The treatment of melasma: A review of clinical trials

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Melasma is an irregular brown or grayish-brown facial hypermelanosis, often affecting women, especially those living in areas of intense UV radiation. The precise cause of melasma remains unknown; however, there are many possible contributing factors. Because of its dermal component and tendency to relapse, melasma is often difficult to treat. The use of broad-spectrum (UVA + UVB) sunscreen is important, as is topical hydroquinone, the most common treatment for melasma. Other lightening agents include retinoic acid (tretinoin) and azelaic acid. Combination therapies such as hydroquinone, tretinoin, and corticosteroids have been used in the treatment of melasma, and are thought to increase efficacy as compared with monotherapy. Kojic acid, isopropylcatechol, N-acetyl-4-cysteaminylphenol, and flavonoid extracts are other compounds that have been investigated for their ability to produce hypopigmentation, but their efficacy, safety, or trial design indicates that the interventions would need further study before they could be recommended. Chemical peels, laser treatments, and intense pulsed light therapy are additional therapeutic modalities that have been used to treat melasma. (J Am Acad Dermatol 2006;55:1048-65.)

Melanin is produced in melanocytes and stored in melanosomes within the keratinocytes. The number, melanin content, and location of these melanized cells (along with oxygenated and deoxygenated hemoglobin) help determine the color of the skin. Melanosomes contain tyrosinase, a copper-containing enzyme, that catalyzes the conversion of L-tyrosine to L-dopa and L-dopa to L-dopa-quinone in melanin synthesis.[1] Melasma is a dysfunction of this pigmentary system, resulting in an irregular brown or grayish-brown facial hypermelanosis. Although it can occur in both sexes and any skin type, it is more commonly seen in women[2] and those with darker complexions—Fitzpatrick's skin types IV to VI—especially those living in areas of intense UV radiation, such as Hispanics/Latinos, Asians, and African Americans.[3-6] The condition usually develops slowly and symmetrically, and can last for many years, with worsening in the summer and improvement during the winter.[7]

Melasma is sometimes used interchangeably with the term "chloasma," which is a hyperpigmentation that often results from pregnancy or changes in uterine and ovarian hormones; melasma, however, can have a variety of possible causes. The common contributing factors include genetic predisposition,[4,8] pregnancy,[9] use of oral contraceptives,[10]

Abbreviations used:

AEs:	adverse effects
AzA:	azelaic acid
CO_2:	carbon dioxide
FA:	fluocinolone acetonide
GA:	glycolic acid
HQ:	hydroquinone
IPC:	isopropylcatechol
IPL:	intense pulsed light
MASI:	Melasma Area and Severity Index
MKF:	modified Kligman's hydroquinone formula
PIH:	postinflammatory hyperpigmentation
RA:	retinoic acid
RCT:	randomized controlled trial
SWC:	skin-whitening complex
TCA:	trichloroacetic acid
YAG:	yttrium-aluminum-garnet

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Funding sources: None.

Disclosure: Dr Taylor has received previous honoraria/grants or acted as a consultant or an investigator for the following companies: Allergan, Astellas, Barrier Therapeutics, Bieresdorf, Connetics, Dermik, Doak (Bradley), Galderma, Intendis, Johnson & Johnson, L'Oreal, Medicis, Palomar, Stiefel.

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Published online October 4, 2006.
0190-9622/$32.00

doi:10.1016/j.jaad.2006.02.009

endocrine dysfunction or hormone treatments,[11,12] and exposure to UV light.[4,8,13] In addition, cosmetics and drugs containing phototoxic agents (eg, antiseizure medications) have also been linked to melasma.[3] Interestingly, Wolf et al[14] suggests that some cases of melasma could be stress induced, because the release of melanocyte-stimulating hormone can be influenced by stress.

When melasma occurs with pregnancy, also termed "the mask of pregnancy," it can resolve within a few months after delivery and treatment may not be necessary. However, there are many cases in which the disorder persists indefinitely.[15] Pregnancy-associated melasma may be caused by an increase in placenta, ovarian, and pituitary hormones.[16] Melasma has also been attributed to an elevation of melanocyte-stimulating hormone, estrogen, and progesterone leading to increased melanogenesis.[10]

Vazquez et al[8] reports that melasma in men shares the same clinicohistologic characteristics as in women, with the exception that hormonal factors may not play a major role. The main associated factors among men appear to be sun-induced aggravation and a significant family history of the condition.[8] A study of melasma in Indian men implicated sun exposure and cosmetic use including topical mustard oil.[17]

It is helpful, before treatment, to perform an examination using Wood's lamp; this will identify the depth of the melanin pigmentation, thus, helping to delineate the type of melasma.[18] Generally, melasma is classified into one of 3 histologic types: epidermal, dermal, and mixed.[13] However, some also include a fourth type known as Wood's light inapparent.[4] Under Wood's light the epidermal type often shows a darkening of color when examined, as the light emitted by Wood's lamp is absorbed by the excess melanin. The dermal type, however, will not show this accentuation.[1,4] The mixed type involves a deposition of melanin in both the epidermis and the dermis and color enhancement with Wood's light is seen is some places of the skin, but not others.[4]

It is interesting to note that when histologically assessing 56 patients, Kang et al[13] did not find any cases of entirely dermal-based melasma. Furthermore, Sanchez et al[4] describe dermal type melasma as having melanin-laden macrophages in the perivascular array, both in the papillary and reticular dermis. Epidermal hyperpigmentation in the dermal type was found to be similar to the epidermal type, but not as prominent.[4] It has, thus, been suggested that there may be no truly pure dermal type of melasma.[13]

There are 3 clinical patterns recognized on the basis of clinical examination. These include a centrofacial, malar, and mandibular pattern. The centrofacial is the most common pattern of melasma and involves the cheeks, forehead, upper lip, nose, and chin. The malar pattern has lesions limited to the cheeks and nose, and the mandibular pattern has lesions that occur over the ramus of the mandible.[4] Other sites (eg, forearm and neck) may also be involved in any of these patterns.[7]

METHODS

MEDLINE (1966-2005) was searched using the key words melasma, chloasma, hyperpigmentation, and hypermelanosis. This article outlines published randomized controlled trials (RCTs) of the interventions that have been studied for use in the treatment melasma. When RCTs were not present, nonrandomized or open clinical trials were reviewed.

General management

Because of its refractory and recurrent nature, melasma is often difficult to treat. The goals of treatment often include prevention or reduction in the severity of recurrence, reduction of the affected area, improvement in the cosmetic defect, and reduced time to clearance, all with the fewest possible side effects.[19] The principles of therapy include protection from UV light, inhibition of melanocyte activity and melanin synthesis, and the disruption and removal of melanin granules.[20]

General management recommendations that assist in the clearing of melasma include discontinuation of birth control pills, scented cosmetic products, and phototoxic drugs, coupled with UV protection with use of broad-spectrum (UVA + UVB) sunscreens.[20] Solar exposure exacerbates melasma, and its avoidance is fundamental for the successful management of the disease.[21] Most patients using bleaching agents can expect a recurrence of the disease on exposure to sunlight and artificial UVA and UVB light.[21] This supports the importance of the use of broad-spectrum sunscreens (SPF $>$ 30) in melasma therapies. Broad-spectrum sunscreens must be applied daily throughout the year and continued indefinitely to minimize the reactivation of melanocytes by incidental exposure to the sun.[21]

Although sunscreens are a vitally important component of therapy, other forms of treatment are nonetheless necessary.[22] Topical treatments include the application of creams such as hydroquinone (HQ). Although some negative reactions have been described, HQ remains one of the most prescribed agents for melasma and is considered the gold standard of therapy, especially for epidermal melasma. The epidermal type generally has a good response to topical therapy, whereas skin with

Table I. The mechanisms by which various treatments for melasma achieve their depigmenting effect

Mechanism of action	Therapy
Tyrosinase inhibitor	Hydroquinone
	Tretinoin*
	Azelaic acid
	Kojic acid
Nonselective suppression of melanogenesis	Corticosteroids
Inhibition of ROS	Azelaic acid
Removal of melanin	Chemical peels
Thermal damage	Laser treatments

ROS, Reactive oxygen species.
*Tretinoin may also disperse keratinocyte pigment granules and accelerate epidermal turnover.[31]

mainly dermal deposition of melanin responds poorly.[4] Alternative therapies such as chemical peeling agents or laser therapy are sometimes also used. Table I outlines the various treatments for melasma and their proposed mechanism of action. Table II outlines efficacy studies for the most common forms of topical treatment, whereas Table III focuses on the efficacy studies for chemical peeling agents.

