Melasma and Its Newest Therapies

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A wide range of options is included in the armamentarium for melasma, but the condition is recalcitrant. Sun-protective behavior is necessary, and patients should halt use of oral contraceptives and avoid skin care products that facilitate pigmentation.[1] The author prefers using a regimen that combines hydroquinone 4% in the morning and a triple-combination cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) in the evening. The hydroquinone product contains Tyrostat™-09, which is derived from extracts of field dock (*Rumex* spp). Tyrostat-09 has been shown to be an effective tyrosinase inhibitor used alone or in combination, outperforming hydroquinone and arbutin, according to one study.[2] This product also contains avobenzone, a strong UVA-blocking sunscreen agent.

In recalcitrant patients, the previously mentioned regimen can be combined with glycolic peels, Jessner peels, modified Jessner peels, or intense pulsed light therapies to hasten resolution. Serial glycolic acid peels were found, in one study, to provide additional improvement when combined with a modification of Kligman's topical formulation (hydroquinone 5%, tretinoin 0.5%, hydrocortisone acetate 1% in a cream base).[3]

Although there is no cure for melasma, the triple-combination products have been shown to at least temporarily treat the condition. Because they combine 3 effective ingredients in one cream, they likely improve patient compliance by simplifying the regimen. Patient education about sunscreen and sun avoidance is still paramount.

Melasma

Known to be extremely refractory to treatment, melasma, also called *chloasma* and "the mask of pregnancy," is a common, chronic cutaneous discoloration typically affecting women of childbearing age. *Chloasma* is derived from the Greek word meaning "to be green"; *melasma* comes from the Greek word meaning "to be black."[4] Given the actual color of the dyschromia, *melasma* is the preferred term. Although its appearance is most frequently linked to pregnancy or use of oral contraceptives, melasma is known to develop at any time during a woman's reproductive years. Melasma has been diagnosed in premenstrual girls as well as menopausal women, but these instances are rare. Women with darker skin types are more often affected. Approximately 10% of melasma presentations occur in men, more often in those of Middle Eastern, Caribbean, or Asian descent. In an age-matched comparison of men with melasma and control subjects, the men with idiopathic melasma were found to have significantly higher levels of circulating luteinizing hormone and lower levels of testosterone.[5] Melasma is a common pigmentary problem among Asians, particularly women.[6,7]

Melasma typically presents as discrete, irregularly shaped tan to dark-brown macules, appearing most often on the upper lip, nose, cheeks, chin, forehead, and, occasionally, the neck. There are 3 identifiable patterns of presentation, with a centrofacial distribution, involving the cheeks, forehead, upper lip, nose, and chin, being the most common.[8,9] The other distribution patterns seen are the mandibular pattern, involving the chin line, and the malar pattern, which involves the nose and cheeks. Melasma most often emerges in skin regularly exposed to the sun, but it reportedly has been observed on the nipples and around the external genitalia.[10,11]

Etiology

The pathogenesis of melasma is not yet clearly understood. Solar exposure, genetic predisposition, and hormonal influences are considered among the primary causal factors, but a precise etiology has not yet been ascertained.[10,11] The hormones estrogen and progesterone, nutritional deficiency, and certain antiepilepsy drugs have been identified as playing significant causal or exacerbating roles in the development of melasma.[12] Indeed, some authors consider the root cause to be stimulation of melanocytes by endogenous or exogenous estrogen,[13] implying that other factors serve only to worsen the condition. Hydantoin and phenytoin have also been cited as contributing factors in both women and men.[11,14]

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A necessary precondition for the pathogenesis of melasma appears to be a history of frequent, protracted exposure to the sun, which is also well known to aggravate the condition.[9,12] Indeed, UV exposure is believed to be the leading exogenous factor in the development of melasma.[12,15] In a study of 56 Korean patients, the lesional skin of melasma was shown histologically to be characterized by more prominent solar elastosis than was normal skin, with melanosomes greater in number and more diffusely spread in keratinocytes.[16] It is not surprising, then, that melasma is usually less conspicuous in the winter months, when there tends to be less sun exposure.[11] A few familial melasma cases have been reported, suggesting that there may be a genetic etiologic component, but there are not many supportive data on this point.[12]

The application of hot wax for the removal of unwanted hair has been reported to precede the appearance of melasma on the upper lip in some women. In fact, this phenomenon occurs frequently enough that the author postulates that heat might influence the development of melasma in a fashion similar to erythema ab igne (a reticulated erythematous hyperpigmented eruption induced by chronic heat exposure).

