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Skin Lightening Agents

Wen-Yuan Zhu
Department of Dermatology, The First Affiliated Hospital, Nanjing Medical University, Nanjing, P.R. China

Ru-Zhi Zhang
Department of Dermatology, The Affiliated Hospital, BangBu Medical College, BangBu, P.R. China

The ideal depigmentating compound should have a potent, rapid, and selective bleaching effect on hyperactivated melanocytes, carry no short- or long-term side effects, and lead to a permanent removal of undesired pigment. Depigmentation can be achieved by regulating (i) the transcription and activity of tyrosinase, tyrosinase related protein-1 (TRP-1), tyrosinase related protein-2 (TRP-2), and/or peroxidase, (ii) the uptake and distribution of melanosomes in recipient keratinocytes, and (iii) melanin and melanosome degradation and turnover of "pigmented keratinocytes" (1).

TYROSINASE INHIBITION

Tyrosinase is a copper enzyme, which catalyses both the hydroxylation of monophenols to o-diphenols and the oxidation of o-diquinones to o-quinones. Most whitening agents act specifically to reduce the function of this enzyme by means of the following mechanisms (2): (i) interference with its transcription and/or glycosylation, (ii) inhibition by different modalities, (iii) reduction of by-products, and (iv) post-transcriptional control.

Hydroquinone

Hydroquinone (HQ), which is a hydroxyphenolic chemical, has been the gold standard for treatment of hyperpigmentation for over 50 years. Its therapeutic efficacy alone or in association with other compounds (3) seems to exert mainly in melanocytes with active tyrosinase activity. HQ may interfere with pigmentation even through: (i) the covalent binding to histidine or interaction with coppers at the active site of tyrosinase, (ii) the inhibition of DNA and RNA synthesis, (iii) the alteration of melanosome formation and melanization extent, and (iv) selectively damaging melanosomes and melanocytes.

The effectiveness of HQ is related directly to the concentration of the preparation. Concentrations of HQ vary from 2% (over the counter) to as high as 10% that are prescribed extemporaneously for resistant cases. It was known that the higher concentrations of HQ were more effective, but the irritating and toxin for melanocytes sign were obvious. There was a reduction in the effectiveness of HQ preparation due to oxidation so that stabilizing agents like sodium bisulphate and ascorbic acid were used as antioxidants. The most suitable vehicle for the formulation is a hydroalcoholic solution (equal parts of propylene glycol and absolute ethanol) or an hydrophilic ointment, or a gel containing 10% alpha-hydroxy acids (AHAs), taking into consideration the desired 3% to 5% HQ concentration in ethanol and propylene glycol 1:1 (or in a cream base or an AHA 10% gel).

The skin lightening effect of HQ can be enhanced by adding various topical agents such as tretinoin and corticosteroids. The following combination has been proposed by Kligman and Willis (5): HQ 5%, tretinoin 0.1%, dexamethasone 0.1%, in ethanol and propylene glycol 1:1 or in hydrophilic ointment. In this formula, tretinoin stimulates the cell turnover promoting the rapid loss of pigment via epidermopoieses, and acts as a mild irritant facilitating the epidermal penetration of HQ and as an antioxidant preventing the oxidation of HQ. Corticosteroids can eliminate the irritation caused by HQ and/or tretinoin (6).

Depigmentation of HQ preparation begins within three weeks after twice-daily application and it is used for a maximum of five to seven weeks. The formulation without antioxidants should never be more than 30 days old. A slight modification of the Kligman and Willis formula is the following: HQ 4%, tretinoin 0.05%, fluocinolone acetonide 0.01% (or hydrocortisone 1%), in ethanol and propylene glycol 1:1 or in hydrophilic ointment. In this formulation the concentration of tretinoin is lowered to 0.05%, and the aim is to minimize the irritation caused by tretinoin and eliminates local steroid side effects (7). The improvement rate of melasma was ranging from 40% to 87.5% in two to four months.

The side effects of HQ include allergic contact dermatitis, irritant contact dermatitis (more probable with the higher concentrations), and post-inflammatory hyperpigmentation and nail discoloration. Irritation, stinging, and/or burning were observed transiently during the first day of application and disappeared with use of the medication after a few days.

Kojic Acid

Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyrane-4-one, KA) (8), a naturally occurring hydrophilic fungal derivative evolved from certain species of Acetobacter, *Asperigillus* and *Penicillium*, is used in the treatment of hyperpigmentation disorders (9). Its molecular formula is $C_6H_6O_{4,5}$, and its molecular weight is 142.1. It also eliminates free radicals, strengthens the activity of cells and keeps the food fresh.

The depigmetation action of kojic acid is attributed to the chelating ability (10), even if an interference with different steps of melanin synthesis (11) and inhibition of nuclear factor-kappa B (NF-kappa B) activation in keratinocytes, contrasting with the hyperpigmentation associated with inflammatory response (12). It is a kind of specialized inhibitor for melanin for preventing the tyrosinase activity through synthesizing with copper ion in the cells after it enters skin cells. KA and its derivative have better inhibitory effect on tyrosinase than any other skin whitening agents. At present it is assigned into various kinds of cosmetics for curing freckles, age spots, pigmentation, and acne. It has been used alone in concentration 2–4% and it has also been combined with HQ 2% in an AHA gel base (13).

KA dipalmitate is a modified kojic acid derivative, which not only overcomes the instability to light, heat, and metallic ion, but also keeps the inhibitory tyrosinase activity

and prevents the forming of melanin. As fat-soluble skin whitening agent, it is more easily absorbed by skin. Kojic acid has the potential for causing contact dermatitis and erythema (14). The heterozygous p53-deficient CBA mice were fed a diet containing 0%, 1.5%, and 3% KA for 26 weeks. KA induced diffuse hypertrophy and hyperplasia of the thyroid follicular epithelial cells and tumorigenic potential in the liver (15).

Azelaic Acid

Azelaic acid (AZA) is a naturally occurring 9-carbon dicarboxylic acid compound isolated from cultures of *Pityrosporum Ovale*. It inhibits tyrosinase activity in vitro ($K_i = 2.73 \times 10^{-3}$M) and may also interfere with DNA synthesis and mitochondria activity in hyperactive and abnormal melanocytes. AZA has been used to treat melasma and post-inflammatory hyperpigmentation and to arrest the progression of the lentigo maligna to melanoma. This specificity may be attributed to its selective effects on abnormal melanocytes (16). AZA produced ultra structural damage to normal melanocytes (17).

AZA cream has been reported to be of benefit in the treatment of melasma. The cream is applied twice daily and most patients report a mild but transient irritation and dryness of the skin at the beginning of the treatment. In the treatment of melasma, a 24-week study in South America found that a 20% concentration of AZA was equivalent to 2% HQ (18). In the Philippines, a study found that 20% AZA was better than 2% HQ. Three hundred and twenty nine patients with melasma were treated with 20% AZA and 4% HQ. Fifty six percent of the AZA group had good or excellent results while 73% HQ had a similar result (19).

Topical potent steroids and 20% AZA cream combines the beneficial effects of both besides perhaps increasing the compliance of the patients (20). AZA with tretinoin caused more skin lightening after three months than AZA alone, and a higher proportion of excellent responders at the end of treatment (16). The combination of AZA 20% cream and glycolic acid 15% or 20% lotion was as effective as HQ 4% cream in the treatment of hyperpigmentation in darker skinned patients, with only a slightly higher rate of mild local irritation (21).