Hydroquinone

Mechanism of action. HQ (1,4-dihydroxybenzene) is a hydroxyphenol, which, in the presence of catalytic amounts of dopa, will compete with tyrosine, the natural substrate of tyrosinase. This process prevents the enzymatic oxidation of tyrosine to dopa, thus, preventing the synthesis of melanin. This is consistent with the selective mode of action toward cells with active tyrosinase activity.[23]

Efficacy. Amer and Metwalli[24] assessed the efficacy of HQ 4% cream used in conjunction with broad-spectrum sunscreen in patients with various pigmentary disorders. Of the 70 patients entered into the study, 50 had melasma, 10 freckles, and 10 postinflammatory hyperpigmentation (PIH). The pigment intensity relative to nonaffected areas of skin was determined on a 4-point scale with 1 being no difference, 2 mild pigmentation, 3 moderate pigmentation, and 4 severe pigmentation. From week 0 to 12 (treatment end) the number of patients with melasma and moderate pigmentation decreased from 28 (56%) to 1 (2.1%), and patients with severe pigmentation decreased from 22 (44%) to 4 (8.4%). In addition, the number of patients with melasma with no difference between affected and nonaffected areas increased from none at week 0 to 41 patients (85.4%) at week 12. The study deemed that there was a good to excellent response achieved in 89.5% of patients with melasma and that treatment with HQ is beneficial in patients with hyperpigmentary disorders.[24] However, these results should be considered with caution, as this study is not randomized or placebo controlled. Furthermore, the study seems to lack a detailed description of the methods undertaken and there appears to have been no statistical analysis of the results.

Haddad et al[25] in a double-blind, randomized, placebo-controlled study of 30 patients with melasma, assessed the efficacy of a skin-whitening complex (SWC) 5% cream versus HQ 4% cream. Patients were randomized into two groups; group 1 received HQ 4% and placebo, and group 2 received SWC and placebo, each to be applied to opposite sides of the face. Efficacy was measured based on two independent investigator evaluations and a patient questionnaire. Of the 30 patients enrolled, 25 completed the study. Group 1 (HQ vs placebo) showed an improvement of 76.9% and group 2 (SWC vs placebo) showed an improvement of 66.7%. This difference was not statistically significant (Fisher's test, $P = .673$). Patient satisfaction levels were 66.7% for group 1 and 69.2% for group 2. Despite being a RCT, this study opts to evaluate the compounds involved through a more qualitative approach, rather than using measures of pigment intensity or Melasma Area and Severity Index (MASI) scores. Furthermore, the study fails to provide a description of what comprises SWC. Nonetheless, with a 76.9% improvement rate in those treated with HQ, this study does support earlier evidence that HQ is effective in treating hyperpigmentation.

Interestingly, while testing glycolic acid (GA) peels for melasma, Hurley et al[26] discovered that 4% HQ monotherapy with daily application of sunscreen not only improves melasma, but is as effective as their proposed peeling regimen plus HQ. In this randomized, investigator-blind, split-face prospective trial, 21 Hispanic women (18 of whom completed the study) were treated with 4% HQ and 4 GA peels (20% concentration on first two visits then 30% at next two) on one side and 4% HQ only on the other. Both sides had a statistically significant treatment effect ($P < .001$). However, between the two groups, there was no significant difference in either the degree of pigmentation lightening or in the MASI scores from baseline to treatment end. HQ 4% cream as a monotherapy was concluded to be an adequate agent for treating melasma.[26]

The available concentrations of HQ vary from 1.5% to 4% (Table IV). Concentrations of 2% or less are available in the United States in over-the-counter preparations and those with concentrations greater that 2% are available only by prescription. In the

Table II. Studies involving commonly used topical agents for the management of melasma

Treatment	Study	Design	No. of patients E	No. of patients C	R1	R2	Duration	Results
Sunscreen	Vazquez et al (1983)[22]	R, DB	59	53	Sunscreen + HQ	Placebo + HQ	3 mo	R1: 96.3% showed improvement. R2: 80.8% showed improvement. No significant difference between R1 and R2.
HQ	Amer et al (1998)[24]	O	50*	48*	HQ 4%		12 wk	Good to excellent response in 89.5% of those with melasma.
	Haddad et al (2003)[25]	R, DB, SF	30 R1 = 15 R2 = 15	25 R1 = 12 R2 = 13	HQ 4% vs placebo	SWC 5% vs placebo	3 mo	R1: improvement of 76.9% on HQ side. R2: improvement of 66.7% on SWC side.
Tretinoin	Griffiths et al (1993)[32]	R, DB	50 R1 = 26 R2 = 24	38 R1 = 19 R2 = 19	Tretinoin 0.1%	Vehicle	40 wk	R1: 68% improved; significant over baseline ($P = .0003$). R2: 5% improved. Epidermal pigment reduced by 36% in R1, but increased by 50% in R2 ($P = .002$).
	Kimbrough-Green et al (1994)[33]	R, DB	30 R1 = 15 R2 = 15	28 R1 = 15 R2 = 13	Tretinoin 0.1%	Vehicle	40 wk	R1: 73% improved. R2: 46% improved; 15% worsened. R1 marginally significant better than R2 ($P = .07$).
Steroid	Neering (1975)[38]	R, O	17	16	Betamethasone 17-valerate 0.2%		3 mo	Depigmentation in 12 patients, attributed to betamethasone ($P < .05$). 25% Showed no depigmentation.
Combination	Gano et al (1979)[15]	O	20		Tretinoin 0.05% + betamethasone valerate 0.1% + HQ 2%		10 wk	65% Showed improvement. 35% Showed no improvement.
	Taylor et al (2003)[40]	R, SB	641		HQ 4% Tretinoin 0.05% + FA 0.01%	HQ 4% + tretinoin 0.05% or tretinoin 0.05% + FA 0.01% or HQ 4% + FA 0.01%	8 wk	Significantly more patients (28.6%) in R1 cleared completely ($P < .001$). Significantly more patients (77%) R1 experienced complete/near-complete clearing ($P < .001$).
AzA	Lowe et al (1998)[46]	R, DB, PG	52 R1 = 25 R2 = 27	45 R1 = 21 R2 = 24	AzA 20%	Vehicle	24 wk	R1: treatment response in 55% of patients. R2: treatment response in 12.5%.

