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Evaluation of the Efficacy and Safety of A New Pigment Correction Cosmetic Protocol in Caucasian Women with Melasma

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Abstract

Melasma is one of the most prevalent acquired pigmentation disorders, especially among women due to its hormonal background. There is a wide variety of therapeutic alternatives available for its treatment given its multifactorial origin and complexity. Cosmetic protocols based on depigmenting agents remain one of the cornerstones of melasma treatment.

Aim: To evaluate the efficacy and safety of a new cosmetic pigment correction protocol in the treatment of melasma in Caucasian women.

Methods: A single-blind, prospective, single-center study was conducted in 20 women between 25 and 65 years of age, phototypes II-IV with mildmoderate facial melasma.

For 90 days patients applied a sunscreen and moisturizing cream in the morning and a pigment correction protocol at night consisting of a skin retinization regime combining two formulations with *Retinsphere*[®] technology. (Neoretin DC Ultra emulsion and Neoretin DC transition cream).

Treatment results were evaluated by clinical assessment, Observ[®] photography and non-invasive instrumental measurements such as the erythema and melanin index by Mexameter. The Melasma Area and Severity Index (MASI) were recorded, and patients completed both a quality of life questionnaire (MELASQoL) and a subjective evaluation.

Results: MASI score was significantly reduced at all study visits, with a significant reduction in the area and severity of melasma already observed at 30 days and a 48% reduction at the end of treatment.

In the opinion of the investigator and patients, some degree of improvement was reported in 95% of patients at the end of treatment and neither patients nor the investigator reported worsening of melasma at the end of treatment as compared to baseline. The degree of melasma improvement observed by patients increased progressively and significantly from day 45 onwards, reaching an improvement of almost 70% at the end of the treatment.

The adverse effects evaluated, (peeling, erythema, burning, tightness, irritation, and itching) increased gradually, being higher at T45 and T60, coinciding with the greater frequency of application of the formulations. Effects were however transient and in no case reached statistical significance or required treatment discontinuation.

Conclusion: The cosmetic pigment correction protocol under study appears to be an effective therapeutic option for the treatment of melasma. The retinization regime, which consisted in the gradual application of the more powerful formulation alternated with a transition formulation, made it possible to achieve both efficacy and good tolerability to the therapeutic regimen.

Introduction

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, checks, jaw, and chin. Although the pathogenesis is still not fully understood, hyper-reactive melanocytes activated by ultraviolet (UV) radiation is the most widely accepted cause. Other causes such as genetics, environmental pollutants, sensitizing drugs and hormones can also play a major role in melasma onset and development [1] as well as the combination of several of these factors [2].

Skin inflammation, such as pronounced erythema, has also been demonstrated by colorimetry and thermography to worsen melasma pigmentation [2,3]. In addition, there is histological data demonstrating the presence of a moderate lymphohistiocytic infiltrate, increased mast cell infiltration in adjacent elastotic areas,



augmented vascularity, and up-regulation of pro-angiogenic factors [4,5].

It has been observed that melasma pigmentation worsens during summer and improves in winter, reporting a 50% reduction in its intensity during this time. Although UVA radiation has been shown to stimulate melanogenesis through a direct effect on melanocytes, visible light from solar radiation and even blue light emitted from electronic devices can also cause hyperpigmentation. Therefore, to prevent its appearance, it is essential to select sunscreens against the entire solar spectrum and not only against UV radiation [6,7].

Its multifactorial etiopathogenesis and recurrent nature has led to the adoption of a wide variety of therapeutic alternatives for the approach to melasma, with variable and transitory results. Therefore, treatment decisions depend on the interrelation between improvement in quality of life and symptoms [8]. The different therapeutic approaches in the treatment of melasma include depigmenting cosmetic products, drugs such as Hydroquinone (HQ), and even dermo-aesthetic techniques such as laser or peeling.

With respect to cosmetic treatments, there are numerous active pigment correction and control agents such as retinol, kojic acid, tranexamic acid and niacinamide, which act at different stages in the synthesis of melanin [9]. Other natural ingredients such as Edafence[°] (anti-pollution technology) or Fernblock^{*} (photoprotective technology) can help prevent the development of hyperpigmentation disorders [10,11].