Particular advantages of AZA therapy include its favorable safety and side effect profile. It is non-teratogenic, is not associated with systemic adverse events or photodynamic reactions, exhibits excellent local tolerability, and does not induce resistance in *Propionibacterium acnes* (22). Adverse effects from the AZA included irritant contact dermatitis that was usually mild and transient, but occasionally was pronounced.

Paper Mulberry Extract

Mulberry (*Morus alba* L.) leaves containing many nutritional components are the best food for silkworms. The extracts from mulberry leaves have a potent antihyperglycemic activity in diabetic mice. Many phenolic compounds have been identified from the root bark of mulberry tree. *Morus alba* L. also contains rutin, isoquercitrin, and astragalin. The root bark of *Morus alba* has been shown to have a skin whitening effect.

Lee et al. (23) investigated the in vitro effects of an 85% methanol extract of dried *Morus alba* leaves on melanin biosynthesis. These extracts inhibited the tyrosinase activity that converts dopa to dopachrome in the biosynthetic process of melanin. Mulberroside F (moracin M-6, 3′-di-O-beta-D-glucopyranoside), which was obtained after the bioactivity-guided fractionation of the extracts, showed inhibitory effects on tyrosinase activity and on the melanin formation of melan-a cells. But its activity was low and weaker than that of KA.

Aloesin

Aloesin, a natural hydroxymethylchromone derivative isolated from aloe vera, acts by two different mechanisms of action on tyrosinase activity, e.g., aloesin inhibits the formation of DOPA quinone by competitive inhibition at the DOPA oxidation site, reduction of copper ions at the hydroxylase site, and consequently tyrosine hydroxylation by non-competitive inhibition (24). In comparison with other depigmenting agents, aloesin shows no cytotoxicity in cell-based assays, no skin irritation in preliminary human studies and any genotoxicity or mutagenicity in the Ames assay. Cultured cells used in tyrosinase activity assays show no morphologic abnormalities when treated with aloesin, and human melanocytes appear normal with multiple dendrites (24).

Thus aloesin is a potent inhibitor of human tyrosinase. However, because of the hydrophilic nature of the compound and moderately high molecular weight, penetration of human skin was poor. Jones et al. (24) demonstrated aloesin dissolved in ethanol penetrates the skin slowly with approximately 1.59% of a finite dose penetrating the skin over a 32-hour period. At non-cytotoxic concentration aloesin probably acting as a competitive inhibitor on DOPA oxidation and as a non-competitive on tyrosine hydroxylase activity. Aloesin treatment showed pigmentation suppression in a dose-dependent manner; thus, aloesin might be used as an agent that inhibits melanin formation induced by UV radiation (25). In vivo, aloesin and arbutin co-treatment inhibits UV-induced melanogenesis in a synergistic manner.

The mixture of aloesin and arbutin showed a significant inhibition on tyrosinase activity of human melanocytes and reduced significantly melanin content, and had little influence on melanocytes viability (26).

Arbutin

Arbutin was first discovered in Arctostapylos uva-ursi (L.) Spreng and then in the leaves of Vaccinicum vitis-idaca L., Pyrus pyrifolia (Burm.f.) Kakai. and Saxifraga stolonifera (L.) Meerb. It is a naturally occurring HQ beta-D-gluconopyranoside, which causes depigmentation at non-cytotoxic concentrations. In both normal human melanocytes and melanoma, arbutin induces a decrease of tyrosinase activity without affecting messenger RNA (mRNA) expression, inhibits the 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase activity (pmel 17/*silver* protein) (27), and exerts an inhibitory effect on melanosome maturation. It was found to inhibit the oxidation of l-tyrosine catalyzed by mushroom tyrosinase (28). The kinetics and mechanism for inhibition of tyrosinase confirms the reversibility of arbutin as a competitive inhibitor of this enzyme (29). Arbutin was much less cytotoxic than HQ to cultured human melanocytes.

A clinical trial performed with Japanese women with melasma found a 3% arbutin-containing skin lotion, milky lotion and cream, applied twice daily for three months, to be effective in reducing melasma intensity and lesion size (good-to-excellent clinical response in 71.4% of patients) (30). Higher concentrations are more efficacious than lower concentrations, but they may also result in a paradoxical hyperpigmentation.

Licorice Extract

The licorice extract includes liquiritin, isoliquertin (a chalcone) that occurs as a glycoside and during drying is partly converted into liquiritin, liquiritigenin, isoliquiritigenin, and other compounds. Liquiritin causes depigmentation by two mechanism: (i) via melanin dispersibility by means of the pyran ring of the color dispersing flavonoidal nucleus of

liquiritin, and (ii) via amelanodermic and epidermal stain removing property. Acute and chronic toxicity studies have been carried out with no adverse effects. Glabrene and isoliquiritigenin (2′, 4′, 4-trihydroxychalcone) in the licorice extract can inhibit both mono- and diphenolase tyrosinase activities. The IC_{50} values for glabrene and isoliquiritigenin were 3.5 and 8.1 μM, respectively, when tyrosine was used as substrate. The effects of glabrene and isoliquiritigenin on tyrosinase activity were dose-dependent and correlated to their ability to inhibit melanin formation in melanocytes (31).

Liquiritin cream is a new bleaching agent. Amer et al. (32) described that topical liquiritin cream applied at 1 g/day for four weeks is therapeutically effective in melasma. Good to excellent results with complete disappearance of melasma were observed in 18 (90%) out of 20 patients. Yasuaki (33) described the formulation of a liquiritin cream containing 20% liquorice. The cream was applied at 1 g/day to patients with melasma for one to four months and showed good efficacy. Side effects were minimal with mild irritation, which disappeared with continuation of treatment.

Ellagic Acid (Copper Chelation)

A polyphenol widely distributed in plants, is capable of preventing pigmentation caused by sunburn (34). Ellagic acid inhibits tyrosinase non-competitively in a dose-dependent manner, through its capacity to chelate copper, even if other mechanisms, such as a scavenger effect have been suggested. Interestingly, in brownish guinea pigs (34), ellagic acid induced a reversible inhibition of melanin synthesis only in UV-activated melanocytes (34).

PRODUCT REDUCTION AND REACTIVE OXYGEN SPECIES

Compounds with redox properties can have depigmenting effects by interacting with o-quinones, thus avoiding the oxidative polymerization of melanin intermediates, or with copper at the active site. Therefore, that melanin cannot be formed by the action of tyrosinase until all ascorbic acid is oxidized.

Ascorbic Acid

Ascorbic acid (AsA) interferes with the different steps of melanization, by interacting with copper ions at the tyrosinase active site and reducing dopaquinone and DHICA oxidation. Melanin can be changed from jet black to light tan by the reduction of oxidized melanin (35).

AsA is an effective reducing agent, which, at high concentrations, can momentarily retard the melanin-biosynthesis pathway, but never eliminate it. On the contrary, the resultant accumulation of diphenol produces an indirect activation on this pathway when the reductant is completely depleted (36). However, AsA is highly instable, being quickly oxidized and decomposed in aqueous solution and, because of its prevalent hydrophilic nature, has a low degree of penetration into the skin. Vitamin C iontophoresis may be an effective treatment modality for melasma (37).