Continued

Table II. Cont'd

Treatment	Study	Design	No. of patients E	No. of patients C	R1	R2	Duration	Results
	Verallo-Rowell et al (1989)[29]	R, DB	155 R1 = 77 R2 = 78	132 R1 = 65 R2 = 67	AzA 20%	HQ 2%	24 wk	R1: 56.9% achieved good overall improvement; 16.9% excellent; 23% fair. R2: 17.9% good; 1.5% excellent; 50.8% fair; 29.8% treatment failures. R1 differed significantly from R2 ($P < .001$).
	Balina et al (1991)[47]	R, DB	329 R1 = 164 R2 = 165	243 R1 = 122 R2 = 121	AzA 20%	HQ 4%	24 wk	R1: 64.8% good/ excellent overall result; 7.4% treatment failures. R2: 72.5% good/ excellent; 8.3% failures. No significant difference between R1 and R2.
	Kakita et al (1998)[48]	R, DB, PG	65 R1 = 31 R2 = 34	59 R1 = 29 R2 = 30	AzA 20% + GA 15%-20%	HQ 4% GA vehicle	24 wk	R1 and R2 produced equivalent overall improvement scores; no significant difference.
KA	Garcia et al (1996)[50]	R, O, SF	39	39	KA + GA	HQ + GA	3 mo	51% Had equal reduction with both regimens. 28% Had more reduction with R1. 21% Had more reduction with R2. R1 and R2 not significantly different ($P > .05$).
	Lim (1999)[49]	R, DB, R/L	43	40	KA 2% + HQ 2% + GA 10%	HQ 2% + GA 10%	12 wk	R1: more than half clearance in 60% of cases. R2: more than half clearance in 47.5% of cases. Improvement not statistically different ($P = .9$).

AzA, Azelaic acid; *C*, completed; *DB*, double-blind; *E*, enrolled; *FA*, flucinolone acetonide; *GA*, glycolic acid; *HQ*, hydroquinone; *KA*, kojic acid; *O*, open; *PG*, parallel group; *R*, randomized; *R1*, regimen 1; *R2*, regimen 2; *R/L*, right/left comparison; *SB*, single-blind; *SF*, split-face; *SWC*, skin-whitening complex.

*The study enrolled 70 patients with various pigmentary disorders, only 50 possessed melasma.

treatment of melasma, it is recommended that the HQ preparations be applied uniformly and twice daily to the affected area. It has been recommended that if no improvement is evident after an initial 2 months of use, then the drug should be discontinued[27]; however, in some cases it can take as long as 6 months for a change to appear.

Safety and tolerability. The most frequently observed reactions are mild skin irritation and sensitization, characterized by itching, burning, stinging,

Table III. Studies involving chemical peels used in the management of melasma

Treatment	Study	Design	No. of patients E	No. of patients C	R1	R2	Duration	Results
GA	Lim et al (1997)[67]	SB, R/L	10	10	Serial GA peeling (20%-70%) + GA 10% + HQ 2%	GA 10% + HQ 2%	26 wk	R1: 6 patients had slight lightening of melasma (independent assessor evaluation); 4 had moderate. R2: 7 had slight; 1 had moderate; 2 showed no change.
	Javaheri et al (2001)[66]	O	25	23	3 GA peels 50%		3 mo (peels) 3 mo (follow-up)	Improvement observed in 91% ($P < .01$).
	Hurley et al (2002)[26]	R, SB, SF	21	18	1 GA peel 20% + 1 GA peel 30% + HQ 4%	HQ 4%		Both R1 and R2 sides showed significant treatment effect compared with control ($P < .001$). No significant difference in MASI scores between R1 and R2.
	Sarkar et al (2002)[68]	O, PI	40 R1 = 20 R2 = 20	40 R1 = 20 R2 = 20	GA peels 30%-40% + MKF	MKF	21 wk	R1 had significantly better response than R2 ($P < .01$).
SA	Grimes (1999)[61]	PI	6*		2 SA peels 20% + 3 SA peels 30% + HQ 4%	HQ 4%		R1 resulted in moderate to significant improvement in 4 of 6 patients with melasma.
TCA	Chun et al (2004)[63]		20†	20	TCA peels 10%-50%			55% of those with melasma experienced a good clinical response.

C, Completed; *E*, enrolled; *GA*, glycolic acid; *HQ*, hydroquinone; *MASI*, Melasma Area and Severity Index; *MKF*, modified Kligman's HQ formula; *O*, open; *PI*, pilot investigation; *R*, randomized; *R1*, regimen 1; *R2*, regimen 2; *R/L*, right/left comparison; *SA*, salicylic acid; *SB*, single-blind; *SF*, split-face; *TCA*, trichloroacetic acid.

*The study enrolled 25 patients with various dermatologic disorders, only 6 possessed melasma.

†The study enrolled 106 patients with various pigmentary disorders, only 20 possessed melasma.

and allergic dermatitis, and have been reported to occur more frequently with 4% than 2% concentrations. Chronic use of high concentrations of HQ ($\geq$5%) have been reported to produce ochronosis and colloid milium.[27]

In the study by Amer and Metwalli,[24] local irritation was noted in most patients, but exogenous ochronosis was not observed. The randomized, controlled study by Haddad et al[25] reported that the incidence of side effects was greater among the HQ group than the SWC group, where 25% of the HQ group reported an itchy eruption. This was not statistically significant from the SWC group, which had no reports of side effects.

Bentley-Phillips and Bayles[28] conducted a 6-year investigation designed to assess the safety of HQ in cosmetic skin-lightening products and to determine an optimal concentration. Through the use of open and closed patch testing of 840 volunteers (resulting in 7000 test areas) they determined that HQ is a suitable for use in cosmetics, provided that the content is kept below a certain limit. HQ 3% concentration was determined to be the optimal strength. Interestingly, their impression from clinical observations was that many of the side effects experienced may occur from misuse, excessive use, and the application of multiple preparations.[28] It has also been suggested that patients may use unsuitable cleansing agents, carry out vigorous rubbing of the affected areas, and apply excessive amounts of medication.[29]

Tretinoin

Mechanism of action. Retinoids, such as vitamin A acid and retinoic acid (RA) or tretinoin, were

Table IV. Products available in North America containing hydroquinone as the active ingredient[27,84]

	Vehicle	Concentration	Name
OTC	Cream	1.5%	Esoterica Unscented, Medicis Canada Ltd Esoterica Sensitive Skin, Medicis
		1.8%	Drula Fade Cream Medium-Medicated, Drula-Fabrik,Dr. O. Druckery GMBH
		2%	Banishing Cream 2%, Avon Canada Inc Creme Blanchissante 2%, Dr. Daniel Products Eldopaque Cream 2%, ICN Canada Ltd Eldopaque, Valeant Eldoquin Cream 2%, ICN Canada Ltd Eldoquin, Valeant Esoterica Facial Cream, Medicis Canada Ltd Esoterica Regular Cream, Medicis Canada Ltd Esoterica Sunscreen Fade Cream, Medicis Canada Ltd Esoterica Regular with papabens propylene glycoland sodium bisulfite, Medicis Esoterica Facial, Medicis Esoterica Sunscreen, Medicis Obagi Protocols Clear, Obagi Medical Products Inc Palmer's Skin Success Fade Cream, E. T. Browne Drug Co Inc Seequin 2 IDS, Vivier Canada Inc Solaquin 2% Cream, ICN Canada Ltd Solaquin, Valeant Ultraplus Skin Lightening Cream—2%, Ultracare Laboratories Inc Vantex Skin Bleaching Cream with Sunscreen 2%, Fashion Fair Cosmetics
	Lotion	2%	Clairissime Clear Complexion Lotion, Ayotai Canada Inc Fading Fluid, Flageoli Limited Rodan and Fields Proactiv Solution: Skin LighteningLotion, Guthy Renker Corp
	Gel	2%	Conditioning Gel, Laboratoires La Roche-Posay Canada Neostrata HQ AHA Gel 2%, Canderm Pharma Inc
Prescription	Solution	3%	Melanex, Neutrogena Melquin-3, Stratus Hydroquinone Solution, Glades
	Cream	4%	Drula Fade Cream Superforte Medicated, Drula-Fabrik,Dr. O. Druckery GMBH Eldopaque Forte Cream 4%, ICN Canada Ltd Eldopaque Forte, Valeant Eldoquin Forte Cream 4%, ICN Canada Ltd Eldoquin Forte, Valeant Glyquin XM, ICN Canada Ltd Hydroquinone Cream, Ethex, Glades Hydroquinone with Sunscreens, Ethex, Glades Lustra, Taropharma, A Division Of Taro Pharmaceuticals Inc Lustra-AF, Taropharma, A Division Of Taro Pharmaceuticals Inc Melpaque HP, Stratus Melquin HP, Stratus Neostrata Canada HQ Plus Cream, Canderm Pharma Inc Nuquin HP, Stratus Solaquin Forte 4% Cream, ICN Canada Ltd Solaquin Forte, Valeant Ultraquin Cream 4%, Canderm Pharma Inc Ultraquin Plain Cream 4%, Canderm Pharma Inc Viquin Forte With Moisturizing AHA-Cream, ICN Canada Ltd Viquin Forte, Valeant
	Gel	4%	Hydroquinone Forte Gel, Glades Neostrata Canada Hq Plus Gel, Canderm Pharma Inc Nuquin HP, Stratus Seequin 4 IDS, Vivier Canada Inc Solaquin Forte, Valeant Ultraquin Gel 4%, Canderm Pharma Inc

