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New Horizons in Treating Disorders of Hyperpigmentation in Skin of Color

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Pigmentary abnormalities are among the most common reasons why patients with skin of color visit a dermatologist. Hydroquinone has been a cornerstone for the treatment of hyperpigmentation; however, concerns regarding adverse effects have prompted a search for alternative agents. Some promising topical treatments include soy, licorice, rucinol, mulberry, niacinamide, ellagic acid, resveratrol, and dioic acid. Oral agents, primarily used for the prevention of postprocedural hyperpigmentation, include procyanidins, tranexamic acid, and *Polypodium leucotomos*. Advances in Q-switched lasers, intense pulse light, fractional photothermolysis, and the advent of tretinoin peeling add to the clinician's armamentarium for treating hyperpigmentation.
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Disorders of hyperpigmentation, including melasma and postinflammatory hyperpigmentation (PIH), are frequently encountered yet frustrating problems in the skin of color population. Indeed, pigmentary disorders rank among the top 5 most common skin complaints in several ethnic groups, including blacks, Arabs, and South Asians.[1-4] Management is often challenging due to the limited number of currently available successful treatment options. Some currently available medical, surgical, and laser- and light-based therapies may be adapted for new indications. Other modalities are still in development and could potentially represent new ways of approaching hyperpigmentation in skin of color.

Treatment of Hyperpigmentation Disorders With Newer Topical Agents

Hydroquinone has long been a mainstay for the topical treatment of hyperpigmentation. However, concerns regarding ochronosis, allergic and irritant contact dermatitis, melanocyte toxicity, difficulty formulating stable preparations, and carcinogenicity (when given orally in rodents) have prompted a search to find alternative agents.[5,6] In addition, many formulations of hydroquinone currently available have never been tested for safety or efficacy.[6] Other agents that have already been used topically to treat hyperpigmentation in skin of color include azelaic acid, arbutin, and kojic acid. None of these agents or hydroquinone will be discussed. Newer topical agents that have been shown to have partial or total efficacy in treating hyperpigmentation in skin of color include soy, licorice, aloesin, mequinol, rucinol, mulberry, niacinamide, ellagic acid, resveratrol, dioic acid, green tea, and N-acetyl glucosamine. These will be described and published studies that indicate effectiveness in skin of color are detailed.

Topical Agents

Soy

Nondenatured soy extracts are derived from the soybean, a species of legume originally native to East Asia, and contain serine protease inhibitors and isoflavones. The serine protease inhibitors, soybean trypsin inhibitor, and Bowman-Birk protease inhibitor, affect skin pigmentation by inhibiting protease-activated receptor-2 (PAR-2)-mediated phagocytosis of melanosomes by keratinocytes.[7] They also have a role in the apoptosis of keratinocytes and other skin cells. PAR-2 is expressed on the cell surface of keratinocytes, and its activation produces multiple changes characteristic of phagocyto-

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sis, including cytoskeletal reorganization and morphologic changes.[8] Serine protease inhibitors can also inhibit the pigmentation caused by UVB radiation, suggesting that ultraviolet (UVB)-induced pigmentation may be regulated by PAR-2 activation.[9]

Thirty healthy South-East Asian women treated solar lentigines on one limb, with twice-daily application of a soy extract. After 2 months, treated solar lentigines had an insignificant 4.4% decrease in the melanin index, a significant 15.1% decrease in the melanin density, and a significant 12.3% decrease in the size of melanin spots.[10] More recently, Wallo et al[11] studied 63 women with skin types I–III, with moderate facial photodamage over 12 weeks and found soy moisturizer was significantly more efficacious than the placebo vehicle in improving dermatologists' evaluations of percentage improvement from baseline of mottled pigmentation (90% vs 53%) and blotchiness (84% vs 34%) at 12 weeks.

