

A Stepwise Approach to Melasma Management and Treatment

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Melasma, an acquired disorder of hyperpigmentation, has long frustrated those it affects and the health care professionals who attempt to treat it. Its cause is not clear, but exposure to UV radiation (especially UVA), heat, and visible light all appear to play roles, as do female hormones. Existing treatments lighten the skin through inhibition of melanin synthesis, reduction of melanin, and disruption of melanin granules.

The authors attended a roundtable discussion group and discussed a therapeutic approach to melasma in an effort to render analysis and recommendations for its treatment and management. The summary of discussion and information presented at this meeting is detailed within this article. In general, the authors opined that, while a variety of monotherapies, including hydroquinone, retinoids, and kojic and azelaic acids, have been used to treat melasma, the best results appear to be obtained with combination therapy in a program of sun protection and elimination of exogenous estrogens. Other effective adjunctive treatment modalities include microdermabrasion, chemical peels, and laser and light therapies. The concluding result of their discussion and presentation as presented within this article is a practical stepwise treatment approach for the treatment of mild, moderate, severe, and resistant melasma.

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Melasma is an acquired disorder of hyperpigmentation and has been estimated to affect more than 6 million women in the United States.^{1,2} It presents as irregular brown, tan, or gray macules on sun-exposed skin. It appears most frequently in women, although approximately 10% of cases occur in men. Causative factors associated with melasma are female hormones (both endogenous and exogenous) and UV, infrared, and visible radiation. Although melasma occurs in all skin types, it is most common in more deeply pigmented skin, particularly among women of Hispanic, Asian, and East Indian origin.³ It occurs most commonly on the centrofacial area, although it may also occur in the mandibular area, as well as the forehead, nose, neck, and forearms.

Melasma is chronic and relapsing, can be severely disfiguring, and may negatively impact one's quality of life.⁴ Epidermal melasma, which is limited primarily to the basal and suprabasal epidermis, is much more amenable to treatment than dermal melasma, which consists of melanin-laden macrophages in the superficial and deep dermis.^{5,6} A mixed type with clinical features of each also exists. The types may be differentiated on the basis of Wood lamp examination, with only the lesions of epidermal melasma accentuated.³

Current treatments for melasma include limiting sun exposure and taking steps to inhibit melanin synthesis, remove melanin, and disrupt melanin granules.^{6,7} Available topical melasma treatments include hydroquinone (HQ) alone or in combination with tretinoin, corticosteroids, retinol, glycolic acid, topical kojic acid, azelaic acid (AZA), licorice extract, arbutin and mulberry extract, as well as resorcinol. The authors discussed that microdermabrasion, chemical peels, and laser and light sources are frequently used adjunctive procedures that are employed with topical therapy. Less frequently used are dermabrasion and liquid nitrogen.^{1,3}

A PROPOSED STEPWISE APPROACH TO MELASMA MANAGEMENT

The pathogenesis of melasma is not well understood, and lack of a standardized system of therapy has frustrated both patients and physicians. A group of dermatologists with expertise in the management of melasma and other skin diseases met in 2006 to discuss their clinical experiences with and relevant data for melasma treatment. The authors reviewed available data, discussed clinical patterns, and developed a general approach for the management of melasma based on their own best practices.

The consensus from the authors is presented in this article, beginning with recommendations for preventive measures to be undertaken in all patients with melasma,

followed by specific additions of topical agents and procedures according to the level of melasma severity. Melasma severity may be quantified using the Melasma Area and Severity Index, which takes into account melasma area, amount of involvement, darkness of melasma, and homogeneity of hyperpigmentation.

RECOMMENDATIONS FOR MELASMA OF ALL LEVELS OF SEVERITY

Sun avoidance and sun protection are of primary importance in melasma management.^{6,8,9} Sun protection includes avoiding peak solar radiation between 10 AM and 2 PM, modifying outdoor behavior, and wearing a hat. To optimize sun protection, the authors recommend wearing a hat with a 7-cm-wide brim in order to provide the best facial protection.¹⁰

It is important, however, for individuals with melasma to understand that they continue to receive damaging doses of UV, sufficient enough to cause relapse or exacerbation, even through glass windows; therefore, sunscreen must be worn at all times, even when indoors. It was discussed that movable or permanent UVA shields for car windows may be an option for patients.