OTC, Over the counter.

first used in combination with HQ to enhance the penetration of HQ, but were later recognized to have their own effect on the pigment.[30] Tretinoin's ability to depigment is based on its ability to disperse keratinocyte pigment granules, interfere with pigment transfer, and accelerate epidermal turnover and, therefore, pigment loss.[31] In addition, there is also evidence that it can inhibit the induction of tyrosinase, DOPAchrome conversion factor, and melanogenesis.[1]

Efficacy. Griffiths et al[32] randomized 50 Caucasian women (38 of whom completed treatment) with facial melasma into a 40-week study of topical 0.1% tretinoin versus vehicle. Efficacy was assessed based on overall clinical response, graded on a scale ranging from −2 (much worse than baseline) to 2 (much improved). The color of melasma was graded as −3 much darker than baseline, −2 darker, −1 slightly darker, 0 no change, 1 slightly lighter, 2 lighter, and 3 much lighter. Overall severity under Wood's light was assessed on a scale where 0 was no melasma, 1 to 3 was mild, 4 to 6 moderate, and 7 to 9 severe melasma. Colorimetry and histologic analysis were also performed. In the tretinoin-treated group, 68% (13 of 19) were rated as improved or much improved, versus 5% of the vehicle group. Reduction of overall severity in the tretinoin group was significantly greater than the vehicle group ($P = .0003$). Furthermore, tretinoin significantly lightened areas of melasma to a value of 1.5 ± 0.3 U, but the vehicle-treated areas were actually darkened to a value of -0.1 ± 0.1 U ($P < .0001$). These results were consistent with the results of colorimetry, which also showed lightening with tretinoin and darkening with the vehicle. Histology showed that epidermal pigment was reduced by 36% after tretinoin treatment, but there was a 50% increase with the vehicle.[32]

Kimbrough-Green et al[33] randomized 30 African American patients (28 of whom completed treatment) with moderate to severe melasma into a double-blind 40-week study involving 0.1% tretinoin cream versus vehicle. At study end, the average MASI score for the tretinoin group decreased by 32%; the vehicle group experienced a 10% decrease. Overall response at week 40 was only marginally statistically significant compared with vehicle ($P = .07$). Of the 15 (73%) patients treated with tretinoin, 11 were considered improved or much improved, whereas 6 of 13 (46%) patients using vehicle improved. No clinical worsening was observed with tretinoin, but 15% of patients using vehicle rated as worse at trial end. Colorimetric analysis revealed a 40% lightening toward normal skin color within the tretinoin group, compared with a 4% lightening in the vehicle group. Histologic analysis indicated that tretinoin therapy produced an 8% decrease in epidermal pigmentation, whereas there was a 55% increase with the vehicle.[33]

Tretinoin is available in 3 forms: gel, cream, and liquid, at strengths ranging from 0.01% to 0.1%[27] and is approved for the treatment of acne vulgaris and photoaging.[27,34] As a monotherapy it is not an approved treatment for melasma; however, it is part of a combination HQ, tretinoin, and fluocinolone acetonide (FA) cream (Tri-Luma, Galderma, Fort Worth, Tex) which is an approved treatment for melasma.[34]

Safety and tolerability. The most common side effects of tretinoin include a retinoid dermatitis characterized by burning or stinging, erythema, scaling, and dry skin.[35] Given that tretinoin can be irritating, the dose must be adjusted to prevent inflammation. This inflammation may cause hyperpigmentation, especially in those with dark skin. Fortunately, most adverse effects (AEs) are reversible on discontinuation of therapy, although the hyperpigmentation/hypopigmentation may persist for many months.[36]

Cutaneous reactions reported by Griffiths et al[32] were considered moderate in 88% of patients treated with tretinoin and 29% of those receiving vehicle. In 5 members (20%) of the tretinoin group the reaction was considered to be severe (grade 4); this was not seen with the vehicle.[32] Kimbrough-Green et al[33] reported that cutaneous reactions were limited to erythema, peeling, or both of the area of application and were observed in 67% (10 of 15) of the patients treated with tretinoin and in one patient treated with vehicle. The side effects were characterized as generally mild and resulted in no patient withdrawals. No patient experienced hyperpigmentation.[33]

Those sensitive to acitretin, etretinate, isotretinoin, or other vitamin A derivatives may also be sensitive to tretinoin.[36] In addition, patients using vitamin A acid can also be at an increased risk for sunburn and are more susceptible to irritation from wind, cold, and dryness.[35] Topical tretinoin is not considered mutagenic or carcinogenic, however, animal tests have demonstrated evidence for teratogenicity. There have not been adequate and well-controlled studies performed in pregnant women. In addition, the safety of tretinoin gel has not been established in children younger than 12 years, neither has the safety of the emollient cream in patients younger than 18 years.[27]

Corticosteroids

Mechanism of action. It has been suggested that corticosteroids may directly affect the synthesis of melanin, although the mechanism by which the skin is lightened is not completely known. Melanocytes respond to a variety of chemical mediators such as prostaglandins and leukotrienes and, thus, it has

been theorized that steroids might alter melanocyte function by inhibition of prostaglandin or cytokine production by various cells of the epidermis.[30] Corticosteroids may suppress secretory metabolic products from melanocytes without causing their destruction, and this could be the reason for their short-lived effect on pigmentation disorders.[37]

Efficacy. The use of corticosteroids in the treatment of melasma is seen more often in conjunction with other topical therapies (eg, tretinoin and HQ). As a monotherapy there has been little published research, resulting in only two small-scale studies.

Neering[38] investigated betamethasone 17-valerate 0.2%, twice-daily application for 3 months, as a monotherapy for melasma. In this randomized, double-blind, split-face study of 15 patients with melasma and one with secondary pigmentation, there was a significant depigmentation effect from betamethasone ($P < .05$). A gradual depigmentation was noted in 12 patients, where 9 patients achieved a good improvement and 3 displayed a moderate improvement. Four patients had no depigmentation. Unfortunately, the study failed to assess whether the improvement caused by steroid treatment was a long-term benefit.[38]

In a letter to the editor, Kanwar et al[37] outlined the treatment of 10 patients with melasma and the topical corticosteroid clobetasol propionate (0.05%), reporting fading of pigmentation after 2 weeks, with 80% to 90% clearance of pigment observed in 7 patients after only 6 to 8 weeks. This initial clearance of pigment was, however, short lived, lasting at maximum 6 months and in some only a couple of weeks.[37]

Safety and tolerability. With steroid use patients can develop a rosacea-like eruption with persistent erythema, pustules, and papules in a centrofacial distribution (which can flare when steroid is withdrawn, but then clear after 1-3 months). Perioral dermatitis, seen predominately in adult women, is also possible. Occasionally and paradoxically, corticosteroids, which are often used to treat allergic disorders, can themselves produce allergic contact dermatitis.[39] Neering[38] noted that the side effects with betamethasone consisted mainly of an itching sensation.[38]

Atrophic changes are a commonly encountered side effect.[39] Even in a small-scale study, such as that of Kanwar et al,[37] 3 patients had to cease treatment after 4 weeks because of local atrophy and the appearance of telangiectasias after application of clobetasone propionate 0.05%. However, in the trial with betamethasone,[38] atrophy was not seen. Because of atrophy and other side effects, monotherapy with topical steroids, especially high-potency steroids, for melasma is not a recommended therapeutic option.

