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Melasma, Novel Treatment Modalities

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Abstract

Treatment of melasma remains challenging due to frequent relapses and the occurrence of post-inflammatory hyperpigmentation (PIH) following many interventions. Treatment goals are inhibition of melanin synthesis and transfer by sunscreens, sun avoidance and the use of bleaching agents on one hand and removal of already present pigment by peeling, lasers and light on the other hand. Triple combination creams (TCC) (also known as Kligman's formula utilizing hydroquinone and modifications of Kligman's formula) remain the mainstay of treatment. Newer bleaching agents derived from plants and synthetic compounds have been introduced and many of them are promising safe substitutes for hydroquinone.

Peeling agents especially superficial and medium depth peels are effective treatment modalities for melasma. Newer peeling agents are less irritating and may thus lead to fewer side effects.

Q-switched lasers, which target melanin, have led to PIH until the innovation of "laser toning" and fractional Q-switched ruby, which have better outcomes. Fractional non-ablative and ablative lasers are useful at lower fluencies. Pulsed dye laser, which targets the vascular component in melasma, is promising with less melasma rebound.

Combinations of the above-mentioned modalities usually have a better treatment outcome than either alone. This review will focus on the more recently introduced therapies.

Keywords: Melasma; Bleaching; Peeling; Laser; Combination therapy

Introduction

Melasma is a common, acquired facial skin disorder, mostly involving sun-exposed areas like cheeks, forehead and upper lip. It is clinically divided according to its distribution into centrofacial, malar and mandibular patterns [1].

Histopathologically, melasma is associated with epidermal hyperpigmentation due to increased melanin formation and deposition rather than increased melanocyte numbers, weak basement membrane, elastosis, vascular proliferation with mild lymphohistiocytic infiltrates increased numbers of mast cells and dermal melanophages [2,3].

The pathogenesis of melasma is complex. Increasing evidences show that melanocytes are not the only cells involved, and that other players like keratinocytes and fibroblasts probably have a key role in the development and the relapses of melasma [4]. Ultraviolet (UV) light from sun exposure has a major role in induction and relapse of melasma. Pregnancy, oral contraceptive pills, family history and dark skin types remain among the major predisposing factors [5]. Interestingly, visible light, especially that in the blue-light range, can increase skin pigmentation adding to the burden of melasma relapse [6,7].

Melasma is usually diagnosed clinically. Wood's light or, more recently, confocal laser microscopy help in localizing melanin level [8].

For evaluating the severity and degree of melasma, several scoring systems and tools have been proposed. The Melasma Area and Severity Index (MASI) is the most popular scoring system [9]. To calculate the MASI score, the sum of the severity rating for darkness (D) and homogeneity (H) is multiplied by the numerical value of the areas involved (A) and by the various percentages of the four facial areas. These values are added to obtain the MASI score. Melasma Severity Scale (MSS) is a simpler way to grade melasma [10]. Colorimetry quantifies the melanin that is present in melasma lesions and the changes associated with improvement from the treatment using the L*a*b* color system, as determined by the Commission International de I'Eclairage. There are also the mexameter and the dermaspectrometer that can quantify melanin using melanin index [11]. Patient's subjective evaluation of improvement after treatment is graded into mild, less than 25%; moderate, 25 to <50%; good, 50 to <75%; excellent, >75%, [12].

Due to the complex pathogenetic nature of melasma, treatment is challenging and relapses are the hallmark of the disease. Herein we will present the current therapies available for melasma with focus on newer treatment modalities. The main goal of therapeutic modalities is either suppression of melanogenesis and melanin transfer from the active melanocytes or removal of already present pigment in epidermis and dermis.

Treatment of Melasma

Suppression of melanogenesis

Sunscreens: Strict avoidance of sunlight is mandatory. The use of tinted, mineral sunscreens is more beneficial than non-tinted, since they protect not only against ultraviolet but also against visible light [4]. In a recently published study, patients with melasma applying iron oxide-containing sunscreens in the morning and hydroquinone 4% in the evening obtained significantly better bleaching compared to those applying ordinary sunscreens and hydroquinone (Table 1) [13].

