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New oral and topical approaches for the treatment of melasma

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ABSTRACT

Melasma is a common, therapeutically challenging, and universally relapsing disorder of hyperpigmentation that is most often observed in women and individuals with Fitzpatrick Skin Types III through VI. The pathogenesis of melasma is complex and protean. Contributing factors that are often implicated in the etiopathogenesis of this condition include a genetic predisposition, intense ultraviolet radiation exposure, and hormonal influences. Therapeutic interventions for melasma include a multimodality approach incorporating photoprotection agents, topical and oral skin lighteners, and resurfacing procedures. Given our expanding knowledge of the pathogenesis of melasma, new and effective treatments are expanding our therapeutic armamentarium. This article reviews new and emerging oral and topical treatments for melasma.

Introduction

Melasma is a common acquired disorder of hyperpigmentation that is characterized by irregular light to dark brown patches on the forehead, cheeks, upper lip, and chin areas of the face. Prevalence rates vary from 1% to 50% in high-risk populations (Grimes, 1995, 2009; Halder et al., 1983; Kim et al., 2007; Moin et al., 2006; Werlinger et al., 2007). High-risk populations include individuals with darker skin types, pregnant women, and those residing in global locations with intense ultraviolet (UV) exposure.

Patterns of distribution of melasma include a centro-facial, malar, and mandibular pattern with the centro-facial distribution as the most common. In some instances, the neck, extensor arms, and upper back are also affected. These nonfacial areas are most commonly observed in menopausal women. Recent studies have documented an increase in erythema and telangiectasias in the affected areas, which suggests a vascular component for this condition (Kim et al., 2007). Melasma occurs in all races and ethnicities, but the overwhelming majority of patients are women and individuals with Fitzpatrick skin types IV through VI, including Hispanic, Asian, and individuals of African descent (Halder et al., 1983; Kang, 2012; Kim et al., 2007; Moin et al., 2006; Rodrigues and Pandya, 2015). Men comprise the minority of patients with melasma, and account for <20% of cases. The clinical and histologic features of melasma in men are similar to those in women as reported in the literature (Sarkar et al., 2018; Vachiramon et al., 2012). One study reported low testosterone levels in men with melasma (Sarkar et al., 2018).

Myriad quality-of-life studies report on the emotional turmoil and psychological devastation that is experienced by affected individuals (Balkrishnan et al., 2003; Ikino et al., 2015; Pawaskar et al., 2007). Patients experience significant emotional impact and often feel bothered, frustrated, embarrassed, and depressed about their skin appearance (Ikino et al., 2015).

Histologic features of melasma include an increase in the content of both epidermal and dermal melanin, but the quantity varies with the intensity of hyperpigmentation. In addition, most studies show no quantitative increase in melanocytes; however, the cells are enlarged with prominent and elongated dendrites and more abundant melanosomes. Additional features of the involved skin include solar elastosis and increased mast cells, dermal blood vessels, and expression of vascular endothelial growth factor (Grimes et al., 2005; Kang et al., 2002).

The pathogenesis of melasma is complex. Multiple pathways have been implicated in the induction of hyperpigmentation. Etiologic factors include a genetic predisposition, UV light exposure, and hormonal influences. Increased expression of stem cell factor, c-Kit, and α-melanocyte-stimulating hormone have been reported in the lesional skin (Kang et al., 2006; Lee et al., 2017). Recent studies suggest that patients with melasma express markers, which suggests

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increased oxidative stress (Seçkin et al., 2014). Alterations in the Wnt pathway and abnormal barrier function have also been documented (Lee, 2015). The observations of solar elastosis, increased mast cells, vascular defects, barrier dysfunction, and fatty acid abnormalities suggest that melasma may well represent a phenotype of photodamage (Passeron and Picardo, 2018).

