# Treatment of melasma

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Treatment of melasma involves the use of a range of topical depigmenting agents and physical therapies. Varying degrees of success have been achieved with these therapies. The Pigmentary Disorders Academy (PDA) undertook to evaluate the clinical efficacy of the different treatments of melasma in order to generate a consensus statement on its management. Clinical papers published during the past 20 years were identified through MEDLINE searches and methodology and outcome assessed according to guidelines adapted from the US Preventive Services Task Force (USPSTF). The consensus of the group was that first-line therapy for melasma should consist of effective topical therapies, mainly fixed triple combinations. Where patients have either sensitivity to the ingredients or a triple combination therapy is unavailable, other compounds with dual ingredients (hydroquinone plus glycolic acid) or single agents (4% hydroquinone, 0.1% retinoic acid, or 20% azelaic acid) may be considered as an alternative. In patients who failed to respond to therapy, options for second-line therapy include peels either alone or in combination with topical therapy. Some patients will require therapy to maintain remission status and a combination of topical therapies should be considered. Lasers should rarely be used in the treatment of melasma and, if applied, skin type should be taken into account. ( J Am Acad Dermatol 2006;54:S272-81.)

Melasma is a pigmentary disorder of the face involving the cheeks, forehead, and commonly the upper lip. This condition is more common in women, accounting for 90% of all cases. It appears in all racial types, but occurs more frequently in those persons with Fitzpatrick skin types IV to VI who live in areas of high ultraviolet radiation; sun exposure deepens these hyperpigmented areas. Treatment of melasma involves the use of topical hypopigmenting agents, such as hydroquinone (HQ), tretinoin (RA), kojic acid, and azelaic acid. Physical therapies, such as chemical peels (glycolic acid [GA], trichloroacetic acid [TCA]), laser therapy and dermabrasion, similar to that used in other hyperpigmentary disorders, have also been evaluated with varying degrees of success.

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*Abbreviations used:*

| | |
|---|---|
| FA: | fluocinolone acetonide |
| GA: | glycolic acid |
| HQ: | hydroquinone |
| KF: | Kligman's formula |
| MASI: | Melasma Area and Severity Index |
| RA: | tretinoin |
| TCA: | trichloroacetic acid |

One aim of the Pigmentary Disorders Academy was to estimate the clinical efficacy of the different treatments of melasma in order to generate a consensus statement on its management. A MEDLINE search was conducted on therapeutic options for melasma. Clinical studies (excluding case studies) that have been published over the past 20 years were reviewed and the data classified according to specific criteria (see below). Subsequent treatment recommendations were generated on the basis of this published clinical evidence and expert opinion.

## TOPICAL THERAPIES

### Hydroquinone

HQ inhibits the conversion of dopa to melanin by inhibiting the activity of tyrosinase. Other proposed mechanisms of action are inhibition of DNA and RNA synthesis, degradation of melanosomes, and destruction of melanocytes.[1] HQ can cause permanent depigmentation when used at high concentrations for a long period of time. It is commonly used at concentrations ranging from 2% to 5%, the higher concentrations trading off greater efficacy with

greater skin irritation. Adverse effects of HQ include irritant dermatitis, contact dermatitis, postinflammatory pigmentation, ochronosis, and nail bleaching.

Because hydroquinone is a commonly used therapy for melasma, two representative placebo-controlled studies plus one comparative study have been chosen for inclusion in this review. Ennes, Paschoalick, and Mota De Avelar Alchorne[2] reported on the use of HQ 4% in a double-blind, placebo-controlled trial involving 48 patients with melasma on the face. HQ or placebo was applied twice daily for 12 weeks; both contained a sunscreen with a sun protection factor of 30. Evaluation of efficacy was based on clinical observations and photographic evaluations. Total improvement was defined as complete disappearance of the spot; partial improvement as partial disappearance, and failure as no change or worsening. Results indicated total improvement of melasma in 38% of patients treated with HQ as well as partial improvement and no treatment failures in 57% of patients; 5% of patients discontinued therapy. In the placebo group, 8% of patients had total improvement, 58% had partial improvement, but 17% were classified as treatment failures. Both therapies were well tolerated, with no serious adverse events reported. In a more recent placebo-controlled study, HQ 4% was compared with a skin whitening complex consisting of a mixture of uva ursi extract (a competitive inhibitor of tyrosinase that provokes chemical decoloration of melanin), biofermented *Aspergillus* (chelates copper ion needed for tyrosinase activity), grapefruit extract (exfoliative action), and rice extract (hydrating function) in 30 patients over a 3-month period.[3] Treatment evaluation consisted of patient questionnaires and two independent observers. According to the observer evaluations, HQ use resulted in a 77% improvement with a 25% side-effect rate, primarily pruritus, compared with a 67% improvement and 0% side effects with the skin-whitening complex.