Suppression of melanogenesis	Removal of already present melanin in the epidermis and dermis
Sunscreens Tinted sunscreens (UV and visible light)	**Peeling (superficial and medium depth peels)** Trichloroacetic acid (10-35%)
Preparations that inhibit melanin production Hydroquinone	Glycolic acid (20-70%)
Arbutin	Salicylic acid (20-30%)
Ellagic acid	Jessner's solution
Rucinol	Tretinoin peels
Azelaic acid	Newer peels
Licorice extract (glabridin and liquitrin)	Phytic acid peels
Kojic acid	Amino fruit peels
Ascorbic acid	
Retinoids	**Lasers**
Newer preparations	**Q-switched lasers**
Dioic Acid	Ruby
N-Acetyl Glucosamine	Alexandrite
Mulberry extract	Nd-YAG
Silymarin	**Ablative lasers**
Other botanicals	CO2
Resveratrol	Erbium
Oligopeptides	**Fractional lasers**
Tranexamic Acid	Fractional non-ablative
Metformin	Fractional ablative
	Fractional Q-switched ruby laser
Preparations that inhibit melanin transfer	**Pulsed dye laser**
Soy	**Intense pulsed light**
Niacinamide	

Table 1: Treatment modalities for Melasma

Preparations that inhibit melanin production and transfer

Bleaching agents: Bleaching agents work mainly be inhibiting tyrosinase enzyme, which is the key enzyme in melanogenesis. The benchmark of bleaching agents is hydroquinone (HQ) 2-5%. It is applied alone or better in combinations [14]. The classical combination, termed Kligman's formula consists of a bleaching agent (hydroquinone 5%), an exfoliating agent (tretinoin 0.1%) and topical steroid (dexamethasone). Topical steroids are not only anti-inflammatory; they also inhibit melanocyte activity [15]. Other combinations and modifications on the original Kligman's formula

have been developed over the years using different ingredients and/or different concentrations of ingredients. Kligman's formula or similar combinations will be referred to in this review as triple combination cream (TCC). In the United States, a TCC consisting of 4% HQ, 0.01% fluocinoloneacetonide, and 0.05% tretinoin is currently the only HQ-containing drug that the Food and Drug Administration (FDA) has approved for the treatment of melasma [16].

The most significant adverse effects of HQ are irritation, confetti-like depigmentation and ochronosis. Moreover, HQ is potentially cytotoxic, mutagenic and its metabolite may cause bone barrow toxicity in vitro and in laboratory animals [14,17].

Due to the reported side effects of HQ, research has been in action to find other agents with hypo-pigmenting activity and yielded a vast amount of naturally occurring and synthetic compounds. A summary of such compounds with focus on the newer ones will be mentioned herein.

Arbutin is a naturally occurring derivative of HQ derived from the extract of the bearberry plant and has fewer adverse effects than HQ [18].

Ellagic acid is an antioxidant found in certain plants and fruits. It is also a substrate of tyrosinase, suggesting a possible inhibitory effect on the melanogenesis pathway [18,19].

Rucinol is a resorcinol derivative and has been shown to inhibit tyrosinase and tyrosinase related protein-1 (TRP-1) [20].

Azelaic acid is a naturally occurring dicarboxylic acid synthesized by the yeast Malassezia. It weakly inhibits tyrosinase and has shown cytotoxic and anti-proliferative effects in abnormal melanocytes. Twenty percent azelaic acid cream applied twice daily may be more effective than hydroquinone 4% in reducing mild melisma [21].

Licorice extract; the main active ingredients in licorice roots are glabridin and liquitrin, both decrease pigmentation. Glabridin has additional anti-inflammatory activity [22,23].

