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A Cosmeceutical Retinoid-Based Depigmentant Formula for Different Skin Types and Ethnicities

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Abstract

Disorders in skin pigmentation are a common cause of consultation for dermatologists and other physicians. Psychological distress is a usual feeling in many patients, especially when the affected area is visible such as the face. Thus, an effective treatment is important for both, the patient and the professional. A lot of scientific research has been performed in order to elucidate the mechanisms that controls and regulate skin pigmentation and also to discover new treatments to prevent, reduce or remove such dermatosis. However, different types of dyschromia are triggered by sun exposure, hormonal imbalance, pregnancy, drugs, toxics, trauma, etc.

Keywords: Skin pigmentation disorders; Dyschromia

Background

The principal dyschromia disorders are post-inflammatory hyperpigmentation, melasma and facial lentiginosis. All of them are conditions that mean a great aesthetic problem, due the persistence of them once they appear and also the difficulty to achieve a successful treatment in some cases.

Post inflammatory hyperpigmentation (PIH) is secondary to the induction of melanin synthesis when several inflammatory pathways are activated. Many situations can trigger inflammation in the skin, which results in a further skin hyperpigmentation, especially in people with dark skin [1]. Among such situations we can find acne lesions, insect bites, scratches and also skin contact to irritants as illustrated in the review of Orthone et al. [2], subjects exposed to lauryl sulfate sodium, resulted in hyperpigmentation over the course of 1-2 weeks even in Caucasian skin.

Melasma is one of the most prevalent acquired pigmentation disorders, especially among women. It is characterized by symmetrically distributed darker brownish macules and patches in sun-exposed areas of the face such as the forehead, cheeks, jaw and chin. Although the pathogenesis is still not fully understood, hyper-reactive melanocytes activated by UV radiation is the most widely accepted cause. Other causes such as genetics, drugs, and hormonal background also play a major role in melasma development [3]. It has been reported a higher melasma prevalence among several ethnicities such as East Asians, Indian, Pakistani, Middle Eastern, Mediterranean-African and Hispanic Americans, especially those who live in areas with greater sun radiation exposure as intertropical regions [4]. Since UV- radiation seems to be the main trigger factor, melasma pigmentation worsens during summer and improves in winter. It has been reported in the scientific literature a reduction of the intensity of the disease in 50% and its incidence during pregnancy in more than 90% with a daily use of high SPF sunscreen Recently it has been shown that visible light is involved in the worsening of melasma [5].

Solar lentigos are shown in photoexposed areas due to the chronic solar exposure. Several studies indicate the participation of keratinocyte growth factor (KGF) in the formation of lentigines, which is also involved in the synthesis of melanin [6]. In addition we can observe alterations in the epidermal architecture, which is due to the DNA damage caused by ultraviolet light.

Melasma and postinflamatory hiperpigmentation may appear in all skin types and all ethnicities, but occur more often and severely in skin-of-color subjects, including African Americans, Hispanics, Asians, native Americans, Pacific Islanders and those of Middle Eastern descendent [7]. Solar lentigos due to chronic solar exposure have an etiology that differs slightly from the other two entities, so it is usually observed on all skins damaged by the sun [8].

We must emphasize the importance of ethnicity in the development, progression and maintenance of dyschromias, since not only is the phototype of Fitzpatrick the determining factor. Within the same phototype we can distinguish different ethnicities. The prevalence of melasma and post inflammatory hiperpigmentation (PIH) is higher in those indiviuals with ethnic mix. Additionally, it can be refractory to treatment. Thus, in this group of patients is necessary to avoid aggressive treatments that may worsening the situation [9].

Most patients that develop melasma have a hypersensitivity to ultraviolet radiation, as their minimum erythema dose is lower than in the rest of the population, even if they have dark skin phototypes [2]. In these patients, a very short solar exposition can stimulate the disease. We also know that there is an important hormonal component in the development and progression of this hypermelanosis, which is usually related to gestation and oral contraceptive medication. There are also some triggering factors such as use of cosmetics, photosensitizing drugs, certain food items, hepatopathies and inflammatory processes of the skin [10,11].

In melasma lesions, the excess of melanin can be present in the epidermis, the upper dermis or a combination of both. This deeper accumulation of melanin is normally associated with the extravascularization of macrophages that phagocyte extracellular melanin granules and migrates to deeper layers of the skin making the treatment much more difficult that the epidermal manifestation. It is important to mention that dermal vasculature exhibits, similar features to chronic sun damage and there is an important role of dermal inflammation secondary to ultraviolet radiation in the hyperpigmentation and reactivation of melasma lesions through the production of melanogenic cytokines and growth factors [12].

