The treatment of melasma: A review of clinical trials

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Melasma is an irregular brown or grayish-brown facial hypermelanosis, often affecting women, especially those living in areas of intense UV radiation. The precise cause of melasma remains unknown; however, there are many possible contributing factors. Because of its dermal component and tendency to relapse, melasma is often difficult to treat. The use of broad-spectrum (UVA + UVB) sunscreen is important, as is topical hydroquinone, the most common treatment for melasma. Other lightening agents include retinoic acid (tretinoin) and azelaic acid. Combination therapies such as hydroquinone, tretinoin, and corticosteroids have been used in the treatment of melasma, and are thought to increase efficacy as compared with monotherapy. Kojic acid, isopropylcatechol, N-acetyl-4-cysteaminylphenol, and flavonoid extracts are other compounds that have been investigated for their ability to produce hypopigmentation, but their efficacy, safety, or trial design indicates that the interventions would need further study before they could be recommended. Chemical peels, laser treatments, and intense pulsed light therapy are additional therapeutic modalities that have been used to treat melasma. (J Am Acad Dermatol 2006;55:1048-65.)

Melanin is produced in melanocytes and stored in melanosomes within the keratinocytes. The number, melanin content, and location of these melanized cells (along with oxygenated and deoxygenated hemoglobin) help determine the color of the skin. Melanosomes contain tyrosinase, a copper-containing enzyme, that catalyzes the conversion of L-tyrosine to L-dopa and L-dopa to L-dopa-quinone in melanin synthesis.[1] Melasma is a dysfunction of this pigmentary system, resulting in an irregular brown or grayish-brown facial hypermelanosis. Although it can occur in both sexes and any skin type, it is more commonly seen in women[2] and those with darker complexions—Fitzpatrick's skin types IV to VI—especially those living in areas of intense UV radiation, such as Hispanics/Latinos, Asians, and African Americans.[3-6] The condition usually develops slowly and symmetrically, and can last for many years, with worsening in the summer and improvement during the winter.[7]

Melasma is sometimes used interchangeably with the term "chloasma," which is a hyperpigmentation that often results from pregnancy or changes in uterine and ovarian hormones; melasma, however, can have a variety of possible causes. The common contributing factors include genetic predisposition,[4,8] pregnancy,[9] use of oral contraceptives,[10]

Abbreviations used:

AEs:	adverse effects
AzA:	azelaic acid
CO_2:	carbon dioxide
FA:	fluocinolone acetonide
GA:	glycolic acid
HQ:	hydroquinone
IPC:	isopropylcatechol
IPL:	intense pulsed light
MASI:	Melasma Area and Severity Index
MKF:	modified Kligman's hydroquinone formula
PIH:	postinflammatory hyperpigmentation
RA:	retinoic acid
RCT:	randomized controlled trial
SWC:	skin-whitening complex
TCA:	trichloroacetic acid
YAG:	yttrium-aluminum-garnet

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endocrine dysfunction or hormone treatments,[11,12] and exposure to UV light.[4,8,13] In addition, cosmetics and drugs containing phototoxic agents (eg, antiseizure medications) have also been linked to melasma.[3] Interestingly, Wolf et al[14] suggests that some cases of melasma could be stress induced, because the release of melanocyte-stimulating hormone can be influenced by stress.

When melasma occurs with pregnancy, also termed "the mask of pregnancy," it can resolve within a few months after delivery and treatment may not be necessary. However, there are many cases in which the disorder persists indefinitely.[15] Pregnancy-associated melasma may be caused by an increase in placenta, ovarian, and pituitary hormones.[16] Melasma has also been attributed to an elevation of melanocyte-stimulating hormone, estrogen, and progesterone leading to increased melanogenesis.[10]

Vazquez et al[8] reports that melasma in men shares the same clinicohistologic characteristics as in women, with the exception that hormonal factors may not play a major role. The main associated factors among men appear to be sun-induced aggravation and a significant family history of the condition.[8] A study of melasma in Indian men implicated sun exposure and cosmetic use including topical mustard oil.[17]

It is helpful, before treatment, to perform an examination using Wood's lamp; this will identify the depth of the melanin pigmentation, thus, helping to delineate the type of melasma.[18] Generally, melasma is classified into one of 3 histologic types: epidermal, dermal, and mixed.[13] However, some also include a fourth type known as Wood's light inapparent.[4] Under Wood's light the epidermal type often shows a darkening of color when examined, as the light emitted by Wood's lamp is absorbed by the excess melanin. The dermal type, however, will not show this accentuation.[1,4] The mixed type involves a deposition of melanin in both the epidermis and the dermis and color enhancement with Wood's light is seen is some places of the skin, but not others.[4]

It is interesting to note that when histologically assessing 56 patients, Kang et al[13] did not find any cases of entirely dermal-based melasma. Furthermore, Sanchez et al[4] describe dermal type melasma as having melanin-laden macrophages in the perivascular array, both in the papillary and reticular dermis. Epidermal hyperpigmentation in the dermal type was found to be similar to the epidermal type, but not as prominent.[4] It has, thus, been suggested that there may be no truly pure dermal type of melasma.[13]

There are 3 clinical patterns recognized on the basis of clinical examination. These include a centrofacial, malar, and mandibular pattern. The centrofacial is the most common pattern of melasma and involves the cheeks, forehead, upper lip, nose, and chin. The malar pattern has lesions limited to the cheeks and nose, and the mandibular pattern has lesions that occur over the ramus of the mandible.[4] Other sites (eg, forearm and neck) may also be involved in any of these patterns.[7]

METHODS

MEDLINE (1966-2005) was searched using the key words melasma, chloasma, hyperpigmentation, and hypermelanosis. This article outlines published randomized controlled trials (RCTs) of the interventions that have been studied for use in the treatment melasma. When RCTs were not present, nonrandomized or open clinical trials were reviewed.

General management

Because of its refractory and recurrent nature, melasma is often difficult to treat. The goals of treatment often include prevention or reduction in the severity of recurrence, reduction of the affected area, improvement in the cosmetic defect, and reduced time to clearance, all with the fewest possible side effects.[19] The principles of therapy include protection from UV light, inhibition of melanocyte activity and melanin synthesis, and the disruption and removal of melanin granules.[20]

General management recommendations that assist in the clearing of melasma include discontinuation of birth control pills, scented cosmetic products, and phototoxic drugs, coupled with UV protection with use of broad-spectrum (UVA + UVB) sunscreens.[20] Solar exposure exacerbates melasma, and its avoidance is fundamental for the successful management of the disease.[21] Most patients using bleaching agents can expect a recurrence of the disease on exposure to sunlight and artificial UVA and UVB light.[21] This supports the importance of the use of broad-spectrum sunscreens (SPF $>$ 30) in melasma therapies. Broad-spectrum sunscreens must be applied daily throughout the year and continued indefinitely to minimize the reactivation of melanocytes by incidental exposure to the sun.[21]

Although sunscreens are a vitally important component of therapy, other forms of treatment are nonetheless necessary.[22] Topical treatments include the application of creams such as hydroquinone (HQ). Although some negative reactions have been described, HQ remains one of the most prescribed agents for melasma and is considered the gold standard of therapy, especially for epidermal melasma. The epidermal type generally has a good response to topical therapy, whereas skin with