A comparative study has recently been completed involving 4% HQ and the triple fixed combination therapy HQ 4%, RA 0.05%, and fluocinolone acetonide (FA) 0.01% (see below).[4] A total of 120 patients were randomized to one of the two treatment arms and treatment was applied for 8 weeks. Efficacy assessments involved the investigator's static evaluation of melasma severity at each visit using a scale from 0, indicating melasma lesions that were very similar to the surrounding normal skin or with minimal residual hyperpigmentation, to 3, severe (markedly darker than the surrounding normal skin). Primary success was defined as a melasma severity score of 0 at week 8. Evaluation of overall improvement was conducted by the investigator at each visit on a scale from 5, completely cleared (100%), to 1, worsening; hyperpigmentation darker than that of baseline melasma. Secondary success was defined as an improvement score between 3 and 5. Overall evaluation by the patient at week 8 involved a scale from 1, excellent, to 4, poor. At baseline, more than 98% of all patients had moderate (grade 2) or severe (grade 3) melasma. At weeks 4, 6 and 8, melasma severity scores were significantly lower in the triple therapy groups than in the hydroquinone group ($P < .003$). Primary success was achieved for 35% of patients (21/60) and for 5.1% of patients (3/59) in the triple therapy and HQ groups, respectively ($P = .0001$). Secondary success was achieved for 73% (44/60) and 49% (29/59) of patients treated with triple therapy and HQ, respectively ($P = .007$). The proportion of patients who considered that the treatment was "excellent" was greater for triple therapy (50%) than for HQ (34%). There were no significant differences between the two treatment groups for the incidence of the reported adverse events.

## Retinoids

**Tretinoin.** Tretinoin (retinoic acid [RA] or vitamin A acid) is thought to have an inhibitory effect on tyrosinase by inhibiting the enzyme's transcription, as well as on dopachrome conversion factor, with a resulting interruption of melanin synthesis.[5] RA reduces hyperpigmentation through the induction of desquamation. Concentrations ranging from 0.05% to 0.1% have been used and the associated side effects are erythema and peeling in the area of application; postinflammatory hyperpigmentation has also been reported.

RA 0.1% has been used to treat melasma in 30 black patients, with results indicating that the average Melasma Area and Severity Index (MASI) score of the tretinoin-treated group decreased by 32% from baseline compared with a 10% decrease in the vehicle control group.[6] Histological examination of treated skin revealed a significant decrease in epidermal pigmentation in the RA group compared with the control group (Table I). Side effects were limited to a mild retinoid dermatitis in 67% of RA-treated patients. Another randomized controlled study of 0.1% RA once daily in 38 Caucasian women indicated that 13 of 19 tretinoin-treated patients (68%) were clinically rated as improved or much improved, compared with 1 of 19 patients (5%) in the vehicle group ($P = .0006$).[7] Significant improvement first occurred after 24 weeks of tretinoin treatment. Colorimetry (an objective measure of skin color) demonstrated a 0.9 unit lightening of tretinoin-treated melasma and a 0.3 unit darkening with vehicle ($P = .01$); these results

**Table I.** Melasma in black skin: Histologic results after 40 weeks of topical 0.1% tretinoin versus vehicle therapy*

| Variable | Tretinoin cream 0.1% (n = 14) | | | Vehicle (n = 12) | | | *P* value† |
|---|---|---|---|---|---|---|---|
| | Baseline | Posttreatment | % Change | Baseline | Posttreatment | % Change | |
| Epidermal thickness ($\mu$m)‡ | 47 ± 2 | 66 ± 4 | +41 | 47 ± 5 | 44 ± 3 | −7 | .006 |
| Epidermal pigmentation | 1.8 ± 0.2 | 1.7 ± 0.3 | −8 | 1.8 ± 0.3 | 2.8 ± 0.1 | +55 | .0007 |
| Thickness of granular cell layer | 0.4 ± 0.1 | 2.1 ± 0.3 | +445 | 0.5 ± 0.1 | 1.2 ± 0.2 | +115 | .004 |
| Stratum corneum compaction | 0.5 ± 0.1 | 2.4 ± 0.3 | +415 | 0.8 ± 0.3 | 1.1 ± 0.3 | +44 | .003 |
| Dermal pigmentation | 2.3 ± 0.3 | 1.9 ± 0.3 | −18 | 1.5 ± 0.3 | 1.7 ± 0.3 | +11 | .16 |
| Dermal inflammation | 0.9 ± 0.2 | 1.1 ± 0.2 | +24 | 1.0 ± 0.2 | 1.0 ± 0.2 | +4 | .63 |

*All measurements represent mean ± standard error and, except for epidermal thickness, are based on a semiquantative scale of 0 (none) through 4 (maximum). Percentages were determined before rounding off the means. (From Kimbrough-Green CK, Griffiths CE, Finkel LJ. Arch Dermatol 1994;130:727-33, page 730, Copyright © 1994, American Medical Association. All rights reserved.)

†Represents significance of change from baseline in tretinoin versus vehicle groups.

