A Review of Melasma, Part 2: Therapy

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Melasma is a common, acquired, and progressive form of hyperpigmentation that occurs most often on the faces of healthy adult women. It also presents in men and in other sun-exposed areas, however.

The true pathogenesis of melasma remains unknown, although persistent exposure to sunlight is among the most important factors when associated with hormonal changes and a genetic predisposition. Melasma may be triggered by multiple stimuli sufficient to cause functional changes in specifically predisposed melanocytes.

Noninvasive subsidiary methods may render clinical examination more objective and accurate, aiming at better diagnosis, prognosis, and therapeutic control. Treatment consists of hypopigmenting agents, chemical peels, microdermabrasion, lasers, and intense pulsed light. A regimen of daily broad-spectrum sun protection is essential to control the progression of melasma and improve treatment.

The aim of the treatment is not to cure melasma, but to control it. Several treatments are available, including hypopigmenting agents, chemical peels, microdermabrasion, lasers, and intense pulsed light.

Hypopigmenting Agents

Hydroquinone is a hydroxyphenolic chemical and has been used as first-line treatment of hyperpigmentation for more than 50 years. It acts by inhibiting the enzyme tyrosinase, thereby reducing the conversion of dopa to melanin.[1] Other mechanisms described are degradation of melanosomes, inhibition of DNA and RNA synthesis, and destruction of melanocytes.[2] Hydroquinone may be used in concentrations from 2% (over-the-counter agents) to 4%. Higher formulations (5%–10%) may be unstable and irritating.[3] Adverse reactions include allergic and irritant contact dermatitis and postinflammatory hyperpigmentation, nail discoloration, hypopigmentation of normal skin surrounding treated areas, and exogenous ochronosis. The latter has been reported with the use of higher concentrations of hydroquinone in dark-skinned South African women.[1] These adverse reactions improve (sometimes slowly in exogenous ochronosis) after discontinuation of hydroquinone.[4]

Hydroquinone combined with other chemicals has been found to be more effective than hydroquinone alone in treating hyperpigmentation disorders.[5] The first combination was described by Kligman and Willis[6] in 1975; it consisted of tretinoin (retinoic acid) 0.1%, hydroquinone 5%, dexamethasone 0.1%, and hydrophilic ointment. To reduce adverse reactions, this combination has been modified with different concentrations of tretinoin or different corticosteroids.[7] Tretinoin improves epidermal penetration and prevents the oxidation of hydroquinone. It also increases keratinocyte proliferation and pigment elimination[5] and reduces corticosteroid-induced skin atrophy.[1] The corticosteroids reduce the hydroquinone- and retinoid-induced irritation and also inhibit melanin synthesis.[5,8] The first triple-combination topical treatment with safe, favorable results approved by the Food and Drug Administration for treating melasma was a formulation containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%.[9]

Another combination that has been shown to be effective and safe is hydroquinone 4%, buffered glycoid acid 10%, ascorbic acid (vitamin C) and tocopherol (vitamin E), and sunscreen.[10] The authors believe that the glycolic acid may play an important role in removing the stratum corneum, enhancing hydroquinone penetration.

N-acetyl-4-*S*-cysteaminylphenol is a phenolic agent that also inhibits tyrosinase activity and is considered more stable and less irritating than hydroquinone. It has been used at 4% and 8% concentrations to treat melasma.[11]

Azelaic acid is a dicarboxylic acid (1,7-heptanedicarboxylic acid) that is isolated from *Pityrosporum ovale*. Its mechanism of action is to inhibit mitochondrial oxidoreductase

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activity and DNA synthesis, inducing cytotoxic effects on hyperactive melanocytes.[12,13] Used at a 15% to 20% concentration, azelaic acid has demonstrated efficacy in treating melasma.[14,15] Balina and Graupe[16] compared the efficacy of azelaic acid 20% with that of hydroquinone 4% and found no significant differences.