Although, certain mechanisms of melanin synthesis and maturation are still unknown, advances in this field allow us to develop several active ingredients that are able to act in different stages of melanogenesis.

In the management of pigmentary disorders, it is important to highlight the treatment of melasma be challenging and long-term approach. In addition the avoidance of aggravating factors like contraceptive medication and ultraviolet exposure, topical therapy has remained the mainstay of treatment. There are multiple choices for topical treatment, of which hydroquinone (HQ) is the most commonly prescribed drug. It is an effective treatment, well tolerated but must be used with caution in some patients. It is well known that a prolonged HQ usage may lead to secondary effects like depigmentation and exogenous ochronosis. The search for safer alternatives has led to the development of many new topical agents for managing hypermelanosis. In addition to HQ, there are other topical agents with variable efficacy including azelaic acid, kojic acid, retinoids, topical steroids, glycolic acid, mequinol, and arbutin. These topical substances modify different stages of melanogénesis. The most common mechanism of action is the inhibition of the enzyme tyrosinase. Combination therapy is the preferred mode of treatment for the synergism of their activities and the reduction of untoward effects. The most popular combination consists of HQ, a topical steroid, and retinoic acid known as Kligman formula. Treatment with demelanizing agents must be continued for several months before significant clinical benefits become noticeable.

Several recent studies have shown the efficacy of some new active ingredients, such as topical and oral tranexamic acid [13,14] and cinnamic acid [15]. New approaches to melasma treatment based on the combination of ingredients are also becoming increasingly popular. We must also consider that in addition to topical treatments different types of laser and light therapy have been studied in the treatment of melasma. Intense pulsed light (IPL), low fluence Q-switched lasers, and non-ablative fractionated lasers are the most commonly used nowadays [16]. In addition, chemical peels such as glycolic tretinoin and others, are classic treatments that continue to be used in the daily clinical practice [17].

There are evidences in the literature of acosmeceutical product combining different ingredients that demonstrated good tolerance and effectiveness. This formula is based on RetinSphere® technology, the association of two retinoid derivatives: retinol in glycospheres and hydroxypinacolone retinoate. The vehiculization of the retinol within the glycospheres improves the tolerance and facilitates the delivery into the cell. The retinoic acid ester, hydroxypinacolone retinoate, has similar action to tretinoin, but does not cause the irritation typically observed with this retinoid. RetinSphere® technology has been combined with other depigmenting active ingredients such as N-acetylglucosamine able to inhibit glycosylation of tyrosinase, kojic acid, a fungi metabolite with strong tyrosinase inhibitor able to chelate metal ions [18] such as Cu^{+2} and Fe^{+3} Cromabright® and Natriquest® (also chelators able to uptake the copper and iron ions needed by tyrosinase for its activation), albatin and alistin® (acting synergistically inhibiting melanin synthesis), and Niacinamide (vitamin B3 that prevents the transfer of melanosomes to keratinocytes). Furthermore, the formulation contains hydrating,anti-irritant and anti-inflammatory active ingredients [19].

It is interesting to highlight the relevance of photoprotection in the treatment of melasma and other pigmentary disorders. Topical sunscreens are very important due to the relevant role of ultraviolet radiation and visible light in the maintenance and worsening of these alterations [20]. Recently we have been able to verify that oral photoprotection, specifically Fernblock®, is very useful during the treatments with depigmenting actives, since better results are obtained with their use [21]. Furthermore, Fernblock® demonstrated to be effective against UVB and Visible light skin damaged [22,23].

Neoretin® in Melasma Treatment in Caucasian Population

A double-blind, split-face placebo control clinical study conducted in 30 Caucasian patients phototype II-IV diagnosed with melasma [18] employed the same regimen consisting in Neoretin® DC Gelcream SPF50 in the morning and the serum at bedtime during a period of three months. Subjects were their own control as the active formula was applied over half of the face and vehicle in the other split face.

Photographic assessment was performed using RBX images and MASI evaluation. Twenty-eight out of 30 subjects conclude the study. The two dropped outs were due to reasons unrelated to the study product. The analysis of data, concluded that the 89% of the side of the face treated with the active formula showed improvement. The reduction of the MASI at the end of the study was 74% on the treat side and 55% on the side that received placebo with photoprotector SPF50, which is statistically significant=0,009). At the end of the study, the degree of satisfaction was scored in 8-9 out of 10 in 70% of patients. PGA was classified as a great or excellent improvement in 60% of patients.