Licorice

Licorice extract derived from the root of *Glycyrrhiza glabra* is known to contain depigmenting compounds. The main active ingredient is glabridin, which has been shown to inhibit tyrosinase. UVB-induced pigmentation and erythema in guinea-pig skin were inhibited using topical 0.5% applications for 3 weeks. In addition, glabridin has demonstrated antiinflammatory activity through inhibition of cyclooxygenase and superoxide anion production, which may prevent postprocedural PIH in skin of color patients.[12] However, clinical evidence of the efficacy of glabridin in the treatment of hyperpigmentation is limited. Glabridin is currently available in commercial formulations in concentrations from 10% to 40%.[13]

Another compound found in licorice extract is the flavonoid, liquiritin, which is thought to cause depigmentation through dispersion of melanin. In a split-face trial, liquiritin cream applied at 1 g/d for 4 weeks produced excellent results in 16 out of 20 Egyptian women with epidermal melasma. Mild skin irritation was seen in 2 patients treated with liquiritin cream, which disappeared with ongoing treatment.[14]

Rucinol

Rucinol (4-n-butylresorcinol) is the first substance shown to inhibit the activity of both tyrosinase and tyrosinase-related protein-1, which catalyzes the oxidation of the melanogenetic intermediate 5,6-dihydroxyindole-2-carbolylic acid. Rucinol inhibits B16 mouse melanoma tyrosinase in vitro more effectively than kojic acid, hydroquinone, and arbutin by factors of 5.6, 100, and 380, respectively.[15] Khemis et al[16] conducted a double-blind, randomized, split-face comparative trial comparing the efficacy of twice-daily application of 0.3% rucinol serum or vehicle. At 12 weeks, 28 women with skin types III-IV with melasma had significantly lower mean pigmentation scores with rucinol (6.2 ± 2.3) than with vehicle (6.7 ± 2.1). Another double-blind, randomized, split-face study had 23 Korean women with melasma apply liposome-encapsulated rucinol 0.1% cream or vehicle twice daily and showed a significant decrease in the melanin index on the rucinol-treated side (−7.51%) compared with the vehicle-treated side (−3.26%) at 8 weeks.[17]

Mulberry

Mulberroside F (moracin M-6, 3'-di-O-beta-D-glucopyranoside) is isolated from the extract of dried *Morus alba* leaves. Inhibition of mushroom tyrosinase activity is 71% compared with 78.9% from *Glycyrrhiza glabra* extract and 91.4% from kojic acid. Mulberry extract, like kojic acid, can scavenge reactive oxygen species but to a lesser degree.[18,19] A recent randomized placebo-controlled study in Filipinos assessed the efficacy of 75% mulberry extract in the treatment of melasma in 50 subjects. After 8 weeks, the treatment group exhibited a significant mean melasma area and severity index (MASI) score reduction from 4.08 at baseline to 2.89, as well as improvement in Mexameter readings and quality of life scores compared with placebo.[20]

Niacinamide

Niacinamide (vitamin B3) is naturally found in vegetables and seeds, and it is part of the niacin coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are involved in cellular oxidation and reduction reactions. Niacinamide at a 10 μM dose inhibits melanosome transfer to keratinocytes in vitro by 14% after 3 days of treatment and is partially reversible to 2% at 3 days post-treatment.[21] A randomized, double-blind, split-face study had 18 Japanese women with lentigines, melasma, or freckles apply 5% niacinamide moisturizer or vehicle moisturizer for 8 weeks with a significant decrease in hyperpigmentation.[22] A similar study in Caucasian women for 12 weeks found topical 5% niacinamide prevented an increase in seasonal-induced hyperpigmented spot area in facial skin versus placebo control.[23] Niacinamide can be combined with N-acetyl glucosamine for a greater effect on hyperpigmentation.[24]

Ellagic Acid

Ellagic acid is a polyphenol antioxidant found in a variety of foods, such as strawberries, grapes, cherries, walnuts, and green tea.[25] The mechanism by which ellagic acid suppresses melanogenesis is related to tyrosinase inhibition secondary to chelation of copper. In vivo analysis on brownish guinea pigs has shown 1% ellagic acid to be a more efficient skin whitener and suppressor of pigmentation than kojic acid or arbutin at the same concentration.[26] A study in Turkish subjects found 1% gel formulations of naturally occurring ellagic acid, synthetic ellagic acid, and arbutin to be similarly effective in the treatment of melasma in 29 subjects.[25]