From a historical perspective, commonly used agents for the treatment of melasma include hydroquinone, azelaic acid, kojic acid, glycolic acid, salicylic acid, and tretinoin. Of these treatments, hydroquinone remains the gold standard. Multiple studies suggest that combination formulations offer the best results (Halder et al., 1983; Kim et al., 2007; Moin et al., 2006; Werlinger et al., 2007). These triple combination formulas usually contain hydroquinone, a retinoid, and a corticosteroid in varying concentrations. The aforementioned commonly used therapies are often associated with universal relapses. Second-line treatments, such as chemical peels and lasers, are efficacious in some patients, but these approaches can be associated with acute and long-term complications, particularly in individuals with darker skin types. Given the global negative impact of melasma on the quality of life, a quest to find more efficacious treatments that offer sustained long-term remission for patients with this frustrating and therapeutically challenging disorder is ongoing.

Therapeutic interventions

The treatment of melasma should include a multimodality approach that incorporates photoprotective agents, antioxidant treatments, skin lighteners, exfoliants, and resurfacing procedures, as needed. Evidence-based studies suggest that first line therapies for melasma encompass intense photoprotection and topical lightening agents (Jutley et al., 2014; Rivas and Pandya, 2013; Sarkar et al., 2013; Sarma et al., 2017). Additionally, many studies have addressed the safety and efficacy of chemical peels and laser/light sources for pigment reduction in melasma. Such procedures are most often considered second- and third-line therapeutic approaches.

Lasers should be used with care and caution given the high rate of recurrence of melasma. In addition, laser intervention is often complicated by postinflammatory hyperpigmentation in individuals with darker skin types.

This review addresses new and emerging oral and topical agents for the treatment of melasma.

Photoprotection

Daily photoprotection is key in the management of this therapeutically challenging and universally relapsing disorder. The use of broad spectrum sunscreens is essential. Caregivers of patients with melasma often report the common occurrence of rapid and frequent relapses after intense UV exposure. Lakhdar et al. (2007) assessed the role of a broad-spectrum sunscreen in the prevention and treatment of chloasma in pregnant women during a 12-month clinical trial. Of the 185 patients who completed the study, only five new cases of chloasma (melasma) were noted, an occurrence rate of 2.7% and much lower than the 53% previously observed during pregnancy.

In addition to the deleterious impact of UV light as a trigger and relapsing factor, recent studies have implicated a role for visible light (Duteil et al., 2014, 2017; Mahmoud et al., 2010). Visible blue light has been shown recently to stimulate opsin-3, which activates the melanogenesis-associated transcription factor and other melanogenic enzymes such as tyrosinase and dopachrome tautomersae (Regazzetti et al., 2018). Tyrosinase and dopachrome form a protein complex that is mainly generated in the melanocytes of dark-skinned individuals. Hence, the sustained effects of visible blue light irradiation in individuals with darker skin types are thought to induce long-lasting hyperpigmentation in individuals with skin type III and above (Regazzetti et al., 2018). Therefore, photoprotection that incorporates visible light, such as iron oxide sunscreens, is essential. There are few readily available iron oxide formulations, and such formulations optimally block UV light in the visible spectrum.

Castanedo-Cazares et al. (2014) compared the effects of a UV-visible light sunscreen to a UV-only sunscreen, both with sun protection factor ≥50. Sixty-eight patients were included in this 8-week study (Castanedo-Cazares et al., 2014). The UV-only sunscreen contained mexoryl SX, titanium dioxide, octocrylene, Tinasorb–S, and avobenzone. The UV-visible light sunscreen contained the same regimen plus iron oxide. Both groups received hydroquinone 4% daily. Significantly greater improvement was observed in the group that was treated with the UV-visible light regimen.

In a 6-month study of 40 patients, Boukari et al. (2015) assessed the efficacy of a UV–visible light sunscreen that contained iron oxide. The control group used the same UV sunscreen that provided the same UV-B and UV-A protection without the iron oxide. A significantly greater reduction in Melasma Area Severity Index (MASI) score occurred in patients treated with the combination UV-visible light formula. Both studies document the beneficial effects of visible light protection in patients with melasma.

