Original Contribution

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Assessment of the efficacy and tolerance of a new combination of retinoids and depigmenting agents in the treatment of melasma

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Summary

Background Melasma is a dermatosis with significant repercussions on patients' quality of life, and there is currently no standard treatment. Hydroquinone is deemed the treatment of choice, but its safety has been questioned in certain cases.
Aims To determine the efficacy and safety of a new combination of retinoids in the improvement of melasma.
Patients/Methods Prospective, double-blind, vehicle-controlled, and randomized study in 30 patients with melasma. The product was applied on one side of the face and the vehicle on the other, twice daily during 3 months. Standardized photographs were taken using RBX technology on the three visits (basal, at one and a half months and at 3 months). The main variable to determine the efficacy was the improvement of the hemifacial Melasma Area Severity Index (MASI). Other variables were determined such as improvement perceived by the investigator, improvement perceived by the patient, impact on quality of life or side effects.
Results The MASI improvement at 3 months of treatment was significant on the treated side *vs.* the vehicle side, reaching an improvement of 70%, which is comparable to the percentage of improvement described with hydroquinone. No notable side effects were detected, in spite of a significant percentage of patients included in the study citing a history that could be compatible with sensitive skin.
Conclusions This new combination of retinoids and depigmenting agents proved to be effective and safe in the treatment of melasma.

Keywords: melasma, treatment, retinoids

Introduction

Melasma is a hyperpigmentation condition distributed generally symmetrically in the facial area, which can have a very negative impact on patients' quality of life.[1] It mainly affects women with a high phototype. It often persists indefinitely, remaining active for several years. [2–4]

The exact etiology is unknown, but certain trigger factors have been suggested such as genetics, ultraviolet radiation, visible radiation, hormone alterations (pregnancy, oral contraceptives), and increase of the melanocyte-stimulating hormone (MSH).[2]

Melasma is often resistant to treatments, and therefore, it is a frustrating dermatosis for both patients and dermatologists. [5,6] The results are variable, often imperceptible.

Conventional treatment includes avoiding possible trigger factors, daily application of suitable photoprotection as well as depigmenting products. The efficacy of sun protection is backed by the study of Ennes *et al.* [7] where 8.3% of the patients showed total disappearance of the melasma and 58% partial improvement when treated exclusively with photoprotection cream.

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Lakhdar observed an incidence of melasma of 2.7% in pregnant women who used photoprotection [8] compared to 53% in pregnant women of that same population who did not use it as demonstrated by Khadir.[9]

Depigmenting agents exert their action through different mechanisms: elimination of excess melanin, regulation of the activity of melanocytes, control of the dispersion of melanin granules, or inhibition of the transfer of melanin to keratinocytes. Most commonly used depigmenting agents include hydroquinone, retinoids, mequinol, azelaic acid, arbutin, kojic acid, oleosin, liquorice extract, ascorbic acid, n-acetyl-glucosamine, niacinamide, etc.[10–16]

A new product has been designed recently, based on RetinSphere Technology, which encompasses the association of two topical retinoids: retinol glycospheres and hydroxypinacolone retinoate.

Retinol encapsulated in glycospheres has been used previously in patients with acne.[13] The retinoic acid ester, hydroxypinacolone retinoate, has similar action to tretinoin, but does not cause the irritation observed with this retinoid. Recently, Veraldi demonstrated that use at 0.1% during 2 weeks in patients with acne can improve skin roughness by 50% and scaling by 40%.[14] Unlike retinol and other derivatives that must be converted into the biologically active form of retinoic acid, hydroxypinacolone retinoate binds directly to retinoic acid receptors (RAR).[17]

RetinSphere technology has combined with other depigmenting active ingredients such as N-acetylglucosamine (inhibits glycosylation of tyrosinase), kojic acid, Cromabright® and Natriquest® (they uptake the copper and iron ions needed by tyrosinase for its activation), albatin® & alistin® (they act synergistically inhibiting melanin synthesis), and niacinamide (vitamin B3 that prevents the transfer of melanosomes to keratinocytes). Furthermore, the formulation contains 10% of hydrating active ingredients and 3% anti-irritant, anti-inflammatory active ingredients.