Combination therapy: HQ, tretinoin, and a steroid

An effective treatment for epidermal hypermelanosis is a combination of HQ, a steroid, and tretinoin. The combination strongly inhibits the production of melanin without the destruction of melanocytes. Kligman and Willis[31] proposed a preparation containing HQ 5%, tretinoin 0.1%, and dexamethasone 21-acetate 0.1%, to be applied daily for 5 to 7 weeks, and it was found to be effective in the treatment of melasma. In addition, they discovered that omitting any one component resulted in a loss of effectiveness. Lowering the concentrations of the components decreased the frequency of irritancy, but also decreased the potency of the mixture.[31] Despite its effectiveness, this preparation contains high concentrations of tretinoin and HQ, and uses dexamethasone, which is a potent fluorinated steroid.

Over the years this combination has been altered to obtain a formulation with less severe side effects, while maintaining or improving efficacy. Gano and Garcia[15] treated melasma with tretinoin 0.05%, betamethasone valerate cream 0.1%, and HQ cream 2.0% for 10 weeks and found a 65% improvement. The side effects were frequent but minimal in severity and the treatment was considered to be successful even during the spring and early summer when there is an increase in UV light exposure.[15] Pathak et al[21] evaluated treatment regimens that included 2% to 5% HQ creams, with or without 0.05% or 0.1% RA, applied twice daily for 3 months. The enhanced pigment-producing activity of melanocytes was best diminished by the avoidance of sunlight and the use of the combination formula containing low concentrations of HQ and RA.[21]

More recently, Taylor et al,[40] with 641 patients, investigated the effects of 4% HQ in combination with 0.05% tretinoin (RA), and 0.01% FA. This combination (Tri-Luma) is currently approved in the United States for the treatment of melasma. This multicenter, randomized, investigator-blind, 8-week trial found that significantly more of the patients treated with RA, HQ, and FA (77%) experienced complete or near complete clearing when compared with each of the dual therapies (HQ + FA, RA + FA, RA + HQ) ($P < .001$). Application-site erythema, desquamation, burning, dryness, and pruritus were the most frequently experienced side effects. This triple combination was considered to be well tolerated overall and skin atrophy was seen in only one patient in the trial. This patient was in the group that received HQ and steroid but not tretinoin.[40] There is

evidence that suggests that retinoids used in conjunction with steroids will help prevent the skin atrophy associated with topical steroid use[41,42]; however, caution should still be exercised when using treatments that involve a steroid component, especially on facial skin.

Torok et al[43] in an open-design study of this combination cream therapy (HQ 4%, tretinoin 0.05%, FA 0.01%) followed up 228 patients with facial melasma (173 of whom completed the study). The cream was applied once daily and patients were assessed on a monthly basis until there was a satisfactory resolution (severity score of 0 or 1), at which time treatment was stopped. If melasma worsened patients were retreated for 8 weeks. Some patients received several courses of treatment during the 12-month study. Of patients who received treatment, 129 (57%) experienced treatment-related AEs, the most frequently reported of which were application-site desquamation and erythema, occurring in approximately a third of patients. Most treatment-related AEs were considered mild and transient and did not result in withdrawal from the study. The incidence of application-site AEs increased as the number of courses of treatment increased, up to 6 months, at which time this trend stabilized. There were no cases of skin atrophy or thinning, rosacea, or hypopigmentation. Other AEs included acne/acne breakouts, perioral dermatitis, hyperpigmentation, and telangiectasia.[43]

Azelaic acid

Mechanism of action. Although the entire mechanism of action for azelaic acid (AzA) is not fully understood, AzA has anti-inflammatory, antibacterial, and antikeratinizing effects, which make it useful in a variety of dermatologic conditions. It is a naturally occurring 9 carbon straight chain dicarboxylic acid, which acts on hyperactive and abnormal melanocytes by competitively inhibiting tyrosinase.[44] Furthermore, part of its effect may result from its inhibitory effects on reactive oxygen species, allowing for a reduction in oxidative tissue injury at sites of inflammation and in melanin formation.[45]

Efficacy. Lowe et al,[46] in a 24-week multicenter, randomized, double-blind, parallel-group study of 52 patients, assessed the efficacy, safety, and tolerability of AzA 20% cream compared with its vehicle for the treatment of facial hyperpigmentation in individuals of phototypes IV to VI. Of the 25 patients treated with AzA and the 27 treated with vehicle, 21 and 24 patients, respectively, completed the study. The investigator's subjective scale found that the AzA group had a significantly greater decrease in pigment intensity than the vehicle group at both weeks 16 (P = .044) and 24 (P = .021). At week 24 mean pigment intensity scores significantly decreased in the AzA group (20.0% decrease) over the vehicle group (3.9% decrease) (P = .021). By study end, 55% of patients treated with AzA versus 12.5% of those treated with vehicle experienced an improvement of pigment intensity by one or more grades. The AzA group showed a significant improvement in pigment intensity as measured by a chromometer over the vehicle group (P = .039). Pigment intensity decreased from 4.29 to 3.39 in the AzA group, whereas it increased from 5.35 to 5.41 in the vehicle group. Overall global improvement was graded significantly higher in the AzA group compared with vehicle at weeks 12 (P = .026), 20 (P = .030), and 24 (P = .008). Despite other measures of efficacy showing AzA superiority, there were no significant between-group differences with respect to lesion area during the study.[46]

A double-blind comparison between 20% AzA and 2% HQ creams performed by Verallo-Rowell et al[29] randomized 155 patients (n = 77 AzA, n = 78 HQ) with melasma into a 24-week study. Pigment intensity was assessed using a 5-point grading scale in comparison with the patient's typical skin color, where 1 represented no difference, 2 slightly more pigmented, 3 moderately more pigmented, 4 markedly more pigmented, and 5 intensely more pigmented. In all, 65 (84.4%) and 67 (85.9%) of patients from the AzA and HQ groups, respectively, completed the study. Of the patients in the AzA group, 57% had a reduction by 2 or 3 levels in pigment intensity. The HQ group experienced reduction of 2 or 3 levels of pigment intensity in 37% of patients; this was significantly different from the AzA group ($P < .5$; χ^2 test). Reduction of lesion size was seen in more patients treated with AzA than HQ. In all, 48 patients using AzA possessed a favorable therapeutic response after 24 weeks (11, excellent overall improvement; 37, good; 15, fair; 2 failures), whereas the HQ group yielded 1 excellent improvement, 12 good, 34 fair, and 20 patients were treatment failures. The overall results were significantly different between the AzA and HQ groups ($P < .001$; χ^2 test).[29]

A 24-week randomized double-blind study involving 329 women by Balina and Graupe[47] compared 20% AzA cream with a 4% formulation of HQ. In all, 122 patients in the AzA group and 121 in the HQ group completed treatment. There was a 71% reduction in median lesion size in the AzA group and a 78% reduction in the HQ group. A more than 50% reduction in initial lesion size was seen in 60% and 66% of patients using AzA and HQ, respectively. A reduction by 1 to 3 levels of pigment intensity

appeared in 84.2% and 89.2% of patients using AZA and HQ, respectively. There was no significant difference between the two groups for either lesion size or pigment intensity. Good or excellent overall results were achieved by 64.8% (79 patients) of the AzA group, versus 72.5% (87 patients) of the HQ group (*P* not significant).[47]