Currently, the use of topical depigmenting agents is the "gold standard" in the treatment of melasma [12]. Within the therapeutic arsenal, the best results are obtained with HQ at different concentrations (normally 2% to 4%), Tranexamic Acid (TA), glycolic acid, trichloracetic acid, kojic acid, salicylic acid, azelaic acid, ascorbic acid, mandelic acid, niacinamide, corticoisteroids, arbutin, resveratrol, resorcinol, and retinoids. Some of them are often combined in the same formulation [13,14].

HQ, also known as dihydroxybenzene, is a hydroxyphenolic compound that is structurally like melanin precursors. It inhibits the conversion of DOPA to melanin by inhibiting the enzyme tyrosinase. HQ affects the formation, melanization, and degradation of melanosomes [12]. Topical HQ can cause adverse effects such as irritant and allergic contact dermatitis, post-inflammatory pigmentation and ochronosis. Therefore, it should be used with special caution in patients with sensitive skin or dermatitis and under medical supervision. HQ is often combined with a retinoid and topical corticosteroid, known as the Kligman Willis formula. This triple combination is more effective and better tolerated than HQ monotherapy [15].

TA, a synthetic derivative of lysine, is a fibrinolytic agent that blocks the conversion of plasminogen to plasmin, thus preventing the binding of plasminogen to keratinocytes and inhibiting the release of paracrine melanogenic factors that normally act to stimulate melanocytes [14,16]. In several studies topical TA appears to be as effective as topical HQ [17].

Topical retinoids, used long-term alone or in combination with HQ, can also be effective and safe in the treatment of melasma. Several topical retinoids such as tretinoin or all-trans-Retinoic Acid (RA), 13-cis-retinoic acid (isotretinoin), retinol, retinaldehyde, tazarotene, and adapalene have been used with success in melasma therapy. The action mechanism is thought to involve the stimulation of keratinocyte turnover, inducing a decrease in melanosome transfer [18] and allowing greater penetration of other active ingredients. RA has been commonly used in the treatment of disorders of hyperpigmentation

[19]. It is thought to inhibit tyrosinase transcription, interrupt melanin synthesis, inhibit tyrosinase-related proteins 1 and 2 (TRP-1 and TRP-2), and has been shown to decrease post-transcriptional levels of tyrosinase and TRP-1 after UVB exposure [18]. In a randomized, vehicle-controlled study of 0.1% RA cream versus vehicle cream applied nightly to the face of Caucasian women with melasma for 40 weeks, 68% of RA-treated patients were rated as improved or greatly improved as compared to just 5% of those patients treated with vehicle [20]. When retinoids are used as depigmenting agents, they must be stable and applied progressively to avoid irritation, although the development of retinoid dermatitis remains common with some retinoids [21]. This gradual application by which skin increases tolerance to retinoids is called "retinization" [5,19].

In addition to these topical treatments, there are several chemical peels and pigment correction masks that can be very useful. However, these treatments must be tailored to each patient according to type of melasma, phototype or ethnicity of the patient, and his/her activity. The most frequently performed peels in offices are glycolic acid (20-70%), salicylic acid (20-30%), and Trichloracetic Acid (TCA) (15-35%), alone or in combination with Jessner's solution, kojic acid, glycolic acid, retinol and many others. The main adverse effect of these peels is exaggerated irritation which increases the probability of developing Post-inflammatory Hyperpigmentation (PIH).

Another approach can be the use of laser procedures. However, laser therapy should be used with extreme caution when treating melasma as it can in some cases worsen its severity. There is evidence of the benefits of Pulsed Dye Laser (PDL) and picosecond alexandrite laser using special lens [22]. Each case should be carefully studied according to specific individual characteristics before considering the use of light sources.

In any treatment it is essential to avoid melanogenesis-triggering factors such as intense exposure to solar radiation (UVA, UVB, IR and visible light), as well as the use of hormonal contraceptives and photosensitizing drugs. All patients, regardless of the degree of severity of the melasma, should use daily photoprotection with an SPF 50 or 50+, reapplying frequently and in an appropriate amount (2mg/ cm²). In addition, for a correct control of the disease it is important to use physical measures such as clothing, sunglasses and hats. It is also important to mention that beneficial effects of oral supplementation with Fernblock®, a standardized extract of the ferm Polypodium leucotomos have been demonstrated in pigmentary disorders such as melasma [13]. Fernblock's action mechanisms include the promotion of the p53 suppressor gene, modulation of inflammatory cytokines, upregulation of endogenous antioxidant systems, blocking of UV radiation-induced cyclooxygenase-2 expression and inhibition of the activation of Opsin-3 [10,23]. It works as a powerful antioxidant due to its high content of phenolic compounds, and has demonstrated beneficial effects in photo aging, photoprotection and the treatment of pigmentary disorders [24,25].