This study aimed to determine the efficacy of the protocol with the study products (Neoretín®) *vs.* a vehicle in the treatment of patients with melasma. A secondary objective was to determine the safety of the product *vs.* the vehicle.

Materials and methods

A prospective, randomized, double-blind, vehicle-controlled study was carried out. 30 patients were selected.

Inclusion criteria were as follows:

- Aged over 18 years.
- Absence of treatment for melasma in the last 3 months.
- No desire to get pregnant in the forthcoming months and use of contraceptives.
- No concomitant diseases.
- No administration of another topical or systemic product that may interfere or affect the process.
- No allergy to the product ingredients.

Treatment

The treatment protocol included the application of the active cream with sun protection factor SPF 50 (Neoretin® discrom control gelcream—IFC Pharmaceuticals) during the day and active serum (Neoretin® discrom control serum booster fluid—IFC Pharmaceuticals) at night on one side of the face *vs.* vehicle gelcream with SPF 50 during the day and vehicle serum during the night on the other side of the face; thus, the patient was also the control group. The vehicle had the same photoprotector as the study product.

Clinical assessment

The observation period was 3 months, organized into visits at baseline (T0), at one and a half months (T1) and at 3 months (T2).

Classical clinical photography was carried out and with polarized light via Reveal® System with RBX technology (Red/Brown/X identified).

To determine the efficacy, the percentage of improvement in the Melasma Area Severity Index (MASI) after treatment was deemed as principle variable.

The MASI is calculated based on the percentage of relative surface of involvement (A), the intensity of darkness (D) of melasma, and the homogeneity (H) of the hyperpigmentation.

The area of involvement is given a numerical value of 0–6 (0 indicates no involvement; 1, 0–9%; 2, 10–29%; 3, 30–49%; 4, 50–69%; 5, 70–89%; and 6, 90–100%). The intensity of darkness (D) and the homogeneity of melasma (H) were rated on a scale from 1–4 (0 indicates absent; 1, slight; 2, mild; 3, marked; and 4, maximum). The global MASI (0–48) and the MASI on each side of the face (0–24) were calculated. A coefficient of correlation was applied according to location: Each cheek corresponds to 30% of the total face, the forehead corresponds to 30%, and the chin corresponds to 10%. On the unilateral MASI, the forehead corresponds to 15% and the chin to 5%, and only one cheek is taken into account (30%). The higher the score, the more intense the melasma.[18]

The following were included as secondary variables:

- Intensity of the cutaneous pigmentation: intense (+++), moderate (++), mild (+), and null (−).
- Improvement in the intensity of pigmentation on vehicle side and treated side: excellent, moderate, mild, no change, or worsening.
- Roughness: scored as 0: null, 1: mild, and 2: intense.
- Luminosity: scored as 0: null, 1: mild, and 2: intense.
- Degree of global improvement perceived by the investigator: from −2 to 3, where −2: great worsening, −1: minimum worsening, 0: no improvement, 1: minimum, 2: moderate, and 3: intense improvement.
- Quality of life and patient improvement: During the first and last visit, the MELASQOL quality of life scale (10–70) and patient satisfaction according to a scale from 0 to 10 were carried out as well as the perceived improvement of the patient with the PGA validity scale from 0 to 4, where 0: worsening or no change; 1: mild improvement; 2: moderate improvement; 3: great improvement, and 4: excellent improvement.
- Secondary effects: description and intensity: null, mild, or intense.

Statistical analysis

The statistical analysis involved a descriptive analysis of the set of variables, obtaining the frequency tables for the qualitative variables and usual descriptive data of centralization, dispersion, and position for those of quantitative or ordinal nature. To compare the possible significant differences between the three times of the result variables, Friedman nonparametric tests were used for a global comparison between the three times and the Wilcoxon nonparametric test for comparisons in pairs. The same Wilcoxon test was used to study the relation between the treated and control sides for paired samples.