Resveratrol

A potential topical agent to treat hyperpigmentation in skin of color is resveratrol. Resveratrol is a phytoalexin and nonflavonoid polyphenolic antioxidant that is synthesized in plant cells subjected to stress, such as fungal invasion or nutrient depletion. It can be found in grape skin extracts, red wine, purple grape juice, peanuts, mulberries, bilberries, blueberries, cranberries, and the Japanese knotweed. Resveratrol initially came to the forefront when wine was found to be cardioprotective in the French population. Its mechanism of action is unknown, and current data are conflicting. Galgut and Ali studied the effects of topical ethanolic extracts

of *Arachis hypogaea*, or peanuts, on the tail melanophores of *Bufo melanostictus*.[27] Peanuts have half the amount of resveratrol found in red wine. Treatment with *A. hypogaea* extract resulted in distinct aggregation of pigment cells leading to skin lightening, which was reversible after reimmersion in physiological saline. There have not been any studies with oral resveratrol; however, when this research is eventually translated to human clinical trials, its effects will likely be tested via the oral route.

Dioic Acid

Octadecenedioic acid is a recently developed monounsaturated dicarboxylic acid that is structurally similar to azelaic acid. Its lightening effect occurs through the binding of peroxisome proliferator-activated receptor gamma (PPAR-γ), which results in reduced tyrosinase mRNA expression.[28] One study compared twice-daily application of 1% dioic acid to 2% hydroquinone cream in 96 Mexican female subjects with melasma. Both agents demonstrated equal efficacy in reducing MASI scores over 40% after 12 weeks of treatment. Although adverse effects were similar between the 2, pruritus occurred more in hydroquinone group, whereas acneiform reactions were more prevalent in those using dioic acid. The latter was attributed to the oilier vehicle.[29]

N-Acetyl Glucosamine

N-Acetyl glucosamine (NAG) is an amino-monosaccharide that inhibits enzymatic glycosylation, which is required to convert inactive protyrosinase to the active tyrosinase. It reduces melanin production and downregulates the gene expression of several intracellular cytoskeletal proteins that are involved in melanosome transport within the cell.[30] An 8-week, double-blind, placebo-controlled, split-face study treated 50 Japanese female patients with solar lentigines, melasma, or freckles with topical 2% NAG twice-daily for 8 weeks and found a reduction in facial hyperpigmentation based on computer image analysis of the percentage change of hyperpigmented spot areas.[24] Although formulating a topical agent has been difficult due to its instability, a recent study has demonstrated the potential for niosomes for improved NAG localization to the skin.[31]

Treatment of Hyperpigmentation Disorders With New Oral Agents

There are new oral agents that may be effective for preventing PIH in skin of color or treating other forms of hyperpigmentation after it has developed in skin of color. These agents include procyanidins, tranexamic acid, and *Polypodium leucotomos* (PL). Relevant references to studies using these in skin of color are described.

Procyanidins

Proanthocyanidins, or condensed tannins, can be found in apples, maritime pine bark, cinnamon, *Aronia* fruit, cocoa beans, grape seeds and skin, and red wine. The French maritime pine (*Pinus pinaster*) bark extract, otherwise known as Pycnogenol, has been postulated as a possible treatment for hyperpigmentation. It contains a standardized mixture of phenolic compounds, including catechin, epicatechin, taxifolin, procyanidins, caffeic acid, ferulic acid, and *p*-hydroxybenzoic acid as important constituents.[32] Pycnogenol has been shown to protect against UV-induced erythema possibly though inhibition of nuclear factor (NF)-κB-dependent gene expression.[32] Additionally, Pycnogenol has proven to be an antioxidant more potent that vitamins C and E based on in vitro data. An open-label trial of 30 Chinese women with melasma taking oral Pycnogenol 25 mg 3 times a day for 30 days demonstrated an 80% response rate with no significant side effects observed.[33]

Grape seed extract is a powerful antioxidant, which exhibits 78%-81% inhibition of superoxide anion and hydroxyl radical at concentrations of 100 mg/L.[34] Yamakoshi et al[35] administered oral grape seed extract to 12 Japanese women with melasma for 6 months and found improved or slightly improved melasma in 10 of the 12 women (83%, $P < .01$).