Kojic acid (derivative of several fungal species) and ascorbic acid (vitamin C) inhibit melanogenesis by interacting with copper, which acts at the enzyme's active site [17]. Additionally, the antioxidant effects of ascorbic acid prevent the production of free radicals, which trigger melanogenesis and reduce oxidized melanin, changing the pigmentation from black to tan. Preparations containing 5 or 10% ascorbic acid alone are available, as well as combinations with other bleaching agents. When used alone, 5% ascorbic acid has a slow onset of action compared to 4%HQ but with fewer adverse effects [24].

Kojic acid is used in 1-4% concentrations, usually in combination with other agents [25,26]. It is a known sensitizer and has been claimed to be mutagenic [17].

Retinoids, increase epidermal cell turnover, inhibit melanosome transfer, enhance the penetration of other topical agents, inhibit tyrosinase transcription and interrupt melanin synthesis. Topical tretinoin proved effective in melasma after its use for 40 weeks [9,27]. However, topical tretinoin commonly causes skin irritation and inflammation, which often results in worsening of melasma.

In the author's opinion, irritation caused by TCC containing HQ-and/or tretinoin could be minimized by using them day after day instead of their daily use. Patients could use moisturizer during the rest of the week. Additionally, the use of potent topical steroid initially (first 2 months) followed by a less potent one will not only decrease

the irritation, but will also boost the response. We noticed that potent steroids have a stronger melanocyte inhibitory action compared to low potency steroids.

Newer topical bleaching formulations

Soy: Soy interferes with melanin transfer by inhibiting the protein-activated receptor 2 (PAR-2) pathway. Two soybean-derived proteins, namely soybean trypsin inhibitor and the Bowman-Birk inhibitor, interfere with melanosome transfer by inhibiting the PAR-2 activation. In a blinded controlled 12-week study, authors evaluated the efficacy of a soy moisturizer containing soybean trypsin inhibitor and Bowman-Birk Inhibitor on 65 women with moderate facial photodamage. There was significant improvement in mottled pigmentation, blotchiness, dullness, fine lines, overall texture, and overall skin tone [28].

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. 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 acne-form eruption was 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. In a double-blind, placebo-controlled split face study, 2% NAG proved effective (30). 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 [30,31].

Mulberry extract: Several species of the Moraceae family exhibit antioxidant activity [32,33]. The focus here, though, will be on the skin-lightening activity of various parts of Morus (commonly known as mulberry) trees. Extracts of parts of white mulberry, paper mulberry and Chinese mulberry trees (leaves, stem, bark, fruits or roots) can actively inhibit tyrosinase enzyme that could even supersede the activity of hydroquinone and kojic acid [34,35].

A randomized, single-blind, placebo-controlled trial on the safety and efficacy of 75% mulberry (Morus alba) extract oil versus placebo as a topical treatment for melasma, showed that the mean MASI score significantly improved for the 75% mulberry extract oil group (mean difference, 1.19), compared to placebo (0.06). Mexameter and Melasma Quality of Life (MelasQOL) scores also showed statistically significant differences in the mulberry extract group [36].

Silymarin: Silymarin "Milk Thistle" is classically used as liver support in liver cirrhosis and chronic liver disease. Silymarin was also found to prevent photocarcinogenesis, and significantly prevents melanin production.

Altei et al. [37] published an experimental work on albino rabbits and melasma patients using silymarin (SM) cream. Twenty-four Albino rabbits were randomly divided into 4 equal groups. [A] No treatment, [B] received placebo, [C] treated with SM cream (0.1), & [D] treated by SM (0.2), were applied topically before UV sun light exposure for 30 days, assessed clinically &histopathologically. Ninety-six adults diagnosed with melasma were randomized to three equal groups to receive one of the tested drugs applied twice daily for 4 weeks, evaluated by the response; lesion size, MASI score, physician global assessment, and subjective assessment.

The clinical and histopathological observations were reduced significantly in SM groups. Topical SM showed tremendous improvement of melasma in a dose-dependent manner, and was effective in prevention of skin damage caused by UV sunlight. Authors concluded that it is a safe new candidate effective treatment for melasma.