Polypodium leucotomos

There has been much interest recently in the use of *Polypodium leucotomos* (PL) as an adjunct photoprotective agent in melasma. Polypodium is a fern of the Polypodiaceae family that is unique to Central and South America. PL's mechanisms of action include the promotion of the p53 suppressor gene expression, modulation of inflammatory cytokines, upregulation of endogenous antioxidant systems, and blockade of UV radiation-induced cyclooxygenase–2 expression (Nestor et al., 2014; Siscovick et al., 2008).

Several recent studies have documented a beneficial effect in patients with melasma (Goh et al., 2018; Martin et al., 2013). In a randomized, placebo-controlled study of 40 patients, Martin et al. (2013) assessed the efficacy of PL 240 mg twice daily versus placebo. The authors reported a statistically significant effect of PL compared with placebo. In a recent double-blind, placebo-controlled trial, Goh et al. (2018) reported the effectiveness of PL in melasma. Patients were randomized to receive either oral PL 240 mg twice daily or placebo for 12 weeks. The active and placebo groups were also treated with a broad spectrum sunscreen and hydroquinone 4% daily. The group treated with PL achieved a significantly greater reduction in MASI score at 56 and 84 days of treatment (Goh et al., 2018).

Frequently used topical agents

A variety of topical agents have been used for melasma. Historically, hydroquinone has been the gold standard. Others agents include azelaic acid, kojic acid, retinoid treatments, niacinamide, corticosteroid medications, salicylic and glycolic acid, arbutin, resveratrol, and resorcinol. These agents and their mechanisms are cited in Table 1 (Al-Niaimi and Chiang, 2017; Birk, 1985; Bissett, 2002; De Caprio, 1999; Deo et al., 2013; Glowka et al., 2018; Grimes, 1995, 2009; Hashim et al., 2018; Huh et al., 2010; Kang, 2005; Keeling et al., 2008; Lajis et al., 2012; Menter, 2004; Monteiro et al., 2013; Navarrete-Solís et al., 2011; Niwano et al., 2018; Nordlund et al., 2006; Olejnik et al., 2018; Paine et al., 2001; Picardo and Carrera, 2007; Pires et al., 2018; Schulte et al., 2015; Tse, 2010; Videira et al., 2013; Wargniez et al., 2017; Wohlrab and Kreft, 2014). Evidence-based studies have suggested that combination products that contain hydroquinone 4%, tretinoin, and a steroid produce the best response (Jutley et al., 2014; Rivas and Pandya, 2013; Sarkar, 2013; Sarma et al., 2017). (See Table 2.)

Table 1
Common lightening agents for melasma

Name	Mechanism of action	Side effects	Reference
Hydroquinone	Tyrosinase inhibition	Erythema, irritation, exogenous ochronosis	De Caprio, 1999; Grimes, 2009; Nordlund et al., 2006; Tse, 2010
Azelaic acid	Tyrosinase inhibition	Stinging, burning, itching, dryness	Hashim et al., 2018; Schulte et al., 2015
Kojic acid	Tyrosinase inhibition	Irritation, contact dermatitis	Deo et al., 2013; Lajis et al., 2012; Monteiro et al., 2013
Ascorbic acid	Inhibition of reactive oxygen species	No significant adverse event	Al-Niaimi and Chiang, 2017; Pires et al., 2018
Retinoids	Downregulation of Tyrosinase	Irritant reaction, dryness, hyperpigmentation	Kang, 2005
Corticosteroid treatments	Antiinflammatory and nonselective inhibition of melanogenesis	Telangiectasias, epidermal atrophy, steroid-induced acne, striae, hypopigmentation	Menter, 2004
Niacinamide	Inhibition of melanasome transfer	Irritation	Bissett, 2002; Navarrete-Solís et al., 2011; Wohlrab and Kreft, 2014
Licorice	Melanin dispersion, tyrosinase inhibition	No significant adverse event	Picardo and Carrera, 2007; Videira et al., 2013
Undecylenoyl phenylalanine	Antagonist of α-melanocyte-stimulating hormone, β-adrenergic, stem cell receptors	No significant adverse event	Glowka et al., 2018; Olejnik et al., 2018
4-N-butylresorcinol	Tyrosinase inhibition, antioxidant, antiinflammatory	Mild erythema and itching	Huh et al., 2010; Wargniez et al., 2017
Soybean	Inhibits melanosome transfer to keratinocytes	No significant adverse event	Birk, 1985; Paine et al., 2001
Arbutin	Inhibition of tyrosinase	Skin irritation	Sarma et al., 2017
Glucosamine	Inhibition of tyrosinase activation	Skin rash	Niwano et al., 2018
Mequinol	Inhibition of tyrosinase	Skin irritation, redness, peeling	Keeling et al., 2008