Tranexamic Acid

Tranexamic acid is an oral agent that has been shown to prevent UV-induced plasmin activity in guinea pig skin, which leads to a decrease in arachidonic acid and subsequently prostaglandins, thereby decreasing tyrosinase activity.[36-38] Lee et al[39] found that weekly intradermal injections of tranexamic acid into lesions of melasma in 85 Korean women significantly reduced mean MASI score from 13.22 at baseline to 7.57 at week 12. Oral tranexamic acid has shown mixed results; 1 study found it to be ineffective in preventing PIH in Japanese women after Q-switched (QS) ruby laser treatments for senile lentigines on the face, whereas another found it to improve the efficacy of intense pulsed light (IPL) and Q-switched neodymium:yttrium-aluminum-garnet laser (QSNYL) laser treatment of Korean patients with melasma.[40,41]

Polypodium leucotomos

PL is an extract of a fern species that contains polyphenols, which are potent inhibitors of reactive oxygen species with antiinflammatory, antioxidant, and photoprotective properties. PL inhibits matrix metalloproteinase-1-photoinduced membrane damage and reduces psoralen/UVA-induced phototoxicity.[42] A total of 10 patients with skin phototypes II-III were exposed to PUVA alone and then to PUVA with 7.5 mg/kg of oral PL extract.[43] PL significantly diminished the cutaneous pigmentary response in 4 of the 6 cases evaluated. Although further studies are needed in darker skin phototypes, PL extract may be a useful adjunctive topical treatment to prevent further hyperpigmentation in disorders, such as melasma, which can be exacerbated by UV light.

Treatment of Hyperpigmentation Disorders With Lasers

Laser technology for dermatologic disorders has advanced remarkably during the past decade. Presently, several lasers are available with the potential of safely treating disorders of

hyperpigmentation in skin of color. Studies supporting the use of lasers in these disorders are reviewed.

Q-Switched Ruby

The QS ruby laser emits red light with a wavelength of 694 nm. There have been conflicting results with the QS ruby laser for treating melasma and PIH. Taylor and Anderson treated 8 subjects of different skin types, including black patients, with refractory PIH and melasma and found either no improvement or worsening of hyperpigmentation.[44] In contrast, a recent study treated 15 Korean women with melasma and documented a decrease in pigmentation and mean (MASI) scores.[44,45] A drawback is that a deeply pigmented epidermis can impede light penetration to the dermis and unwanted epidermal injury may result in dyspigmentation. In general, the QS ruby laser is not recommended for the treatment of hyperpigmentation disorders in skin of color.

Q-Switched Alexandrite

The longer 755-nm wavelength of the QS alexandrite laser allows for deeper penetration into the skin. A study of 32 Chinese women demonstrated that combination low-energy QS alexandrite and QS Nd:YAG laser can be effective in treating melasma. Pigmentation decreased by ≥90% in 21 patients after an average of 10.2 treatments and by 60%-89% in 11 patients after an average of 11.4 treatments. Better results were seen in those with "light brown" melasma and whose duration of disease was <2 years. No hyperpigmentation or scarring was seen, although 1 patient experienced transient pigment loss.[46] There have also been studies with small sample sizes investigating the combination of pulsed CO_2 and QS alexandrite lasers for the treatment of melasma.[47,48] Combination treatment may have unpredictable results, and in some cases, a worsening of hyperpigmentation. Neither modality is safe enough to recommend for routine use in the treatment of melasma.