A multicenter, randomized, double-blind, parallel-group study of patients with facial hyperpigmentation involving the combination of AzA 20% and GA 15% or 20% in comparison with HQ 4% was conducted by Kakita and Lowe.[48] At week 24, overall improvement, reduction in lesion area, pigment intensity, and disease severity were comparable between the two groups. The combination of AzA and GA was as effective as 4% HQ cream, with a slightly higher rate of local irritation in the latter group. Unfortunately, the impact of GA on the efficacy of AzA was not reported and, thus, it is difficult to accurately determine whether these data would support the findings of other RCTs involving AzA and HQ.[48]

The vehicle-controlled study indicates that AzA may be helpful in improving melasma and data suggest that in the treatment of melasma 20% AzA cream is more effective than 2% HQ, and of comparable efficacy to 4% HQ. Topical AzA 20% cream is used as an off-label treatment for melasma. Available by prescription, it should be applied on a twice-daily basis and treatment maintained over a period of at least 2 to 3 months.[36]

Safety and tolerability. Topical administration of 20% AzA has produced pruritus, burning, stinging, and tingling in 1% to 5% of patients. Other adverse reactions, such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis, have been reported in less than 1% of patients. Rarely asthma, vitiligo, small depigmented spots, hypertrichosis, development of keratosis pilaris, and exacerbation of recurrent herpes labialis may occur.[34]

Lowe et al[46] found that mean severity scores of signs and symptoms were less than 1 (below trace levels) for all signs and symptoms throughout the study. However, AzA caused significantly more burning at weeks 4 ($P = .046$) and 12 ($P = .021$), and significantly more stinging at week 4 ($P = .002$), than the vehicle. There were no significant between-group differences for oiliness, dryness, erythema, or peeling.[46] Verallo-Rowell et al[29] found that mild, transient, local irritant sensations were reported by 11 patients using AzA and that 5 patients using AzA experienced pronounced primary irritant reactions. Local side effects presenting as scaling or erythema were seen in only two cases (AzA).[29] Balina and Graupe[47] reported pronounced local irritant effects in 18 patients using AzA. However, the study characterized most of the irritant effects as mild and transient.[47]

Other topical agents

Kojic acid is not an approved treatment for melasma and we could not retrieve any RCTs comparing kojic acid as a monotherapy to either vehicle/placebo or any current melasma treatments. However, because both kojic acid and HQ are tyrosinase inhibitors, the combination should be expected to augment efficacy.[49] Thus, those who do not respond to HQ and GA may benefit from the addition of kojic acid to the treatment regimen.[49,50] There have been two studies performed in which kojic acid has been used in combination with other therapies to treat facial hyperpigmentation. In a randomized, split-face, study of 39 patients with facial hyperpigmentation, Garcia and Fulton[50] found that 51% of patients had an equal reduction on both the kojic acid 2% plus GA 5% side and the HQ 2% plus GA 5% sides of their faces. Furthermore, 28% and 21% of patients improved with kojic acid and HQ, respectively ($P > .05$), suggesting that kojic acid and 2% HQ are similarly effective in melasma. Every patient experienced some burning and desquamation during an initial accommodation phase; however, kojic acid was considered to be more irritating.[50] In a double-blind right/left comparison of 40 Chinese women performed by Lim,[49] melasma cleared in 60% of patients using kojic acid 2%, HQ 2%, and GA 10%; however, there was clearance in 47.5% of patients using HQ and GA alone. Although the addition of kojic acid did not worsen melasma, 45% of patients had an equal reduction in melasma on both sides of the face and neither formulation was effective in clearing the melasma completely. Furthermore, although the methods of the study state that nonparametric Wilcoxon's rank sum test for paired samples was used for statistical analysis, the results of this study were presented with no mention of *P* values or that significance had been attained between the two groups. Side effects were seen regardless of the kojic acid content and all patients experienced redness, stinging, and mild exfoliation.[49]

Four-isopropylcatechol (4-IPC) is a phenolic compound that relies on selective melanocyte toxicity, which results in cutaneous depigmentation from a loss of functional melanocytes. The probable mode of action is competitive inhibition, because 4-IPC acts as a substrate for tyrosinase.[51] In a study of 68 patients with various pigmentary disorders, 54 of whom possessed melasma, patients were treated with either 1% or 3% 4-IPC.[51] Treatment with 3% IPC was noted

to be more effective than 1%, as it produced an earlier detectable depigmentation; however, this higher concentration was noted as being more irritating, and it more frequently produced side effects. Treatment response to 4-IPC was considered good, as 42 of 54 showed improvement; however, many patients reported redness and scaling of the skin, especially with the 3% formulation. Patch testing indicated that 4 patients experienced allergic contact dermatitis. One patient experienced confetti-like areas of depigmentation in the IPC-treated areas after 5 months of treatment.[51] There have been no published studies involving the treatment of hypermelanosis with 4-IPC since this study in 1976[51] and it is not a recommended mode of treatment.

N-acetyl-4-S-cysteaminylphenol works specifically on melanocytes with active synthesis of melanin to inactivate their function.[52,53] Jimbow,[52] in a small-scale study including 12 patients using 4% N-acetyl-4-S-cysteaminylphenol in an oil-in-water emulsion applied twice daily for up to 6 months, found marked improvement in 8 patients, and almost complete clearance of melasma in one patient. Light microscopy showed that N-acetyl-4-S-cysteaminylphenol–treated skin had a marked decrease in visible melanin pigment in the epidermis. None of the patients reported side effects such as local irritation. There was, however, recurrence of pigmentation in one patient after withdrawal of treatment.[52]

Leenutaphong et al,[54] using a 40-week, randomized, vehicle-controlled clinical trial of 30 Thai patients (23 of whom completed treatment), found that there was no difference between topical 0.05% isotretinoin and its vehicle in the treatment of melasma.

Adapalene is a stable naphthoic acid derivative that controls cell proliferation and differentiation, and has significant anti-inflammatory action.[55] Dogra et al,[55] in a preliminary report of a randomized clinical trial comparing the efficacy and patient acceptability of tretinoin 0.05% and adapalene 0.1% in 30 Indian female patients, found no significant statistical difference between the two groups with regard to efficacy. Side effects were more frequent in the tretinoin group.

Recent study has shown that certain components, or flavonoids, from licorice roots, such as glabrene and isoliquiritigenin, are effective tyrosinase inhibitors and can, thus, act as bleaching agents.[56] Liquirtin, also a flavonoid found in licorice extracts, is available in a 2% cream and has the ability to cause depigmentation by two different mechanisms, through melanin dispersibility and by its amelanodermic and epidermal stain-removing property.[57] A split-face study of 20 women with idiopathic melasma evaluating the efficacy of liquirtin reported that 80% of the treated cases had an excellent response, with mild irritation (erythema and a slight burning sensation) occurring in 20% of those tested, suggesting a possible regimen of 1 g/d for 4 weeks.[57]

L-ascorbic-2-phosphate (magnesium-L-ascorbyl-2-phosphate; VC-PMG) is a stable vitamin C derivative that suppresses melanin production. Kameyama et al[58] found that applying VC-PMG cream 10% twice daily to the skin of 34 patients with pigmentary disorders (including chloasma, senile freckles, ephelides, and nevus of Ota) produced an improvement in 55% of those treated, suggesting that it may be effective in reducing hyperpigmentation.