For those who suffer from nonfacial melasma, protective clothing is essential. Normal clothing may provide a sun protection factor (SPF) level between 6 and 15, which drops to less than 5 if the fabric is wet. Sun-protective clothing lines, fabrics, or sun-protective laundry aids offer protection of SPF 30 or higher.¹⁰

A broad-spectrum UVA/UVB sunscreen with SPF 30 or higher and long-acting broadband UVA protection is paramount to melasma prevention and treatment because sun exposure can result in relapse of successfully treated melasma.^{6,8,9} Traditional UVB blockers include *p*-aminobenzoic acid, salicylates, and cinnamates. Benzophenones (oxybenzone) block UVB and UVA radiation, while dibenzoylmethanes (avobenzone) block UVA radiation.¹¹ Avobenzone is capable of a high degree of UVA absorption; however, it is unstable in sunlight.¹¹ The newest generation of sunscreens addresses the need for broad-spectrum protection and stabilization of active ingredients. Other technologies add a chemical to produce photostable avobenzone combined with conventional UVB filters.^{12,13} Other emerging technologies use fewer chemical sunscreens to provide UVB protection along with photostable UVA protection.¹⁰

Physical sunscreens, which scatter light, are not considered as effective as chemical sunscreens at protecting skin. Moreover, because they consist of inorganic white particulates such as titanium dioxide and zinc oxide, they may be cosmetically unacceptable to patients with more deeply pigmented skin. If used, the micronized formulations are preferred.¹⁴ Chemical sunscreens act by

transforming UV energy to heat, and there is some evidence that heat may play an important, underrecognized role in the development of melasma. In fact, it is increasingly suggested that all patients with melasma refrain from physical exertion in high temperatures and limit their exposure to hot ovens and fires if possible.¹⁵

Patient education on proper application of sunscreen is paramount, and SPF measurement is based on sunscreen applied at a concentration of 2 mg/cm². Studies show that most people apply a layer as thin as 0.5 mg/cm², resulting in an SPF significantly lower than what is stated on the label.¹⁶

Sunscreen should be applied to the face every morning, whether it is sunny or overcast. After washing the face, a thin layer of sunscreen or daily moisturizer with SPF 30 or higher should be applied and allowed to dry, followed by a second layer. Sunscreen application should be repeated every 4 hours and immediately after excessive perspiration or swimming.

It is often recommended that patients of childbearing age refrain from using hormonal forms of birth control because of their potential ability to trigger melasma.¹⁷⁻¹⁹ The authors recommend an oral contraceptive/hormone replacement therapy consult if germane. Melasma that occurs during pregnancy typically fades in a few months, but it can become persistent, and repeated pregnancies can deepen the pigmentation associated with melasma.²⁰

Patient education regarding melasma, its treatment, exacerbating factors, and the importance of sun protection is essential for all melasma patients. As has been shown to be true for other chronic skin diseases, treatment success depends on the patient's commitment to and understanding of the prescribed regimen.^{21,22} Physician-prescribed treatment protocols should be reviewed at each visit to ensure understanding and maximize compliance.

TREATMENT REGIMEN FOR MILD MELASMA

Step 1

The Figure illustrates the recommended treatment regimen for mild, moderate, and severe melasma. The authors recommend that patients with mild melasma start on a 3-month course of the currently available triple-combination (TC) cream that contains HQ 4%, tretinoin 0.5%, and fluocinolone acetonide 0.01% in a hydrophilic cream base. This formulation, indicated for the short-term intermittent treatment of moderate to severe facial melasma, has been shown in several large, controlled studies to be effective in reducing hyperpigmentation in test subjects with moderate to severe melasma. Treatment with TC cream typically

includes side effects of mild to moderate redness, drying, peeling, burning, and itching during the first weeks of treatment.²³⁻²⁶

The patient should be reevaluated within 1 to 3 months of starting treatment. If the melasma has cleared, the authors agreed that treatment should be stopped or tapered and a retinoid should be added to the protocol of sun protection and sun avoidance. Treatment compliance should be assessed and the treatment protocol reinforced as required.