Q-Switched Nd:YAG

Cho et al[49] conducted a retrospective analysis of 25 Korean women with melasma treated with the QSNYL and found 18 (72%) had marked to near-total improvement. Another study enrolled 20 Korean melasma patients and treated them with 5 sessions of QSNYL during the course of a week and found an increase in lightness value and a significant decrease in melanin index.[50] Recurrence rates at 3-month follow-up are as high as 64%, and adjunctive therapy may be helpful in preventing recurrence.[51] The QSNYL with its longer wavelength is the safest type of laser to treat dark-skinned patients.

Intense Pulsed Light

IPL is a nonlaser light source that emits light, with a range from 515 nm (red/yellow) to 1200 nm (infrared). Zoccali et al[52] treated 38 patients with melasma with skin types III and IV with 3-5 IPL sessions over 40-45 days, and results were good to excellent in 29 patients (76%). Another study treated 89 Chinese women with melasma with 4 IPL treatments at 3 week intervals and found 69 (77.5%) women obtained 51%-100% improvement with a substantial decrease in mean MASI scores from 15.2 to 4.5.[53]

Fractional Photothermolysis

Fractional photothermolysis (FP) by erbium laser emits a wavelength from 1440 to 1550 nm that creates hundreds of microthermal treatment zones, which are full-thickness microscopic columns of coagulation in regularly spaced arrays separated by islands of untreated skin. This allows for rapid migration and proliferation to repair the damaged areas within 1 day, and postoperative erythema usually resolves in 3-4 days.

Rokhsar and Fitzpatrick[54] reported 6 of 10 subjects attaining 75%-100% clearing of their melasma and 1 subject developing PIH. Likewise, Naito found 50% improvement in 3 of 6 Chinese subjects with melasma after 3-4 treatments at 4-week intervals.[55] Lee et al[56] reported 25 Korean subjects with melasma treated monthly for 4 months with FP. Of these, 60% improved at 4-weeks follow-up, which decreased slightly to 52.2% at 24-weeks follow-up, whereas 13% experienced PIH. Similarly, Katz et al[57] published a trial of 8 women with skin types II-IV with melasma who underwent 2-7 treatments of FP at 3-8 week intervals. More than 50% improvement was witnessed in 5 subjects with sustained efficacy during a mean follow-up period of 13.5 months compared with 3 subjects whose lesions recurred after initial improvement. However, a split-face study found FP to be inferior to triple topical therapy (hydroquinone 5%, tretinoin 0.05%, and triamcinolone acetonide 0.1% cream) for the treatment of 29 patients with skin types II-V with melasma.[58] Recently, 14 patients with skin types II-IV with melasma received 3-4 treatments at 4-week intervals with a novel 1927 nm fractional thulium fiber laser. A 51% and 34% reduction in MASI scores was observed at the 1- and 6-month follow-up visits, respectively, without evidence of scarring or PIH.[59]

For PIH, success with FP remains largely confined to case reports. Katz et al[60] reported the case of a 50-year-old woman, skin type IV, who experienced near total clearance of a recalcitrant hyperpigmented patch on the neck after 3 treatments spaced apart 4-8 weeks. Likewise, a 42-year-old woman, skin-type II, attained 50%-75% improvement of her CO_2 laser-induced PIH on the face after 5 treatments every 1 to 2 weeks.[61] Finally, Cho et al[62] published the case of 27-year-old Korean woman, skin-type IV, with arcuate hyperpigmentation resulting from a 1450-nm diode laser, which responded well to FP.

Lasers will become more useful in treating disorders of hyperpigmentation in skin of color. The lasers available currently are the QS ruby, QS alexandrite, QSNYL, erbium, and thulium with variability in results. In addition, IPL is an available nonlaser modality. Selection of an optimal laser or light source depends on if the hyperpigmentation has an epidermal component, dermal component, or both. Lasers with shorter wavelengths, such as the QS ruby and QS alexandrite lasers, have a limited depth of penetration and com-

pete with endogenous melanin chromophores, which can result in unwanted dyspigmentation. Lasers generating longer wavelengths, such as the QSNYL, are less efficiently absorbed by endogenous melanin and simultaneously allow a greater margin of safety and satisfactory results in skin of color. IPL may provide a modest benefit as an adjunctive treatment. FP has significant potential in the treatment of hyperpigmentation, and more studies are required to evaluate its efficacy and safety. In the future, laser treatment of hyperpigmentation in skin of color may be based on the protection of normal melanocytes from laser energy, with some of the topical or oral agents described earlier.