Kojic acid is a fungal metabolic product that inhibits the catecholase activity of tyrosine.[17] It is used at a 2% to 4% concentration.[18] In a comparative study of Chinese women with melasma, the addition of kojic acid 2% to a gel containing glycolic acid 10% and hydroquinone 2% further improved melasma.[19]

Topical tretinoin helps to eliminate the dispersed pigment in the keratinocytes by accelerating the turnover of epidermal cells and inducing dispersion of pigment granules in the keratinocytes.[5] Topical tretinoin 0.1% has been used successfully as monotherapy for melasma.[20,21] Adapalene, at a concentration of 0.1%, is another retinoid that has been proven to be effective in treating melasma, with fewer side effects than tretinoin 0.05% cream.[22]

Other hypopigmenting agents that have been used are ascorbic acid and tocopherol.[5] Ascorbic acid inhibits melanin production by reducing *o*-quinones[18] and oxidized melanin.[23] Iontophoresis enhances ascorbic acid penetration and its effectiveness in treating skin with melasma.[23]

Arbutin,[24] licorice extract,[25] and liquiritin[26] also have been described as hypopigmenting agents.

Chemical Peels

In treating melasma, the main purpose of chemical peels is to reduce epidermal thickness and remove melanin, both via the stratum corneum. Chemical peels enhance penetration of topical medications to the basal layer of epidermis and hasten their effects. Deep peels are generally not used because they are frequently associated with hypopigmentation, hyperpigmentation, scarring, and keloid formation.[27]

Salicylic acid peels have demonstrated safety and efficacy in treating melasma and other disorders in patients with Fitzpatrick skin types V and VI when formulated in a hydroethanolic vehicle at 20% to 30% concentrations as a superficial peeling agent.[28]

Glycolic acid peel is an α-hydroxy acid that, in high concentrations (50%–70%), causes epidermolysis. When associated with daily use of hypopigmenting agents (hydroquinone, tretinoin, or combination therapy) in patients of different Fitzpatrick skin types, it produces satisfactory results, improving clinical treatment.[27]

Tretinoin peel may be used in a concentration of 1% to 5%. Cucé et al[29] showed improved clinical and histological results when using tretinoin peels to treat melasma and other disorders. These peels were safe in patients with Fitzpatrick skin types I through IV.

Other chemical peels are Jessner solution[30] and lactic acid.[31]

Microdermabrasion

Microdermabrasion has become a popular method of superficial resurfacing and may produce changes in epidermal barrier function. It may be useful in treating melasma because it enhances penetration of topical medications.[32]

Laser and Intense Pulsed Light

Lasers are not widely used for treating melasma. Although dermal-type melasma is difficult to treat, laser therapy has produced positive results.[4] Lasers should only be considered when other therapeutic options have failed since lasers often produce postinflammatory hyperpigmentation, which usually causes the recurrence of melasma.[5]

In a study by Angsuwarangsee and Polnikorn,[33] combining the UltraPulse® carbon dioxide laser and the Q-switched Alexandrite laser produced better results than using the Q-switched Alexandrite laser alone. However, the combination was associated with more adverse reactions (severe postinflammatory hyperpigmentation, contact dermatitis, and transient hypopigmentation). The erbium:YAG laser has also been associated with postinflammatory hyperpigmentation and should be reserved for refractory patients.[34]

Intense pulsed light is effective for superficial melanocytic lesions. Postinflammatory hyperpigmentation has been observed in patients with melasma.[35] Some patients under treatment for skin rejuvenation experience intense pulsed light–induced melasmalike hyperpigmentation despite the appearance of normal skin. Negishi et al[36] believe that these patients seem to have very subtle *epidermal melasma*, a latent melasma that is exacerbated by intense pulsed light treatment.

Fractional resurfacing is a new laser treatment that has been used recently for managing melasma. It shows promising results, with minimal adverse reactions and no downtime.[37,38] The authors suggest further studies with long-term follow-up and multiple patients.

Conclusion

All the treatments described in this article may improve melasma, but because of the refractory nature of the condition, there is no cure. Combination treatments have been shown to be more effective in treating melasma than the use of individual methods. Successful

treatment involves maintenance medication and regular follow-up care. Daily broad-spectrum sun protection is essential in controlling the progression of melasma and improves treatment.

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