Results

A total of 30 patients were included, 28 of whom completed the study. The two withdrawals were for reasons unconnected with the study. Of the 28 patients who completed the study, 27 were female and one male. The mean age was 39 years. The mean evolution of the melasma at the start of the study was 57 months. 63% of the patients did not take oral contraceptives. 60% presented phototypes II or III and almost 40% presented dark phototype (IV). 67% of patients cited a history of sensitive skin.

The photographic analysis with RBX technology showed that 89% of the side of the face treated with the study product showed a certain degree of improvement, qualified as very good improvement in 50% of the cases. While on the vehicle side, only 56% showed some degree of improvement with the majority qualified as good improvement (53%). Said improvement was significant *vs.* the basal level on both sides ($P < 0.001$), but was significantly greater on the treated side *vs.* the vehicle side ($P = 0.005$) (Figs 1–9).

As regards the MASI measurement, there were no significant differences at basal time between either side of the face, with the mean score of 9.4 ± 4.6. At the end of the study, the mean score on the treated side of the face was 2.4 ± 3, while on the vehicle side, the mean was 4.2 ± 4.2. This difference between the MASI of the treated side and that of the vehicle side was significant ($P = 0009$). (Fig. 10).

In percentage terms, the reduction of the MASI at the end of the study on the side treated with the product was 74% (±31%) *vs.* a reduction of 55% (±36%) on the side that received the vehicle with SPF, with this being a significant difference ($P = 0.009$). (Fig. 11).

Furthermore, on visit T1, a reduction of 53% (±31%) of the MASI was observed on the side treated with the study product *vs.* a reduction of 36% (±29%) on the vehicle side. These differences were significant ($P = 0.008$) and show a rapid response to treatment with the active product in most patients (Fig. 11).

The degree of improvement perceived by the investigator at 3 months of treatment was moderate or intense in 60% of the sides of the face treated with the product, *vs.* 42% of moderate or intense improvement in the vehicle-treated sides of the face, without this difference being statistically significant ($P = 0.1$).

The satisfaction with previously received treatments according to the assessment scale from 1 to 10 (with 10 being the maximum satisfaction and 1 the minimum) failed to reach 3 of 10. After completing 3 months of treatment, the degree of satisfaction was 70% of patients or 8/10 or 9/10.

The degree of improvement perceived by the patient on the PGA scale (0–5) in T2 was classified as great or excellent improvement in 60% of patients.

Tolerance to treatment was very good, with a degree of acceptability, tolerance, and side effects without differences *vs.* the vehicle side. Both dark phototypes and sensitive skins with high risk of hyperpigmentation and low tolerance to products such as hydroquinone