The nature of the pathology and its evolution must be carefully explained to patients during the first visit to ensure optimal adherence to treatment and avoid false expectations of radical results in a short time. The patient must understand and accept that, although in-office treatments are normally performed in the autumn/winter periods, they must continue treatment at home for the rest of the year to maintain the results and avoid worsening of their condition.

Melasma has a significant impact on physical appearance, generating a strong emotional impact and reducing the quality of life of affected patients, which often motivates them to visit a dermatologist [12]. Sci Forschen

In relation to the above, there is a need to find safe and effective products and treatment regimens for melasma that can be maintained over a long period without causing damage to the treated areas.

The pigment correction protocol we propose combines the action of different active ingredients to block the synthesis and transfer of melanin, as well as eliminating the excess of pigment retained in the epidermis.

Study Population, Materials and Methods

The aim of this study was to evaluate the tolerance, safety, and efficacy of a cosmetic retinization protocol in the treatment of melasma in Caucasian women.

In this single-blind, prospective, single-center study, we evaluated 20 women, aged 25 to 65 years, phototypes II-IV with mild-moderate facial melasma.

None of the subjects had received pigment control or correction treatment during the 3 months leading up to the study, were suffering from concomitant diseases, had allergies to any of the ingredients in the formulations or were seeking to become pregnant in the following months. In additional to the inclusion criteria, patients discontinued use of cosmetic products at least one week prior to the start of the study, and refrained from using any other topical products during the study period.

The treatment protocol featured two formulations with Retinsphere* technology, one (Neoretin Discrom Control Ultra emulsion) being more powerful with Retinsphere Technology with 0.5% retinol, offering greater pigment correction activity, and the other, a transition product (Neoretin Discrom Control Transition cream) with the same active ingredients but at lower concentrations, and with additional soothing and repairing ingredients to facilitate retinization and increase tolerance to the more active product [21].

The formulations used for the intensive pigment correction protocol feature the following active ingredients with safety and efficacy demonstrated in previous studies [26-29].

1. RetinSphere[®] Technology (retinoid combination) is an innovative combination of two cosmetic retinoids (retinol in microsponges and hydroxypinacolone retinoate) that induces effects on the skin analogous to those of retinoic acid, but without the well known irritant side effects.

Retinol: Retinol or vitamin A is a liposoluble vitamin which is less stable than RA, but which offers similar results with fewer side effects. In the tested formulations, retinol is transported in a microsponge system that maintains the stability of the molecule against external aggressions (oxidation) and provides sustained release, thus increasing the efficacy of the retinoid and producing less irritation.

Hydroxypinacolone retinoate: Is a RA ester that reduces the potentially irritating effect on skin. The ester form is one of the most stable retinoids [30] and acts on the same receptor as RA, providing similar efficacy but with better tolerance.

The combination of these two retinoids has pigment reduction activity through mechanisms which regulate melanogenesis, normalize epidermal proliferation and enhance penetration of other active ingredients. The technology has been shown to increase skin elasticity and radiance and decrease wrinkles and pigmentation in photoaged skin [27]. To ensure retinoid tolerance, it is essential to follow a skin retinization schedule [21].

2. Anti-pollution technology; Edafence® this compound originates

from the extract of *Deschampsia antarctica*, a plant native to the Antarctic continent. It is a plant capable of surviving in hostile environmental conditions, such as high radiation, high salinity, high oxygen concentration, low temperature, and extreme dryness, due to protection mechanisms against environmental aggression. Edafence[®] has been shown to reduce the effects of various pollutants on the skin and it strengthens the skin's barrier function, thus improving overall pigment control efficacy [31,32], as clinical studies have shown that environmental pollution can worsen pigmentation disorders such as melasma [33].

3. The ingredients of the pigment correction system are acting to contrast different stages of melanogenesis:

1) Inhibition of tyrosinase glycosylation: N-acetylglucosamine and Hexylresorcinol.

2) Inhibition of tyrosinase activation: Natrilquest, chelators able to sequester copper and iron ions needed by tyrosinase for its activation.