Sixteen women with idiopathic melasma were instructed to use, at night, 5% ascorbic acid cream on one side of the face and 4% HQ cream on the other side, for 16 weeks. The improvement was observed on the HQ side with 93% good and excellent results, compared with 62.5% on the ascorbic acid side. Side effects were present in 68.7% with HQ versus 6.2% with ascorbic acid (38).

The numbers of DOPA-positive melanocytes of guinea pigs treated with VC, VE, and cystine were significantly decreased compared with those in VC group. In B16 melanoma cells, simultaneous treatment of VC, VE, and N-acetyl-cysteine was the most effective to decrease the melanin contents and to inhibit tyrosinase activity (39).

A multi-clinical, double-blind study on therapeutic effect of combination preparation of vitamins E and C was undertaken in comparison with single preparation of vitamin E and vitamin C in the treatment of chloasma or pigmented contact dermatitis (PCD). Objective data revealed significantly better results with combination treatment in chloasma than vitamin C alone and, in PCD, than vitamin E or C alone. The total serum lipoperoxide level and its ratio to total serum lipids tended to decline in the combination group and decreased significantly in vitamin E group. The sebum lipoperoxide level decreased significantly only in the combination group (40).

Magnesium-L-Ascorbyl-2-Phosphate (VC-PMG)

AsA is quickly oxidized and decomposed in aqueous solution and thus is not generally useful as a depigmenting agent. To resolve that problem, Magnesium-L-ascorbyl-2-phosphate (VC-PMG) was synthesized. VC-PMG is stable in water, especially in neutral or alkaline solution containing boric acid or its salt. VC-PMG is hydrolyzed by phosphatases of liver or skin to AsA and thus exhibits vitamin C-reducing activity (41). VC-PMG significantly suppressed melanin formation on purified tyrosinase or cultured cells and inhibited melanin formation without cell growth suppression on cultured human melanoma cells. Inhibition of melanogenesis was stronger when the activity of melanogenic enzymes was relatively high.

VC-PMG is absorbed percutaneously, stays in the skin, and inhibits tyrosinase activity of melanocytes. The addition of 1% to 3% 1,1-methyleneglycol-bis increases the absorption of VC-PMG. In situ experiments demonstrated that 10% VC-PMG cream was absorbed into the epidermis and that 1.6% remained 48 hours after application. When the 10% VC-PMGcream was topically applied to the patients, the lightening effect was significant in 19 of 34 patients with chloasma or senile freckles and in three of 25 patients with normal skin (42).

Thioctic Acid (Alpha-Lipoic Acid)

A disulfide derivative of octanoic acid, it exhibits several biologic effects, which include the quenching of ROS, metal chelation, interaction, and the regeneration of other antioxidants, redox regulation of protein thiol groups, and effects on gene expression and apoptosis (43). Thioctic acid has been reported to prevent UV-induced photo-oxidative damage, mainly through the down-modulation of NF-kappa B activation and to inhibit tyrosinase activity probably by chelating the copper ions (44).

Dihydrolipoic acid, lipoid acid, and resveratrol reduced microphthalmia-associated transcription factor and tyrosinase promoter activities. Dark skinned Yucatan swine treated with these agents showed visible skin lightening, which was confirmed histological, whereas ultraviolet B-induced tanning of light skinned swine was inhibited using these agents (45).

Alpha-Tocopherol (α-Toc)

Alpha-Tocopherol (alpha-Toc) and its derivatives inhibit tyrosinase in vitro and melanogenesis in epidermal melanocytes. The antioxidant properties of alpha-Toc,

which interferes with lipid peroxidation of melanocyte membranes and increases the intracellular glutathione content, could explain its depigmenting effect. Alpha-Toc has a more effective and long-lasting antioxidant response. Topical application of alpha-Toc and AsA, in vivo, decreases the tanning response inhibiting the UV-induced melanogenesis and proliferation of melanocytes. An alternative compound is alpha-Tocopherol ferulate (alpha-Toc-F), a derivative of alpha-Toc linked by an ester bond to ferulic acid, an antioxidant, which provides stabilization to alpha-Toc, similar to AsA. Alpha-Toc inhibited melanogenesis in cultured normal human melanocytes, although it did not influence melanin synthesis in enzyme solution prepared as cell homogenates. In addition, alpha-Toc stimulated intracellular glutathione (GSH) synthesis (46).

Thirty μ/ml of alpha-TF dissolved in 150 μg/ml of lecithin inhibited melanization significantly without inhibiting cell growth. No significant effect on DOPA chrome tautomerase (DT) activity was observed (47).

INHIBITION OF MELANOSOME TRANSFER

The activation of protease-activated receptor-2 (PAR-2), a seven *trans*-membrane G-protein coupled receptor, which is expressed in keratinocytes and not in melanocytes, was found to activate keratinocyte phagocytosis, enhancing the melanosome transfer (48). Inhibition of PAR-2 cleavage by serine protease inhibitor, such as RWJ-50353, completely avoids the UVB-induced pigmentation of epidermal analogs (49,50).

Niacinamide

Niacinamide or nicotinamide is a biologically active form of niacin (vitamin B_3) involved in over 200 enzyme reactions in the form of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate.

Hakozaki et al. (51) suggested that niacinamide has no effect on tyrosinase activity, melanin synthesis, or cell number in melanocyte monoculture system, and no effect on the proliferation of keratinocytes. The research results showed that niacinamide down-regulated the amount of melanosomes transferred from melanocytes to surrounding keratinocytes in a coculture system by approximately 35–68%.

Daily use of a niacinamide moisturizer was effective in reducing hyperpigmentation and in increasing lightness of basal skin color compared with control moisturizer. The efficacy of topical niacinamide for decreasing facial hyperpigmentation and lightening skin color in vehicle-controlled protocols was evaluated (51).

RWJ-50353

RWJ-50353, a serine protease inhibitor that reduced melanosome uptake in culture, is shown to have a dose-dependent depigmenting activity in vivo with no irritation or other side effects. Treatment with increasing concentrations of RWJ-50353 did not affect tyrosinase mRNA levels. Interestingly, this treatment led to decreased levels of TRP-1 and increased levels of TRP-2 mRNAs (49). The downregulation of TRP-1 by RWJ-50353 should lead to reduced tyrosinase activity and reduced pigment production.

RWJ-50353 inhibits melanosome transfer from melanocytes to keratinocytes by its inhibitory effect on the keratinocyte PAR-2 signaling pathway. RWJ-50353-treated keratinocytes are unable to actively take or receive melanosomes from the presenting dendrites. Electron microscopy studies illustrated an accumulation of immature

melanosomes inside melanocytes and abnormal dendrite dynamics in RWJ-50353-treated epidermal equivalents.

In vivo RWJ-50353 (up to 10mM, twice-daily treatment to swine skin) could not completely inhibit melanogenesis or pigment transfer, and the transferred melanosomes are of poor quality (50). Treatment of dark skinned Yucatan swine for eight weeks with RWJ-50353 induced visible skin lightening. Histological analysis of treated sites at eight weeks shown only minimally stained melanin granules dispersed in the basal layer of epidermis (50).

