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Melasma treatment: A novel approach using a topical agent that contains an anti-estrogen and a vascular endothelial growth factor inhibitor

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ABSTRACT

Melasma is an acquired disorder of pigmentation that presents with asymptomatic symmetric darkening of the face. The pathogenesis of this condition is multifactorial and influenced by several factors including female sex hormones, genetic predisposition and ultraviolet light exposure. The management of melasma is usually directed at more than one of the causative etiologic factors and often incorporates a combination of topical agents, with or without the addition of physical modalities. Estrogen and angiogenesis are significant factors in the etiology of melasma. A useful addition to the therapeutic armentarium for treating melasma would include a topical agent that could effect both of these causative factors. Specifically, a topical preparation consisting of an anti-estrogen and a vascular endothelial growth factor inhibitor would accomplish this goal. Suitable candidates that target estrogen receptors and vascular endothelial growth factor are currently used in medical oncology as systemic antineoplastic agents. The anti-estrogen could be either a selective estrogen receptor modulator (such as tamoxifen or raloxifene) or an aromatase inhibitor (such as anastrozole or letrozole or exemestane). The vascular endothelial growth factor inhibitor would be bevacizumab. In conclusion, a novel–topically administered–therapy for melasma would combine an anti-estrogen and a vascular endothelial growth factor inhibitor.

Introduction

Melasma is an acquired disorder of pigmentation that presents as symmetric darkening on the face; it has a multifactorial etiology and influencing factors include estrogen and angiogenesis. Selective estrogen receptor modulators (SERMs) and aromatase inhibitors are used in the management of estrogen receptor positive breast cancer. A vascular endothelial growth factor (VEGF) inhibitor is approved for the treatment of colorectal, kidney and lung cancer. A topical agent that incorporates both an anti-estrogen and a vascular endothelial growth factor inhibitor might provide a novel therapeutic intervention for the successful management of melasma.

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Discussion

Melasma

Epidemiology

Melasma occurs in all ethnic groups. It is particularly common in individuals of darker pigmented skin phenotypes (such as Fitzpatrick skin types III to IV). It is more common in women than men; the prevalence ranges from 1% to 35% [1–3].

In pregnancy, the prevalence is up to 70%; it often persists after delivery. Melasma also often recurs with subsequent pregnancies. Similarly, oral contraceptive use is associated with melasma [1–3].

Clinical presentation

Melasma presents as an acquired symmetric hyperpigmentation in sun exposed areas. It most commonly affects the face (centrofacial pattern, malar pattern, mandibular pattern or mixed).

However, less frequently, it may occur on the forearms—with or without facial involvement [4–7].

A Wood lamp examination (emitting ultraviolet A radiation at 320 nm to 400 nm) may be used to demonstrate the difference in pigmentation between the effected and the non-effected areas. However, this examination may not accurately reflect the location of pigment (epidermal, dermal or mixed). More recently, dermoscopy and reflectance confocal microscopy have been used in the diagnosis of melasma [1,6].

Pathology

Melasma lesions were found to have two basic patterns: an epidermal form and dermal form. Melanin deposition in the basal and suprabasal layers of the epidermis accompanied by heavily pigmented melanocytes that were highly dendritic had been observed in the epidermal form. In contrast, the dermal form has perivascular melanophages in the superficial and deep perivascular dermis with less epidermal pigmentation [8].

Additional pathology results of melasma lesions have also been described. Increased deposition of melanin has been found in both the epidermis and dermis (in lesions that the Wood lamp indicated as epidermal melasma) [9]. In addition, microscopic examination has shown that the melanocytes were larger and more prominent; however, the melanocytes were not increased in number [9]. However, in Asian patients with melasma, the lesions showed not only melanin in all layers of the epidermis, but also an increased number of melanocytes, melanin and melanophages in the dermis, and severe solar elastosis [10].

More recently, it was demonstrated that melisma lesions had increased vascularization as compared to surrounding normal skin without melasma [11].

Pathogenesis

Melasma is a disorder of melanogenesis dysfunction resulting in the presence of more biologically active melanocytes in the affected skin. The definitive pathogenesis remains to be established; however, it is likely to be complex and multifactorial. Classical influencing factors in melasma are female sex hormones, genetic predisposition, and ultraviolet light. However, several additional factors have been associated with the etiology of melasma including autoimmune thyroid disease (and endocrinopathies), cosmetics, hormone replacement therapy, inflammatory processes, oral contraceptives, ovarian tumors, photosensitizing drugs, pregnancy, stressful events, vascularization, and visible light [6,12,13].

