Current and New Strategies for Managing Non-Responders to Laser Toning in the Treatment of Melasma

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Melasma is one of the most common forms of acquired hyperpigmentation in Asians. It is often intractable with a high rate of recurrence. Several years ago, the collimated low-fluence 1,064 nm Q-switched neodymium-doped yttrium aluminum garnet laser was introduced as the "laser toning" for the treatment of melasma. Laser toning has been established as an excellent treatment option for melasma with proven efficacy, and it has gained widespread usage. Compared to the early days of laser toning, recent laser toning treatment is associated with lower fluence, fewer passes, wider intervals between treatment sessions, and a minimal and milder tissue response. This recent approach can reduce the risk of mottled hypopigmentation, postinflammatory hyperpigmentation, rebound hyperpigmentation, and recurrence of melasma. However, there are a growing number of non-responders to the recent laser toning technique, which can be problematic for some doctors. Dermatologists should be aware of the various ways to manage non-responders. Moreover, they should also have an accurate understanding of the mechanisms and principles of these modalities to apply optimal treatment methods for each patient condition and melasma state. Further research and updates are necessary to improve the safety and efficacy of laser therapy for melasma.

Key words

Laser toning; Melasma; Non-responders; Q-switched neodymium-doped yttrium aluminum garnet laser

Received June 4, 2016
Revised June 17, 2016
Accepted June 19, 2016

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Melasma is a common acquired skin disease characterized by symmetrical hyperpigmented macules and patches involving sunexposed areas.¹ The lesions are irregular in shape and light to dark brown in color.¹ Etiology and pathophysiology of melasma are not yet clearly understood, though various factors and complicated pathophysiological processes are thought to be involved.² Melasma tends to affect more women than men, but also people with darker skin. It is particularly common in East Asians including Koreans, Chinese, and Japanese. In this population, the desire to treat the condition is also very high. Melasma is often difficult to treat. Conventional treatments include topical sunblock, topical whitening agent, and peeling.³ Several lasers or intense pulsed light (IPL) have been used in melasma in the past. Traditional laser therapies in melasma had a high risk of postinflammatory hyperpigmentation (PIH), rebound hyperpigmentation, or recurrence/worsening of melasma.⁴ High fluence levels were thought to cause excessive thermal reaction and inflammation, leading to such complications.⁵ A new method using the top-hat beam mode, short pulse width, high peak power, and low fluence of a 1,064 nm Q-switched (QS) neodymium-doped yttrium aluminum garnet (Nd:YAG) laser was introduced under the name of 'laser toning' for treatment of melasma. This new method has the benefit of minimizing thermal damage to tissues.⁶ Laser toning reduces the number of melanosomes (particularly, stage IV melanosomes), and induces structural change in them. While it does not destroy melanocytes, it does reduce the volume and dendrite count of melanocytes.⁷ In addition, laser toning was reported to down-regulate the expression of tyrosinase-related protein (TRP)-1, TRP-2, nerve growth factor, α -melanocyte-stimulating hormone, tyrosinase, and stem cell factor in the lesion site.⁸ In other words, laser toning improves melasma not by lowering the melanocyte count but by reducing melanin, melanosomes and melanocyte functions.⁶⁻⁸

In our previous article '*Mottled hypopigmentation from laser toning in the treatment of melasma: a catastrophic or manageable complication?*', we performed a systematic literature review of publications reporting the development of hypopigmentation after laser toning.⁶ Some reports focused on the occurrence of hypopigmentation following laser toning treatments, with an estimated incidence of around 10% in the Asian population. This led to a growing concern about the risk of laser toning.⁹⁻¹³ However, most of the reported cases were collected during the early days of laser toning when more aggressive approach was used with a high fluence, excessive

cumulative energy, a high number of passes and short treatment intervals. Recent laser toning treatment uses a lower fluence and fewer passes that cause milder tissue responses compared to the old days and the treatment interval is adjusted depending on the patient responses. Such modifications have helped to greatly reduce the incidence of mottled hypopigmentation, skin irritation, PIH and rebound hyperpigmentation. In the previous article, we concluded that excessive concern and fear of laser toning are unwarranted.⁶ Meanwhile, one may still wonder about the impact of using gentle parameters on the efficacy. In this article, we will discuss limitations of the current laser toning techniques and suggest various ways to overcome these limitations through literature review and our own clinical experience.