Resveratrol: A potential topical agent to treat hyperpigmentation in skin of color is resveratrol. Resveratrol is a phytoalexin and nonflavonoidpolyphenolic antioxidant that is synthesized in plant cells subjected to stress. It can be found in grape skin extracts, red wine, purple grape juice, peanuts, mulberries, bilberries, blueberries, cranberries, and the Japanese knotweed. Its mechanism of action is unknown, and current data are conflicting. Animal studies have shown that resveratrol led to skin lightening in Bufomelanostictus due to distinct aggregation of pigment cells [38].

Other botanicals as potential bleaching agents

A number of flavonoids and polyphenols are under trial as future bleaching agents. They generally have anti-inflammatory activity and decrease reactive oxygen species. These are extracts of belides, green tea, coffee fruit, orchid, emblica, cabbage palm fern, ground ivy, French pine and German chamomile in addition to the above-mentioned extracts of soybean, licorice, mulberry and silymarin [39].

Niacinamide: Studies on niacinamide have demonstrated a suppression of melanosome transfer suggesting the reduction of cutaneous pigmentation [40]. Topical niancinamide has other beneficial effects on the skin, including prevention of photoimmunosuppression and photocarcinogenesis, anti-inflammatory effects in acne, rosacea, and psoriasis. It also increases biosynthesis of ceramides, as well as other stratum corneum lipids with enhanced epidermal permeability barrier function. Moreover, it has antiaging effects [41].

Twenty-seven melasma patients were randomized to receive 4% niacinamide cream on one side of the face, and 4% hydroquinone cream on the other side for eight weeks. Sunscreen was applied along the observation period. They were assessed by noninvasive techniques for the evaluation of skin color, as well as subjective scales and histological sections initially and after the treatment with niacinamide. All patients showed pigment improvement with both treatments. Colorimetric measures did not show statistical differences between both sides. However, good to excellent improvement was observed with niacinamide in 44% of patients, compared to 55% with hydroquinone. Niacinamide reduced the mast cell infiltrate and showed improvement of solar elastosis in melasma skin. Side effects were present in 18% with niacinamide versus 29% with hydroquinone [41].

Oligopeptides: Investigators have begun to explore the role of oligopeptides, as these molecules are easily degraded to naturally occurring, and thus non-toxic, amino acid constituents. The aim was to produce oligopeptides with high tyrosinase inhibiting activity, that

are neither cytotoxic nor mutagenic A number of peptide fragments have been shown to reduce pigment production [42-44].

In an attempt to find suitable oligopeptides, Ubeid et al. [45] studied a series of penta-, hexa- and octapeptides. Octapeptides P16-18 were found to be potent competitive tyrosinase inhibitors with minimal toxicity toward the major cell types of human skin.

Lumixyl (0.01%) is a decapeptide, with a tyrosinase inhibitory activity. In a split-face, randomized, double-blind and placebo-controlled pilot study, the effect of twice-daily topical application of this oligopeptide (0.01% w/w) on moderate, recalcitrant melasma over a 16-week course was studied in 5 females (skin phototype IV) with recalcitrant melasma [46]. Treatment was well tolerated with no visible signs of irritation or allergy. All five participants demonstrated statistically significant improvement in the appearance of melasma and overall facial aesthetics with high patient satisfaction.

In two further studies, Lumixyl (0.01%) was incorporated with antioxidant cleanser, 20% glycolic acid lotion and physical sunscreen in Caucasian [47] as well as Hispanic melasma patients [48]. The brightening system was well tolerated with no adverse events reported. Mean decreases of 36%, 46%, 54%, and 60% in MASI scores were observed at weeks 4, 8, 12, and 16, respectively, which were further corroborated by standardized photography showing visible reduction in the appearance of melasma [48].

The tetrapeptide, Pro-Lys-Glu-Lys (PKEK) has proven skin-lightening benefits on skin discoloration from melasma and PIH in subjects with skin types V-VI in South Africa, making it a good candidate for all racial groups [49].