‡For each patient specimen, measurements from the top of granular layer to epidermal basement membrane at 5 interrete sites were averaged.

correlated with clinical lightening. Histologically, epidermal pigment was reduced by 36% following tretinoin treatment, compared with a 50% increase with vehicle ($P$ = .002). Reduction in epidermal pigment also correlated with clinical lightening. Moderate cutaneous side effects of erythema and desquamation occurred in 88% of tretinoin-treated and in 29% of vehicle-treated patients.

**Isotretinoin.** Isotretinoin 0.05% has been studied in 30 Thai patients with moderate to severe melasma. Patients were randomized to treatment with isotretinoin plus sunscreen or vehicle plus sunscreen for 40 weeks.[8] Results showed that the MASI and Melasma Area and Melanin Index scores of treated patients decreased by 68.2% and 47%, respectively, compared with decreases of 60% and 34% for controls; although these differences were clinically important, they were not statistically significant. Side effects were limited to mild transient retinoid dermatitis in 27% of patients.

**Adapalene.** Adapalene is a naphthoic acid derivative with potent retinoid activity; it controls cell proliferation and differentiation and has significant anti-inflammatory action.[9] A randomized trial of 0.1% adapalene versus 0.05% tretinoin for 14 weeks in 30 Indian patients indicated a 41% and 37% reduction in MASI scores with adapalene and tretinoin, respectively (not significant).[10] Side effects were significantly more frequent with tretinoin than with adapalene; 63% of patients treated with tretinoin suffered with pruritus, burning, dryness, erythema and scaling compared with mild erythema and a burning sensation in 8% and dryness in 13% of patients treated with adapalene.

## Azelaic acid

Azelaic acid has antiproliferative and cytotoxic effects on melanocytes, which are mediated via inhibition of mitochondrial oxidoreductase activity and DNA synthesis.[11] It is also a weak competitive inhibitor of tyrosinase in vitro. Azelaic acid is available as a cream at a concentration of 15% to 20%. A 20% azelaic acid–based cream has been used to treat 39 patients for 6 months with two applications per day. A reduction in melasma intensity was obtained in 37 patients. A mean reduction in pigmentation of 51.3% was reported. The overall judgment of physician and patient were excellent or good in 79% and 85%, respectively.[12] A randomized, double-blind comparative study in 155 patients of Indo-Malay-Hispanic origin found that 20% azelaic acid was superior to HQ 2%.[13] Over a period of 24 weeks, 73% of the azelaic acid patients compared with 19% of the HQ patients had good to excellent overall results, as measured by the reduction of the pigmentary intensity of melasma and lesion size ($P < .001$). In a double-blind study by Balina and Graupe[14] involving 329 women, 20% azelaic acid was shown to be as effective as HQ 4%, without the latter's undesirable side-effects. In the azelaic acid–treated patients, 65% of outcomes were graded as good or excellent compared with 72.5% of those of HQ-treated patients. Azelaic acid 20% plus tretinoin 0.05% or 0.1% has been shown to be more effective in enhancing the skin lightening effects of azelaic acid alone. In an open-label randomized study of 50 patients, 24 weeks of treatment with azelaic acid 20% and azelaic acid 20% plus tretinoin 0.05% resulted in excellent results in 5.3% and 34.8% of patients, respectively.[15] Sarkar, Bhalla, and Kanwar[16] have also studied sequential therapy of the potent topical steroid clobetasol propionate and azelaic acid. Thirty Indian patients with melasma had azelaic acid 20% applied to one half of the face twice daily for 24 weeks and to the other half, clobetasol propionate 0.05% for just 8 weeks followed by azelaic acid

20% for the remaining 16 weeks. Results showed no difference at 24 weeks in the lightening produced by either treatment; 96.7% and 90% of patients had good to excellent responses with azelaic acid plus steroid and azelaic acid, respectively. Side effects of the treatments were mostly mild, transient, local itching and burning. Acneiform eruptions were observed in 5 patients receiving clobetasol propionate, but these disappeared once the steroid treatment was discontinued. Three patients withdrew from the trial because of atrophy and telangiectasia resulting from clobetasol propionate treatment, and 4 patients withdrew because of burning, erythema, and itching due to azelaic acid. The authors recommend that sequential treatment only be carried out under the supervision of a dermatologist.

### Vitamin C iontophoresis

Vitamin C inhibits melanin formation as well as reducing oxidized melanin.[17] Iontophoresis has been used to increase the penetration of vitamin C into the skin. In a comparative study, 29 patients were treated with vitamin C iontophoresis to one side of the face and water placebo to the other twice a week for 12 weeks.[18] Luminance (L) value was measured by using a colorimeter to obtain an objective parameter of the brightness of the pigmentation. A significant decrease in L value was reported on the treated side of the face (from 4.8 at baseline to 2.78 after 12 weeks) compared with placebo (4.45 at baseline to 3.87 at 12 weeks) ($P < .01$). Side effects in a small number of patients included a mild sense of electric shock, itching, erythema, burning sensation, and dryness of the face.