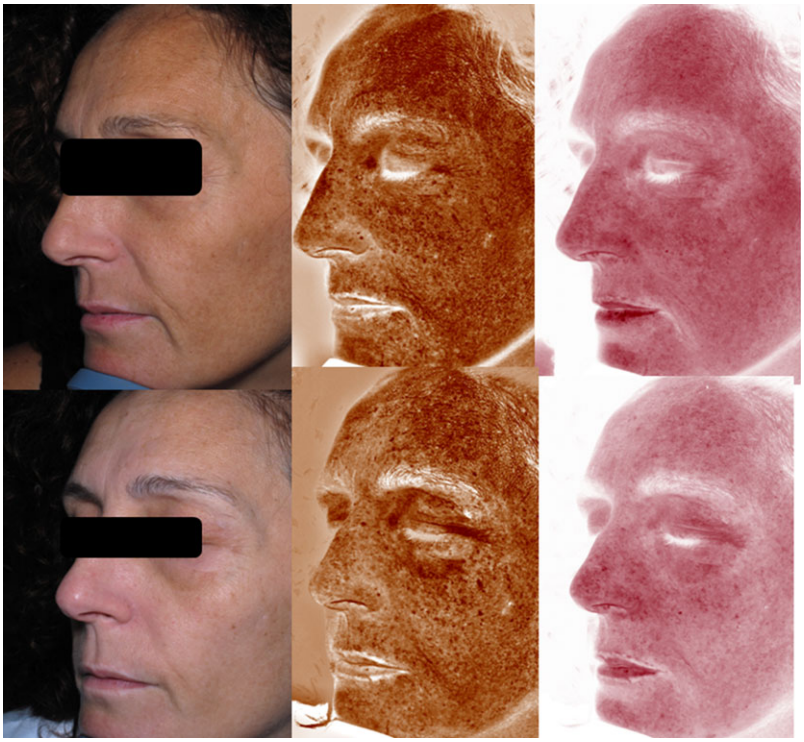

Figure 1 Photography with RBX technology before treatment and 3 months after the treatment on the side treated with the new combination of retinoids (Neoretín®).

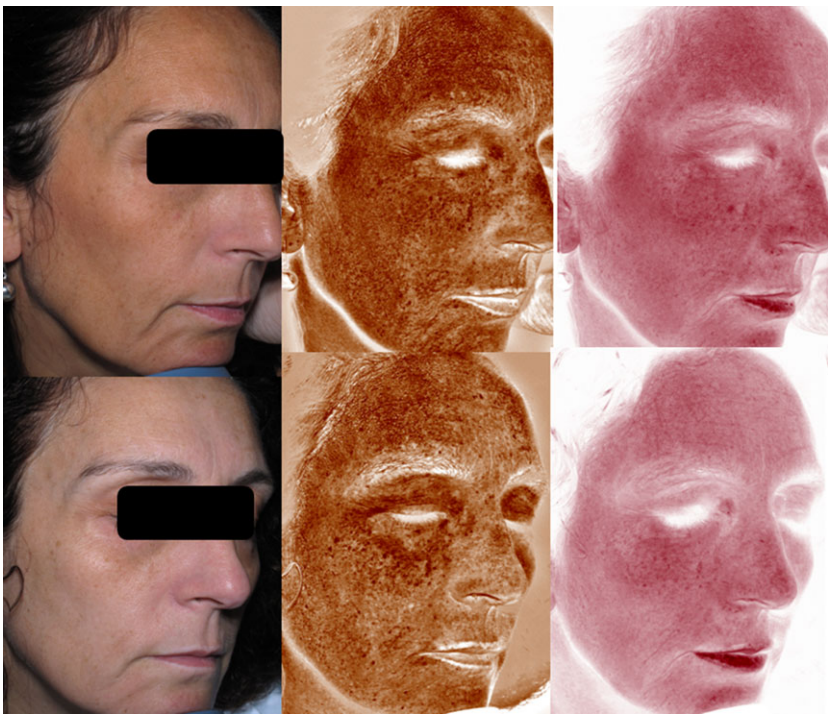

Figure 2 Photography with RBX technology before treatment and 3 months after the treatment on the vehicle-treated side. It shows more improved depigmentation on the side treated with Neoretín® than on the vehicle side.

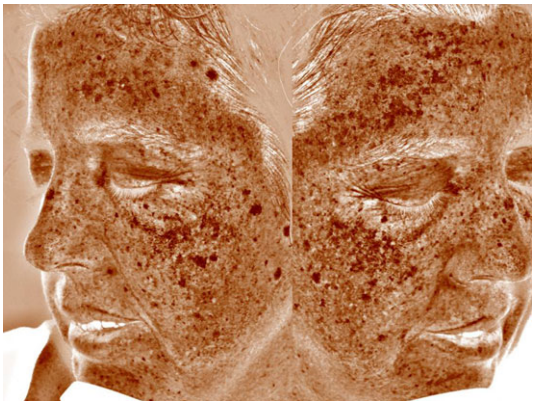

Figure 3 Basal photography (T0) with RBX technology for pigment, highlighting the lesions on the vehicle side (left) and treated side (right).