Estrogen and melasma

Melasma tends to develop in women during their reproductive lifespan. It commonly occurs as a physiologic skin change of pregnancy. It also often appears after initiating treatment with oral contraceptives. Hence, female sex hormones have been implicated in the development of melasma [4,12,13].

Estrogen receptors (estrogen receptor-alpha and estrogen receptor-beta) are expressed in human skin [14,15]. In addition, increased estrogen receptor expression has been demonstrated in melasma lesions as compared to nearby normal skin [16,17]. The increased expression of estrogen receptors implies that estrogens have a role in the pathogenesis of melasma.

Estrogens are able to stimulate melanogenesis of cultured human melanocytes. This occurs since the hormone induces the synthesis of enzymes that result in melanin production. The enzymes include tyrosinase, tyrosinase-related protein-1 (TRP-1), tyrosinase-related protein-2 (TRP-2), and micropthalmia-associated transcription factor (MITF) [18–20].

Estrogen receptors are also expressed in the nucleus and cytoplasm of melanocytes from healthy skin [19,21]. Reduction in melanogenesis has been observed when estrogen is inhibited by its antagonist [19]. Hence, estrogen-induced melanogenesis seems to be an etiologic component of melasma and an intervention that diminishes the effect of estrogens by blocking their receptors may have an efficacious role in the management of this condition.

Melasma-associated angiogenesis

Increased vascularity of melasma lesions has been demonstrated not only histologically [11], but also using dermoscopy [1,22] and reflectance confocal microscopy [6,23]. Indeed, staining of melasma lesions with factor VIII-related antigen demonstrated both larger blood vessels and more numerous blood vessels as compared to normal skin [11]. In addition, keratinocytes of melasma lesions had greater expression of vascular endothelial growth factor as compared to those of nearby non-lesional skin [11].

The essential role of angiogenesis in the pathogenesis of melasma is also demonstrated by two therapeutic approaches that primarily effect vessels within the lesions. Specifically, the combination of pulsed dye laser and a topical preparation consisting of hydroquinone, retinoid, and corticosteroid was more effective than the topical therapy alone [24]. Also concurrent oral and topical transexamic acid (an anti-fibrinolytic) for eight weeks decreased melasma lesion hyperpigmentation; post-treatment histologic examination showed not only diminished melanin content, but also decreased vascularization of the treated sites [25].

Hence, a modality that diminishes the vascular component of melasma by targeting vascular endothelial growth factor might be effective in treating melasma.

Treatment

Several modalities have been utilized for the management of patients with melasma [26–29]. The approach to therapy is often based upon interfering with an aspect of the pathogenesis of melasma [25,30]. Treatment interventions predominantly encompass either topical therapies (such as botanicals, corticosteroids, hypopigmenting agents and retinoids—either as individual drugs or combination therapy) [31–33] or physical modalities (such as acupuncture, chemical peels, dermabrasion and lasers) [33–35].

Treatment may be directed at the hormonal etiology of melasma. Discontinuation of oral contraceptives may be helpful; up to 25% of women develop melasma after beginning these drugs [36,37]. Several women showed spontaneous improvement of their melasma after switching from a combined oral contraceptive to a levonorgestrel-releasing intrauterine device [37].

Management has also been directed at the angiogenesis aspect of melasma. Intense pulsed light is a non-laser light source that emits light with wavelengths between 515 and 1200 nm. In addition to targeting deeper pigmentation, treatment with intense pulsed light targets the increased vasculature associated with melasma [38].

Anti-estrogens

Selective estrogen receptor modulator (SERM)

Tamoxifen is a first generation selective estrogen receptor modulator. Selective estrogen receptor modulators are a class of compounds that interact with estrogen receptors; however, each selective estrogen receptor modulator has a unique tissue-specific profile. Tamoxifen acts as an estrogen receptor antagonist in breast tissue and is used in the adjuvant management for women who have estrogen receptor positive breast cancer. Second and third generation selective estrogen receptor modulators have been developed for the management of osteoporosis. Raloxifene, a second generation selective estrogen receptor modulator, has been approved for breast cancer prevention in postmenopausal women [39–41].