The therapeutic efficacy of laser toning in melasma can be considered in two aspects; the degree of initial improvement from treatment, and how long this improvement is maintained without recurrence. The recent approach of laser toning with gentle parameters is superior to the more aggressive method in terms of the latter aspect of efficacy; maintaining the improvement without recurrence. The gentle approach with a lower fluence carries a much lower risk of complications including PIH or hypopigmentation, and causes less rebound hyperpigmentation or recurrence. Many studies already found that the initial therapeutic effect of the gentle approach was maintained for a longer period of time compared to the more aggressive method.¹⁴⁻¹⁶ Experienced doctors agree that using high fluences, many passes, and shorter intervals to achieve quick results can cause quicker and more common recurrences of melasma.

When it comes to the other aspect of efficacy, the degree of initial improvement from treatment, the recent laser toning method with gentle parameters may seem to fall short. The non-responder rate has not yet been shown to be higher with a gentle approach compared to the more aggressive one. However, many dermatologists who have switched to the gentle parameters more frequently experience patients showing poor initial improvement to laser toning. They sometimes complain that they are seeing a growing number of non-responders.

While it is true that clinical dermatologists encounter considerable number of non-responders and it may be an annoying problem to practitioners, there is a paucity of clinical studies that systematically analyzed or reviewed this phenomenon. It seems impossible to systematically assess and analyze the non-responder rate associated with laser parameters and other diverse treatment techniques. What is worse, the term "non-responder" is not

yet clearly defined. However, it generally refers to patients with less than 25% clinical improvement after about 7-15 laser toning treatments.^{12,17} We also use this definition in this article.

Generally, studies mentioning the non-responder reported a rate around 10% of non-responders in melasma patients treated by laser toning; 2 out of 25,¹² and 4 out of 50.¹⁷ These studies used relatively aggressive parameters with the fluence of 2.5-5 J/cm² and 2.8 J/cm², respectively. Recent studies that used lower fluence levels rarely mentioned non-responders. This might be due to the fact that recent studies did not use global assessment grading system but the mean Melasma Area and Severity Index (MASI) score, or melanin index as a measure of clinical improvement. They also tended to compare mean values of groups rather than treatment outcomes of individual patients. The non-responder rates reported in literature varied; 7.7%,¹⁵ 26.9%,¹⁶ and 15%.¹⁸ Based on our clinical experience, we estimate that about 20% of all patients treated with gentle laser toning parameters are non-responders.

The problem of non-responders has become a tiresome concern for clinicians. When faced with such a problem, less experienced doctors often make a common mistake of increasing the fluence of laser toning until stronger response is seen. The fluence can be raised slightly for a short period of time, however, consistently raising fluence levels to induce strong tissue response should be avoided. Treatment response may improve immediately but repetitive exposures to raised fluence levels have a higher risk of complications such as PIH, mottled hypopigmentation, rebound hyperpigmentation and worsening of melasma.

Laser toning has been shown to be very effective in melasma and many doctors favor this modality when treating melasma. However, the problem of non-responders remain with the safer and milder laser toning treatment. Various methods have been developed to manage non-responders. To achieve optimal safety and efficacy, clinical dermatologists should be well-versed in the variety of methods available for treatment of melasma and be able to apply and adjust suitable modalities to each individual patient with melasma. Let us take a look at various therapeutic methods that can be used alone or in combination with laser toning to tackle the problem of non-responders.

COMBINATION THERAPY WITH LASER TONING (EXCEPTING OTHER LASER TREATMENTS)

A large percentage of non-responders can benefit from

a therapy combining laser toning with another modality. Most dermatologists can successfully treat non-responders through this combination therapy, and obtain superior outcome and a long-term remission in most of melasma patients. Recently, many studies on combination therapy are being published. Topical whitening agent, one of the most conventional therapeutic modalities, is commonly used with laser toning as combination treatment for melasma. Most commonly used whitening agents include azelaic acid and the triple combination (TC) cream containing 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide.^{18,19} Combining laser toning with vitamin C iontophoresis²⁰ or peeling agents^{16,21} has also been reported to bring favorable synergistic effects.