### N-acetyl-4-S-cysteaminylphenol

Phenolic and catecholic compounds are potent depigmenting agents of the skin. A melanocytotoxic agent, N-acetyl-4-S-cysteaminylphenol, was synthesized consisting of phenol, catechol, and sulfur.[19] A retrospective observation of 12 patients treated with 4% N-acetyl-4-S-cysteaminylphenol, a tyrosinase substrate, showed a complete loss (8%), a marked improvement (66%), or a moderate improvement (25%) of melasma lesions.[19] Visible changes in the melanin in the dermis were seen 2 to 4 weeks after daily topical application. This depigmentation was associated with a decrease in the number of functioning melanocytes and in the number of melanosomes transferred to keratinocytes.

### RA plus HQ

A study of 0.1% RA, HQ 5% plus lactic acid 7% or ascorbic acid 10% twice daily for 16 weeks in 10 Oriental patients with melasma indicated a 70% success rate assessed by using spectrophotometry.[20] Included in this group were 6 patients who needed a second course of treatment. Erythema and scaling were observed during treatment. RA 0.1% plus 3% HQ has been evaluated in 40 female Korean women in a 20-week open label study.[21] Overall, 59% of patients were rated as having excellent to good improvement by physician and patient evaluations after therapy. The majority of patients (96%) noted mild to moderate reactions to tretinoin cream. The sensations of burning, itching, erythema, and scaliness lessened with continued therapy.

### GA plus HQ

Another combination study compared 10% GA plus 4% HQ in a cream containing vitamins C and E and sunscreen with a cream containing sunscreen alone.[22] A total of 39 Hispanic women with Fitzpatrick skin types III-V and bilateral epidermal melasma were enrolled in this randomized, controlled 12-week trial. Changes in pigmentation were measured by means of a Mexameter (CK Electronic, Cologne, Germany) (spectrophotometric skin coloration measure of melanin and hemoglobin levels), the MASI, and a global evaluation by the patient and a blinded investigator. Results indicated a significant decrease in the degree of pigmentation using the study cream compared with sunscreen alone; 75% versus 13% of patients improved ($P < .0001$). Irritation was more common with the study cream, but this resolved on cessation of use and the application of moisturizers.

### GA, HQ, or kojic acid

Kojic acid, a compound derived form the fungus *Aspergillus oryzae*, has been shown to inhibit tyrosinase[23] and has been studied in combination with other agents. GA 5% combined with either 4% HQ or 4% kojic acid daily for 3 months has been compared in a split-face design in 39 patients with melasma.[24] Although none of the patients was completely cleared, both combinations proved equally effective, with reduction of pigmentation in 51% of patients; dramatic results were noted in 28% of patients treated with GA/kojic acid and in 21% treated with GA/HQ.

### HQ, RA, and steroid combinations

HQ has been studied in combination with other agents to provide greater therapeutic success than HQ alone.[4,25] The addition of tretinoin 0.05% to 0.1% prevents the oxidation of HQ, as well as improving epidermal penetration, allowing pigment elimination and increasing keratinocyte proliferation. First proposed in 1975, Kligman's formula (KF; HQ 5%, tretinoin 0.1%, and dexamethasone 0.1%) has been the most widely used combination therapy for