Tranexamic Acid (TXA): Tranexamic acid (Cyklokapron ®) is an antifibrinolytic widely used to treat haemorrhage. TXA is a plasmin inhibitor and lysine analog. It inhibits UV-induced plasmin activity by preventing the binding of plasminogen to the lysine binding sites on keratinocytes, which decreases free arachidonic acid and its metabolites (prostaglandins) decreasing melanocyte tyrosinase activity. TXA decreases vessel numbers by antagonizing vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b FGF). Additionally it decreases mast cell numbers [50].

Trials using oral, topical and intralesional TXA in melasma and hyperpigmentation have been performed on TXA alone and in conjunction with other modalities [50-53].

Intradermal injection of TXA (4 mg/ml) at weekly intervals for 12 weeks yielded a significant decrease in MASI score from baseline to 8 and 12 weeks. The patients' self-assessment of melasma improvement showed that 9.4% had good (51-75% lightening) and 76% had fair improvement (26-50% lightening). Side effects were minimal and all the patients tolerated the treatment well [51].

Na et al. (2012) [50] evaluated the efficacy of oral and topical TXA in melasma patients both clinically and histologically. Twenty-five melasma patients were instructed to take TXA tablets (2 tablets tds) and apply the cream twice daily for 8 weeks (each TXA tablet contained 125 mg of TXA, 50 mg of ascorbic acid, 40 mg of L-cysteine, 4 mg of calcium pantothenate and 1 mg of pyridoxine chloride. The topical agent was 2% TXA and 2% niacinamide). Subjects were asked to use standard sunscreen on the whole face during the study period. TXA decreased epidermal pigmentation associated with melasma and also reversed melasma-related dermal changes, such as vessel number and increased numbers of mast cells. Combining other agents may contribute to the good outcome of treatment.

On the other hand, topical 5% TXA cream failed to produce an effect on melasma in a split face, placebo controlled trial [52].

In combination with intense pulsed light (IPL) and low fluence Q-switched Nd:YAG laser, oral TXA improved the clinical efficacy in light- or laser-based melasma treatment especially during the period of relative high sun exposure without serious adverse effects [54].

In our experience, oral tranexamic acid (250 mg) together with oral vitamin C (500 mg) twice daily together with TCC were well tolerated and improved cases with melasma not responsive to topical treatment alone (unpublished data).

Metformin: Recently, the effects of metformin, a widely used drug in the treatment of type 2 diabetes, were investigated on melanogenesis both in vitro and in vivo (Lehraiki et al.). Metformin led to reduced melanin content in melanoma cells and in normal human melanocytes by decreasing cAMP accumulation and cAMP-responsive element-binding protein phosphorylation. This inhibitory effect is correlated with decreased expression of master genes of melanogenesis, microphthalmia-associated transcription factor, tyrosinase, dopachrometautomerase, and tyrosinase-related protein 1. Interestingly, topical application of metformin induced tail whitening in mice and had as anti-melanogenic effect on reconstituted human epidermis and on human skin biopsies. These data emphasize the depigmenting effect of metformin and suggest a clinical strategy for using metformin in the topical treatment of hyperpigmentation disorders. Removal of already present melanin in the epidermis and dermis [55].

Chemical Peels: Chemical peeling or controlled chemical burns result in destruction of a portion of the epidermis and/or dermis followed by its exfoliation and subsequent resurfacing of epidermis along with remodeling of collagen, and elastic fibers during the repair process in the dermis. Superficial, medium depth and deep peels are available [56   ]. Since most melasma patients have a dark complexion and due to their melanocyte hypersensitivity, treatment is restricted to superficial and less to medium depth peels. Various chemical peeling agents like glycolic acid (20-70%) [57], trichloroacetic acid (10-35%) [56,58], salicylic acid (20-30%) [59], Jessner's solution [60], tretinoin peels [12] and others have been proposed to treat melasma. They proved effective but with the risk of inflammation, PIH and or melasma rebound.

The value of priming the skin before treatment with bleaching creams, tretinoin (0.025-0.1%), glycolic acid (<15%) creams individually or as TCC and the use of TCC together with sunscreens during and after treatment sessions would add to the efficacy and decrease melasma relapse [61]. The more recently introduced phytic acid peels [62] and amino fruit peels [63] are better tolerated with less side effects than the classical peels [61].