Whitening agents such as topical TC and azelaic acid are considered first-line therapy of melasma in evidence-based medicine.²² When used alone in clinical practice, however, they have many limitations such as low efficacy, low patient compliance and side effects including irritation. Combining whitening agents with laser toning has been shown to overcome these limitations and achieve a superior outcome in previous studies.^{18,19}

Vitamin C (ascorbic acid) is known to inhibit malanogenesis.²³ Vitamin C, however, has poor delivery to the skin through both oral intake and topical application. Its unstable chemical structure makes it difficult to maintain stability in a solution form. Various methods have been used to overcome these problems, the most common of which is vitamin C iontophoresis. Vitamin C iontophoresis is widely used as a basic treatment of melasma. Among clinicians, the synergistic effect of combining vitamin C iontophoresis and laser toning has been recognized for a long time. Lee et al.²⁰ found that the thermal effect of laser increased blood circulation of the skin and improved penetration of topical vitamin C.

Chemical peeling is an important treatment of melasma that has been in long use due to its effective removal of melanin in keratinocytes and acceleration of epidermal turnover.²⁴ Therefore, some doctors argue that laser toning and peeling make an excellent combination therapy. They believe that pigments destroyed by laser toning can be more effectively removed with a chemical peel. However, a chemical peel and laser toning both directly inhibit tyrosinase which may create an overlap.²⁵ The combination of chemical peel and laser toning has been in common use for a long time and we have also experienced excellent efficacy using this method in our practice. On the other hand, this combination may have a higher risk of complications compared to monotherapies.²¹ One should also be aware of a report that superior effect of this com-

bination is only short-lived and the combination brings an outcome similar to that of laser toning used alone after about 10 treatments.¹⁶ This combination therapy can result in various levels of efficacy and complications depending on the doctor's experience and methods of combination. Therefore, it is advisable to have deep knowledge of the peeling agents and laser properties before using this combination.

Tranexamic acid (trans-4-amino-methylcyclohexanecarboxylic acid, TA) has been used for treatment of hyperpigmented lesions including melasma.^{26,27} TA is an anti-fibrinolytic agent that inhibits the plasmin/plasminogen system. In addition to its anti-fibrinolytic effect, it is also known to have anti-allergic and anti-inflammatory effects which are presumed to inhibit melanogenesis.²⁷ It is also thought to inhibit interactions between melanocytes and keratinocytes, thereby bringing lightening effects. However, the mechanism by which TA reduces melanin is not yet clearly understood.²⁸ TA is used in various formulations including topical creams, localized microinjections and oral agents for the treatment of hyperpigmentation.

TA can be used alone in melasma and is known to be a safe and effective treatment.^{26,29} Due to low efficacy and poor patient compliance, however, TA is commonly used in combination with laser toning and other modalities. The combination of TA and laser toning has a wealth of clinical experience with many studies reporting its efficacy and safety.^{30,31} Unlike other combinations, the two components can be used simultaneously without an increase in the risk of complications. Recent studies have reported that TA can decrease laser-induced melanogenesis.²⁸ Since a long time ago, TA was combined with lasers to increase its skin permeation.³² Thanks to recent development of transepidermal drug delivery, TA is expected to be more effectively used in treatment of melasma.

Besides non-laser modalities, laser therapies are also being combined to laser toning to obtain better results than those of laser toning alone. Many clinical dermatologists including ourselves have been combining laser toning with other melasma therapies and there has been a great deal of clinical experience on combination treatment. Research on combination therapy is increasing in the recent years as laser toning is considered a mainstay of treatment in melasma. Clinical data on the safety and efficacy of laser toning has increased and recent laser toning method uses a lower fluence, milder tissue response and fewer passes compared to the old days. These allow other therapeutic modalities for melasma to be combined with laser toning for better efficacy.

FRACTIONAL LASER TONING

Applying more aggressive laser toning in melasma patients with poor response may bring immediate improvement, however, the long-term disadvantages outweigh the immediate benefits. On the other hand, with fractional laser toning, increasing the fluence can have a different impact. Because tissues damaged from irradiation are surrounded by non-irradiated healthy tissues, it is expected to reduce skin irritation and promote healing. It means fractional laser toning may have a lower risk of complications. We used the 1,064-nm fractional laser toning mode with 50% coverage and kept the fluence about twice as high as a regular laser toning mode. As the fractional mode settings and parameters differ depending on the manufacturer, it is important to exquisitely adjust the parameters for each patient and lesion site. As fractional laser toning uses a higher fluence, it is expected to bring better results in non-responders. Moreover, when hypopigmented macules occur, hypopigmented lesions can be less visible by virtue of the small beam size. Scattered, fine spots of hypopigmentation may create an overall whitened look rather than ungainly depigmented macules.