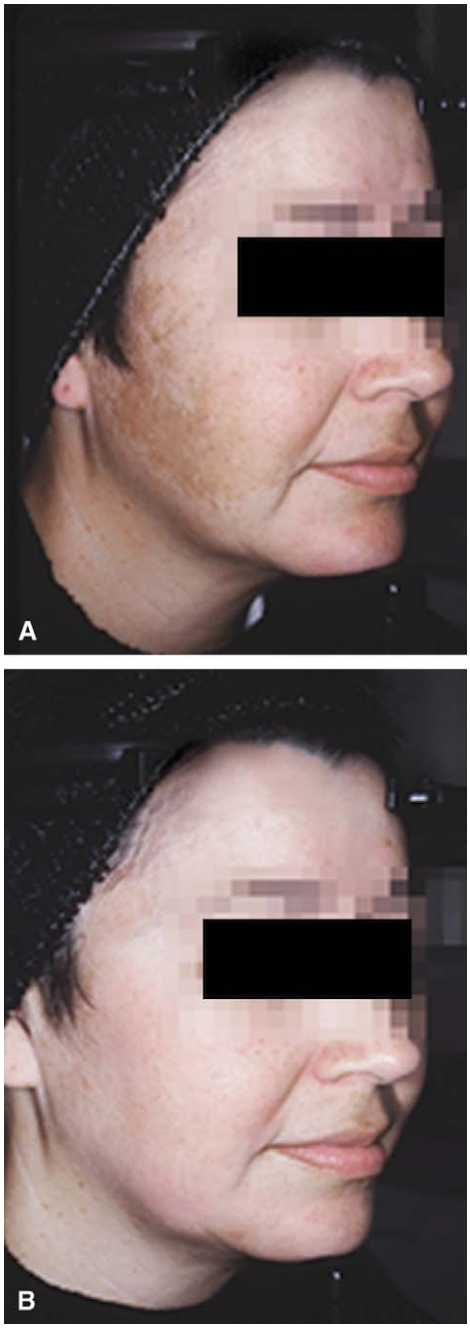


**Fig 1.** Appearance of melasma in patient at baseline (**A**) and after 8 weeks of treatment (**B**) with a triple fixed combination of hydroquinone 4%, retinoic acid 0.05%, and fluocinolone acetonide 0.01%. (From Taylor SC, Torok H, Jones T, Lowe N, Rich P, Tschen E, et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. Cutis 2003;72:67-72, page 71. Copyright 2003, Quadrant HealthCom Inc. Reprinted with permission.)

melasma worlwide.[25] The addition of corticosteroids to a combined therapy involving HQ caused a decrease in the irritative effects of the hypopigmenting agents, as well as inhibiting melanin synthesis by decreasing cellular metabolism. Tretinoin has been found to abrogate the epidermal atrophy that can occur with topical corticosteroids. Various modifications to the original formula have subsequently been studied.

A triple fixed combination of HQ 4%, RA 0.05%, and FA 0.01% has been studied in 641 patients with moderate to severe melasma and Fitzpatrick skin types I to IV.[26] The study compared the triple combination with HQ/RA, FA/RA, and FA/HQ over a period of 8 weeks; sunscreen with a sun protection factor of 30 was used in all patients. Complete clearing on or before day 56 was reported in 26.1%, 9.5%, 1.9%, and 3.1% of patients on a regimen of HQ/RA/FA, HQ/RA, FA/RA, and FA/HQ, respectively (Fig 1). Comparative results for percentages of cleared/almost cleared lesions were 77%, 46.8%, 27.3%, and 42.2%. Importantly, efficacy was consistent across all racial and ethnic groups. Adverse events were mild to moderate; the most common reactions observed with all treatment groups were erythema, skin peeling, burning, and/or stinging sensation. No skin atrophy was reported.

Two long-term safety studies have been conducted on the triple fixed combination of HQ 4%, RA 0.05% and FA 0.01%.[27,28] These were multicenter, long-term (1 year), open-label studies involving a total of 797 patients with mild, moderate, or severe melasma. Of these, 569 patients had already completed the 8-week study already discussed and 228 were newly enrolled patients.[27] The treatment was used for an average of 6.8 months and the majority of patients received two or more courses; all patients used a broad-spectrum sunscreen. A total of 96 patients used the treatment for 360 days. It was observed that each time the patient was treated, a shorter period was required to achieve a benefit so that by month 12, more patients had mild and cleared melasma (94%) compared with any month on study drug. In terms of safety, there was no significant increase in severity or the incidence of adverse events when compared with the 8-week controlled clinical study and only 3 patients (1%) discontinued the study because of treatment-related adverse events. A total of 129 patients (57%) experienced at least one treatment-related adverse event. Most were expected application site reactions, mild and transient in nature, and did not require remedial therapy. Two cases of skin atrophy were recorded in patients who had been treated for 180 days (out of 797 patients) at the end of the study, confirming the idea of abrogating the epidermal atrophy that can occur with topical corticosteroids.

A phase IV community-based study in 1260 patients with moderate to severe melasma and

Fitzpatrick skin types I to VI involving the triple combination has been conducted in the United States.[29] The efficacy parameters were melasma severity (MASI score) and the change in the MASI. Results showed that the triple fixed combination of HQ/TA/RA produced a highly significant reduction in MASI scores ($P < .0001$). The majority of patients had "complete to nearly complete" (75%-99%) improvement in MASI score by weeks 4 and 8. Efficacy was consistent across racial and ethnic groups. It was interesting to note that 60% of patients reported an adverse event, which was mainly skin irritation. There was no report of skin atrophy in any patient; a few cases of telangiectasia were reported.

A modification to KF in which HQ level was reduced to 2% has been assessed in a comparative clinical trial with GA 30% to 40% (chemical peel).[30] Forty Indian patients with Fitzpatrick skin types III to IV with moderate to severe melasma were randomized to treatment with the modified KF daily plus 6 serial GA treatments at 3-week intervals or to modified KF alone. A significant decrease in the MASI score at 21 weeks compared with baseline was observed in both groups. The group receiving GA showed a trend toward more rapid and greater improvements than the group only receiving the modified KF. At 12 weeks there was a 46% reduction and at 21 weeks an 80% reduction in MASI in the combined therapy group. This compared with a 33% and 63% reduction with KF alone at 12 and 21 weeks, respectively. Adverse events were minimal in both groups.