In addition to the good results obtained with this cosmeceutical regimen, tolerance results were also satisfactory for all phototypes and also in those patients with sensitive skin.

Neoretin® in Melasma Treatment in Mexican Population

Another study was performed in Mexican population [24] who owns intrinsic and specific racial features that makes the melasma treatment particulary difficult. The 90% of this population has indigenous ancestors, and this origin predisposes to the development of melasma and post–inflammatory hyperpigmentation. For these reasons the treatment and prevention of these hypermelanosis in such population constitutes a big challenge for physicians who must balance the risk and benefits of the different therapeutic strategies in order to achieve the best results avoiding as much as possible the inflammatory component that may worsen the aesthetic results of the melasma treatment.

A total of 30 subjects with facial melasma were recruited for this prospective, open and observational study. Eligibility criteria included men or women over 18 years old, in good health status and absence of melasma treatment in the previous two months. Pregnant or nursing women were not allowed to participate in this study.

The depigmentant capacity of the described protocol of treatment was carried out through the assessment of Melasma Area and Severity Index (MASI), the taking of clinical and dermoscopic photographs (Dermlite II Pro), the analysis of the skin with the Reveal System (RBX technology), and the skin brightness measurement (Chromameter, Minolta CR 400). Subjective global evaluation of the patients and the investigators were also registered at the end of the study.

The results showed a significant reduction of the MASI score in more than 65% of the patients ($p<0,0001$) and the average of the MASI score reduction was 50% ($p<0,0001$).

The skin brightening experienced a significant increase ($p<0,05$) reached to 76,9% of patients at the end of the treatment and the dermoscopy findings showed an improvement in pigmentation in 57,7% of patients.

The subjective global evaluation performed by the patients and the investigators was in accordance with the good results previously described. Ninety percent of the patients observed some degree of improvement and 55% of them score it as a "marked improvement". Regarding tolerance, one of the major issues of most of the treatments for melasma and PIH, results were excellent with no serious adverse events reported. Just a slight, transient and self-limited erythema was observed in 23% of subjects that did not require treatment discontinuation.

Neoretin® in Solar Lentigo Treatment in Filipino Population

In a prospective, double blind, placebo-controlled clinical trial study recently conducted in Filipino population [21] the synergic effects of a combined regimen consisted in Neoretin® DC Gel Cream SPF50 in the morning and Neoretin® DC Serum at night in addition to oral photoprotection with Fernblock® was Fernblock® is a specific extract obtained from the leaves of the fern Polypodium leucotomus that is targeting the different ethiopatogenic mechanisms of melasma and others sun skin blotches. Specific extract obtained from the leaves of the fern *Polypodum leucotomus* in order targeting the different ethiopatogenic mechanisms of melasma and other sun-exposure derived skin blotches. This clinical trial was designed with four arms to evaluate the effects of different options of treatment.

A total of 80 women (20 per arm) were recruited for this study. Eligibility criteria included patients over 35 years old, in good health status and presence of skin blotches due to photoaging. Pregnant or nursing women were not allowed to participate in this study.

To assess the efficacy of the explained treatment options, different parameters were assessed: brightness, lightening, hydration, moisturization, firmness, wrinkle reduction, smoothness and thickness. The observational period was 90 days long with follow-up visits at day 30, and 90 after study entry.

The good results obtained in both, topical and oral+topical combined arms, demonstrated that Neoretin® regimen not only improves the appearance of the hyperpigmented skin blotches but also exerts global antiaging activity ameliorating all the parameters measured previously mentioned. Topical treatment alone achieved statistical significance improving in

most parameters. After 90 days of treatment a skin lightening scored +19%, skin brightening +8.9%, transepidermal water loss (TEWL) -10,2%, moisturization +21,7%, wrinkles -10% and skin smoothness +32,6%. The results of the combined treatment were similar or even greater in some of the parameters: skin lightening scored +15.1%, skin brightening +11,6%, transepidermal water loss (TEWL) -14,2%, moisturization +22,5%, wrinkles -9.4% and skin smoothness +32,6%.

In general terms, tolerance was very good for most of the patients. Only two of them were dropped out Due to adverse events because of the development of erythematous patches on the cheeks and tightening that lasted for three days without sequelae after resolution. A third patient was dropped out due to reasons not related to the study treatment.

Neoretin® in Caucasian and Asian Population with Solar Lentigo

The prospective, open-label study of Vitale et al [23] included 40 patients (30 Caucasian and 10 Asian) over 18 years old and diagnosed with solar lentigo and photoaging features received the Neoretin® regimen for 60 days. Objective measurements were made to determine the skin hydration (Corneometer®), brightness (Colorimeter®) and melanin content of the skin blotches (Mexameter®).