INTENSE PULSED LIGHT

IPL was one of the most commonly used treatment of melasma before the introduction of laser toning. In the early 2000s, studies started reporting therapeutic efficacy of IPL in melasma,³³ and others followed suit, reporting favorable results of IPL.^{34,35} A review published in 2006 also provided a favorable evaluation of IPL in melasma.³ However, in clinical practice, patients without visible melasma lesions often developed melasma-like hyperpigmentation after receiving IPL treatment for photorejuvenation or lightening of solar lentigines and freckles. Negishi et al.³⁶ proposed that latent melasma that was not visible with the unaided eye might have exacerbated after IPL therapy. They called this latent melasma 'very subtle epidermal melasma' (VSEM) and found that about 30% of all women without visible melasma had VSEM in ultraviolet (UV) photography.³⁶ In other words, subtle melasma can be often present in patients without visible lesions and can develop into noticeable melasma after aggressive IPL treatment. As IPL therapy was too often followed by development of visible hyperpigmentation,^{36,37} or worsening of existing melasma lesions,³⁸ the notion that IPL is risky in patients with melasma began to spread widely among dermatologists.

We are of belief that an appropriate use of IPL can be very effective in the treatment of melasma. Melasma may worsen after IPL because improper parameters, which are more suitable for treating solar lentigines or freckles, are used. Excessive heating of tissues can worsen melasma. In fact, dermatologists who frequently utilize IPL in melasma use lower fluences than those used in solar lentigines or freckles. This is similar to the difference between high-fluence 1,064-nm QS Nd:YAG laser and low-fluence laser toning. However, unlike laser toning, IPL used in melasma does not target destruction of melanin pigments or melanosomes. IPL has a longer pulse width than that of the QS Nd:YAG laser and delivers thermal energy to the entire epidermis through melanin pigments and melanosomes to increase epidermal turn-over and improve degenerated skin environments.

Therefore, the mechanism of action differs between IPL and laser toning, which allows them to complement each other. As most patients with melasma also present other pigmented lesions, combining IPL with laser toning can bring superior and faster improvement than using laser toning alone. For these reasons, we prefer combining laser toning with IPL. In agreement with our experience, recent studies have reported that low-fluence IPL therapy is safe and effective,³⁹ and combining IPL and laser toning can bring excellent outcomes and rapid improvement.⁴⁰⁻⁴² We expect fractionated IPL will be soon introduced for treatment of melasma,⁴³ and additional research should be performed to support its use.

FRACTIONAL LASERS

The concept of fractional photothermolysis (FP) was first introduced by Manstein et al.⁴⁴ in their paper published in *Lasers in Surgery and Medicine* in 2004. Early fractional lasers were developed to reduce the complications of traditional laser skin resurfacing. In the early days, the key indication of FP was skin rejuvenation of photodamaged skin and rhytides. However, some studies reported of successfully treating melasma using a 1,550 nm fractional erbium-doped laser.^{45,46} Afterwards, generation and excretion of micro epidermal necrotic debris (MEND), and removal of melanin in this process were clarified,^{47,48} which served as an underlying principle of fractional laser therapy in melasma. Favorable reports of ablative and nonablative fractional lasers in melasma followed,⁴⁹⁻⁵² and review papers described that fractional lasers were effective in treatment of melasma.⁵³⁻⁵⁵

However, Korean dermatologists who applied fractional lasers in melasma came to experience much more side

effects including PIH and rebound pigmentation than those reported in previous literature. When the energy and density were lowered to reduce side effects, the actual efficacy was much lower than what was reported in clinical studies. Many dermatologists started to be skeptical of the benefits of FP in melasma. By the late 2000s, skepticism regarding the effects of fractional laser in melasma had grown and many studies reported of a high risk of side effects and low efficacy.^{2,56-58} These negative results were particularly pronounced in studies involving Asian patients. The discrepancy in the results between Asians and Caucasians may stem from racial and genetic differences. Lee et al.⁵⁶ reported that melasma initially improved in the early phase of the treatment but worsened starting with the third treatment. They raised questions about the long-term results. Nonspecific thermal stimulation is inevitable to remove melanin through MEND and inflammation takes place as a reaction to the excess heat. Therefore, FP may bring temporary improvement of melasma but is likely to worsen melasma through inflammatory response in the long run.