Another modified KF consisting of HQ 5%, RA 0.1%, and hydrocortisone 1% has been studied in 25 Korean female patients with therapy-recalcitrant facial melasma.[31] Therapy was applied twice per week for 4 months. The severity of melasma was scored at baseline, 4 weeks, and 4 months after treatment using a modified version of the MASI.[6] As early as 4 weeks after treatment, 12% of patients had a definite improvement of more than 50% in the modified MASI score, 20% of patients had a 30% to 50% improvement, and 16% of patients had a 10% to 29% improvement. At 4 months 52% and 19% of patients had a 50% or a 30% to 50% improvement, respectively; 29% showed no improvement.

### Miscellaneous treatments

Less commonly used depigmenting agents include bearberry extract, paper mulberry plant extract, arbutin, licorice extract, melawhite (leukocyte extract), ascorbic acid, mercury, and indomethacin. At present there are no controlled studies investigating the efficacy of these compounds and data are insufficient to make a conclusion about the efficacy of these therapies for melasma.

**Table II.** Patients showing more than 50% improvement in melasma at the end of the study involving 12 weeks of treatment with kojic acid 2% gel plus glycolic acid 10% and hydroquinone 2% or glycolic acid 10% and hydroquinone 2%

| Improvement in melasma | Kojic acid + GA + HQ | GA + HQ |
|---|---|---|
| <50% | 16 (40.0%) | 21 (52.5%) |
| >50% | 24 (60.0%) | 19 (47.5%) |
| Total | 40 (100%) | 40 (100%) |

*GA,* Glycolic acid 10%; *HQ,* hydroquinone 2%.
Reproduced from Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. Dermatol Surg 1999;25:282-4, page 283, with permission from Blackwell Publishing.

## PHYSICAL THERAPIES

### Chemical peels

Chemical peels can be used to treat melasma and include such agents as GA, TCA, Jessner's solution (lactic acid, salicylic acid, resorcinol, and ethanol), salicylic acid, tretinoin, and kojic acid. GA peels at concentrations ranging from 10% to 70% are popular and can be used in dark-skinned patients. A 91% improvement in melasma (reduction in MASI score) was found in a study involving 25 nonpregnant women treated with 50% GA once per month for 3 consecutive months.[32] Patients enrolled had a minimum MASI score of 15 and those with epidermal-type melasma had a better response to therapy than those with mixed-type melasma. In terms of side effects, one patient developed a mild degree of hyperpigmentation, reported to be the most common side effect of GA peels.

GA 70% has been compared with Jessner's solution in a split-face design trial with 16 patients.[33] Colorimetric analysis showed an average lightening of $3.14 \pm 3.1$ on the GA-treated side and $2.96 \pm 4.84$ on the Jessner solution—treated side (no statistical significance). The only adverse events reported occurred on the GA-treated area, which consisted of crusting, postinflammatory hyperpigmentation, and erythema. Follow-up of 5 patients at 16 months indicated that patients who continued topical therapy maintained their improvement, whereas those who discontinued experienced relapse.

The addition of GA 20% to 30% to 4% HQ has been studied in 21 Hispanic women with bilateral epidermal and mixed melasma.[34] Patients underwent twice-daily full-face application of HQ plus GA 20% to 30% to one side of the face only every 2 weeks and pigmentation was measured by means of a mexameter (spectrophotometric skin coloration measure of melanin and hemoglobin levels) and

**Table III.** Quality of evidence

| | |
|---|---|
| I | Evidence obtained from at least one properly designed, randomized control trial |
| II-i | Evidence obtained from well designed controlled trials without randomization |
| II-ii | Evidence obtained from well designed cohort or case control analytic studies, preferably from more than one center or research group |
| II-iii | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin in the 1940s) could also be regarded as this type of evidence |
| III | Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees |
| IV | Evidence inadequate owing to problems of methodology (eg, sample size, or length or comprehensiveness of follow-up or conflicts in evidence) |

From Stevens A, Raferty J, editors. Health care needs assessment. New York: Radcliffe Medical Press; 1997, page 304. Reproduced with permission.

**Table IV.** Level of evidence

| | |
|---|---|
| A | There is good evidence to support the use of this procedure |
| B | There is fair evidence to support the use of this procedure |
| C | There is poor evidence to support the use of the procedure |
| D | There is fair evidence to support the rejection of the use of the procedure |
| E | There is good evidence to support the rejection of the use of this procedure |

From Stevens A, Raferty J, editors. Health care needs assessment. New York: Radcliffe Medical Press; 1997, page 340. Reproduced with permission.

the MASI. Results indicated that both treatments significantly reduced ($P < .001$) skin pigmentation compared with baseline; however, no difference was observed between the two regimens.