Some authors have suggested that women who use oral contraceptives are the patients who most often present with this painless but stressful pigmentary condition.[11,12] Melasma also frequently affects pregnant women. Together, these groups comprise the majority of patients with melasma. Estrogen by itself is an unlikely source of origin, as suggested by the low incidence of melasma among postmenopausal women on estrogen replacement therapy,[12] but estrogen clearly plays a role in the pathogenesis of melasma. In fact, it is believed that 17β-estradiol is partially responsible for maintaining the pigmentary disorder.[17] Melasma is exceedingly idiopathic, characterized by differences from patient to patient and within individuals, even from pregnancy to pregnancy.[12] Melasma is also characterized by a high degree of recalcitrance and, after subsiding in the months succeeding a patient's pregnancy or after cessation of an oral contraceptive regimen, can recur, taking years to resolve.[11,14] Some authors have speculated about an endocrine etiology,[10] but such a pathogenesis has not been established.[14] Likewise, no causal relationships have been attributed to ovarian disorders being correlated with an increased incidence of melasma. The likelihood of experiencing a recurrence of this dyschromia among patients with melasma is greater than the likelihood of initial onset of melasma among a general population.

Disorders of pigmentation, although not usually representative of serious threats to health—though they are sometimes manifestations of significant underlying systemic disease—cause no shortage of stress and anxiety among their sufferers. At the cellular level, pigmentation disorders are engendered, endogenously or exogenously, by a rise in the production of melanin by melanocytes, the increased transfer of melanosomes from melanocytes to basal and suprabasal keratinocytes, or both.[15,18] The hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine through the enzymatic action of tyrosinase and the subsequent oxidation of 3,4-dihydroxyphenylalanine to dopaquinone produces the 2 chemically discrete types of the pigment melanin (the brown-black eumelanin and red-yellow pheomelanin).[19,20] Melanin is transferred to keratinocytes or into the dermis through 3 different processes: (1) damage to melanocytes in the basal layer renders the cells susceptible to phagocytosis by melanophages, which results in release of melanin into the dermis; (2) melanosomes are directly deposited, through their dendrites, into the dermis; or (3) macrophages migrate into the epidermis and phagocytize melanosomes, returning them to the dermis. Treatments for melasma are aimed at preventing the production of melanin, inhibiting the transfer of melanosomes, or hastening the removal of melanosomes and melanin from the epidermis.[21] This article will focus on the treatment of melasma using combination therapy containing a corticosteroid, a retinoid, and a tyrosinase inhibitor.

Treatment With a Corticosteroid, a Retinoid, and a Tyrosinase Inhibitor

Introduced in 1975 and popular since then for the treatment of melasma, the "Kligman formula" consists of tretinoin 0.1%, hydroquinone 5%, dexamethasone 0.1%, and hydrophilic ointment.[19] Complete depigmentation of normal adult skin in black males treated for melasma, ephelides, and postinflammatory hyperpigmentation resulted from the daily application of this formulation for 5 to 7 weeks. Kligman and Willis[19] found that omission of any one component of the regimen resulted in failure to achieve depigmentation. The combination is no longer available commercially but can be formulated by a pharmacy. The success of the Kligman formula, however, laid the foundation for melasma treatment, as topical combination remains the mainstay therapy for this vexing pigmentary disorder despite the advent of new approaches stemming from technologic innovation. The 3 components of the Kligman formula have been used both individually and in combination to successfully treat pigmentation disorders.

Corticosteroids

Corticosteroids have been combined with other agents in the treatment of melasma for years. They exert an

antimetabolic effect, resulting in decreased epidermal turnover and, thus, may produce a mild depigmenting effect. In early studies by Kligman and Willis,[19] topical dexamethasone as monotherapy produced little depigmentation, even after 3 months of therapy. A significant concern is that topical corticosteroids used alone in this setting, especially on the face, may result in epidermal atrophy, telangiectasia, rosacealike erythema, acne, and perioral dermatitis. Several studies have demonstrated that epidermal atrophy does not occur when topical corticosteroids are combined with retinoids.[22-25] When used in combination with tretinoin and hydroquinone in the treatment of melasma, fluocinolone acetonide 0.01% suppresses biosynthetic and secretory functions of melanocytes and, thus, melanin production, leading to early response in melasma, synergy among the 3 agents, and no significant side effects over an 8-week period.[23]

Tretinoin

Topical retinoids were first used in 1960 for the treatment of epidermal keratinization diseases, and a significant improvement was observed in patients suffering from ichthyosis.[1] Since then, retinoids have been used for everything from cancers to wrinkles. Many studies have shown the efficacy of retinoids in treating pigmentation disorders as seen in photoaging and melasma.[26]

Retinoids have not been found to suppress melanogenesis in pigmented skin equivalents and monolayer cultures of murine and human melanocytes.[27] It is thought that the role of retinoids in bleaching treatments appears to be in other specific actions, such as promotion of keratinocyte proliferation and acceleration of epidermal turnover.