Hydroquinone is used globally for melasma (De Caprio, 1999; Grimes, 2009; Nordlund et al., 2006; Tse, 2010), and although used for more than 60 years, it remains our most efficacious topical agent. Hydroquinone inhibits tyrosinase, which is the rate-limiting enzyme for pigment production, and is well tolerated in most patients. The most common side effect is irritant contact dermatitis.

The majority of clinical trials that have assessed the efficacy and safety of hydroquinone have not extended beyond 6 months. Nonetheless, physicians have enormous variability in prescribing practices for hydroquinone, so there is no universal standard of treatment. In the authors' experience, hydroquinone can be safely and effectively used beyond 6 months. However, optimal results are often best achieved using a 6-month rotational algorithm that cycles on and off hydroquinone. Other lightening agents are often essential to maintain the results achieved with hydroquinone use. Hydroquinone should not be used in pregnant or breastfeeding women due to its Category C characterization.

Hydroquinone has been banned in some countries due to concerns of ochronosis and possible cases of depigmentation. Ochronosis is characterized by hyperpigmented lichenoid, which are cavier-like papules that appear in cutaneous areas treated with hydroquinone. Ochronosis was first reported in Africa and is usually caused by the long-term use of high concentrations of hydroquinone with inadequate sun protection (Bhattar et al., 2015; Grimes, 2009). In contrast to common case reports from Africa, this condition is uncommon in the United States where most cases are secondary to the prolonged use of over-the-counter, low-concentration, cosmetic formulations of 2% hydroquinone. Cases of depigmentation caused by hydroquinone are rare.

Additional concerns with regard to the safety of hydroquinone is based on studies that suggest that benzene, which is a known leukemogenic agent, is metabolized into hydroquinone as a major byproduct (Norlund et al., 2006). Benzene metabolites, including hydroquinone, phenol, or benzoquinone, do not exhibit the potency and level of the myelotoxic effect of benzene. In addition, individuals who are occupationally exposed to long-term hydroquinone have not demonstrated myelotoxic changes (De Caprio, 1999; Tse, 2010). Hydroquinone has now been used and manufactured for more than 60 years, and a review of the literature reveals no cases of skin cancer, internal malignancies, or liver damage related to the topical application of hydroquinone for skin lightening.

New oral and topical treatments

Tranexamic acid

Tranexamic acid (TA), a synthetic derivative of lysine, is a fibrinolytic agent that blocks the conversion of plasminogen to plasmin and thereby impedes the binding of plasminogen to keratinocytes (Fig. 1). Downstream effects include diminished arachidonic acid release and decreased prostaglandin and fibroblast growth factor synthesis. Prostaglandins and fibroblast growth factor both stimulate melanin synthesis. TA also decreases mast cells and angiogenesis (Kim et al., 2015). Nijo Sadako first reported the efficacy of TA in 1979 in a patient with melasma treated for chronic urticaria (George, 2016).

TA is currently used via a spectrum of delivery routes including oral, topical, intradermal, and microneedling (Taraz et al., 2017). The current oral dosing is significantly less than doses used to treat hemophilia, heavy menstrual bleeding, or other hemorrhagic conditions. Oral dosing for melasma is, on average, 250 mg twice daily compared with 3900 mg daily for bleeding diatheses (Taraz et al., 2017). Multiple studies have documented the efficacy of TA in patients with melasma (Banihashemi et al., 2015; Del Rosario et al., 2018; Ebrahimi and Naeini, 2014; Kim et al., 2017; Lee et al., 2016; Na et al., 2013; Perper et al., 2017; Wu et al., 2012).