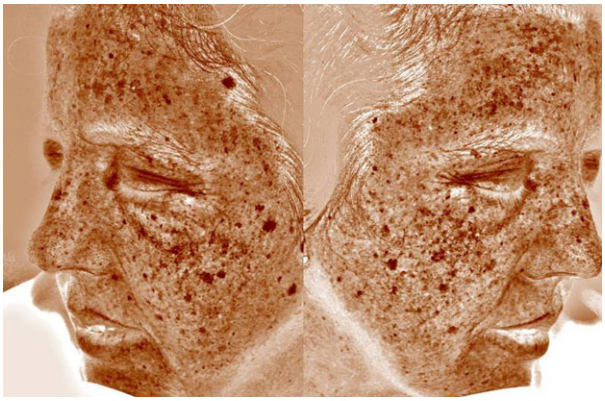

Figure 4 Photography at the end of treatment (T2) with RBX technology for pigment, highlighting the lesions on the vehicle side (left) and treated side (right), showing the improvement on the side treated with the product.

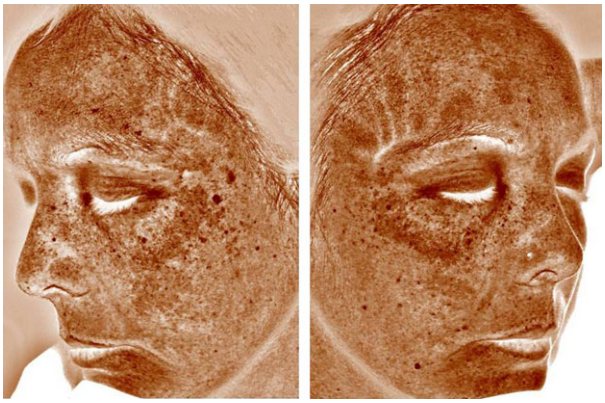

Figure 5 : Basal photography (T0) with RBX technology for pigment, highlighting the lesions on the vehicle side (left) and treated side (right).

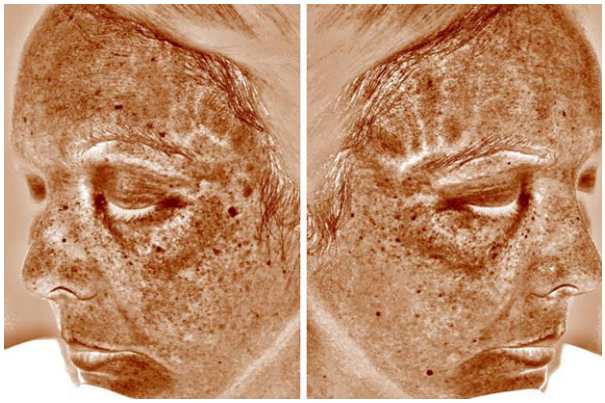

Figure 6 : Photography at the end of treatment (T2) with RBX technology for pigment, highlighting the lesions on the vehicle side (left) and treated side (right), highlighting the improvement of the side treated with product.

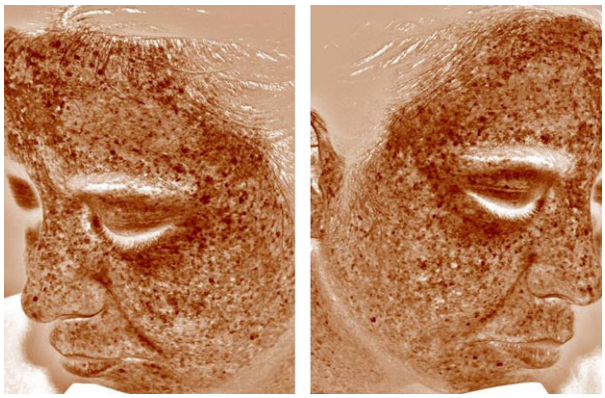

Figure 7 : Basal photography (T0) with RBX technology for pigment, highlighting the lesions on the vehicle side (left) and treated side (right).