Controversy still exists over the use of fractional laser in treatment of melasma. We believe that fractional lasers can play a significant role if they are combined with laser toning. As mentioned earlier, there is a high probability of low effect and high risk of side effects in the treatment conducted on the basis of the old concept that FP can be effective in melasma by removing melanin pigments through MEND. However, when combined with laser toning for the purpose of improving the dermal environment, fractional lasers may bring excellent long-term benefits.

As for histopathology of melasma, basic characteristics of the condition include increased melanin in all epidermal layers, basal hyperpigmentation, solar elastosis, and epidermal flattening.⁵⁹⁻⁶¹ Melanocytes in the melasma lesion are larger and have more developed dendrites compared to those in the normal tissues.⁵⁹⁻⁶¹ The basement membrane is also damaged, presenting pendulous melanocytes that protrude into the dermis.^{62,63} Along with these findings, other noticeable histochemical characteristics include increased inflammatory cytokines, elevated levels of melanogenesis-associated proteins, and signs suggesting UV-induced skin damage. Dermal inflammation caused by accumulated UV irradiation stimulates fibroblasts which increase dermal stem cell factors and various cytokines.⁶⁴ These seem to lead to increased melanogenesis.⁶⁴ UV irradiation also activates matrix metalloproteinases which results in the damaged basement membrane.⁶³ For these reasons, it has been proposed that the treatment goal of FP in melasma should be the

improvement of the altered dermal environment to rectify the aberrant signals between dermis and epidermis.

Therefore, laser toning which is effective in removing melanin, and fractional laser which is effective in improving the dermal environment can be combined to enhance the therapeutic effect in melasma. As the benefits and risks can differ greatly across patients and lesion types, parameters should be delicately adjusted to maximize the effect and minimize complications.

LONG-PULSED LASERS

There is a growing interest in applying the “dual mode” or “dual toning technique” of laser toning in melasma and studies have reported favorable results on this technique.⁶⁵⁻⁶⁷ The dual toning technique, which is not an official term, refers to the combination therapy using low-fluence QS Nd:YAG laser and long-pulsed Nd:YAG laser. The theoretical basis of this technique is, as discussed above, using long-pulsed laser to improve the altered dermal environment of the lesion site to obtain superior short-term and long-term results than with laser toning alone.

Most studies used 0.3-ms quasi-long pulsed Nd:YAG lasers,⁶⁵⁻⁶⁷ however, the millisecond domain long-pulsed lasers are also being used in clinical practice. As discussed above, IPL or fractional laser can be combined with laser toning for the purpose of improving the dermal environment and such combination can be regarded, in principle, as dual toning technique. It is important to select the effective wavelength and pulse width of laser to achieve skin rejuvenation and dermal remodeling. The long pulse 1,064-nm Nd:YAG laser may offer particular benefits considering its absorption coefficients of melanin and water.

1,927-NM FRACTIONAL THULIUM FIBER LASER

The 1,927-nm fractional thulium fiber laser was introduced in 2009 and has about 10 times higher absorption coefficient of water compared to the 1,550-nm erbium-doped fiber laser. Due to this property, its photothermal effect is limited to the dermoepidermal junction and upper dermis, which enables effective removal of epidermal pigments. The stratum corneum has a relatively lower water content than the epidermis and tends to have lower thermal reaction to the fractional thulium laser, which enables its preservation. As this may help rapid recovery and reduce inflammation, the fractional thulium laser is expected to be beneficial in the treatment of melasma.

Studies have reported that as the fractional thulium laser is able to preserve the stratum corneum and deliver the photothermal effect to a limited depth, the risk of side effects such as PIH and rebound hyperpigmentation is minimized, while melasma is effectively improved.⁶⁸⁻⁷¹ The fractional thulium laser has superior efficacy in removing melanin compared to other fractional lasers, however, long-term follow-up is needed to evaluate its long-term efficacy and safety in melasma.

DUAL-PULSED LASER TONING

It is interesting that no studies so far have actually examined the impact of the pulse width in laser toning therapy. That may be because laser toning is generally performed using the 1,064-nm QS Nd:YAG laser which provides a fixed pulse width. Studies on the pulse width have been performed only recently. Alsaad et al.⁷² compared the 5-nanosecond (ns) QS Nd:YAG laser and 50 ns QS Nd:YAG laser in terms of pain and efficacy. They found the difference in MASI scores between two groups was not statistically significant but the pain score was significantly lower in the 50-ns QS group.⁷² Considering the principles of laser toning treatment and thermal relaxation time (TRT) of melanosomes, the 50-ns QS Nd:YAG laser may be useful in laser toning therapy of melasma. Few studies have looked at the importance of pulse width in laser toning for melasma but future research on this topic will help bring new innovations in the treatment of melasma.