Treatment of Hyperpigmentation Disorders With Chemical Peels

A range of chemical peels is effective in treating disorders of hyperpigmentation in skin of color and is reviewed.

Salicylic Acid

Typically, a concentration of 20%-30% salicylic acid is used to induce superficial peeling. There are mixed results with regards to the efficacy of salicylic acid (SA) peels in the treatment of dyschromias. In a large, randomized, double-blinded trial, Ejaz et al[63] found SA peels to be equally effective to Jessner solution in terms of treating Pakistani patients with epidermal melasma. However, Joshi et al[64] conducted a smaller, randomized, split-face trial with 10 subjects with skin types IV-VI and found no significant difference in the treatment of PIH between the sides peeled by SA and the untreated sides.

Trichloroacetic Acid

Medium-level concentrations of 35%-50% trichloroacetic acid (TCA) will penetrate between the superficial papillary and midreticular dermis.[65] There is an increased risk of PIH in dark-skinned patients using higher TCA concentrations for deeper peels. However, focal application of higher TCA concentrations has been found to be successful without significant complications in the treatment of 106 dark-skinned patients with seborrheic keratoses, solar lentigines, freckles, and melasma with 10%-65% focal TCA peels.[66] In another study, 20 Indian women with melasma were treated with TCA (10%-20%) peels and a 79% reduction was found in MASI scores after 12 weeks without major side effects.[67]

Jessner Solution

Lawrence et al found Jessner solution and 70% glycolic acid to work equally well in the treatment of melasma, with an overall 63% reduction in MASI seen.[68] Some authors prefer to use a modified Jessner solution by substituting citric acid for resorcinol to avoid contact allergy and subsequent PIH, especially in skin types V and VI. The addition of TCA 15% to a modified Jessner solution allows a more uniform penetration and has been shown to decrease MASI by 71.7%, which was superior to TCA 15% peeling alone.[69]

Tretinoin

Tretinoin peels have emerged as a new method of peeling capable of causing the same histologic changes after 2.5 weeks that would normally require 4-6 months with topical tretinoin.[70] Weekly peeling with 1% tretinoin solution was found to be equally effective as 70% glycolic acid at weeks 6 and 12 of treatment in 10 Indian subjects.[71] Likewise, an Iranian trial with 63 subjects found similar results, but with less discomfort, associated with 1% tretinoin peels compared with 70% glycolic acid after 4 peeling sessions biweekly.[72] Using a 10% concentration of tretinoin allows a reduction in skin contact time to 1 hour compared with the usual 4-8 hours required for the 1% concentration while still maintaining efficacy.[73]

Chemical peels should be used with caution in skin of color given, as excessive peeling and exfoliation can cause irritation, which can worsen PIH. Sun avoidance and sunscreen application are recommended after a chemical peel to avoid PIH. Although SA peels are not efficacious as monotherapy or adjunctive therapy in the treatment of hyperpigmentation, Jessner solution and tretinoin peels are efficacious.[68,71] TCA peels in varying concentrations improve hyperpigmentation; however, deeper peels with higher concentrations should be used judiciously due to the risk of PIH. The depth of a chemical peel is the most important parameter to consider when treating hyperpigmentation in skin of color.

Conclusions

Therapies that have been discussed in this article represent new horizons for the treatment of disorders of hyperpigmentation in skin of color. Often, multimodality treatment will offer the best chance of resolution. Future studies should include larger sample sizes, direct comparisons between agents, and further delineation of side effects and tolerability for many of the emerging modalities discussed so that the best evidence can be obtained for treatment of these psychologically devastating disorders of hyperpigmentation in skin of color.

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