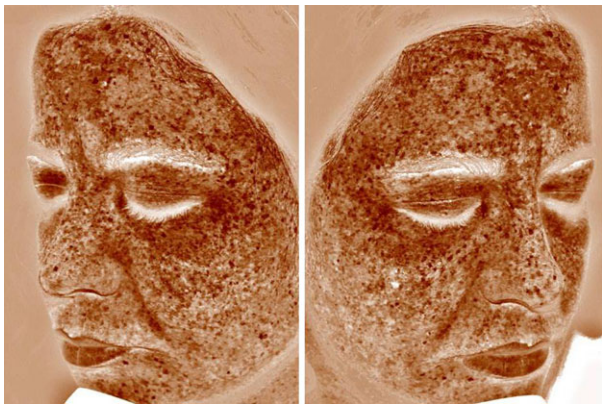

Figure 8 : Post-treatment photography (T2) with RBX technology for pigment, highlighting the lesions on the vehicle side (left) and treated side (right), highlighting the improvement of the side treated with the product.

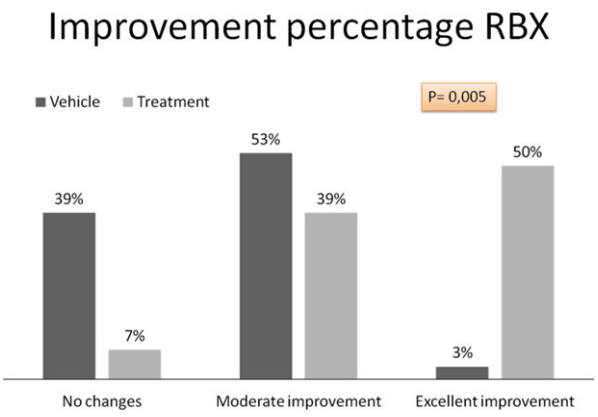

Figure 9 Improvement of pigmentation diagnosed with RBX technology, showing better results on the side treated with the new combination of retinoids (statistically significant).

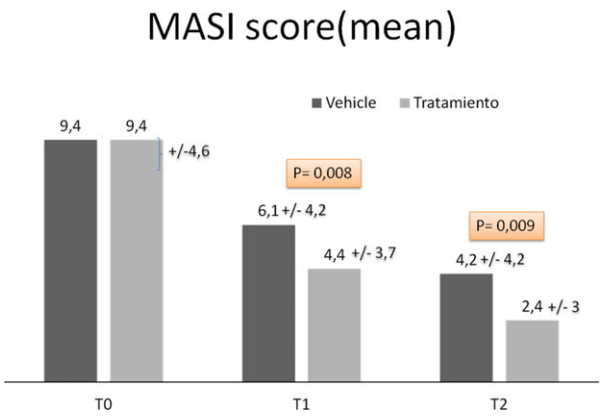

Figure 10 Melasma Area Severity Index (MASI) score (mean) during the different visits, showing significantly lower MASI mean score on the side treated with the new combination of retinoids.

presented very good tolerance to the depigmenting retinoid combination, differential factor *vs.* other retinoids. As regards the side effects, just two patients cited intense pruritus on both sides of the face on visit T1. Intense burning sensation was only cited by one patient on T1 on the treatment side, and finally only one patient presented intense erythema on visit T1 on the treatment side. In no case was it necessary to suspend treatment and at 3 months no side effects were recorded.