A recent study examined a new pulse mode of laser toning called dual-pulsed laser toning or photoacoustic therapy pulse (PTP). This novel QS pulse-to-pulse mode is operated as a dual pulse at half fluence and 50-150-microsecond intervals.⁷³⁻⁷⁵ Some research suggests that the delay time between two subpulses allows melanocytes to cool down while destroying melanosomes. Kim et al.⁷³ reported that the PTP technique resulted in less hypopigmentation compared to the traditional technique in treatment of PIH. In another study demonstrating the effect of the PTP mode in Riehl's melanosis, Chung et al.⁷⁴ proposed that the dual-pulsed mode caused less proinflammatory transcription factors and cytokines to be able to provide a safer treatment than the conventional laser toning. There is only one published paper reporting the therapeutic effect of the PTP mode in melasma.⁷⁵ Better clinical outcomes with less treatment-associated pain were obtained with the QS PTP-treatment than the QS single pulse-treatment.⁷⁵ They suggested that the QS PTP mode might be useful in treatment of melasma,

especially on the thin skin of the periorbital lesions, and to erythema-prone and sensitive patients. In our practice, we are using the PTP technique with excellent results and hope that more research will be performed on this new technique in the near future.

NEW LASER THERAPIES

The low-fluence QS alexandrite laser, QS ruby laser, QS ruby fractional laser, copper bromide laser, and picosecond alexandrite laser have been proposed as alternatives to laser toning using the QS Nd:YAG laser.⁷⁶⁻⁸⁰ Although the conventional laser treatment of melasma using QS alexandrite laser and QS ruby laser has brought poor results, lowering the fluence or using the fractional mode is expected to widen the application of these lasers in melasma. The copper bromide laser was consistently reported to have disappointing results in the literature with the exception of a Korean study published in 2010.⁸⁰⁻⁸²

In the late 1990s, a study reported that the picosecond laser had superior efficacy than the nanosecond laser in tattoo removal.⁸³ The picosecond alexandrite laser was developed and shown to be effective in tattoo removal,^{84,85} leading to its recent commercialization. Unlike tattoo removal, it is unclear whether the picosecond alexandrite laser will be superior to the previous nanosecond lasers in melasma treatment. Theoretically, the shorter pulse width of the picosecond laser can minimize the collateral damage and selectively target melanosomes. Considering the TRT of melanosomes, however, it is unclear whether the picosecond laser will have clinically significant superiority over the nanosecond laser. One should also consider the characteristics of the 755-nm wavelength applied to the picosecond alexandrite laser. Newly proposed laser therapies of melasma lack safety and efficacy data and need more research and clinical long-term experience.

CONCLUSION

As mentioned earlier, in patients with melasma that have poor response to laser toning, a clinician can often make the mistake of increasing the fluence for getting strong tissue reactions and initial improvement. Such an approach should be avoided. Various treatment modalities of melasma other than the laser toning have been developed. It is important for dermatologists to clearly understand different mechanisms and properties of each treatment. That allows them to choose the optimal modalities for each patient and lesion state. It can also guarantee better efficacy and safety.

When dealing with a non-responder, it is helpful to switch to another treatment or combine other treatments. However, the first and most important is to check whether the patient follows the basic element of melasma treatment consisting of sun avoidance, regular sunscreen use, and discontinuation of birth control pills, irritating cosmetics or phototoxic drugs. UV is a leading cause of melasma and a fundamental part of its pathophysiology. Patients should be instructed to avoid UV exposure and wear a sunblock. In addition, they should discontinue hormone therapies or oral contraceptives that can trigger or aggravate melasma. The presence of systemic conditions, phototoxic drugs, psychological/physical stress, or the use of irritating cosmetics must also be checked in detail. Even though there is universal agreement that the above elementary approaches are essential in the treatment of melasma, many doctors often neglect to examine thoroughly if a non-responder follows them steadily. We recommend that the basic parts of treatment are checked and identified before applying a new treatment method in non-responders.

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