TA has been predominantly used in Asian patients and was recently evaluated in a cohort of patients in the United States. Del Rosario et al. (2018) assessed the efficacy of TA 250 mg twice daily versus placebo in a 3-month study, followed by 3 months of sunscreen only. Thirty-nine patients completed the trial. At 3 months, there was a 49% reduction in MASI score versus 18% for the placebo control group. No serious adverse events were reported (Del Rosario et al., 2018).

The largest retrospective study of TA treatment was conducted in Singapore. The authors reviewed data from 561 patients with melasma who were treated with TA, and improvement was noted in 90% of patients. Adverse events were reported in 40 patients (7.1%), and most side effects were mild. However, one patient developed deep vein thrombosis and was later discovered to have familial protein S deficiency. There was a personal history of spontaneous miscarriage and a family history of thromboembolic issues in two siblings (Lee et al., 2016).

General concerns linger with regard to the safety profile given TA's propensity to induce thromboembolic phenomena. Hence, TA

Table 2
New oral and Topical Treatments.

	Agent		Reference	Mechanism of action	Dosing	Study outcomes	Adverse events
Photoprotection	Topical	Iron oxide sunscreens	Boukari et al., 2015; Castanedo-Cazares et al., 2014; Duteil et al., 2017; Lakhdar et al., 2007; Mahmoud et al., 2010; Regazzetti et al., 2018	Blocks blue visible light	SPF ≥ 50	UV-visible light regimen had significant improvement	None
	Oral	*Polypodium leucotomos*	Goh et al., 2018; Martin et al., 2013; Nestor et al., 2014; Siscovick et al., 2008	Promotion of p53 suppressor gene expression/modulation of inflammatory cytokines ↑ endogenous antioxidant systems blockade of UV radiation induced cyclooxygenase-2 expression	240 mg BID	Beneficial effect Greater reduction in MASI	Mild gastrointestinal upsets
Lightening agents	Oral and topical	Tranexamic acid	Banihashemi et al., 2015; Del Rosario et al., 2018; Ebrahimi and Naeini, 2014; George, 2016; Kim et al., 2016; Lee et al., 2016, 2017; Na et al., 2013; Perper et al., 2017; Taraz et al., 2017; Wu et al., 2012	Blocks conversion of plasminogen to plasmin Blocks binding of plasminogen to keratinocytes ↓ arachidonic acid release, prostaglandin synthesis and FGF ↓ melanin synthesis ↓ mast cells ↓ angiogenesis	2-5% BID 250 mg BID	Global studies document significant reduction in MASI score	Oral: mild gastrointestinal discomfort, hypomenorrhea, allergic skin rashes, alopecia, and mild elevations in alanine transaminase Topical: erythema, scaling, dryness Propensity to induce thromboembolic phenomena
		Melatonin	Hamadi et al., 2009; Ryoo et al., 2001	Potent antioxidant/free radical scavenger ↑ super oxide dismutase, glutathione reductase, glutathione peroxidase ↓ α-MSH receptors	5% BID 3 mg daily	Decreased MASI, malondialdehyde decreased GSH levels increased	Not reported
		GSH	Handog et al., 2016; Sonthalia et al., 2016; Watanabe et al., 2014	decreases tyrosinase skews conversion of eumelanin to pheomelanin	2% daily 500 mg daily	Melanin index significantly reduced	Intravenous: Stevens-Johnson Syndrome, anaphylaxis Oral and topical: none
		Cysteamine	Besouw et al., 2013; Mansouri et al., 2015	Radio protector (via direct scavenging effects of hydroxy radicals) Tyrosinase peroxidase inhibition	5% daily	Reduced MASI compared to placebo	None reported
	Topical	Pigment-correcting Serum	Makino et al., 2016	Melanocyte activation, melanosome development, melanin synthesis, melanosome transfer keratinocyte differentiation and desquation		Comparable efficacy to hydroquinone	Mild irritation
		Methimazole	Kasraee et al., 2005, 2008	Potent peroxidase inhibitor blocks melanin synthesis	5% daily	No significant changes in serum TSH, free thyroxine, free triiodothymine levels	Minimal cutaneous side effects
		Flutamide	Adalatkhah et al., 2011	Blocks action of endogenous/ exogenous testosterone by binding to androgen receptor	1% daily	MASI/colorimetry effects similar to hydroquinone 4% Patient satisfaction scores significantly high	None