After two months of treatment, 80% of patients showed some grade of improvement. After two months of treatment, the mean melanin index reduction was -16,5% for Caucasian subjects and -20,8% for Asian. Regarding brightness measurements Caucasian subjects experienced an average of improvement of 20.1% and 16% respectively. Hydration measurements were also satisfactory improving a 25,1% in Caucasian and 20.7% in Asian subjects.

The percentage of subjects who showed a positive effect was 70.0% of Caucasian and 80.0% for Asian after 60 days of treatment.

The skin tolerability was 100% in both groups of subjects. No adverse reactions were reported during the trial period.

Discussion

Acquired hyperpigmentation disorders constitute a major concern for most patients who suffer it, especially when it affects the face. Physicians make their best to achieve optimal best results with the combination of different therapies as chemical peelings, laser, and drugs such as hydroquinone. However, response to the different therapeutic options differs from subject to another. Skin phototype is not always accurate enough to predict the response to treatment, being necessary to pay attention to the ethnicity the status of the skin and the tolerance. To achieve the optimum balance between efficacy and safety is not always easy as many variables may alter the course of the treatment, generate a powerful inflammatory response and facilitate the appearance of post-inflammatory hyperpigmentation that would dilapidate the aesthetic improvement obtained by the initial treatment. Occasionally, these therapies are effective in depigmentation but at the same time excessively aggressive and cause adverse events that hinder adherence to the treatment by the patient. Therefore, highly recurrent dermatosis, such as melasma, would reappear soon after, causing a failure of therapeutic success.

In addition to the pigmentary disorders, most of the affected subjects present other signs of photoaging: a moderate to severe degree of solar elastosis was reported in 93% of melasma patients [24] that must be taken into account. Thus, the ideal treatment would not only target to reduce the size and darkness of the spots (melasma, lentigos, etc.) but also to improve the overall state of the skin keeping the hydration, smoothness, and firmness of it. Considering these factors, the desirable depigmenting therapy would be the one with a good efficacy that starts providing results from the beginning, with a good tolerance being gentle with sensitive skin and able to prevent the inflammation and hyperpigmentation related to this process. It should provide reproducible results in different skin types that help the professionals to predict the effect of the therapy in different patients. Finally, the product or therapy should improve the global signs of photoaging to achieve the aesthetic successful outcomes. Due to the safety issues surrounding HQ, the European Committee prohibited the use of this drug in cosmetics due to potential complications such as ochronosis. These suggest that safer and more effective topical ingredients need to be developed [24].

The regimen with Neoretin® Discrom Control has been studied in 140 patients from different ethnicities (Latino, Asian and Caucasian) to assess its ability in ameliorating the appearance of the skin hyperpigmentation such as melasma, lentigo and sun blotches that providing excellent outcomes in most of the patients. In melasma cases, it reached a reduction of MASI scores higher to 60%. In addition, this protocol of treatment has been studied in geographic areas with high sun radiation (main trigger of hypermelanosis and photoaging) as Mexico and Philippines with very good results in all parameters analyzed. This is attributable to the combination of selected active ingredients plus a high SPF included in the daytime use formula. The low incidence of adverse events registered in these trials allows confirming the good tolerability of these cosmeceutical products that postulates it as safe choice specially in those cases that irritation could worsen the initial condition or cause cessation of conventional more aggressive treatments.

The favorable effects of this combination of ingredientes, works ingredientes, works improving fine wrinkles, and skin texture so they should be added to the final outcomes in relation to the pigmentary disorders.

Conclusions

In conclusion, it is important to highlight that pigmentary disorders are very common diseases being one of the most frequent reasons for consultation in the daily clinical practice.

Some of them as melasma tend to be more frequently presented and persistent among darker phototypes and some ethnicities. Although these dyschromias are not potentially life-threatening, they cause deep psychological distress and discomfort in most of the patients. This situation should initiate fundamental thinking about prescribing treatments able to improve able to improve these dermatoses aesthetically without producing adverse effects. Topical treatment continues to be the principal approach on which we support the management of dyschromias. For prescribers, is important to count on topical formulas that work in a synergic manner, with an excellent safety profile that make them a versatile alternative to traditional therapy.

Given this fact we can affirm that the depigmenting regimen of Neoretin® is safe and effective for the treatment of pigmentary disorders in all skin types and ethnicities.

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