Soybean Trypsin Inhibitor

Soybean trypsin inhibitor (STI) inhibited PAR-2 cleavage, and completely inhibited the UVB-induced pigmentation of the epidermal equivalents containing melanocytes (50). Treatment with STI resulted in significant depigmentation, and reduced pigment deposition within the swine epidermis and prevented UVB-induced pigmentation in vivo. STI reduced keratinocyte ingestion of microspheres or *E.coli* particles (48). STI-treated cells showed reduced number and shorter length podia.

STI-treated melanocytes within epidermal increased the number of less mature melanosome and dendrites with mature melanosomes. UV-induced tanning of Yucatan swine was prevented with topical treatments of STI-containing compositions (52).

SKIN TURNOVER ACCELERATION

The capacity of several compounds to disperse melanin pigment and/or accelerate epidermal turnover can result in skin lightening. Chemical substances used as exfoliates, such AHAs, free fatty acids, and retinoic acid, stimulate cell renewal facilitating the removal of melanized keratinocyte, leading to melanin granules loss (53). Topical application has been shown to reduce the visibility of age spots without reducing their size or number (54), and can be useful in the treatment of melasma (55).

Unsaturated fatty acid, such as oleic acid, linoleicacid, or alpha-linolenic acid, suppress pigmentation, in vitro, whereas saturated fatty acids, such as palmitic acid, increase the rate of melanogenesis (56).

Alpha Hydroxy Acids

The benefits of AHAs have long been recognized. Sour milk [contains lactic acid (LA)] and sugarcane juice [contains glycolic acid (GA)] were applied to the face. In low concentrations, AHAs decreased corneocyte cohesion, leading to sloughing of dead cells and stimulation of new cell growth in the basal layer. In higher concentrations, they cause epidermilysis. AHAs have been reported to be effective in treating pigmentary lesions such as melasma, solar lentigines, and post-inflammatory hyperpigmentation. The mechanism of this effect might be due to epidermal remodeling and accelerated desquamation, which would result in quick pigment dispersion. GA and LA might work on pigmentary lesions not only by accelerating the turnover of the epidermis but also by directly inhibiting melanin formation by inhibiting tyrosinase in melanocytes (57). GA or LA (at doses of 300 or 500 μg/ml) inhibited melanin formation in similar dose-dependent manner, without affecting cell growth. The bioavailability of AHAs increases as the pH decreases (desirable pH 2.8–4.8), and they are the only peels that are time-dependent and can be neutralized easily.

A cream containing 4% HQ, 10% buffered GA, vitamins C and E, and sunscreen is safe and effective in the treatment of melasma (58). The addition of kojic acid to a gel containing 10% GA and 2% HQ further improves melasma (59). Javaheri et al. (55) concluded that a prepeel program of daily application of topical sunscreen (SPF-15) and 10% GA lotion at night for two weeks, followed by 50% GA facial peel with a duration of two, four and five minutes once every month for three consecutive months proved to be an effective treatment modality for melasma in Indian patients. The beneficial results achieved can be maintained with topical application of 10% GA and 2% HQ. There are hardly any side effects.

Linoleic Acid

Linoleic acid in vivo showed the greatest lightening effect in UVB-induced pigmentation, without toxic effects on melanocytes (53). Several protease inhibitors caused the accumulation of an approximately 60 kDa tyrosinase doublet promoted the translation of the enzyme to melanosomes (60). The evidence suggests that tyrosinase in selectively targeted by fatty acids, which seem to act on the degradation of the enzyme during the physiologic proteasome-dependent mechanism (61). Linoleic acid accelerates the process whereas palmitic acid works in an antagonistic manner mimicking protease inhibitors (61).

In vitro experiments using cultured murine melanoma cells showed that melanin production was inhibited most effectively by alpha-linolenin acid, followed by linoleic acid and then by oleic acid. Furthermore, the turnover of the stratum corneum, which plays an important role in the removal of melanin pigment from the epidermis, was accelerated by linoleic acid and by alpha-linolenic acid (62). Topical application of linoleic acid is considered to be effective in the treatment of melasma patients (63).

TRADITIONAL CHINESE MEDICINE

Traditional Chinese herbs are a very popular mode for the treatment of hyperpigmentation disorders. Two hundred nineteen kinds of herbs have been screened; among them 19 kinds have been shown to inhibit tyrosinase in vitro (64). The inhibitory effects of tyrosinase activity of *Atractylodes macrocephala, Bombyx mori, Ligusticum sinense, Bletilla striata, Typhonium giganteum, Astragalus complanatus, Serissa erissoides*, and *Diospyros kaki* were either superior or similar to that of arbutin (64).

Cinnamic Acid

Cinnamic acid, a naturally occurring aromatic fatty acid of low toxicity, has a long history of human exposure. The cinnamic acid induces cytostasis and a reversal of malignant properties of human tumor cells in vitro. The cinnamic acid was found to induce cell differentiation as evidenced by morphological changes and increased melanin production in melanoma cells (65). Cinnamic acid does not influence the fungal growth but decreases the yield of the pigment from the mycelium (66).

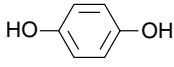
Sophorcarpidine

Tyrosinase activity can be greatly inhibited by cinnamic acid, aloin, and sophorcarpidine, of which sophorcarpidine functions as an uncompetitive inhibitor, compared to aloin and cinnamic acid, which are mixed-type inhibitors (67). Tan et al. (67) demonstrated that

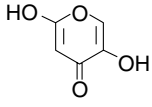
sophorcarpidine, aloin, and cinnamic acid can not only bind to the enzyme, but also to the enzyme-substrate complex as well, leading to the inactivation of tyrosinase.

Chemical structures of some depigmenting agents. Most of the compounds are modulators of melanogenic enzyme activity, their structures show chemical analogy with L-tyrosinase the natural substrate of tyrosinase.

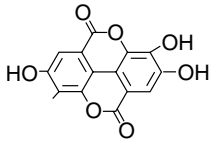
1. Structure of hydroquinone



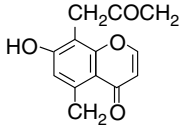
2. Structure of kojic acid



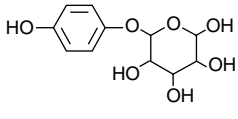
3. Structure of ellagic acid



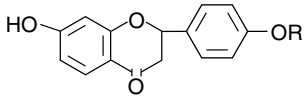
4. Structure of aloesin



5. Structure of arbutin



6. Structures of liquiritin and liquirigenin



Liquiritin, R = Glucosyl liquirigenin, R = H.

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14

Medical and Surgical Approaches to Skin Lightening

Marta I. Rendon
Dermatology and Aesthetic Center and University of Miami, Miami, and Florida Atlantic University, Boca Raton, Florida, U.S.A.

Jorge I. Gaviria
Medical Hair Research Group, Inc. and Clinical Research, Skin Care Research, Inc., Boca Raton, Florida, U.S.A.

INTRODUCTION

When approaching a patient with a pigmentary disorder, four issues must be taken into consideration: the patient's skin type and ethnic background, type of disorder, history of reaction to prior surgical treatments, and post-inflammatory hyperpigmentation (PIH). This information is necessary to determine the most appropriate treatment option. Hyperpigmentation is caused by a wide variety of conditions, diseases, and entities, most of which are acquired. Pigmentary disorders have a tremendous impact on patients' self-esteem and social interactions; therefore, improving patients' quality of life is essential.