Step 2

If the melasma has not cleared, the authors recommend that treatment may be continued and either microdermabrasion, adjunctive HQ in the morning, or a mild glycolic acid or Jessner peel be added to the regimen. Microdermabrasion has been shown to be a useful adjunct to treatment with TC cream because it mechanically helps to remove melanin in the upper dermis and exfoliates melanophage-packed keratinocytes.²⁷ If a chemical peel is used, the authors recommend discontinuing the TC cream for a minimum of 1 to 2 days or for as many as 7 days before the peel to limit the possibility of retinoid-induced skin sensitization decreasing the frost threshold. The patient should be reevaluated within 1 to 3 months.

TREATMENT OF MODERATE MELASMA

Step 1

The patient should start with TC cream and add one additional treatment modality, either microdermabrasion, HQ in the morning, mild glycolic acid, or Jessner solution peel. The patient should be reevaluated within 1 to 3 months. If the melasma clears, the authors noted to discontinue any adjunctive treatments; taper TC cream; add a topical retinoid, such as micronized tretinoin 0.04% or 0.1%, adapalene 0.1%, or tazarotene 0.05% or 0.01% cream; and continue sun protection and sunscreen.

Retinoids have been demonstrated to mildly lighten postinflammatory hyperpigmentation (PIH) without significantly lightening unaffected surrounding skin.^{20,28,29} In the treatment of acne, adapalene gel appears to be uniquely well tolerated by people with Fitzpatrick skin type VI.³⁰ In a small exploratory study, adapalene 0.1% gel data indicated that it was equally as effective as tretinoin 0.05% cream in the treatment of melasma but with fewer instances of cutaneous irritation.³¹

Step 2

If at the 1- to 3-month follow-up visit the melasma is better but not clear, or if the melasma has not responded, continue the TC cream as well as the additional modality of one of the following: microdermabrasion, addition of

can be used, and adjunctive HQ used in the morning at increased concentrations between 5% and 10%. While such concentrations are not commercially available in the United States, they may be compounded extemporaneously. The authors noted their consensus that duration of therapy rather than dosage is more of a factor in increasing the risk for exogenous ochronosis. They do not support long-term HQ therapy at this dosage, but maintain that it is safe in the management of resistant melasma.

Another alternative is to continue both creams and add a localized application of a class I or II topical steroid once daily for 2 to 3 weeks. If this option is chosen, a limited amount of the steroid should be prescribed, and the patient should be carefully instructed in its judicious use and monitored closely by the physician. In lieu of this morning/nighttime regimen, other topical regimens that are potentially useful include HQ 5% to 10%, desonide 0.05% cream, hydrocortisone 2.5%, and ascorbic acid 500 mg, which is available through compounding pharmaceuticals and may be applied twice daily.

LASER AND LIGHT THERAPIES

Another option for severe or resistant melasma is the use of laser and light therapies. Only certain laser and light devices help melasma; others worsen it. Data to support the use of these modalities are limited and its judicious use is recommended.^{10,32,33} In general, the use of traditional short- and long-pulsed, pigment-specific lasers has either a limited role or no role at all in melasma therapy because of the risk for PIH in patients with more deeply pigmented skin and because of the temporary nature of improvement and high risk for melasma recurrence.³⁴

Fractional erbium:YAG resurfacing, such as the Fraxel, may be beneficial.³⁴ In this study, 10 female patients with melasma, with Fitzpatrick skin types III to V, who were refractory to previous melasma treatment received 4 to 6 treatments with the full-face fractional resurfacing laser at 1- to 2-week intervals. Wavelengths of 1535 nm and 1550 nm were both used. Treatment parameters were 6 mJ to 12 mJ per microthermal zone with 2000 to 3500 microthermal zones/cm². The end point was the percentage of lightening achieved as compared with the original pigmentation. Evaluation by 2 physicians found a 75% to 100% improvement in 60% (n=6) of the sample and less than 25% improvement in 30% (n=3) of the sample. Patient evaluations were generally similar to that of the physicians. One patient had PIH, and no patients developed hypopigmentation with treatment. Fractional resurfacing and its long-term efficacy in larger patient populations has yet to be reported.

