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Chemo-Exfoliation with Glycolic Acid, Chitosan, N-acetyl-cysteine, L-carnitine hydrochloride. Therapeutic Protocols for a Highly Socially Presentable Treatment in the Management of Skin Aging, Melasma and Acne

MARINA ROMAGNOLI

• Marina Romagnoli[1] • Carlotta Pastorino[1]

SUMMARY

Over the last few years, the international literature has recognized the validity of protocols that combine outpatient and "at home" keratolytic treatment in several skin diseases [1, 2, 3].

The objective of this study is to prove the efficacy of three protocols for the treatment of acne, melasma and facial skin aging as adjuvant therapy to traditional home therapy: ***outpatient treatment (Treatment A: Sunekos® Tropeel*** *- previously Sunekos® peeling) - Patented formula, of monitored chemo-exfoliation and antiaging and* ***hydrating home therapy (Treatment D: Sunekos® Post-peeling)*** *that has demonstrated to be safe, effective, low-cost and associated with high compliance. This was possible thanks to the use of a patented compound based on 60% non-buffered glycolic acid, N-acetyl-cysteine (NAC), carnitine, chitosan, N-acetyl-glucosamine (NAG), Treatment A: Sunekos® Tropeel (previously Sunekos® peeling) – Patented formula, and a home sun protection cream 15 containing N-acetyl-glucosamine, Vitamin E, ubiquinone, hyaluronic acid and ceramides (Treatment D: Sunekos® Post-peeling).*

In particular, it was possible to successfully treat phototype I to V patients with poor compliance to other outpatient treatments (with chemo-exfoliating agents based on glycolic acid alone or other substances for superficial peeling), who were needle-phobic, without any seasonal interruptions and interference in their relationship life.

KEYWORDS

Melasma, Acne, Aging, Photo aging, Hyperpigmentation, Skin Texture, Bio Stimulation, non invasive, Glycolic Acid, Chemical peel, Bioregeneration peeling, NAC e (N-Acetyl-Cysteine), Trophic Peeling, post peeling, chitosan, Biorestructuring, Socially presentable, socializing peel, needle free

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INTRODUCTION

Acne

Acne is an inflammatory disease of the pilosebaceous follicles; it has a multifactorial pathogenesis, which includes hormonal dysregulation (insulin, insulin-like growth factor 1 (IGF-1 and androgens), Propionibacterium acnes, lipogenetic factors and proinflammatory action-inducing lipids. The synergy of the above factors triggers the activation of the innate immunity, followed by the activation of adaptive immunity. The standard topical therapy is based on the use of benzoyl peroxide, retinoids and topical antibiotics; the systemic therapy is based on the use of tetracyclines, retinoids and antiandrogens in women. The outpatient treatment involves the use of chemical peeling and Energy Mediated Devices (EMD) that have a synergic action on active acne lesions and disease outcomes (hyperchromia, scars). It is clinically characterized by a polymorphism with prevalence of comedones in mild forms, papules-pustules in moderate forms and nodules and cysts in severe forms. Erythematous-macular outcomes, hyperpigmentation and depressed or hypertrophic scars very often coexist with active lesions, especially in long-term cases. The early management of acne lesions effectively guarantees a reduction in the risk of scarring, a problem still difficult to solve despite several available technologies.

The active form of acne affects approximately 80% of adolescents; however, it seems to be strongly increasing in the adult population; it is a disease that compromises the quality of life and has an average response time to therapy of several weeks [4].

Skin Aging

Skin aging results from chronic processes occurring over the years and are related to intrinsic and extrinsic factors; their interaction produces macroscopic, microscopic and biochemical changes that appear in quantitatively different ways in the population. The factors responsible for skin aging include oxidative stress due to free radicals, inflammatory processes, cell senescence and epigenetic changes.

Clinically, all this translates into an altered function of the skin that progressively loses its repair capabilities resulting into clinical alterations ranging from chrono- and photo-aging to neoplastic disease.