Evaluations of tretinoin 0.1% as monotherapy for melasma have been favorable,[22,23] but this approach can take a long time before the condition shows any improvement. A 10-month, randomized, vehicle-controlled clinical study did show that topical tretinoin 0.1% was effective in lightening the melasma in 28 black patients, with only mild side effects.[28]

In a recent study, 10 Indian patients with melasma were treated in a split-face fashion with either a tretinoin 1% solution applied for 4 hours once weekly or a weekly 70% glycolic acid peel for 12 weeks.[29] It was concluded that the tretinoin 1% solution was well tolerated and as effective a therapy for melasma in dark-skinned individuals as a standard and well-tried chemical peel (70% glycolic acid).

Hydroquinone

Tyrosinase, the enzyme that controls the synthesis of melanin, is a unique product of melanocytes. It is considered to be the rate-limiting enzyme for the biosynthesis of melanin in epidermal melanocytes. Therefore, tyrosinase activity is thought to be a major regulatory step in melanogenesis. Hydroquinone has been shown to decrease the activity of tyrosinase by 90%.[20] In addition, hydroquinone is cytotoxic to melanocytes.[30] Jimbow et al[31] elucidated the mechanism of hydroquinone via electron microscopy and histochemistry studies on guinea pigs and showed that the melanosome structure is disturbed after treatment with hydroquinone. This may lead to complete melanocytic degradation; however, keratinocytes are spared and show no apparent injury. Hydroquinone is known to cause reversible inhibition of cellular metabolism by affecting both DNA and RNA synthesis. Although it is useful as a sole agent, hydroquinone is often combined with other agents such as tretinoin, glycolic acid, kojic acid, and azelaic acid. Other products on the market contain ingredients that inhibit tyrosinase and thus decrease melanin formation, but hydroquinone seems to be the most popular. It is found in over-the-counter products, usually at a level of 2%, and in prescription products at a level of 5%. Pharmacies have been known to compound formulations with a level of 12% or higher.

There have been many concerns about the safety of hydroquinone, and, in fact, its use has been banned in Europe and is highly regulated in Asia. This is due, in part, to the fact that it is a metabolite of benzene and has potential mutagenic properties. However, adverse effects related to topically applied hydroquinone are infrequent and predominantly occur with formulation levels greater than 4%. They tend to be temporary and resolve on discontinuation. The most common problems caused by hydroquinone are irritant and allergic contact dermatitis.[32] A small number of cases of exogenous ochronosis, which presents as asymptomatic blue-black macules in the area of hydroquinone application, have been reported.[33,34] It usually occurs after prolonged use of even low concentrations of hydroquinone (eg, 2%). The topical hydroquinone products are thought to cause this disorder by inhibiting the enzyme homogentisic acid oxidase in the skin. This results in the local accumulation of homogentisic acid that then polymerizes to form ochronotic pigment.[35] Exogenous ochronosis seems to occur more commonly among patients with darker skin types.[36] As a monotherapy, hydroquinone remains the most effective topically applied hypopigmenting agent approved for treating melasma by the US Food and Drug Administration (FDA).[36]

Triple-Combination Cream

The Kligman formula was used for many years but required compounding by a pharmacy because it was

not FDA approved. A triple-combination cream using a set of agents similar to those in the Kligman formula has received FDA approval for the treatment of melasma. This medication combines tretinoin 0.05%, hydroquinone 4%, and fluocinolone acetonide 0.01% (a mild anti-inflammatory corticosteroid). Studies have demonstrated that combining a mild corticosteroid with a retinoid prevents corticosteroid-induced atrophy without lessening the anti-inflammatory effect.[22,24]