Oral therapy

Pycnogenol is a French maritime pine (*Pinus pinaster*) bark extract, containing monomeric phenolic compounds and condensed flavonoids.[59] Pycnogenol has both antioxidant and anti-inflammatory properties. UV radiation generates reactive oxygen species, and exposure to the sun can cause erythema and inflammation, with the production of melasma.[59] A 30-day open-design trial of 30 women found that Pycnogenol (25 mg) administered orally 3 times daily decreased the average pigment intensity ($P < .001$) and the average melasma area ($P < .001$). There were no side effects or untoward reactions observed during the treatment. The tolerability of the drug was good and it was considered systematically safe based on evaluation of biochemical and hematologic parameters.[59]

A small-scale, open-design study of 12 Japanese women with facial chloasma (melasma) investigated the effects of proanthocyanidin-rich grape seed extract orally administered for 6 months. Treatment was stopped for 2 months and then 11 of the 12 participants received treatment for an additional 5 months. The first 6 months of grape seed extract treatment showed improvement or slight improvement in 10 of 12 women (83%, $P < .01$). The following 5 months showed improvement or slight improvement in 6 of 11 participants (54%, $P < .01$). The melanin index significantly decreased after 6 months of treatment ($P < .01$); it also decreased at the end of the study ($P < .05$).[60]

Both of these treatments require further study, particularly in the form of large-scale, blinded RCTs, before they can be recommend as therapeutic options.

Chemical peels

The mechanism of action of chemical peeling agents is the removal of melanin, rather than the inhibition of melanocytes or melanogenesis, as in previously discussed treatments. Peels are usually well tolerated by individuals with lighter

complexion; however, dermatologists have been more cautious when performing chemical peels in darker racial-ethnic groups for several reasons, including the risk of PIH and the aggravation of melasma itself.[61] The risk of complications from chemical peels increases proportionately with the depth of the wound. Superficial peels carry the lowest risk of adverse reactions, but have still been associated with hyperpigmentation. Common adverse reactions to all types and depths of peel are persistent postpeel erythema, and the possibility of infection, although these infections are less frequently encountered.[62]

Although several peeling agents have been studied for the treatment of melasma, including salicylic acid,[61] trichloroacetic acid (TCA),[63] tretinoin,[64] and resorcinol,[65] GA peels[26,66-68] remain the most popular. This may be because studies have characterized them as an useful adjunct in the treatment of melasma, as they are easy to administer, generally safe, require little to no downtime, scarring is uncommon, and postpeel hyperpigmentation or persistent erythema is rarely seen.[67]

GA peels. Often used as an ingredient (frequently in a 10% concentration) in skin-lightening creams, GA, an alpha hydroxy acid, is also used at higher strengths (>20%) as a peeling agent. Lim and Tham[67] conducted a 26-week, single-blind, right/left small-scale study involving 10 Asian women who were treated with GA peels 20%-70% every 3 weeks on one side of the face and a HQ 2% plus GA 10% cream applied to both sides. Improvement in color of melasma was graded on a scale of −1 (worse than baseline), 0 (no change), 1 (0-33% lighter), 2 (34%-66% lighter), and 3 (>66% lighter). At study end, both patient and investigator assessment indicated that the side that had experienced the peels was lighter compared with baseline in all patients. Investigator assessment also found that a melasma color score of 1 was attained by 6 patients and a score of 2 by 4 patients on the peel side of the face. On the control side of the face (HQ + GA cream only), 7 patients had a score of 1, one patient had a score of 2, and no change was seen in two patients. Some stinging and redness was experienced during and after each peel. One patient had a burn after a 20% GA peel, which resulted in a transient hyperpigmentation that cleared within 2 months. There was no scarring or worsening of melasma.[67]

Javaheri et al[66] performed a study with 25 women with melasma. The degree of improvement was measured based on changes in MASI scores. The response of each patient was graded as no response (no decrease in MASI score), mild (<25%), moderate (25% to <50%), good (50% to <75%), and very good (>75%). A total of 23 patients completed the study. In the 70% of patients, reduction of pigmentation was apparent after the first peel. At the end of the third peel, 4 patients demonstrated a good response, 11 had a moderate response, and 6 showed a mild response. Two patients did not show improvement. Overall, improvement in melasma (reduction in MASI) was observed in 91% of patients ($P < .01$). Patients with epidermal type melasma demonstrated a better response to treatment than those with mixed type melasma ($P < .05$). At treatment end, one patient experienced a mild degree of treatment-induced hyperpigmentation, but during follow-up no other patient developed any symptoms.[66]

In a randomized, investigator-blind, split-face prospective trial,[26] 21 Hispanic women with melasma were treated with 4 GA peels (either 20% or 30%) plus 4% HQ on one side of the face and 4% HQ cream alone on the other. Of the 18 patients who completed the study there was no significant difference in the degree of lightening, or difference in the MASI scores from baseline to study end, between the two groups. The physician global evaluation showed that 8 patients had more improvement on the peeled side versus 7 patients with more improvement on the nonpeeled side. Most patients felt tingling and some developed mild erythema. From this study it seems that, although GA peels may improve melasma, they are no more effective than HQ alone. However, it should be noted that these investigators recommended that more studies be done comparing the efficacy of HQ with GA peels.[26]

Sarkar et al[68] enrolled 40 Indian patients, Fitzpatrick skin types III to V, with moderate to severe melasma into a 21-week, open pilot study. The addition of GA peels (3 peels with 30% GA, and 3 peels with 40% GA) to a modified Kligman's HQ formula (MKF) produced a significantly better response in the form of lightening of melasma ($P < .01$) than MKF alone. Melasma severity and clinical response was assessed based on MASI scores, and patient subjective assessment of response (excellent, good, fair, or poor). All 40 patients completed the study. The mean MASI score for the peel group decreased from 19.12 ± 6.71 at baseline to 10.17 at week 12 (45.89%), and then to 3.93 at week 21 (77.99%) ($P < .001$). The MKF group's MASI scores decreased from 18.85 ± 5.43 at baseline to 12.52 at week 12 (33.16%), and then to 6.97 (63.14%) at week 21 ($P < .001$). There was also statistical significance between the two treatment groups at both weeks 12 and 21 ($P < .01$), with a better response in the peel group. At study end 80% of patients in the peel group graded their improvement as excellent, whereas 60% of the control group graded their improvement as

excellent. AEs were minimal in both groups; however, almost all patients in the peel group experienced mild erythema and superficial desquamation. Two patients from the peel group developed PIH, which later subsided with application of betamethasone dipropionate 0.05%, and 4 patients receiving MKF had an acneiform eruption.[68]

Other peeling agents. Grimes,[61] while studying the effects of a series of 5 salicylic acid peels (20% and 30%) on 25 patients with various pigmentary disorders (6 of whom had melasma), found that in general superficial peels were well tolerated in the patients with skin types V and VI, that side effects were absent in 84% of those treated, and there was improvement in 66% of those with melasma when treated with a combination of 4% HQ and salicylic acid.[61]

Chun et al[63] explored the use of focal TCA, a derivative of acetic acid, peeling on dark-skinned individuals with various pigmented lesions, including melasma. There was focal application of TCA at concentrations of 10% to 50% to 20 patients with melasma. In all, 11 patients (55%) experienced good clinical response. There were no significant complications reported, such as persistent erythema, hyperpigmentation, herpes simplex flare up, scarring, or keloids. Mild erythema and transient PIH occurred only in rare cases. The study concluded that focal TCA peels are a safe and effective method of treating benign pigmented lesions[63]; however, large-scale RCTs are needed to properly assess its usefulness in conditions of hypermelanosis.

Dermabrasion

Kunachak et al,[69] in a large-scale study of 533 patients with melasma, found that 398 patients (97%) of the 410 patients available for long-term follow-up achieved clearance of melasma without recurrence. Some patients developed hyperpigmentation or increasing hyperemia, which was usually as a result of sun exposure, and was easily controlled by 3% to 5% topical HQ or 0.1% triamcinolone.[69] Other reactions to dermabrasion can include keloid formation, milia, pruritus, enlarged pores, PIH and pigmentary changes, and loss of skin texture. The prevalence of these reactions, especially PIH, may be why dermabrasion has been studied as a possible therapy for melasma but is not a standard treatment modality.