BID, twice daily; FGF, fibroblast growth factor; GSH, glutathione; MASI, Melasma Area Severity Index; MSH, melanocyte-stimulating hormone; SPF, sun protection factor; TSH, thyroid-stimulating hormone; UV, ultraviolet

Fig. 1. Melasma (A) before treatment and (B) after treatment with topical 3% tranexamic acid and hydroquinone. Significant improvement in areas of hyperpigmentation of the cheek and upper lip.

is contraindicated in patients with clotting disorders or a history of thromboembolism (Kim et al., 2017). Major side effects in melasma clinical trials are rarely reported. Other adverse events related to TA use include mild gastrointestinal discomfort, hypomenorrhea, allergic skin rashes, alopecia, and mild elevations in alanine transaminase levels. Oral TA should be prescribed with care and caution. A detailed history should be taken for each patient to exclude individuals at risk for untoward complications.

Several studies have addressed the efficacy and safety of topical TA (Banihashemi et al., 2015; Ebrahimi and Naeini, 2014; Kim et al., 2016). In a 12-week, split-face, prospective trial, Banihashemi et al. (2015) compared the efficacy of a liposomal 5% TA formulation to hydroquinone 4%. Both treatments showed significant clinical improvement without significant differences between the two groups, which suggests comparable efficacy.

In a separate split-face study, a TA 3% suspension was applied to one side of the face and a suspension with hydroquinone 2%, dexamethasone 0.01%, and vitamin C to the opposite side. Both formulations showed significant improvement, which suggests similar topical efficacy for hydroquinone-based formulations (Ebrahimi and Naeini, 2014). Topical side effects included erythema, scaling, irritation, and dryness (Banihashemi et al., 2015; Ebrahimi and Naeini, 2014; Kim et al., 2016).

Melatonin

The hormone melatonin, which is secreted by the pineal gland, is a potent antioxidant and free-radical scavenger that stimulates several antioxidant enzymes, including superoxide dismutase, glutathione reductase, and glutathione peroxidase. Melatonin also inhibits α-melanocyte-stimulating hormone receptors. Oral and topical melatonin were evaluated in a series of 36 patients with melasma and 10 healthy control participants. Patients were randomized to several groups, including topical melatonin only, topical melatonin plus screen, and a combination of topical and oral melatonin and hydroquinone 4% for 90 days. At 90 days, all patients with melasma demonstrated a significant reduction in MASI score. In addition, malondialdehyde, which is a measure of oxidative stress, decreased and glutathione (GSH) levels increased and suggest significant improvement in oxidative stress. These seminal observations also suggest that additional studies to assess the efficacy and safety of melatonin in patients with melasma are warranted (Hamadi et al., 2009l Ryoo et al., 2001).

Glutathione

GSH is one of the most powerful endogenous antioxidants produced by cells in the human body and is a tripeptide of glutamate, cysteine, and glycine. Mechanisms that induce lightening of the skin include inhibition of tyrosinase and the ability to skew production of eumelanin to pheomelanin. There has been enormous recent publicity with regard to the use of intravenous GSH for general skin lightening (Sonthalia et al., 2016). Multiple articles have been published in the lay press on the use of GSH for a variety of diseases including melasma. Intravenous use of GSH has been associated with severe life-threatening reactions including Stevens–Johnson syndrome and anaphylaxis.