Discussion

The basic principles in the treatment of melasma include firstly rigorous photoprotection against UVB, UVA, and visible light radiation. As commented previ-

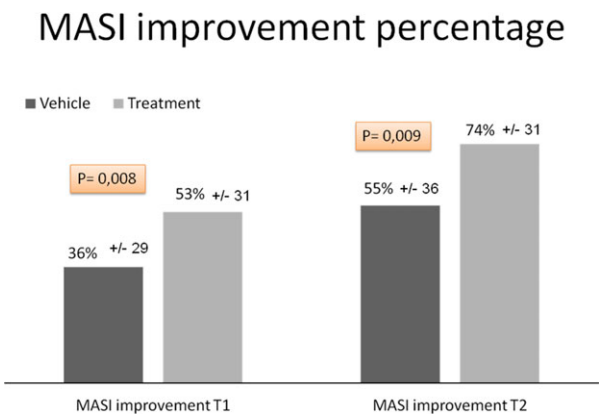

Figure 11 Melasma Area Severity Index (MASI) score (percentage) improvement in T1 and T2. Better MASI improvement is detected on the side treated with the new combination of retinoids in T1 ($P = 0.0008$) and in T2 ($P = 0.009$) compared with vehicle side.

ously, the use of photoprotectors in melasma plays a preventative role and moreover boosts the improvement achieved with regular depigmenting treatments.[7–9] Therefore, the improvement obtained on the vehicle side is largely due to the daily use of SPF 50 (in accordance with that published by Ennes *et al.*).[7] Further to the data from this study, we can state that the product formulated with RetinSphere® technology and other depigmenting agents would boost said improvement by 20%. As well as avoiding trigger factors, it is important to apply depigmenting products for the treatment of melasma. The characteristics of a suitable depigmenting product include effective penetration, good tolerance, and capacity of action via multiple mechanisms, creating synergies that boost the depigmenting effect.[19]

Fifty percent of improvement in the MASI scoring with hydroquinone (treatment with which the best results are obtained) was taken as reference, which is the percentage of significant improvement of reference in the published articles of patients with melasma treated with HQ combined with sun protection SPF 30,[11] although there is one article that discusses the improvement associated with hydroquinone combined with SPF 25 of up to 70%.[12]

Of the treatments regularly used in melasma, we highlight hydroquinone (HQ), which is the depigmenting agent of choice.[7] Various regulatory authorities, however, have recently raised doubts over its safety.[15,16] HQ has been prohibited in certain countries in Europe and Asia due to its long-term side effects,[1,20] which has led to the development of alternative depigmenting agents with similar efficacy but higher

tolerance.[21] Furthermore, care must be taken when it is combined with topical corticoids due to its associated effect on these (epidermal atrophy, hypertrichosis, hypopigmentation, cutaneous fragility, telangiectasia, stretch marks). [22] In spite of the questions raised, other authors defend the safety of HQ given that when reviewing the incidence of exogenous ochronosis in the United States, they found that this was scarce. [23]

In this study, we have demonstrated that the treatment of melasma with the protocol of the new combination product obtains a significant improvement in the MASI *vs.* the vehicle-treated side. Such improvement on the side treated with the study product was 74% (±31%) at 3 months**.** It is therefore greater than that described in different articles with topical retinoids in monotherapy (32–47%) [23,24] and even somewhat higher than that described with hydroquinone (70%). [11]

If we take into account the phototypes in the reduction of the MASI, we have observed that a reduction is found in both fair and dark phototypes without significant different between both groups.

The combination of retinol glycospheres plus hydroxypinacolone retinoate and other depigmenting active ingredients gives the advantage of none of the side effects usually associated with the use of hydroquinone or retinoids such as tretinoin. It is worth highlighting the excellent tolerance, even in dark phototypes and sensitive skins. The product tolerance was rated as very good or good by all patients, wherefore it is of great importance for therapeutic compliance.

Conclusion

Given the efficacy and tolerance detected in this study, we can confirm that this new depigmenting combination product is useful for melasma and furthermore these properties would permit its use in other indications such as the preparation of skin for dermo-esthetic procedures or use between such treatments. Furthermore, this combination of retinoids with depigmenting agents can be used in the anti-aging protocols of combined therapies (with laser, intense pulsed light, peeling, or other techniques), by favouring and accelerating the postprocedure recovery given the cutaneous regeneration and neocollagenesis properties of retinoids [25] and protecting from the damaging effect of solar radiation as the daily use product contains photoprotection.

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