Intense pulsed light (IPL) has been used with some success in the treatment of epidermal melasma.^{35,36} It should be reserved for use in Fitzpatrick skin types I to IV. A slightly

Treatment Options for Resistant Melasma

Increase topical HQ concentration

Higher concentration yields a more gritty consistency

HQ 5%–10% powder in:

Desonide .05% cream (30 g)

Hydrocortisone 2.5%

Ascorbic acid 500 mg

Apply to affected area twice daily

Topical steroid/localized application

Class I or II

Once in the morning

Treat 2–3 wk

Prescribe limited amount and use judiciously

Lasers and light sources

Use caution because these devices may/may not work or may make melasma worse

May be expensive

Limited data to support use

Traditional short- and long-pulsed lasers have no defined role in melasma treatment

IPL

Ideal for Fitzpatrick skin types I–IV

Treat gently

Select slightly lower fluence and longer pulse duration

Fractional laser devices are approved by FDA and may demonstrate some efficacy for resistant melasma

Liquid nitrogen

Ideal for Fitzpatrick skin types I–III

Abbreviations: HQ, hydroquinone; IPL, intense pulsed light; FDA, Food and Drug Administration.

lower fluence and longer pulse duration than is typically employed to treat hyperpigmentation should be used to help prevent the development of PIH. To speed improvement, IPL may be useful as an adjuvant to topical therapy.⁶

OTHER PHYSICAL MODALITIES

Spot treatments with liquid nitrogen may be helpful and is recommended by some authors to be used judiciously in Fitzpatrick skin types I to III.

MELASMA MANAGEMENT AND TREATMENT

HQ in the morning, or a mild glycolic or Jessner peel. Reevaluate the response in 1 to 3 months.

the response within 1 to 3 months and review the treatment protocol, assess patient compliance, and answer questions.


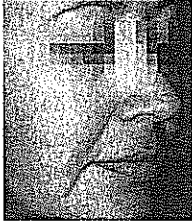

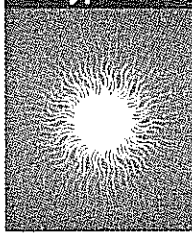
TREATMENT OF SEVERE MELASMA

Initiate treatment with TC cream and one other treatment modality, such as morning application of HQ, superficial peel or microdermabrasion, or laser or light treatment. Reevaluate

OPTIONS FOR RESISTANT MELASMA

Topical Treatment

The authors recommended several options for the management of resistant melasma (Table). At night, TC cream

 <p>Mild</p>	<p>At initial visit, start TC cream once daily for 1-3 mo</p> <ul style="list-style-type: none"> - Begin patient education, review treatment protocol 	<p>Reevaluate at 1-3 mo</p> <ul style="list-style-type: none"> - Continue patient education, review compliance with treatment protocol <p>If clear, stop or taper TC cream and add topical retinoid.</p> <p>If improved but not clear, continue TC cream and add 1 other treatment modality, such as:</p> <ul style="list-style-type: none"> - Microdermabrasion therapy; or - Topical HQ (morning); or - Mild glycolic or Jessner peel 	<p>Reevaluate at 3-6 mo</p> <ul style="list-style-type: none"> - Continue patient education, review compliance with treatment protocol
 <p>Moderate</p>	<p>At initial visit, start TC cream once daily for 1-3 mo and add 1 other treatment modality, such as:</p> <ul style="list-style-type: none"> - Microdermabrasion therapy; or - Topical HQ (morning); or - Mild glycolic or Jessner peel <p>- Begin patient education, review treatment protocol</p>	<p>Reevaluate at 1-3 mo</p> <ul style="list-style-type: none"> - Continue patient education, review compliance with treatment protocol <p>If clear, stop or taper TC cream and add topical retinoid.</p> <p>If improved but not clear, continue TC cream and add 1 other treatment modality, such as:</p> <ul style="list-style-type: none"> - Microdermabrasion therapy; or - Topical HQ (morning); or - Mild glycolic or Jessner peel 	<p>Reevaluate at 3-6 mo</p> <ul style="list-style-type: none"> - Continue patient education, review compliance with treatment protocol <p>If no improvement, continue TC cream and repeat 1 other treatment modality and reevaluate within 3-6 mo.</p>
 <p>Severe</p>	<p>At initial visit, start TC cream once daily for 1-3 mo and add 1 other treatment modality, such as:</p> <ul style="list-style-type: none"> - Topical HQ(morning); or - Superficial peel or microdermabrasion therapy; or - Laser or light treatment <p>- Begin patient education, review treatment protocol</p>	<p>Reevaluate at 1-3 mo</p> <ul style="list-style-type: none"> - Continue patient education, review compliance with treatment protocol 	
 <p>All Types</p>	<ul style="list-style-type: none"> • Encourage sun avoidance behavior <ul style="list-style-type: none"> - Wear broad-brimmed hat and protective clothing - Seek shade • Recommend daily UVA/UVB sunscreen <ul style="list-style-type: none"> - Apply daily SPF 30+ and reapply as needed (ie, after swimming, sweating, or exercise) • Recommend OC/HRT consult, if applicable for female patients • Discuss and provide daily skin care regimen as applicable 		