Treatments for these disorders can be difficult and lengthy, often resulting in a high degree of patient dissatisfaction and causing some patients to seek care from another dermatologist. Therefore, educating patients to have realistic expectations is an important aspect of the therapeutic process. This chapter will discuss the factors essential to choosing the optimal therapeutic approach, and includes a discussion of first-line therapies, when botanicals should be incorporated, and at what point surgical or other procedures should be used.

The treatment of pigmentary disorders is one of the greatest challenges in dermatology (Table 1). The therapeutic armamentarium has been reduced due to the lack of efficacy of most depigmenting agents available on the market. Relapses, as well as lack of permanent remissions, are the norm rather than the exception.

Hyperpigmentation is caused by a wide variety of factors (Tables 1 and 2). The mechanisms inducing hyperpigmentation have not been completely elucidated. Pigmentation is a complex metabolic process that includes tyrosinase activity, melanosome formation, and a cascade of intermediate metabolites that result in the formation of melanin. A rational therapeutic approach should be medications or

Table 1 Causes of Hyperpigmentation

Acanthosis nigricans
Addison's disease
Argyria
Becker's nevus
Café au lait macules
Drug-induced hyperpigmentation (Table 2)
Dyschromatosis symetrica hereditaria
Dyschromia of photoaging
Ephelides
Erythema dyschromicum persistans
Erythromelanosis follicularis
Exogenous ochronosis
Familial periorbital hyperpigmention
Hemochromatosis
Hyperthyroidism
Lentigines
Linea fusca
Liver disease
McCun-Albright syndrome
Melasma
Nevi
Nevus de ota
Photoallergic reaction
Pituitary tumors
Poikiloderma of civatte
Post-inflammatory hyperpigmentation
Polycistic ovarian syndrome
Pregnancy
Scleroderma
Riehl's melanosis
Solar lentigines
Sun exposure
Tinea versicolor
Causes of acquired hyperpigmentation
Skin diseases and conditions
Erythromelanosis follicularis
Linea fusca
Melasma
Poikiloderma of civatte
Postinflammatory hyperpigmentation
Riehl's melanosis
Exogenous causes of acquired hyperpigmentation
Cosmetics
Drugs (Table 2)
Photosensitizing agents (e.g., berloque dermatitis due to bergamot oil, furocoumarins)
Ultraviolet exposure (e.g., melasma, solar lentigines, ephelides)
Ultraviolet tanning beds

compounds acting at different levels of the melanogenesis cascade to produce better aesthetic and clinical results.

Treatment of hyperpigmentation induced by medications should be individualized. In some cases, discontinuation of the drug is impossible, and treatment must be delayed

Table 2 Drugs Known to Induce Hyperpigmentation

Amiodarone
Amitriptyline
Arsenic
Bismuth
Bleomycin
Busulfan
Clofazimine
Cyclophosphamide
Daunorubicin
Dibromomannitol
Doxorubicin
Gold
Mercury
Minocycline
Nitrogen mustard
Phenothiazines
Phenytoin
Silver
Sulfonamides
Tetracyclines
Zodovudine

until that medication is no longer in use. In other cases, progressive discontinuation of the medication is the answer. Use of an alternative medication can solve the pigmentation phenomenon in other patients (1).

No standard therapeutic guidelines exist for treating the most common hyperpigmentation disorders, including lentigines, melasma, pigmentation of aging, and PIH. Due to variations in therapeutic regimes, the different population groups studied, and the limited number of comprehensive studies performed to date, comparison of results is very difficult. This chapter is an overview of topical depigmenting agents and a discussion of physical and combination therapies currently available to treat hyperpigmentation (2).

TOPICAL DEPIGMENTING AGENTS

See Tables 3, 4, and 5.

PHENOLIC DEPIGMENTING AGENTS

Hydroquinone

Hydroquinone, a phenolic compound, is considered the gold standard depigmenting agent. Multiple studies have shown its efficacy in the treatment of many different types of hyperpigmented lesions (3).

Monomethyl of Hydroquinone

Monomethyl of hydroquinone, also known as 4-hydroxyanisole, mequinol, 4-methoxyphenol, hydroquinone monomethyl ether, and p-hydroxyanisole, is a substance widely used in France

Table 3 Cosmeceutical Skin Lightening Agents

Aloesin
Alpha-lipoic acid
Arbutin and bearberry
Ascorbic acid
Azelaic acid
Emblica
Glycolic acid
Helix aspersa müller
Hydroquinone
Idebenone
Kojic acid
Licorice extract—glabridin
Linoleic acid
Liquiritin
Melatonin
Niacinamide-niacin
Oleic acid
Paper mulberry
Retinoids
Soy extract
Tyrostat
Unsaturated fatty acids, oleic acid, linoleic acid, and alpha-linolenic acid
Vitamin C

for melasma and PIH, and throughout the European Union as an alternative to hydroquinone. It was recently approved in the United States for the treatment of lentigines. Reported side effects include contact dermatitis, hypomelanosis at distant sites, leukoderma, and PIH. In a recent study of mequinol in the treatment of solar lentigines, two women diagnosed with solare lentigines were successfully treated with a combined regimen of mequinol 2% and tretinoin 0.01% (4).

Table 4 Prescription Skin Lightening Agents

Hydroquinone
Mequinol
Retinoid monotherapy, tretinoin (all-trans-retinoic acid), tazarotene
Azelic acid
Combination products
Hydroquinone, retinoic acid and steroids
Hydroquinone, retinol
Hydroquinone, retinol and vitamins
Other depigmenting agents
4-N-butylresorcinol
4-Isopropylcatechol
Kojic acid
Monomethyl of hydroquinone
N-acetyl-4-S-cystalminylphenol
Polipodium leucotomos

Table 5 Therapeutic Approaches to Hyperpigmentation

Mild	Moderate	Severe	Sunscreen	Sunscreens	Sunscreens
	Azelaic acid Glycolic acid	Hydroquinone 3%–4% Hydroquinone 4%	Hydroquinone 3%–4% Tretinoin 0.05% and Fluocinolone acetonide 0.01%		
Hydroquinone 4%, Tretinoin 0.05% and Fluocinolone acetonide 0.01%	Hydroquinone 2%–4%	Kojic acid Hydroquinone/Retinol Kojic acid	Hydroquinone/Retinol	Hydroquinone 4%	Tretinoin 0.05% and Fluocinolone acetonide 0.01%
Retinol / Tretinoin	Retinol / Tretinoin Chemical Peels	Hydroquinone+G.A. Hydroquinone + Retinol	Retinol / Tretinoin Microdermabrasion	Kojic acid	
Maintenance: Tretinoin Azelaic acid Kojic acid Cosmeceuticals					

4-Isopropylcatechol

4-isopropylcatechol has been known as a potent depigmenting agent for more than 35 years. Like other phenolic compounds, it is a tyrosinase inhibitor. In a study done in the early 1970s, most of the melasma patients treated showed skin irritation, and atopic dermatitis. Yet two-thirds also showed significant improvement (5). Due to its specific mechanism of action targeting melanocytes, it has promise for use in melanoma and melasma patients (6–8).