Several studies have evaluated oral and topical GSH for general skin lightening. In an 8-week study, Handog et al. (2016) treated 30 healthy Filipino women with a 500 mg buccal glutathione lozenge. The melanin index showed a significant reduction, and global assessments reported moderate lightening in 90% of subjects (Handog et al., 2016). A topical glutathione 2% suspension was assessed in a randomized, double-blind, split-face, 10-week study, in which GSH was applied to one side and a placebo to the opposite side. The melanin index was significantly reduced in the GSH-treated side (Watanabe et al., 2014). Oral and topical GSH are well tolerated with no significant adverse events. The results of these studies suggest the need to test oral and topical GSH for melasma.

New topical agents

Cysteamine

Cysteamine hydrochloride (ß–mercaptoethylanine hydrochloride) is naturally produced in the human body and is a degradation product of the amino acid L-cysteine. Cysteamine is also a radio protector that protects cells from the mutagenic and other lethal effects of ionizing radiation via its direct scavenging effects on hydroxy radicals (Besouw et al., 2013).

Recently, several studies have documented the efficacy of cysteamine in patients with melasma. In a randomized, double-blind trial of 40 patients, a significant improvement in melasma lesions was observed compared with patients who were treated with placebo. Mansouri et al. (2015) assessed the efficacy of 5% cysteamine in 50 patients with melasma. Cysteamine induced significant reductions in MASI scores at 16 weeks compared with placebo.

Pigment-correcting serum

Pigment-correcting serum was recently reformulated to address the multiple pathways involved in the induction of hyperpigmentation. These pathways include melanocyte activation, melanosome development, melanin synthesis, melanosome transfer, and keratinocyte differentiation and desquamation. Pigment-correcting serum contains TA, tetrapeptides, plankton extracts, niacinamide, phenylethyl resorcinol, and undecylenol phenylalanine. In a randomized, double-blind comparison trial of 43 patients, pigment-correcting serum was compared with hydroquinone 4% and showed overall comparable efficacy to hydroquinone in patients with melasma and postinflammatory hyperpigmentation (Makino et al., 2016).

Methimazole

Methimazole is an oral anti-thyroid medication used to treat patients with hyperthyroidism and has been shown to cause depigmentation when applied topically. Methimazole has been used in patients with melasma and postinflammatory hyperpigmentation and causes significant skin lightening. Methimazole is a potent peroxidase inhibitor that blocks melanin synthesis. Absorption studies of topically applied methimazole 5% revealed minimal detectable serum levels and no abnormalities in thyroid function tests (Kasraee et al., 2005, 2008). Methimazole 5% was applied daily in 20 patients with epidermal melasma and did not induce any significant changes in serum thyroid-stimulating hormone, free thyroxine, and free triiodothyronine levels. Methimazole was well tolerated with minimal cutaneous side effects. However, Kasraee et al. (2008) recommend that methimazole only be applied to areas affected by melasma and should not be used as a general cosmetic lightening agent.

Flutamide

A recent paper evaluated the efficacy of topical flutamide in patients with melasma. Flutamide is a nonsteroidal antiandrogen that blocks the action of endogenous and exogenous testosterone by binding to the androgen receptor. Seventy-four women were enrolled in a parallel, randomized, 16-week trial that compared once daily flutamide 1% with hydroquinone 4%. Skin hyperpigmentation improved, and the results of MASI and colorimetry scores revealed similar efficacy for flutamide and hydroquinone 4%. However, patient satisfaction scores were significantly higher in the flutamide group (Adalatkhah and Sadeghi-Bazargani, 2015).

Conclusions

Melasma remains a chronic, therapeutically challenging, and universally relapsing condition. This psychologically devastating disorder should be treated with a multimodality approach that incorporates photoprotective agents, antioxidant treatments, skin lighteners, exfoliants, and resurfacing procedures in severe cases. A myriad of new oral, topical, and combination therapies for melasma have been introduced to expand our repertoire of therapies, and warrant additional trials to substantiate their efficacy and safety.

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