The characteristics of senescent skin include loss of hydration, tone and elasticity with progressive increase in ectatic vessels, alterations in melanin pigmentation, accentuation of the texture, wrinkles, loss of uniformity and accentuation of skin porosity and acne scarring.

Melasma

Today, melasma is considered as a chronic skin disease with a genetic, familiar component, caused by an abnormal production/deposit of melanin in the dermis and epidermis of photo-exposed skin. The histological features of the affected skin cannot be distinguished from those of other diseases due to pigment deposit such as post-inflammatory hyperpigmentation, therefore the differential diagnosis is possible based on the involved site and medical history as well as instrumental investigations (dermatoscopy, EMC) [5].

The skin affected by melasma shows the histological characteristics of photo-damaged skin; moreover, melasma is the most common clinical expression of photo-damage in populations with a high skin phototype. For the above reasons, today there is a tendency not to include melasma among pigmentation disorders, but rather to consider it as an expression of photoaging-induced skin damage.

As a consequence, even the most modern therapeutic strategies, while paying a special attention to the regulation of pigmentogenesis, tend to address it with the remedies typical of actinic aging.

Photo-exposition is one of the trigger factors, though not the only one, along with inflammation and estrogenic influence which makes it a more common disease in women and in specific periods of life when the hormonal influence prevails, such as pregnancy and menopause.

Over the last decade, particular importance has been given to relapse-promoting factors, also in cases with good therapeutic outcome. Several studies have focused on the presence of an accentuated vascular reticulate that is present under the pigment and absent in the surrounding areas. The skin of patients with melasma has shown an upregulation of the vascular-endothelial growth factor (VEGF) and elements of its cascade (wnt, kit-ligand) with increased inflammation, vascularization and stimulation of melanocyte hyperactivity [6].

Thus, the treatment of melasma vasodilation and angiogenesis has become part of the long-term maintenance therapy for this disease.

Study objective

The proposed protocol for the treatment of skin aging, melasma and acne is based on previous evidence [7, 8, 9, 10] that has shown the efficacy and tolerability of a product consisting of a pool of antioxidant agents (N-acetyl-cysteine (NAC), carnitine, chitosan) added to 60% non-buffered glycolic acid for professional use combined with a home therapy with SPF 15 cream containing N-acetyl-glucosamine, Vitamin E, ubiquinone, hyaluronic acid and ceramides with clarifying, sebum regulating and anti-aging properties.

The objective of the study is to propose three therapeutic protocols for

the treatment of skin aging, melasma and acne that combine outpatient therapy with a specific home therapy for each disease. These combined protocols have shown to be efficacious, guaranteeing compliance and safety also in socially unpresentable or needle-phobic patients with poor compliance.

Inclusion and exclusion criteria

Male and female subjects aged more than 18 years, phototype according to Fitzpatrick II, III, IV and V with melasma [11], mild to moderate acne showing comedones, papules and pustules [12] and mild to moderate skin aging [13]. Patients had not followed any outpatient support therapy or systemic drugs in the three months before the study start.

Informed consent to treatment and acquisition of images was obtained from each patient.

Exclusion criteria included pregnancy, breast-feeding, severe comorbidities, ongoing skin diseases (other than those treated in the study), known hypersensitivity and/or allergy to the components of the topical formulations.

Materials and methods

Overall, the study enrolled 20 female and male patients (F:M= 90:10 ratio) (aged between 18 and 46 years (average age 24.87): 10 patients had acne and 10 had melasma; all cases analyzed were with mild to moderate photoaging. The outpatient treatments were administered by specialized personnel at timepoint 0 (T0), after 15 and 30 days (T15, T30), for a total of three sessions.