N-Acetyl-4-S-Cystalminylphenol (NA-CAP)

N-acetyl-4-S-cystalminylphenol (NA-CAP) is one of the four known synthesized phenolic thioether amines that are tyrosine-amine derivative analogues. Their toxicity is tyrosinase dependent and targets only melanocytes. This makes NA-CAP, a promising anti-melanoma and anti-melasma medication (9). In vitro and in vivo studies of NA-CAP have demonstrated its selective melanocytotoxic and antimelanoma effects (10,11), particularly in the selective disintegration of melanocytes in black hair and skin. NA-CAP is more stable than catechols, and its toxicity appears after oxidation by tyrosinase. A small study showed its efficacy in melasma patients (12). Due to the fact that it is less irritating than hydroquinone, this phenolic thioether known for 20 years is a promising stable molecule for use in melasma patients.

4-N-Butylresorcinol

4-N-butylresorcinol has been approved in Japan, where it is used to treat melasma. This compound decreases PIH following laser therapy in melasma patients.

Aloesin

Aloesin a low-molecular-weight ingredient of latex exudates and glycoproteins from aloe vera gel. Aloesin is a hydroxychromone that inhibits tyrosinase at non-toxic concentrations. In vivo, aloesin inhibits UV-induced melanogenesis (13,14).

NON-PHENOLIC AGENTS

Azelaic Acid

Azelaic acid is a 9-carbon dicarboxylic acid used in melasma and PIH. Azelaic acid is often better tolerated in individuals sensitive to hydroquinone. Although its lightening effects are mild, several large studies done with a diverse ethnic background population have compared its efficacy to that of hydroquinone. This has led to the conclusion that although skin irritation is greater, the efficacy of azelaic acid is similar to that of hydroquinone (15–18).

Kojic Acid

Kojic acid is a fungal metabolic product used for the treatment of hyperpigmentation. Kojic acid has been used as an agent to treat melasma (19). When combined with hydroquinone, kojic acid improves the melasma outcome treatment (20). Studies comparing the product to hydroquinone shows kojic acid has the same efficacy (21).

Ascorbic Acid

Ascorbic acid. The stable ester of ascorbic acid (ascorbyl) is used in treating hyperpigmentation. It acts on the melanogenesis cascade, interacting with copper ions to reduce dopaquinone and block dihydrochinindol-2-carboxyl acid oxidation (22). When objective measures were used in a double-blind, randomized trial study to determine efficacy, ascorbic acid (Mg L-ascorbyl-2 phosphate) in a 10% cream base had an efficacy similar to that of hydroquinone in melasma patients (23). Subjective measurements favored hydroquinone. However, these data are limited, and larger studies should be done to verify its efficacy.

Retinoid

Retinoid monotherapy is conducted with tretinoin (all-trans-retinoic acid), which is formed from the oxidation of the aldehyde group of retinene to a carboxyl group. Tretinoin reduces epidermal pigment in a variety of pigmentary disorders (lentigines, melasma, pigmentation of aging, and PIH) in dark skinned people (24). Results are encouraging, but improvement can take from several months to one year (25).

Tazarotene

Tazarotene, an acetylenic topical retinoid, produces good results in pigmented aging spots. Moderate to marked depigmenting effect occurs when used as a gel in a concentration of 0.1%.

TOPICAL COSMECEUTICALS

Topical skin lightening cosmeceuticals are becoming more popular. They have been used alone and in combination therapy. In medical practice they are sometimes used as maintenance agents, and very seldom used in patients who are unable to tolerate various prescription medications or in place of other properties such as antioxidants, anti-aging products, or moisturizers.

Commonly used depigmenting agents include arbutin, ascorbic acid, bearberry extract, idebenone, indomethacin, licorice extract, melawhite, mercury, and mulberry plant extract (Table 3). No controlled studies investigating the efficacy and safety of these compounds have been conducted, and although insufficient data exist to conclude their efficacy, successful results have been published (26).

Thioactic Acid

Thioactic acid (alpha-lipoic acid) is a disulfide derivative of octanoic acid that inhibits tyrosinase activity and prevents UV-induced photodamage. Clinical data proving its efficacy are minimal (27).

Unsaturated Fatty Acids

Unsaturated fatty acids [oleic acid (C18:1), linoleic acid (C18:2), and alpha-linolenic acid (C18:3)], suppress pigmentation in vitro. A clinical study done with Korean women using topical linoleic acid showed significant improvement in melasma (28).

Idebenone

Idebenone, a potent antioxidant, is a benzoquinone that has shown depigmenting properties in pilot studies of patients with melasma and facial hyperpigmentation. Idebenone has been recently introduced to the U.S. market as Prevage.

Licorice Extracts

Licorice extracts (Glycyrrhiza Glabra and Glycyrrhiza Uralensis), marketed as liquiritin, contains flavanoids and a glycoside called glycyrrhizin, and have shown utility in treating melasma (29).

BOTANICALS

In the early 20th century, cosmetics and skin care treatments were made at home from fruits, herbs, and vegetables. A century later, manufacturers and consumers are returning to the notion that natural is healthier, and the holistic approach to skin care is in demand. A 47.3% increase in the demand for alternative remedies occurred between 1990 and 1997, and an estimated 60% of doctors recommend alternative therapies; 47% use alternative therapies themselves (30).

The search for alternatives to hydroquinone led to the discovery of a wide variety of natural depigmenting agents that are now available commercially and are found in cosmetics and in various skin lightening agents sold over the counter.

In addition to their lightening effects, these products can have antiseptic, antioxidant, and moisturizing properties. In many cases, synthetic ingredients are added to enhance results. However, there is a rising tide of patients demanding that all components of skin care products and cosmetics be natural, including preservatives. The challenge is to find naturally derived preservatives that interact with advanced formulations for today's skin care demands. Manufacturers are using all-natural preservatives, such as essential oils, herbs, and fruit extracts that when processed can be 75 to 100 times more potent that their original source.

The research and development departments of cosmeceutical skin companies continually search for new avenues in the treatment of skin pigmentation, new ingredients, and alternate delivery systems.

The use of botanicals should be considered in patients with hypersensitivity to multiple prescription products, patients with contraindications to the use of laser or pulse light therapies, and patients seeking alternative therapies without invasive procedures.

PHYSICAL THERAPIES

This section will focus on physical therapies and lasers, concentrating on the most common hyperpigmenting disorders seen in our daily dermatology practice: lentigines, melasma, pigmentation of aging, and PIH. We will also discuss the use of combination therapies in managing these disorders.

Most authors believe that physical therapies have a place in the treatment of pigmentary disorders. This is also our personal experience. Medium and deep chemical peels with trichloroacetic acid, dermabrasion, and laser therapy may be used in the treatment of hyperpigmentation. However, their success and clinical efficacy are limited.

Medium-depth peels and dermabrasion are rarely used when treating types IV-VI skin phototypes, as these approaches often result in hypopigmentation or hyperpigmentation in this population (31).

CHEMICAL PEELS

Chemical peels with glycolic acid, trichloroacetic acid, Jessner's solution, kojic acid, salicylic acid, and tretinoin are used in the treatment of melasma. Peels are usually done as adjunctive therapy or when faster results are desired. Glycolic acid peels in concentrations ranging from 10% to 70% can produce excellent results in dark skinned patients, as well as in Asians and Latinos. In one study involving 25 non-pregnant women with melasma who were treated with 50% glycolic acid once a month for three consecutive months, a 91% improvement was seen (32).