The combination of 10% GA and 2% HQ has been studied in 10 Asian women with moderate to severe melasma.[35] Combination therapy was applied twice daily to both sides of the face for 26 weeks and 20% GA peels to one side every 3 weeks (total of 8 peels). Assessment by a dermatologist was made using the Munsell color chart. Results indicated that with GA/HQ plus GA peel therapy up to 33% lightening of melasma was found in 6 patients and up to 66% lightening in 4 patients. With the GA/HQ therapy alone, 8 patients had lightening classified as slight ($\leq$33%) in 7 patients and moderate ($\leq$66% lightening) in 1 patient.

Salicylic acid 20% to 30% at 2-week intervals has been used in 25 dark-skinned patients (Fitzpatrick skin types V-VI), including 6 with melasma, with good results.[36] Five peelings were conducted in patients previously treated with 4% HQ for 2 weeks and resulted in moderate to significant improvement in 88% of patients. Minimal to mild side effects occurred in 16%.

Concentrations of 1% to 5% RA have been evaluated in a skin peeling protocol in 15 women with melasma and photoaged skin with Fitzpatrick skin types I to IV.[37] There was a clinical improvement in skin texture and appearance after 5 sessions of treatment applied at 2- to 3-day intervals. Histological examination before and after treatment revealed a decrease in the corneal layer, an increase in the epidermal thickness, and a lengthening of the cristae cutis (skin ridges).

A chemical peel protocol involving GA 50% plus kojic acid 10% has been evaluated in 20 patients with diffuse melasma.[38] Treatment was applied at 2-week intervals for 3 to 6 months. Complete regression was observed in 6 patients (30%), partial regression in 12 (60%), and no regression in 2 (10%). In a comparative study of 40 Chinese women with epidermal melasma, half of the face was treated with kojic acid 2% gel plus GA 10% and HQ 2% and the other half of the face with the same preparation but without the kojic acid twice daily for 12 weeks.[23] Of the patients treated with combination therapy, clearing of melasma was reported in 60% compared with 47.5% receiving GA/HQ (Table II). Side effects included erythema, redness, stinging, and exfoliation, which occurred on both sides of the face but resolved by the third week.

## Laser therapy

The use of a single laser type, the Q-switched ruby laser. has been reported to be ineffective in 11 patients with melasma refractory to other types of therapy.[39] Only two patients showed improvement of their lesions, 3 had no change, and darker hyperpigmentation occurred in 4 patients at 4 weeks. Histopathological examination of pigmented lesions immediately after laser application indicated that not all pigment-producing structures were affected by a single laser treatment. Better results have been shown with a combination of pulsed $CO_2$ laser

**Table V.** Level and quality of evidence for melasma therapies

| Therapy | Level of evidence | Quality of evidence | Reference no(s). |
|---|---|---|---|
| Topical | | | |
| 2% HQ | II-ii | C | 13 |
| 4% HQ | I | B | 2-4, 14 |
| 0.1% tretinoin (RA) | I | B | 6, 7 |
| 0.05% RA | I | C | 10 |
| 0.05% isotretinoin | II-ii | C | 8 |
| 4% N-acetyl-4-S-cysteaminylphenol | III | C | 19 |
| 5% HQ + 0.1%-0.4% RA + 7% lactic acid/10% ascorbic acid | III | C | 20 |
| 3% HQ + 0.1% RA | III | C | 21 |
| 4% HQ + 0.05% RA + 0.01% fluocinolone acetonide | I | A | 4, 26-28 |
| 2% HQ + 0.05% RA + 0.1% dexamethasone (modified Kligman) | III | C | 30 |
| 2% HQ + 0.05% RA + 0.1% dexamethasone (modified Kligman) + 30%-40% GA peel | III | B | 30 |
| 5% HQ, 0.1% RA, and 1% hydrocortisone | III | C | 31 |
| 4% HQ + 5% GA | II-ii | B | 24 |
| 4% KA + 5% GA | II-ii | B | 24 |
| 2% KA + 2% HQ + 10% GA | II-iii | C | 23 |
| 2% HQ + 10% GA | II-iii | C | 23 |
| 4% HQ + 10% GA | I | B | 22 |
| 20% Azelaic acid | I | B | 14 |
| 20% Azelaic acid + 0.05% RA | III | C | 15 |
| Vitamin C iontophoresis | II-i | C | 18 |
| Adapalene | II-ii | B | 10 |
| Chemical peels | | | |
| 10%-50% GA | II-ii/III | C | 32 |
| 10% GA + 2% HQ + 20%-70% GA | II-ii | C | 35 |
| 20%-30% GA + 4% HQ | II-i | B | 34 |
| 70% GA | II-i | B | 33 |
| Jessner's solution | II-i | C | 33 |
| 20%-30% salicylic acid | III | C | 36 |
| 1%-5% RA | III | C | 37 |
| 50% GA + 10% KA | III | C | 38 |
| Laser therapy (+chemical peels and topical therapies) | | | |
| Q-switched ruby | IV | C | 39 |
| Pulsed $CO_2$ + Q-switched alexandrite | IV | C | 40 |
| Q-switched alexandrite | IV | C | 41 |
| Q-switched alexandrite laser + 15%-25% TCA peel + Jessner's solution | III | C | 42 |
| Erbium:YAG | III | D | 43 |
| Dermabrasion | II-iii | E | 44 |

