et al. Efficacy of glycolic acid peels in the treatment of melasma. *Arch Dermatol*. 2002;138: 1578-1582.
32. Taylor SC, Torok H, Jones T, et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis*. 2003;72:67-72.
33. Torok HM. A comprehensive review of the long-term and short-term treatment of melasma with a triple combination cream. *Am J Clin Dermatol*. 2006;7:223-230.
34. Hazel BA, Baum C, Kalf GF. Hydroquinone, a bioreactive metabolite of benzene, inhibits apoptosis in myeloblasts. *Stem Cells*. 1996;14:730-742.
35. Silva Mdo C, Gaspar J, Duarte Silva I, et al. GSTM1, GSTT1, and GSTP1 genotypes and the genotoxicity of hydroquinone in human lymphocytes. *Environ Mol Mutagen*. 2004;43:258-264.
36. O'Donoghue JL. Hydroquinone and its analogues in dermatology –a risk-benefit viewpoint. *J Cosmet Dermatol*. 2006;5:196-203.
37. Westerhof W, Kooyers TJ. Hydroquinone and its analogues in dermatology–a potential health risk. *J Cosmet Dermatol*. 2005;4:55-59.
38. Food and Drug Administration. Skin bleaching drug products for over-the-counter human use: proposed rule. *Fed Regist*. 2006;71:51146-51155.
39. Breathnach AS, Martin B, Nazzaro Porro M, et al. Effect of dicarboxylic acids on normal human melanocytes in dispersed tissue culture. *Br J Dermatol*. 1979;101:641-649.
40. Nazzaro-Porro M. Azelaic acid. *J Am Acad Dermatol*. 1987;17: 1033-1041.
41. Schallreuter KU, Wood JM. Azelaic acid as a competitive inhibitor of thioredoxin reductase in human melanoma cells. *Cancer Lett*. 1987;36:297-305.
42. Fitton A, Goa KL. Azelaic acid. A review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders. *Drugs*. 1991;41:780-798.
43. Nguyen QH, Bui TP. Azelaic acid: pharmacokinetic and pharmacodynamic properties and its therapeutic role in hyperpigmentary disorders and acne. *Int J Dermatol*. 1995;34:75-84.
44. Breathnach AC, Nazzaro-Porro M, Passi S, et al. Azelaic acid therapy in disorders of pigmentation. *Clin Dermatol*. 1989;7:106-119.
45. Breathnach AS. Melanin hyperpigmentation of skin: melasma, topical treatment with azelaic acid, and other therapies. *Cutis*. 1996;57(1 suppl):36-45.

46. Marrot L, Meunier JR. Skin DNA photodamage and its biological consequences. *J Am Acad Dermatol*. 2008;58(5 suppl 2):S139-S148.

47. Miyachi Y. Potential antioxidant mechanism of action for metronidazole: implications for rosacea management. *Adv Ther*. 2001;18:237-243.

48. Piquero-Martín J, Rothe de Arocha J, Beniamini-Loker D. [Double-blind clinical study of the treatment of melasma with azelaic acid versus hydroquinone] *Med Cutan Ibero Lat Am*. 1988;16: 511-514. Spanish.

49. Rigoni C, Toffolo P, Serri R, et al. [Use of a cream based on 20% azelaic acid in the treatment of melasma] *G Ital Dermatol Venereol*. 1989;124(1-2):I-VI. Italian.

50. Verallo-Rowell VM, Verallo V, Graupe K, et al. Double-blind comparison of azelaic acid and hydroquinone in the treatment of melasma. *Acta Derm Venereol Suppl (Stockh)*. 1989;143:58-61.

51. Baliña LM, Graupe K. The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. *Int J Dermatol*. 1991;30: 893-895.

52. Lowe NJ, Rizk D, Grimes P, et al. Azelaic acid 20% cream in the treatment of facial hyperpigmentation in darker-skinned patients. *Clin Ther*. 1998;20:945-959.

53. Kakita LS, Lowe NJ. Azelaic acid and glycolic acid combination therapy for facial hyperpigmentation in darker-skinned patients: a clinical comparison with hydroquinone. *Clin Ther*. 1998;20:960-970.

54. Sarkar R, Bhalla M, Kanwar AJ. A comparative study of 20% azelaic acid cream monotherapy versus a sequential therapy in the treatment of melasma in dark-skinned patients. *Dermatology*. 2002;205:249-254.

55. Draelos ZD. The rationale for advancing the formulation of azelaic acid vehicles. *Cutis*. 2006;77(2 suppl):7-11.

56. Roméro C, Aberdam E, Larnier C, et al. Retinoic acid as modulator of UVB-induced melanocyte differentiation. involvement of the melanogenic enzymes expression. *J Cell Sci*. 1994;107(pt 4):1095-1103.

57. Griffiths CE, Finkel LJ, Ditre CM, et al. Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial. *Br J Dermatol*. 1993;129:415-421.

58. Tadaki T, Watanabe M, Kumasaka K, et al. The effect of topical tretinoin on the photodamaged skin of the Japanese. *Tohoku J Exp Med*. 1993;169:131-139.

59. Kanwar AJ, Dhar S, Kaur S. Treatment of melasma with potent topical corticosteroids. *Dermatology*. 1994;188:170.

60. Erbil H, Sezer E, Taştan B, et al. Efficacy and safety of serial glycolic acid peels and a topical regimen in the treatment of recalcitrant melasma. *J Dermatol*. 2007;34:25-30.

61. Lim JT, Tham SN. Glycolic acid peels in the treatment of melasma among Asian women. *Dermatol Surg*. 1997;23:177-179.

62. Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg*. 1996;22:443-447.

63. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. *Dermatol Surg*. 1999;25:282-284.

64. Nakagawa M, Kawai K, Kawai K. Contact allergy to kojic acid in skin care products. *Contact Dermatitis*. 1995;32:9-13.

65. Serra-Baldrich E, Tribó MJ, Camarasa JG. Allergic contact dermatitis from kojic acid. *Contact Dermatitis*. 1998;39:86-87.

66. Nerya O, Vaya J, Musa R, et al. Glabrene and isoliquiritigenin as tyrosinase inhibitors from licorice roots. *J Agric Food Chem*. 2003;51:1201-1207.

67. Nerya O, Musa R, Khatib S, et al. Chalcones as potent tyrosinase inhibitors: the effect of hydroxyl positions and numbers. *Phytochemistry*. 2004;65:1389-1395.

68. Amer M, Metwalli M. Topical liquiritin improves melasma. *Int J Dermatol*. 2000;39:299-301.

69. Bissett DL, Robinson LR, Raleigh PS, et al. Reduction in the appearance of facial hyperpigmentation by topical N-acetyl glucosamine. *J Cosmet Dermatol*. 2007;6:20-26. ■