Serial glycolic acid peels have been shown to provide additional benefit when added to triple-combination therapy (5% hydroquinone, 0.05% tretinoin, and 1% hydrocortisone acetate) in epidermal melasma. In a study done in 40 dark skinned Indian patients, 20 were given triple combination therapy plus serial glycolic acid peels and 20 received triple therapy alone. Both groups showed statistically significant improvement from baseline. However, there was a trend toward more rapid and greater improvement in the group receiving serial peels (33,34). Further success has been achieved through the combination of glycolic acid peels and hydroquinone with kojic acid (20).

In dark skinned patients, 1% tretinoin peels have shown similar efficacy and tolerance to 70% glycolic acid peels. In a study of Asian women, clinical, and histological improvement was achieved with twice-weekly topical 1% tretinoin peels for two-and-a-half weeks. Minimal skin reactions were noted (35).

The combination of glycolic acid peels with hydroquinone has proven no more effective than hydroquinone alone. However, the combination subjectively improves melasma. In one study, 10 Asian women were treated with a 10% glycolic acid and 2% hydroquinone combination product applied to the entire face twice daily. The patients also received a 20–70% glycolic acid peel every three weeks to one side of the face (eight peels total). All participants were evaluated by an independent dermatologist. Munsell color chart and photographs showed improvement in pigmentation and fine wrinkling on both sides of face. The side receiving glycolic acid peel showed slightly better improvement, but it did not reach statistical significance (25).

Another study of combination therapy involving hydroquinone and glycolic acid peels produced no difference in 21 Latin women with epidermal and mixed melasma. In this split-faced study lasting eight weeks, patients applied 4% hydroquinone to the entire face twice daily and 20%–30% glycolic acid peels hemifacially every two weeks (four peels total). Objective evaluation showed that both treatments significantly reduced skin pigmentation, although no significant difference between the combination therapy and hydroquinone alone were seen (37).

Superficial peels have been shown to hasten the effect of topical treatments. Sixteen women with Fitzpatrick skin types II-VI received pre-treatment peels with 0.05% tretinoin for one to two weeks. They were then given three peels one month apart in which half the face was treated with 70% glycolic acid and half with Jessner's solution. Post-treatment was done with 4% hydroquinone and 0.05% tretinoin. Objective evaluation showed average lightening on both sides of the face (38). Similar improvement was seen in a similar study where topical tretinoin alone was used for 10 months (24).

Topical therapies can also enhance the results of resurfacing techniques. Hevia showed that 0.1% tretinoin accelerates healing after 35% trichloroacetic acid peels in a split-face, placebo-controlled study of 16 male patients. In this cohort, 75% of tretinoin-pretreated hemifaces were completely healed at day 7, as compared with 31% of the placebo-treated hemifaces (39).

Alpha-hydroxy acid peels have been shown to increase efficacy when combined with topical treatments containing bleaching agents on patients with melasma. They have also shown efficacy in patients with pigmentation due to photodamage. Alpha-hydroxy acid peels have proven safe and effective on all skin phototypes (40).

MICRODERMABRASION

Aluminum oxide crystal microdermabrasion was developed in 1995 (41). This process produces superficial epidermal abrasion, and has been used primarily for facial scarring and photodamage. No clinical studies have been done in melasma or any other hyperpigmentation disorder. Although data are lacking in this regard, the effect of microdermabrasion on accelerating the epidermal barrier function makes it a valuable adjuvant therapy (42).

Microdermabrasion is a "feel-good" procedure that can be used to complement topical regimens. We usually alternate the procedure with a series of glycolic acid peels, since their mechanisms of action are different.

DERMABRASION

Dermabrasion is rarely used in pigmentary disorders. One Asian study involving 410 patients with recalcitrant melasma treated with dermabrasion reported 97% clearing. Erythema and PIH was seen following dermabrasion, and partial recurrence of pigmentation can occur following initial clearance of melasma (43).

No clinical trials of combination therapy with dermabrasion and other physical therapies or topical depigmenting agents for melasma or PIH have been performed.

LASERS

CO2 and Erbium

CO2 and erbium resurfacing lasers are commonly used in the treatment of photoaging and acne scarring. They are seldom used for treating pigmentary disorders. Although no general consensus exists on the value of CO2 laser treatment for hyperpigmentation disorders, some authors have reported its use in recalcitrant melasma.

The Combination of CO2 and Q-Switched Alexandrite Lasers

The combination of CO2 and Q-switched alexandrite lasers has produced better results than the Q-switched alexandrite laser alone. In a study done in Thailand, six women were treated on one side of the face with combined ultrapulse CO2 laser and Q-switched alexandrite laser, and on the other side with the Q-switched alexandrite laser alone. The combination of lasers produced a superior and significant reduction in pigmentation, as compared with the single laser (45,46). However, an increase in undesirable side effects,

including PIH, was also seen. Some authors believe that treatment with hydroquinone and retinoic acid prevents PIH after treatment with CO2 laser (47,48).

Pigment-Specific Lasers (Pulse-Dye Pigment, Q-Switched Alexandrite CO2, Q-Switched Ruby, and Q-Switched Nd-Yag)

Pigment-specific lasers (pulse-dye pigment, Q-switched alexandrite CO2, Q-switched ruby, and Q-switched Nd-Yag) are generally recommended only for recalcitrant melasma following the failure of all other therapies. On the other hand, these lasers are the treatment of choice for isolated pigmented lesions, such as lentigos (49).

Q-Switched Ruby Lasers

Q-switched ruby lasers have been successfully used treating specific pigmented lesions such as benign melanosis, labial melanotic macules, mucocutaneous melanosis associated with Peutz-Jeghers syndrome, and phacomatosis pigmentovascularis. Efforts to treat melasma and solar lentigines with the Q-switched ruby laser have not been successful (50–54).

Q-Switched Alexandrite Lasers

Q-switched alexandrite lasers combined with chemical peels have been used to successfully treat acquired bilateral nevus of Ota, freckles, PIH, and recalcitrant dermal melasma in Korean patients with Fitzpatrick skin types IV–VI. The combination is effective and safe (55). Statistically significant results were achieved in a study group of Koreans with Fitzpatrick skin types II–IV and solar lentigines using an alexandrite laser for hair removal (56). When used in combination with CO2 laser, the results in the treatment of refractory melasma were superior to the use of the alexandrite laser alone (45).

Q-Switched Nd-Yag

Q-switched Nd-Yag lasers have proven useful for treating deep-pigmented lesions, such as nevi of Ota and tattoos in dark skinned persons, with a reduction in the risk of epidermal injury (57). Freckles and lentigines in Fitzpatrick prototypes IV or prototypes IV-IV can also be successfully treated with the Q-Switched Nd-Yag laser. Minimum adverse reactions and good cosmetic results can be expected (58).

Tattoos also can be effectively treated and removed with several Q-switched lasers, resulting in minimal scarring (59).

In our clinical practice, a thorough and detailed medical history is performed on each patient seeking treatment for a pigmentary disorder before using any kind of laser. This is done to identify high-risk patients, such as dark skinned patients with Fitzpatrick IV–VI, since post-laser repigmentation and PIH are common occurrences (Table 6).