3) Inhibition of melanin synthesis: TA is an active ingredient that decreases melanin content and tyrosinase, TRP-1 and TRP-2 activity by inhibiting plasminogen binding to keratinocytes.

4) Inhibition of melanosome transport: Niacinamide, vitamin B3 acts as a depigmenting agent by decreasing the transfer of melanosomes from melanocytes to keratinocytes.

Furthermore, the formulation contains hydrating, anti-irritant, and anti-inflammatory active ingredients.

A transition cream with a formulation designed to soothe and reduce potential irritation caused by the retinoids, and SPF 50+ sunscreen with the non-filtering biological active Fernblock^{*}, and a moisturizing cream were also part of the pigment correction protocol used in this study.

Treatment protocol

For 90 days patients applied a sunscreen and moisturizing cream in the morning and at night they followed the pigment correction protocol using the two formulations with Retinsphere* technology.

Skin retinization was carried out for 4 weeks to ensure retinol tolerance. For the first two weeks the transition formula was administered at night, 5 days a week and the intensive treatment formula 2 days a week, then both products were used on alternate nights for two weeks and finally Neoretin DC Ultra emulsion was used 5 nights a week and Neoretin DC Transition cream 2 nights a week, for the next two months (Figure 1).

The investigator performed a clinical assessment of the Melasma Area and Severity Index (MASI) and the degree of melasma improvement. Objective evaluations were performed using clinical photographs (Observ[®]) as well as non-invasive instrumental measurements to determine the erythema and melanin index using Mexameter[®]. Patients also answered a quality-of-life questionnaire (MELASQoL) and a subjective assessment questionnaire.

A total of 6 evaluation contacts were carried out. The first visit was the baseline visit before starting treatment (T0) followed by 3 other in-person visits: T30d, T60d, and T90d. Telephone follow-up were performed at T15 and T45 (Figure 1).

Statistical Analysis

For the efficacy variables of an ordinal nature: clinical assessment of melasma observed by patient and investigator, degree of improvement observed by patient, degree of improvement perceived by investigator

		WEEKS 3-4	MONTHS 2-3
Morning	Moisturizer and SPF 50+ Sunscreen		
Night	NEORETIN DC Transition Cream 5d/week NEORETIN DC Ultra Emulsion 2d/week	NEORETIN DC Transition Cream 4d / week NEORETIN DC Ultra Emulsion 3d/week	NEORETIN DC Transition Cream 2d/week NEORETIN DC Ultra Emulsion 5d/week

and intensity of adverse effects, at each of the measured times of the study, the Wilcoxon test was used.

In the case of quantitative variables of the melanin index and erythema, the Student's t-test for paired variables or Wilcoxon's test was used, depending on the compliance or non-compliance with normality of these variables.

The most usual values of centralization, dispersion and position were used as descriptors in all cases: mean, standard deviation and 25^{th} , 50^{th} and 75^{th} percentiles.

The finding of a significant difference with respect to the baseline value was considered when the level of significance obtained was less than 5% (p \leq 0.05). SPSS V24.0 software was used to perform the statistical analysis.

Results

A total of 20 women, aged 25 to 65 years, with skin phototypes II-IV, and mild-moderate facial melasma were included. All of them completed the study. Average age was 42.3 years.

One of the most important parameters evaluated, MASI, showed a significant reduction at all visits, with a progressive reduction in the area affected by melasma and its intensity, reaching a 48% reduction at the end of treatment (p=0.01) (Figure 2).

The melanin index was reduced at T30 and T60 compared to baseline, but the reduction was not statistically significant.

During the first month (retinization period), the erythema index decreased by 8, 7% compared to baseline (p=0.004) and after the first month of treatment it increased by 4.6% at T60 due to the increased frequency of application of the Neoretin Discrom Control Ultra Emulsion^{*}, although it fell again by 9, 8% at the end of treatment, with values below those of baseline (p=0.014). The Investigator Global Assessment (IGA) and Patient Global Assessment (PGA) indicated that melasma severity decreased over the course of the study by 21%, although the difference was not statistically significant. In over 90% of patients, both investigator and patients noted a reduction in severity over the course of the study. Specifically with respect to PGA, patients reported that melasma severity was significantly reduced at T45 (p=0.03) (Figure 3).