Stepwise recommendations for treating mild, moderate, and severe melasma. Abbreviations: TC, triple-combination; HQ, hydroquinone; SPF, sun protection factor; OC, oral contraceptive; HRT, hormone replacement therapy.

can be used, and adjunctive HQ used in the morning at increased concentrations between 5% and 10%. While such concentrations are not commercially available in the United States, they may be compounded extemporaneously. The authors noted their consensus that duration of therapy rather than dosage is more of a factor in increasing the risk for exogenous ochronosis. They do not support long-term HQ therapy at this dosage, but maintain that it is safe in the management of resistant melasma.

Another alternative is to continue both creams and add a localized application of a class I or II topical steroid once daily for 2 to 3 weeks. If this option is chosen, a limited amount of the steroid should be prescribed, and the patient should be carefully instructed in its judicious use and monitored closely by the physician. In lieu of this morning/nighttime regimen, other topical regimens that are potentially useful include HQ 5% to 10%, desonide 0.05% cream, hydrocortisone 2.5%, and ascorbic acid 500 mg, which is available through compounding pharmaceuticals and may be applied twice daily.

LASER AND LIGHT THERAPIES

Another option for severe or resistant melasma is the use of laser and light therapies. Only certain laser and light devices help melasma; others worsen it. Data to support the use of these modalities are limited and its judicious use is recommended.^{10,32,33} In general, the use of traditional short- and long-pulsed, pigment-specific lasers has either a limited role or no role at all in melasma therapy because of the risk for PIH in patients with more deeply pigmented skin and because of the temporary nature of improvement and high risk for melasma recurrence.³⁴

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OTHER PHYSICAL MODALITIES

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ADJUNCTIVE TOPICAL THERAPIES FOR MILD, MODERATE, OR SEVERE MELASMA

A variety of natural skin-lightening agents has been used with varying degrees of success in melasma, including kojic acid, arbutin, AzA, vitamin C, and mulberry extract.³⁷⁻⁴⁰ While these products may not prove to be fully efficacious, they may add some additional depigmenting activity and may appeal to some patients because the majority are derived from plants and, thus, may be particularly cosmetically acceptable. Arbutin, obtained from bearberry leaves, contains a chemical structure similar to that of HQ. It is widely used in Japan at concentrations of 3% and is not toxic to melanocytes.⁴¹ Kojic acid, while effective, is controversial. It has been reinstated in formulations as a skin lightening agent. It has been shown to be mutagenic in vitro.⁴¹ Licorice, the safest and most widely used pigment-lightening agent, has the lowest level of adverse events.⁴¹ Possessing an excellent safety profile, AzA can be safely combined with retinoids for an enhanced skin-lightening effect; however, it may cause transient stinging in some patients.⁴¹

In a vehicle-controlled study, 39 patients with melasma were treated twice daily for 3 months with kojic acid 2% gel on one side of the face and HQ 2% in a similar gel vehicle on the other side of the face.⁴² Both formulations contained glycolic acid 5%. The average overall reduction in pigmentation intensity was 58% for the entire group. Just more than half (51%) of the subjects responded equally well to both treatments, whereas 21% of the HQ group had a greater reduction in pigment intensity. In a 6-month, open-label, randomized study of 50 Asian patients with melasma, subjects received either a combination of AzA 20% and tretinoin 0.05% cream, or AzA 20% cream alone.⁴³ All subjects used a broad-spectrum sunscreen. The median lesion area decreased by 58% in the AzA monotherapy group and by 65% in the combination therapy group. Skin lightening was more pronounced and occurred earlier in the combination therapy group during the first 3 months of therapy. The combination therapy group also had a higher rate of excellent results (34.8%) as compared with the monotherapy group (5.3%).