Lasers and Light: Lasers proposed to treat melasma are the Q-switched, ablative, fractional (ablative and non-ablative) in addition to pulsed dye laser (PDL) and IPL.

Q-switched lasers (QS): Q-switched (QS) lasers target melanin as chromophore, according to their wavelengths, melanin in epidermis and dermis could be targeted. Preliminary studies onthe treatment of melasma with QS ruby (694 nm), QSalexandrite (755 nm) and QS Neodymium yttrium aluminumgarnet (Nd: YAG) (1064 nm) lasers resulted in worsening of melasma, PIH and sometimes, punctate depigmentation. These results were obtained on using QS lasers alone or in combination with ablative lasers [64-66].

The recent introduction of low energy Q-switched lasers (LEQL) with large spot size and low fluencies do not disrupt the epidermis allowing for selective melanosome damage. LEQL are applied in few passes, weekly or biweekly for 5-10 sessions. The technique is also known as "laser toning" and has become popular in Asian countries [67].

Several studies reported good improvement of melasma [68-71], especially when patients were pretreated with TCC [72] or when combined with glycolic acid peels [73], IPL [74] or dermabrasion [75]. However, reports of patients developing spotty hypopigmentation, depigmentation, leukotrichia, rebound hyperpigmentation and recurrence of melasma are noteworthy especially with too frequent (weekly) and too many sessions (>6-10) [71,76,77].

Ablative lasers: Similarly, ablative non-fractionated carbon dioxide (CO2) and Erbium: yttrium, aluminum, garnet (Erbium: YAG) laser produced initial improvement of melasma, but this was followed by PIH within 3 to 6 weeks of laser treatment [78].

Fractional Lasers: Fractional technology is a technique, where microscopic thermal damage (fractional non-ablative, fractional photothermolysis, FP) or microscopic holes (fractional ablative) are created in the skin, such that neighboring keratinocytes rapidly correct the defects, allowing for less downtime and less complications compared to open wounds. Microscopic injury zones induced by fractional treatments allow transport of necrotic epidermal debris including melanin through a compromised dermoepidermal junction [67,79].

Fractional Non-Ablative Laser: Controversy about the use of fractional erbium glass laser (1550 nm) in melasma has emerged from vast publications [80-85]. FP is a safe and effective treatment for refractory melasma, with long-term remission especially in fair-skinned patients. Treatment of patients with skin types III+ should be with extreme caution, since darker skin types are more prone to develop PIH [80, 81]. Given the high rate of PIH, FP should not be used at higher fluencies (15 mJ/micro beam) in the treatment of melasma[82]. The combination of FP with TCC is useful for patients with melasma resistant to topical therapy alone, but its long-term efficacy is limited [83].

On the other hand, other studies showed that FP does not provide a substantial benefit in treating melasma when compared with the sole application of a broad-spectrum sunscreen [84] and that its effect was comparable to TCA 15% peel treatments when used to treat moderate-to-severe melasma, but neither treatment was long-lasting [85].

Fractional Ablative Lasers: In a case report, fractional CO2 was successful in treatment of refractory dermal melasma in a patient of skin type V [86].

Trelles et al. [79] compared the use of fractional CO2 alone, to TCC to both together in 3 groups of melasma patients. Although one month following treatment the satisfaction index was equal in the three groups, this index continued to decrease for the first two groups. At 6 and 12 months there was a statistically significant difference between the combined use of fractional CO2 laser and TCC, which showed the best results compared to the other two groups as regards MASI score and satisfaction index [79].

Since fractional Erbium: YAG has a better water absorption co-efficient than CO2 and produces less thermal zone, it could be safer to use in treatment of melasma. On **Comparing fractional Erbium:**YAG to 15% TCA in twenty matched melasma patients, we found that both

modalities yielded a significant improvement in MASI score from baseline with no rebound during the 4 months follow up period (accepted as poster presentation in international pigment cell congress, 2014).