*GA,* Glycolic acid; *HQ,* hydroquinone; *KA,* kojic acid; *KF,* Kligman's formula; *RA,* retinoic acid; *TCA,* trichloroacetic acid.

with Q-switched alexandrite laser.[40] The principle behind the treatment was that the $CO_2$ laser would destroy abnormal melanocytes and the alexandrite laser would remove any remaining pigment left in the dermis. Eight patients with dermal-type melasma were pretreated with a 14-day course of tretinoin 0.05%, HQ 4%, and hydrocortisone 1%, after which they were treated with one pass of the $CO_2$ laser and then 4 patients with one pass of the Q-switched alexandrite laser and the other 4 with no treatment. Assessment was by photography and an objective blinded investigator. At 24 weeks after laser therapy, results showed that the combination therapy was more effective in removing all hyperpigmentation areas. No adverse events were noted. The converse of this study has compared the combination of Q-switched alexandrite laser plus $CO_2$ laser with Q-switched alexandrite laser alone.[41] This split-faced design involved treating 6 Thai patients with one pass of each laser treatment as appropriate and assessing outcome at 6 months. Results revealed that combination therapy produced superior improvement in MASI than did monotherapy. Two patients developed severe postinflammatory hyperpigmentation, but this was effectively treated with bleaching agents. Transient hypopigmentation (one patient) and contact dermatitis (one patient) were observed with combination therapy.

Twenty-four patients with recalcitrant facial pigmentary disorders, of whom 6 had melasma, were treated with the Q-switched alexandrite laser in addition to 15% to 25% TCA with or without Jessner's solution.[42] Clinician assessment at 24 months was clear, excellent, or good in 67% of patients, and no significant complications with this combination were noted. Another study examined the use of erbium:YAG laser (2.94 $\mu$m) at 5.1 to 7.6 J/cm$^2$ in 10 women with melasma unresponsive to previous topical therapy or chemical peels.[43] There was marked improvement of the melasma (MASI; melanin reflectance spectrometry measurements) immediately after laser surgery. The baseline mean MASI score of 19.1 decreased to 4.1 on postoperative days 7 to 10. The mean score rose to a maximum of 22.1 at week 6 and was 10.6 at month 6. Mean preoperative melanin reflectance spectrometry measurement was 48.8, which decreased to 41.2 at postoperative day 4 and finally settling at 43.6 at 6 months. Between 3 and 6 weeks postoperatively, all patients exhibited postinflammatory hyperpigmentation.

### Dermabrasion

Kunachak, Leelaudomlipi, and Wongwaisayawan[44] have reported a large-scale study on dermabrasion in 533 patients with facial melasma. Treatment involved local dermabrasion or full-faced dermabrasion with a 16-mm diameter coarse grit diamond fraise with the patient under local anesthesia; the skin was dermabraded down to the level of the upper or mid dermis. Of the 410 patients followed up for a mean of 5 years (range 1-9 years), 398 (97%) achieved persistent clearance of melasma. Partial recurrence occurred in the other 3% of cases. Complications were encountered in 3 cases (0.7%); two patients developed hypertrophic scars and one patient had permanent hypopigmentation. Pruritus was a common consequence in the early postoperative phase. Milia developed in most patients, although it was self-limiting.

## RECOMMENDATIONS

The PDA has reviewed the literature on treatment of melasma and categorized the clinical findings for each treatment according to guidelines adapted from the US Preventive Services Task Force on health care (Tables III and IV).[45] The categorization of each therapeutic option for melasma is shown in Table V.

### Consensus statement

The mechanisms inducing melasma are not completely defined, and pigmentation is a complex process that includes tyrosinase activity, formation of melanosomes, and their transfer and organization in the keratinocytes. Consequently, therapies that can act at different stages of the melanogenesis process can produce better clinical results than a single compound acting at a single stage.

The consensus of the group was that first-line therapy for melasma should consist of effective topical therapies, mainly fixed triple combinations. Where patients have either sensitivity to the ingredients or a triple combination therapy is unavailable, other compounds with dual ingredients (HQ plus GA) or single agents (4% HQ, 0.1% RA, or 20% azelaic acid) may be considered as an alternative. In patients for whom therapy has failed, options for second-line therapy include peels either alone or in combination with topical therapy. Some patients will require therapy to maintain remission status and a combination of topical therapies should be considered. Lasers should rarely be used in the treatment of melasma and, if applied, skin type should be taken into account.

There are currently no guidelines for the management of melasma and given the variations of assessing treatments it is difficult to make effective comparisons between outcomes. The group therefore recommends the development of treatment guidelines for melasma which will establish a uniform set of criteria in scoring systems and allow for critical appraisal of specific treatments.

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