Outpatient Treatment for Aging, Melasma and Acne

Three outpatient sessions at 15-day intervals with a pool of antioxidating agents (6% N-acetyl-cysteine (NAC), 6% L-carnitine chlorhydrate, chitosan) in combination with 60% non-buffered glycolic acid (Treatment A: Sunekos® Tropeel (previously Sunekos® peeling) – Patented formula). The outpatient treatment administration was subject to the integrity of the skin to be treated; if this was not the case, it was recommended to postpone the session. Application time: 4 to 6 minutes with the following mode:

➜ First session with application time no longer than 4 minutes.

➜ Second and third sessions with application time no longer than six minutes, only if no adverse events had been experienced during the procedure.

Inactivation was obtained by applying a buffered solution of sodium bicarbonate in gel and then water and/or thermal water containing bicarbonate and magnesium and application of SPF 15 cream containing N-acetyl-glucosamine, Vitamin E, ubiquinone, hyaluronic acid and ceramides (Treatment D: Sunekos post-peeling).

The onset of the following was considered as a reason for inactivation before the scheduled endpoint: itching, burning, frost, intense or inhomogeneous erythema with the sole exception of frost on active acne lesions.

Home Protocol for Acne

➜ Acne with Comedones [12]: topical keratolytic or retinoid agent to be applied in the evening with a two-day interruption before outpatient treatment, and to be resumed on Day 5 after the outpatient treatment.

➜ Mild to Moderate Acne with Papules and Pustules: benzoyl peroxide (BPO)-BPO+ Adapalene to be applied in the evening only on lesions, with a two-day interruption before the outpatient treatment and to be resumed on Day 5 after ambulatory treatment.

Treatment D, 2 applications a day for 2 days before the session and 4 applications a day for the first 4 days post-treatment and then at least 1 application a day in the morning to be repeated in case of skin xerosis, photoprotection SPF 30 in case of photoexposure.

Home Protocol for Melasma

Clarifying topical agent containing azelaic acid, kojic acid, alpha arbutin, glycirrhiza glabra and ascorbic acid [13] to be applied from 2 evenings a week to every evening, according to tolerability, with a two-day interruption before Treatment A and to be resumed on Day 5 post-treatment.

Treatment D, 2 applications a day for 2 days before the session and 4 applications a day for the first 4 days post-treatment and then at least 1 application a day to be repeated in case of skin xerosis.

Photoprotection SPF 50+ with mixed mineral and physical solar filter, preferably colored, to be applied every two hours in case of outdoor stay, avoiding direct sun exposure.

Home Protocol for Anti-Aging

Topical retinoid agents three nights a week (0.03% to 0.05% according to individual tolerability of retinoic acid) for the first 2 weeks and only in case of good tolerability afterwards every evening with a two-day interruption before the outpatient treatment, and to be resumed on Day 5 post-Treatment A. If the majority of the face was affected by acne or melasma, the protocol therapy relating to the most evident disease was used.

Treatment D, 2 applications a day for 2 days before the session and 4 applications a day for the first 4 days post-Treatment A, and then at least 1 application a day in the morning to be repeated several times during the day in case of skin xerosis, photoprotection SPF 50 in case of photoexposure.

Assessment

Patients underwent a preliminary scan by means of VISIA Canfield 7th Generation Complexion analysis system [14] to confirm the clinical diagnosis of melasma, acne and aging as well as to assess the inflammatory component (RED AREAS), pigmentation and the presence of protoporphyrins by means of different lights by using the RBX® Technology system with polarized light, Wood and UV lights.

The efficacy results were assessed based on the images acquired at T0 and T60, one month after the third treatment, with continuation of home therapy with VISIA, GEA control and acne scales [15] and mMASI [11] for melasma.

All subjects were assessed at T30 and T60for efficacy, safety and tolerability by the administering doctor and at T60 by an independent evaluating specialist based on the images acquired by VISIA.

Results

In the 20 patients enrolled in the study, the perception of heat or stinging did not exceed the value of 5 to 6 on the VAS scale, corresponding to a moderate discomfort during treatment administration. Following the outpatient application of the product, patients reported mild to moderate erythema lasting a maximum of a few hours. In all the treated cases, the application of the proposed home topical therapy and SPF 50 were sufficient to prevent the perception of exfoliation that is normally observed with traditional chemo-exfoliating treatments between Day 3 and 5 post-treatment.