Intense Pulsed Light (IPL): IPL operates in millisecond pulse durations; it is not possible to target dermal melanosomes, which have thermal relaxation times in the nanosecond range. IPL treatment produces transient improvement in epidermal, but not dermal, melasma. Treatment will often result in crusting of the pigmented lesions, and the resultant epidermal disruption may cause PIH [87,88]. However, combining IPL with TCC is a safe and effective treatment for refractory mixed and dermal melisma [89].

Similarly, combining IPL and low energy QS-Nd-YAG resulted in a 59.35% decrease in modified MASI score and no clinical aggravations were observed during the follow-up period [74].

What is New in Laser therapy?

Fractional Thulium fiber 1927 nm

Recently, Polder and Bruce [90] introduced the use of a novel 1927-nm fractional thulium fiber laser to treat melasma. This wavelength has a higher absorption coefficient for water than the 1550 nm laser, hence targets the epidermal pigment with greater efficacy. Four sessions at 4 weeks interval led to statistically significant improvement in melasma without any PIH [90].

In a retrospective study, significant decrease in mean MASI score was reported at 4 weeks after laser treatment in 20 melasma patients. Patient assessment revealed that 12 out of 20 subjects had more than 50% clearance of their melasma. Recurrence was reported by 7 out of 15 patients who were successfully followed-up (mean 10.2 months). Two patients developed PIH that subsided with topical bleaching after 3 months [91].

Ho et al. [92] reported that fractional thulium fiber is safe and effective for Chinese melasma patients at 2 months follow up. Complications were edema, erythema and crusting in the early days and that one patient developed PIH.

Fractional Q-switched ruby laser

Fractional QS ruby laser was designed to treat melasma without getting the usual side effects from previous QS lasers. Low dose fractional QS ruby laser for 6 sessions led to a decrease in MASI and increase in lightness of the melasma lesions in Koreans. Results were maintained at 16 weeks after the last treatment [93]. In a retrospective study, Hilton et al. (2013) [94] reported PIH and melasma rebound in a significant number of Caucasian melasma cases 3 months after 1-3 sessions of fractional QS ruby laser. They recommended more sessions at lower doses and/or the use of TCC and sun avoidance for better treatment outcomes.

Pulsed dye laser (PDL)

Pulsed dye laser aims at targeting the vascular component in melasma. Vascular endothelial growth factor (VEGF) is highly expressed in melasma lesions and the melanocytes VEGF receptors 1 and 2, which are involved in the pigmentation process [95-98]. PDL may decrease melanocyte stimulation and more importantly, decrease subsequent relapses [99].

A study was conducted on 17 patients with melasma who were treated with PDL and topical combination therapy in a split-face comparison. The combination treatment was compared with TCC alone. The laser treatment was started after 1 month of TCC applications. Bleaching cream (HQ 4%, tretinoin 0.05% and flucinoloneacetonide 0.01%) was applied to the whole face and PDL on one half of the face. PDL was applied in 2 doses; one targeting melanin and the other targeting vasculature. Three sessions were performed at 3 weekly intervals. The authors found that the side treated by PDL had a better outcome and showed decreased relapse after summer in skin photoypes SPT II, III. Patients with skin type IV experienced hyper pigmentation, which could be from dose targeting melanin [99].

Combination therapy

Combinations between different treatment modalities have been used. Different topical therapy combinations have been studied and combining topical, oral therapies with each other and/or with peeling and light therapies add to the efficacy of treatment especially in recalcitrant cases. Starting by TCC before other treatment modalities decrease the incidence of PIH and may decrease melasma relapse [54,61, 72,74,75,79,83,89,99].

Maintenance

After successful treatment of melasma, it is very important to maintain the results. This is achieved by continued strict sun avoidance, use of sunscreens (> 50 SPF), especially tinted ones and the use of bleaching creams. To evaluate efficacy of maintenance therapy with TCC, a twice-weekly regimen of TCC versus a gradually decreasing frequency were evaluated. Both were effective in postponing relapse in more than 53% over 6 months. The twice-weekly regimen tended to show better effectiveness in postponing relapse in severe melisma [100].