With respect to perceived improvement in melasma, 65% of patients reported moderate-intense improvement by the end of the study. After the first month of treatment, 62% of the patients had already perceived a slight improvement and 5% a moderate improvement, and the degree of perceived improvement grew steadily, reaching statistical significance at T45 and an improvement of almost 70% at the end of the treatment (p=0.001). All patients reported improvement vs baseline (Figure 4). Clinical photographs taken by Observ^{*} throughout the study confirm this improvement (Figure 5).

The adverse effects detected during the study were mild and transitory, most frequently peeling and erythema. None were significant and there was no drop out. Other adverse effects observed were stinging, tightness and itching. (Figure 6).

Peeling was highest at T60 after having increased the frequency of use of the intensive product with almost 30% of patients reporting moderate-intense flaking. At the end of the treatment peeling had declined (only 18% reported moderate-intense peeling and 77% reported no peeling at all).

Skin erythema increased after periods of increased frequency of use of the high retinol concentration (at T15, T45 and T60), although as the skin became used to the regime, the degree of erythema decreased with 71% of patients experiencing no erythema at T90.

Stinging was greater after the frequency of application of retinoid treatment was increased with approximately 50% of patients experiencing mild to moderate stinging at T30, although it almost immediately disappeared after application. At the end of the treatment, 71% of patients experienced no stinging sensation.

The sensation of tightness was absent in most patients throughout the study. At the end of treatment, 88% of patients reported no sensation of tightness.

Irritation was higher when the frequency of application of intensive treatment was increased (T15, T45 and T60), however at the end of the treatment it was strongly reduced with 60% of patients reporting no irritation and 35% reporting mild irritation.

Itching was perceived by patients at T45, after the initial phase of retinization and after increasing the frequency of application of Neoretin[®] Discrom Control Ultra emulsion. At the end of the treatment 71% of patients reported no itching and just 23% indicated mild itching.

MelasQoL value was significantly reduced by 25.3% after treatment with the pigment correction protocol (p=0.004), indicating improved quality of life for patients.

Discussion

Melasma and other hyperpigmentation disorders represent a major concern for most patients who suffer from them, especially when it affects the face. Physicians work towards achieving optimal results through a combination of different therapies such as chemical peelings, laser, and drugs such as HQ. Response to these different therapeutic options varies however from one subject to another. Skin phototype is not always sufficient to predict treatment

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Figure 2: MASI was significantly reduced at all study visits, with results already observed at 30 days, reaching a reduction of 48% by the end of the treatment. ***p<0,001; **p<0,01



response as other factors such as ethnicity and sensitivity can also play an important role [29].

Pigment correction regimens with similar depigmenting agents to those evaluated in the present study protocol (Neoretin[®] Discrom Control serum) were studied in 140 patients of different ethnicities (Latino, Asian and Caucasian) to assess their ability to improve the appearance of hyperpigmentations such as melasma, lentigo and sun blotches with excellent outcomes in most of the patients [26-29]. The low incidence of adverse events registered in these trials confirmed the good tolerability of the cosmeceutical formulations suggesting they could be a safe choice especially when irritation risks worsening the initial condition or could cause lack of adherence and discontinuation of treatment. The favorable effects of this combination of ingredients also help improve fine wrinkles and smooth skin texture, representing an addition advantage to the pigment correction activity.

Conclusions

In this study, the retinization regime using Neoretin[®] Discrom Control Ultra Emulsion and Transition Cream provided effective pigment correction activity, significantly improving MASI score. It





Figure 4: The degree of improvement of melasma as perceived by patients increased progressively and significantly starting at T45, reaching almost 70% at the end of the treatment. ***p=0,004; **p=0,008; *p=0,001.



Figure 5: Clinical Observ[®] photographs demonstrate clinical improvement. a) before and after treatment. Over the course of treatment with polarized(b) and UV light (c).





Erythema, itching, irritation, stinging and peeling increased gradually, becoming greater at T45 and T60, corresponding to increased frequency of use of the formulation with high retinoid concentration. As retinization proceeded, adverse effects declined and at the end of the treatment the adverse effects were generally null or mild.

is important to note the excellent tolerance to the formulations even with high frequency of application (5 days a week), underlining the importance of gradual introduction of pigment correcting actives (progressive retinization) to avoid undesirable side-effects. The main limitations of this study are the lack of long-term follow-up beyond 90 days of treatment and, furthermore, since the use of sunscreen is known to prevent the worsening of hyperpigmentation, the overall efficacy of the treatment established in this study was limited by the lack of a control group.

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