One patient withdrew from the study due to unknown reasons (drop-out at follow-up).

The assessment by means of VISIA IMAGING SYSTEM RBX® Technology with cross-polarized light, Wood and UV lights allowed to identify a reduction in the erythematous and pigmentary components in patients with melasma and in the erythematous and porphyrin components in the acne population at T60 as compared to the study start.

With regard to the population with acne that was administered the outpatient therapy alone, the ranges of the "GEA acnis scale" were assessed with an average improvement ranging from 14.67 to 8.3 (improvement of 6.58%), while the values of the GEA acnis scale for the outpatient therapy + home therapy ranged from 19 to 10.2 on average (improvement of 53.68%).

In the arm of patients assessed for melasma, the following values of average mMASI were observed: for the patients treated with outpatient therapy alone, we reported a reduction of the average mMASI from 4.12 to 1.415 (improvement of 34.34%), while in the arm of patients treated with outpatient therapy + home therapy the average values ranged from 8.03 to 3.72 (improvement of 46.33%).

During the study period, three cases of frost were reported that resolved without sequelae; no pigmentary, post-treatment persistent erythema and skin hypersensitivity were observed; no worsening as compared to T0 were reported.

Most patients found the treatment both socially presentable and effective, and said they would be available to repeat it and recommend it. In particular, the satisfaction concerned the improvement of texture uniformity, porosity, greater skin firmness and reduced greasiness, with a perceived improvement of the baseline disease according to patient evaluation.

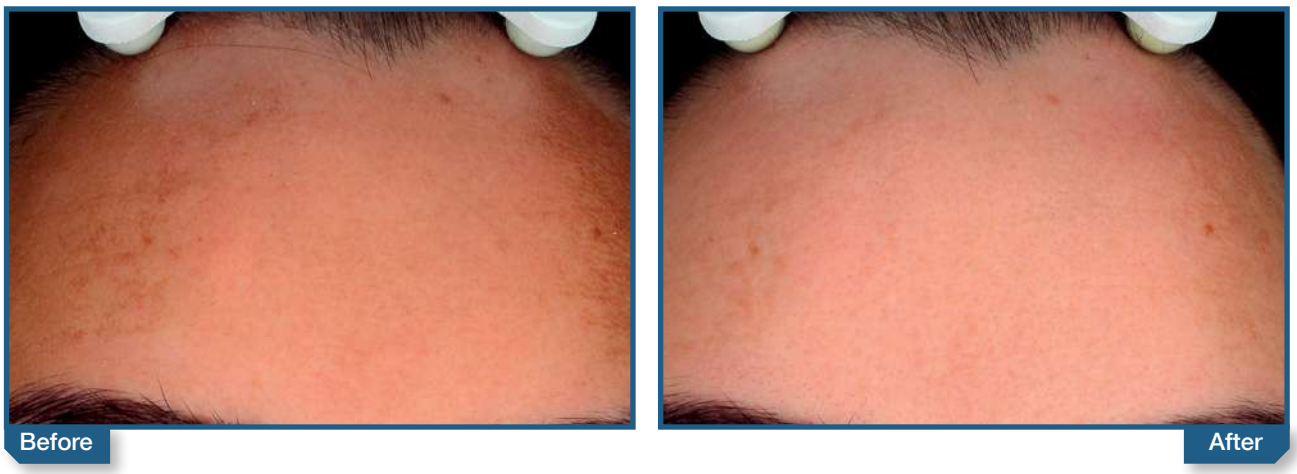

Figure 1.
Patient 1 with melasma – before and after the treatment: decrease of deep pigmentation (VISIA Canfield brown spots).