Conclusions

"Once Melasma, Always Melasma" this quotation is still applicable for melasma patients, since they probably have specialized melanocytes with intrinsic sensitivity to different stimuli. Due to the extreme sensitivity of melanocytes in melisma patients, the main drawback of many treatment tools is post-inflammatory hyperpigmentation and melasma rebound especially if the topical treatment is irritant or if the tool is used aggressively (Table 2). Sun avoidance and the use of sunscreens are crucial. Many new therapies are upcoming. Maybe substances that work on melasma-associated vasculature have a more promising future with less relapses.

Preparation	Mechanism of Action	Indications	Side Effects
Hydroquinone (2-5%)	Tyrosinase inhibitor	Alone or in combination (TCC). First step in melasma treatment, in combination with other tools (priming, maintenance)	Irritation, confetti-like depigmentation, ochronosis. Cytotoxic? Mutagenic?
Kojic acid	Interferes with copper at tyrosinase active site	Alone or in combination with other topical therapies	Contact sensitizer mutagenic?
Azaleic acid 20%	Tyrosinase inhibitor (weak)	Alone or in combination with other topical therapies	Irritation, initial burning sensation.
Retinoids	Peeling, tyrosinase inhibitor, inhibits melanosome transfer	Usually in combination with other topical therapies	Irritation and inflammation, which may result in worsening of melasma, slow onset of action
Dioic Acid	Inhibits melanosometranfer	Still under trial as alternative to older preparations	Pruritus, irritation (mild). Acne-form eruption (oily vehicle)
Tranexamic Acid	TXA inhibits binding of plasminogen to the lysine binding sites on keratinocytes, which eventually decreases prostaglandins & melanocyte tyrosinase activity. TXA decreases vessel numbers & mast cell numbers	Oral and intralesional TXA maybe more beneficial than topical TXA	Oral TXA may lead to nausea, vomiting, diarrhea, or dizziness
Chemical Peels	Increase epidermal turnover, remove already present melanin	Second line treatment, alone or better with TCC	Inflammation, PIH, melasma rebound
Q-switched lasers	Disrupts melanosomes	Could reach dermal melanin removing it (depending on wavelength). Epidermal and dermal melasma	Worsening of melasma, PIH, punctate depigmentation
Low energy Q-switched lasers	Disrupts melanosomes	Nd:YAG laser reaches deep in dermis removing melanin from there	Spotty hypopigmentation, depigmentation, leukotrichia, rebound hyperpigmentation, recurrence of melasma
Fractional Q-switched ruby laser	Disrupts melanosomes.	More superficial than Nd:YAG	PIH, melasma rebound (less than conventional QS)
Ablative lasers	Ablates skin, removing with it melanin particles	Epidermal and dermal melasma	PIH (3 to 6 weeks after laser treatment) especially with deeper, aggressive treatment
Fractional non-ablative laser	Creates microthermal zones through which melanin can be extruded	Epidermal and dermal melasma, less downtime	PIH (darker skin types, higher fluencies), melasma rebound
Fractional Thulium fiber 1927 nm	Non-ablative laser with higher water absorption coefficient	Epidermal and dermal melasma, less downtime	Edema, erythema and crusting (early days), PIH recurrence of

			melasma (less than other lasers)
Fractional Ablative Lasers	Creates small channels through which melanin can be extruded	Epidermal and dermal melasma, less downtime	PIH? Melasma rebound?
Intense Pulsed Light	? Probably targeting vascular component		Crusting of the pigmented lesions, PIH
Pulsed dye laser	Vascular mode, targets dermal blood vessels Pigment mode targets melanin	Decreases the vascular component of melasma	PIH (darker skin types, maybe from pigment mode?)

Table 2: Mechanism of action, indications and side effects of the most commonly used tools in melasma treatment (PIH=post inflammatory hyperpigmentation, QS=Q-switched laser, TCC=triple combination therapy, TXA=tranexamic acid)

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