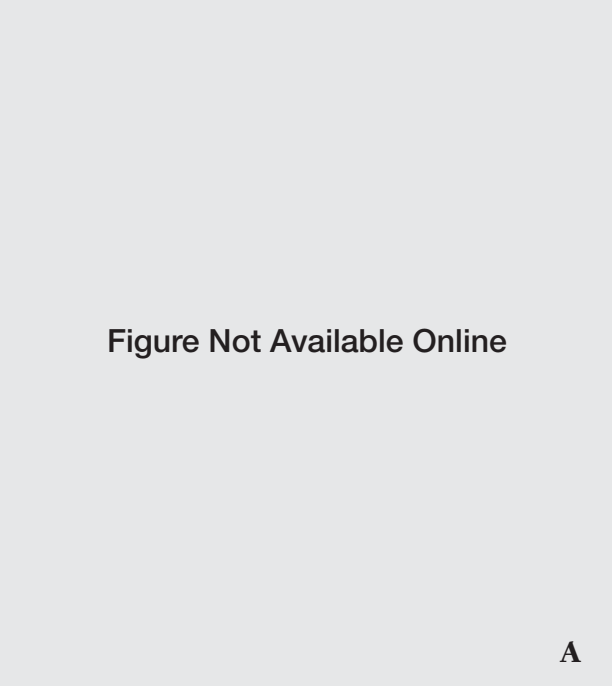
In the 2 phase 3 trials that led to FDA approval of the triple-combination cream, a total of 641 predominantly white women (aged 21–75 years, Fitzpatrick skin types I–IV) with moderate to severe hyperpigmentation were randomized into various treatment groups in two 8-week, multicenter, investigator-blind studies.[25] There were 3 arms of each study that compared dual-combination formulations of tretinoin plus hydroquinone, tretinoin plus fluocinolone acetonide, and hydroquinone plus fluocinolone acetonide. In both studies, all formulations were applied once nightly, and the same drug concentrations and vehicles were used.

Results and Conclusion

At the end of 8 weeks, 26.1% of the patients treated with the triple-combination cream exhibited complete resolution compared with 4.6% of the patients in the 3 dual-combination therapy groups.[25] Complete or near-complete clearing of hyperpigmentation was observed in 77% of the aggregate triple-combination group compared with 46.8% for tretinoin plus hydroquinone, 42.2% for hydroquinone plus fluocinolone acetonide, and 27.3% for tretinoin plus fluocinolone acetonide. Erythema at the application site, desquamation, burning, xerosis, and pruritus were the adverse effects most often cited in response to application of the triple-combination cream, but overall, side effects were mild and of brief duration. The development of ochronosis has been associated with the use of hydroquinone in high concentrations. There were no reported occurrences of ochronosis in this study among patients using any of the treatments containing hydroquinone 4%.

Some authors have argued against the use of topical corticosteroids for melasma because of a correlation with skin atrophy and telangiectasia.[37] However, the combination of a retinoid with a corticosteroid is thought to mitigate the mineralocorticoid effects of glucocorticoids, thereby decreasing the risk of corticosteroid-inducing atrophy.[22] The distinctive triple-combination formulation is believed to have worked in this fashion in preventing skin atrophy. Of the study population, only one patient, in the hydroquinone plus fluocinolone acetonide group, developed skin atrophy. It is important to note that this patient did not receive the formulation containing the retinoid.

The combined results of the 2 studies of the triple-combination cream strongly suggest that the use of



Patient with moderate melasma at baseline (A) and with mild melasma after 8 weeks of treatment with a triple-combination formulation of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% (B).

this agent is more effective than the 3 evaluated dual-combination agents in reversing the hyperpigmentation characteristic of melasma. Apparently safe, effective, and well tolerated for the treatment of melasma, this topical formulation combines 3 components already established as relatively effective agents in monotherapy or dual-therapy regimens (Figure). The 2 multicenter studies evaluated the use of the triple-combination formulation over an 8-week period, but a 12-month open-label extension trial also demonstrated the safety and tolerability of the product.[25]

Another recent study buttresses the findings of this research. Investigators assessed the efficacy of a formula containing tretinoin 0.1%, hydroquinone 5%, and hydrocortisone 1% used to treat 25 female Korean patients with melasma recalcitrant to therapy.[6] Patients applied the triple-combination formulation to their faces for 4 months. They were evaluated before treatment, then assessed 4 weeks and 4 months after treatment. Statistically significant depigmentation in clinical and histologic studies was found, as was elevated subepidermal collagen synthesis, results that were noted as early as 4 weeks after treatment.

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