A standardized extract of French maritime pine bark, *Pinus pinaster*, that contains monomeric phenolic compounds and condensed flavonoids was reported on in a study of 30 women with melasma to decrease both average pigment area ($P < .001$) and pigment intensity ($P < .001$).⁴⁴ There were no side effects, no adverse events, and the drug, taken orally, was well tolerated in this study.

DISCUSSION AND KEY COMMENTARY

The authors noted the importance of treating melasma in the mild early stages because increasing severity is

accompanied by increasing treatment difficulty. The combination of retinoids and sunscreen as the cornerstone of melasma treatment was discussed. Retinoids should be used for all melasma severities. However, one advisor noted that the use of tazarotene appeared to worsen the melasma as some retinoids are more likely to stimulate melanosomes. It was noted that this situation occurred with tazarotene but not with tretinoin. It was generally agreed by the authors that adapalene gel is uniquely well tolerated by African American patients.

There was some discussion regarding the potential use of isotretinoin in recalcitrant melasma in sterilized or postmenopausal patients. However, as this has not been well studied, it is preferable to use a regimen that will not require laboratory follow-up.

The authors do not recommend long-term HQ monotherapy. However, shared clinical experience with HQ 2% to 4% suggests that it is the duration of use rather than potency that is most relevant to the development of exogenous ochronosis. It was suggested that there may be a genetic predisposition for developing this disorder, which may partly explain its relative rarity in the United States. One advisor noted that exogenous ochronosis may be more prevalent among Asians.

It was undecided whether spot treatment with HQ should be advocated versus using it all over the face. Some of the authors suggested that the decision to use spot treatment and risk producing halo depigmentation versus using it all over the face to achieve lightening should be decided on the basis of the patient's skin tone.

Most authors stated their belief that a topical steroid is an important component of TC cream, morning applications of HQ, peels, or microdermabrasion in moderate to severe melasma. It was of note that steroids have a direct effect on melanogenesis by reducing melanocyte proliferation and, also, inflammation.

Some of the authors recommended antioxidants to their patients with melasma whereas others do not. It was generally agreed that either topical or oral antioxidants may help in this setting, and thus several of the authors recommended its use to their patients.

The authors agreed that adjunctive lightening agents such as kojic acid and licorice extracts are only minimally useful in melasma treatment and provide only the potential for additive effects. One author stated that kojic acid and vitamin C are useful adjuncts in mild to moderate melasma but are ineffective in severe melasma. In general, the authors agreed that these agents are best used as part of a maintenance program.

It was generally agreed that laser and light therapies have unpredictable efficacy and that their cost is an important drawback. Data on treating melasma with laser and light therapies are limited.

SUMMARY

Successful melasma treatment depends on effective topical therapy to lighten the hyperpigmented areas and to prevent the development of new ones, as well as the avoidance of risk factors. The most important of these risk factors are UV exposure and exogenous female hormones. Melasma treatment outcomes are optimized by initiating treatment as early as possible when the disease is mild and more amenable to treatment. Severe or long-established melasma is much more recalcitrant to treatment.

One of the most effective therapies to date appears to be topical treatment that combines HQ 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% in a cream formulation. Each component has some skin-lightening activity, but comparisons of the TC versus any 2 of its components suggests an additive, perhaps synergistic activity, of the 3 components. If this TC cream alone does not resolve the condition, other modalities can be added to the topical regimen, such as microdermabrasion, peels, additional HQ, or short-term adjuvant topical corticosteroids. Whereas traditional lasers are generally not recommended, some authors have found that full-face use of fractional resurfacing and IPL shows some promise in Fitzpatrick skin types I to IV. A number of topical skin-lightening agents may be used as adjuncts to the TC cream.

Patient education is essential to successful melasma management. Many patients do not ask for treatment because they do not realize that effective therapies are available for the disease. The importance of sun protection and sun avoidance as a cornerstone of successful melasma management, as well as the correct use of sunscreens and the need for protection even while indoors, must be emphasized. In addition, patients must understand the importance of adherence to their topical regimen.

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