Erbium:YAG Lasers

Erbium:YAG lasers have been shown to improve melasma, but the nearly universal appearance of PIH necessitates prophylactic skin preparation with tretinoin, hydroquinone, and desonide nightly for two to four weeks prior to laser treatment (60).

Intense Pulsed Light (IPL)

Intense pulsed light (IPL) has been successfully used in refractory melasma in Asians, and has been found to be more useful than pigment-specific lasers in severe cases of melasma. It is also an excellent laser for treating lentigenes associated with photoaging (61). In a study of 33 Asian women with refractory dermal or refractory mixed melasma, the combination of IPL with 4% hydroquinone for one month was more effective than hydroquinone alone. Objective measurements were used to evaluate the skin lightening effect. A 39.8% improvement in relative melanin index was seen in the combination treatment group, versus 11.6% in the hydroquinone group at week 16 ($p < 0.05$). Four treatments were done at one-month intervals. Two patients in the IPL group experienced PIH. Partial transient repigmentation was noted 24 weeks after the last treatment session in two patients (62). IPL has also proven effective in the treatment of freckles in Asian patients (61) and in disfiguring lentigines associated with Peutz-Jeghers syndrome (63,64).

Intense pulse light can be safely used in dark skinned people with dermal hyperpigmentation.

Pigment Dye Lasers

Pigment dye lasers have been used with success in café-au-lait macules, ephelides, lentigines, and orange, red, and yellow tattoos. However, they are no longer recommended due to serious secondary reactions reported, including skin discoloration and purpura (66). When topical 0.05% retinaldehyde is used with the 1540 nm erbium:glass laser, the effects of the increasing dermal thickness is potentiated. In one study, half the subjects applied 0.05% retinaldehyde daily after laser treatment and for up to three months after the fifth treatment, and half applied it daily for seven months. Dermal thickness increased in all patients, with a larger increase seen in the retinaldehyde group. A statistically significant increase in forehead dermal thickness was noted in the retinaldehyde group (67).

Although laser treatment has been used in pigmentary disorders in dark skinned patients, their cautious use is warranted. Prospective studies with larger populations of Fitzpatrick phototypes IV–VI are needed to determined their safety and efficacy (68).

OUR THERAPEUTIC APPROACH

As the pigmentary system yields its secrets, and pathogenic disease mechanisms are more intensely investigated and studied, therapeutic options for pigmentary disorders expand.

Once a pigmentary disorder has been diagnosed, the first step is to educate the patient about the condition. This is particularly important if the condition has a chronic nature that will require long-term follow-up, such as melasma.

Table 6 Clinical Parameters to Be Considered Before Using Lasers in the Hyperpigmented Patient

Ethnicity
Medical and surgical history
History of hypertrophic scarring and keloid formation
History of post-inflammatory hyperpigmentation
Skin type (Fitzpatrick phototype)
Use of isotretinoin
Results of previous cosmetic procedures

Sun protection must be the primary preventive measure for all patients. In order for therapy to be successful, counseling patients on sun safety is crucial. A broad-spectrum sunscreen with sun protection factor (SPF) 30 and physical blockers containing titanium dioxide or zinc oxide are preferred. Sunscreens block the stimulatory effect of the sun on melanocytes, as well as the transfer of existing melanosomes to keratynocytes.

In general, therapy for pigmentary disorders must be disease-specific and designed for the individual patient. Due to the complexity of the pigmentary system and the many pathogenic mechanisms involved in most acquired pigmentary disorders, it is only logical to assume that attacking the pigmentary cascade at different levels with different compounds would be the most reasonable approach.

First-line treatment for conditions such as melasma and PIH is topical therapy with a dual- or triple-combination product. Triple combinations contain hydroquinone with a retinoid and a mild corticosteroid; dual combination products contain hydroquinone and a retinoid. In the presence of sensitivity to any of these ingredients, alternative bleaching agents such as kojic acid, azelaic acid, or a cosmeceutical herbal compound can be considered.

Physical therapies are also introduced early in the treatment program. These therapies might include chemical peels, dermabrasion, microdermabrasion, laser, or pulsed light (Table 5). While there is insufficient evidence to conclude that these therapies are indispensable, we feel they are synergistic and help with maintenance control. Their help with the prevention of PIH is an added benefit.

The most commonly used physical therapies are salicylic acid peels, glycolic acid peels, and Jessner's solution. These are primarily superficial peels. Our success rate with these mild procedures used in combination with topical therapies and sunscreen is quite high.

We put all our patients on pre-procedure protocols with skin care products ranging from mild cleansers and moisturizers to products containing active ingredients such as glycolic acid, retinol, Kinerase, or one of the new growth factors (TNS vs. e.g.,). After the procedure, patients are followed closely, and skin care regimens are restarted about a week later.

Light therapies have recently been introduced. We use IPL for treating lentigos. We have not tried IPL on melasma, although several studies have reported success, particularly in Asian patients. IPL provides a more acceptable modality than lasers, as that there is less photothermal injury and, therefore, less risk of PIH in patients with melasma.

Pigment-specific lasers such as Q-switched Nd-Yag are used for isolated lesions such as lentigos, and are only used as a last resort in cases of recalcitrant melasma.

When all other measures have failed, combining topical therapies with procedures is a reasonable approach, especially in recalcitrant conditions. The wisdom of this approach is supported by a handful of trials, although solid evidence is lacking. It is possible that the combination of all available therapies could lead to more rapid and greater improvement and accelerated healing times while reducing the occurrence of PIH.Once their disease has been cleared, patients are always placed on maintenance therapy with a retinoid, a mild lightening agent such as azelaic acid, or a cosmeceutical agent (4,33,56).

CONCLUSIONS

The treatment of pigmentary disorders remains a challenge, as there are no standardized treatments for melasma, PIH, or pigmentation due to photoaging.

The clinical response to pharmacological monotherapy is frequently slow and, in some cases, suboptimal. Whenever possible, the use of a dual- or triple-combination product as a first approach is recommended. The combination of various pharmacologic agents with chemical peels, microdermabrasion, and/or pigment-specific lasers can lead to accelerated healing times and a more rapid and greater improvement, and can reduce the occurrence of PIH. These advantages may enhance compliance.

Scientific evidence exists for a few of the pharmacologic agents, but evidence supporting the use of chemical peels and microdermabrasion for pigmentation disorders is scarce. Lasers have specific uses in the treatment of isolated lesions such as lentigos. Some reports have shown success with light sources including IPL for the treatment of melasma in Asians, specifically dark skinned ones. Pigment-specific lasers should only be reserved for refractory cases.

In general, combining procedural therapy with pharmacologic therapy is logical, although scientific evidence is lacking. Where trials do exist, evidence supports the combination of modalities. The procedures can also improve or hasten the cosmetic results obtained from other conventional therapies.

The choice of therapeutic agents involves assessment of the risk-benefit profile, and regimens should be individualized to specific disease and patient characteristics, as mentioned in Table 6.

Our success rate in the treatment of pigmentary disorders is quite high with the above approaches. However, due to the chronicity of some of these disorders, constant follow-up, patient counseling, and use of sunscreens are critical for long-term improvement and maintenance of results.

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