Intense pulsed light therapy

Moreno Arias and Ferrando[70] followed up 20 patients with various pigmented lesions treated with intense pulsed light (IPL). Those with superficial lesions, such as epidermal melasma, were treated with two pulses, whereas deeper lesions, such as mixed melasma, were treated with 4 pulses. A clearance of 76% to 100% was obtained for superficial lesions (eg, epidermal melasma); however, those with deep pigmented lesions (including mixed melasma) showed only a fair or poor clearance (<50%). PIH was observed in patients with mixed melasma, and the majority of patients had mild to moderate pain and burning sensation. However, burns, scarring, and hypopigmentation were not observed. The study concluded that IPL is an effective therapeutic choice for the removal of melanocytic lesions, especially those epidermal in nature; however, long-term sun protection and bleaching creams should be used after treatment of patients with mixed melasma, because of a higher risk of PIH.[70]

Wang et al[71] enrolled 33 women with melasma unresponsive to previous topical therapies into a RCT studying the effects of IPL. Every patient received 4% HQ and sunscreen to prevent possible PIH. In all, 17 patients were treated with IPL in 4 sessions at 4-week intervals and 16 patients entered the control group (4% HQ cream + sunscreen only). In all, 31 patients completed the study (17 IPL, 14 control) at week 16. After 4 sessions with IPL there was a 39.8% improvement compared with baseline ($P < .005$). Of patients with IPL, 35% received excellent/good improvement level (51%-100%). The control group experienced an 11.6% change in pigment intensity ($P > .05$) from baseline and 14% of the control achieved the good level (51%-75%). The difference in improvement rate between the two groups was significant ($P < .05$), with a better response in the IPL group. However, follow-up to week 36 indicated that additional treatments are necessary to maintain results. Erythema and pain were noted with the first treatment, but were mild and short lived. There were no incidences of infection or scarring. There were two cases of PIH, but this resolved with the use of HQ and further IPL treatment. The study concluded that this modality of treatment is safe and effective for refractory melasma.[71] Furthermore, IPL could be used as an adjuvant to topical therapy to speed improvement of lesions and this may subsequently improve patient compliance.

Laser treatment

The use of lasers for the treatment of pigmentary disorders is based on the theory of selective photothermolysis, which proposes that the specific spectrum of light emitted by a particular laser is absorbed selectively by a cell or tissue type.[72] Pulses of light that are sufficiently brief (ie, shorter than the thermal relaxation time of melanosomes), and are preferentially absorbed by pigmented structures in tissue, can

cause selective heating and thermal damage to the pigmented structures.[72,73] The choice of wavelength determines depth to which the light will penetrate with sufficient energy density to effect tissue change. If the skin is irradiated with wavelengths in the 400- to 600-nm region, oxyhemoglobin will compete strongly with melanin for absorption of photons and predominately vascular damage will occur. At longer visible wavelengths (>600 nm), where absorption by oxyhemoglobin is substantially reduced or absent, absorption by melanin over blood pigments dominates with damage restricted to the melanin pigment-laden structure.[74]

Over the years there have been several different types of laser treatments tried as treatment options for melasma, with varying results. The following is a brief summary of these trials. Many of the studies have a very small patient enrollment and are often single blinded or open design, as it is difficult to blind the patient experiencing a laser treatment, unless two different laser treatments are being compared.

There are two kinds of Q-switched neodymium: yttrium-aluminum-garnet (YAG) lasers, a frequency-doubled (532 nm) and nonfrequency-doubled (1064 nm) laser. Both types of lasers target the pigment for destruction[72]; however, the frequency-doubled laser has a wavelength that is also absorbed by hemoglobin.[75] Tse et al[76] treated 20 patients possessing pigmented lesions (3 of whom had melasma) comparing the neodymium:YAG with that of the Q-switched ruby laser, and reported that neither laser was effective.

Melasma has a variable response to Q-switched ruby laser (694 nm), and most studies report poor results, with recurrences soon after treatment.[77] Goldberg[77] reported that although patients with fair complexion seem to show a greater response, melasma will often recur, sometimes fairly soon after treatment. Taylor and Anderson,[78] in a study of 8 patients with melasma (N = 4) or PIH (N = 4), found that this laser treats melasma ineffectively. Irradiation caused a 2-week worsening of pigment, followed by clearing in one patient. However, melasma began to recur after exposure to sunlight. One patient experienced confetti-like hypopigmentation, which lasted 12 months without improvement. One patient showed no change at all, and the fourth patient experienced no change after the first test and worsening of hyperpigmentation after the final testing.[78]

A combination of Q-switched alexandrite laser (755 nm) and the carbon-dioxide (CO_2) laser in a randomized pilot study containing 8 patients was effective in removing hyperpigmentation as all patients showed complete resolution.[79] The CO_2 laser alone seemed less effective as two patients acquired peripheral hyperpigmentation after treatment. This was thought to occur because of the lower energy at the edges resulting in PIH in the areas that had intact melanocytes. Despite this, the study concluded that this laser therapy is safe, as there was no scarring or infection and that the combination of the two laser therapies was effective in removing hyperpigmentation.[79] However, a split-face study of 6 Thai female patients by Angsuwarangsee and Polnikorn[80] found that with one pass of a CO_2 laser and then one pass of a Q-switched alexandrite laser, PIH was commonly found in darker skin types. In refractory melasma the combination of CO_2 lasers and Q-switched alexandrite laser was unpredictable.[80]

The erbium:YAG laser emits light with 2940-nm wavelength that is highly absorbed by water-containing tissue. This property enables the laser to ablate skin with minimal residual thermal damage, thereby potentially minimizing the risks of PIH.[81] A study by Manaloto and Alster[81] treated 10 patients (skin phototypes II-V) with 3 consecutive full-face passes. Although several properties of the laser are theoretically excellent for cutaneous resurfacing, the resultant inflammatory dermal reaction stimulates the activity of melanocytes in melasma-irradiated skin, leading to temporary worsening of the pigment. However, this study found that any PIH that developed responded well to treatment with peels and topical treatments. The study concluded that erbium:YAG laser resurfacing does effectively improve melasma; however, the almost universal appearance of transient PIH necessitates prompt and persistent intervention. The use of this laser therapy was, thus, recommended only for refractory/recalcitrant melasma.[81]

The pigmented lesion dye laser (500-520 nm) has been found to be ineffective in the treatment of deep dermal pigmented lesions such as melasma, and PIH.[82] Grekin et al[83] found that of the 10 patients treated for melasma, 8 did not obtain improvement and minimal lightening was noted in only two. Melasma does not respond well to this laser, often with hyperpigmentation resulting from treatment.[83]

CONCLUSIONS

Melasma may be treated using monotherapy or with combination therapy. HQ is a reliable treatment and MKF is also effective. These therapies, coupled with regular application of a UVA and UVB blocking sunscreen to avoid UV-induced recurrence, are the most common therapies for epidermal melasma. AzA, currently only used as an off-label treatment, has also shown notable efficacy. There are various other agents that have been studied for their effect on hypermelanosis; although some show potential,

there is also much left unknown about them. In addition, these treatments have often had very little study performed on them or the design of the study was open or pilot, and frequently with an insufficient number of patients to properly assess the validity of the treatment. Alternative treatments to topicals include chemical peels, laser treatment, and dermabrasion. The GA peel seems to have the most promise as an alternative to bleaching creams. Laser treatments seem to show limited efficacy, although in many cases the number of participants with melasma in the studies are very small. IPL has also shown potential, however, combining topical agents such as HQ, tretinoin, and a corticosteroid, in addition to patient education, sun avoidance, and regular sunscreen use is the mainstay of treatment in this difficult and frustrating condition.

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