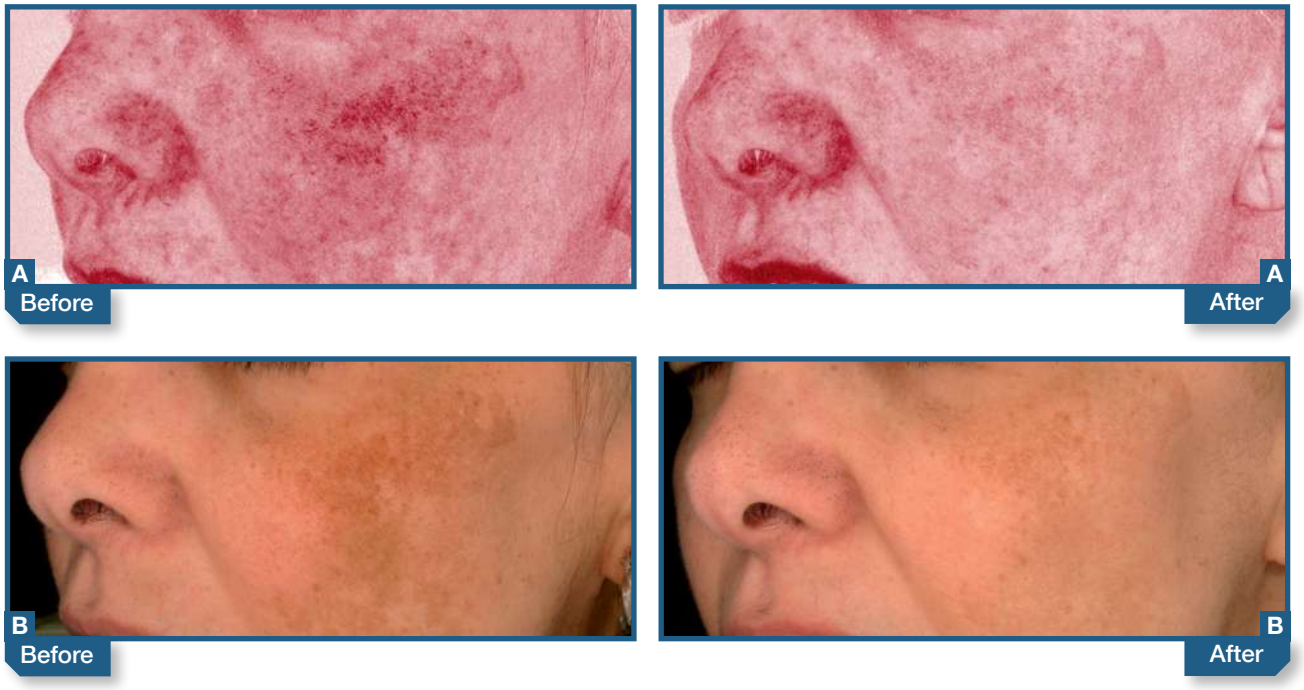

Figure 2.
Patient 2 with melasma – before and after the treatment (VISIA vascular RBX Technology – Red and Brown); ***A:*** *red area represents inflammation under melasma pigmentation (visible reduction of vascular pattern);* ***B:*** *brown area represents deep pigmentation in melasma area (visible reduction of melanin deposit).*

Discussion

Aging, melasma and acne are skin alterations that do not compromise patients' physical health but are highly debilitating for the Quality of Life (DLQIref).

In the absence of early intervention, acne can result in the formation of scars that are still difficult to manage, the persistence of inflammatory lesions and genetic predisposition being its main cause [16].

Therefore, the availability of treatments [17] that speed up the healing of individual lesions is extremely important not only for patients' comfort and compliance to treatment, but especially as a crucial element to avoid scarring outcomes, the prevention of which is considered today as the most effective therapeutic act [18, 19].

Acne lesions and melasma are an important cause of worsening of the quality of life [4, 20] since they hinder self-esteem, the ability to have relationships and to find a job; moreover, they develop during critical periods of life and sum up to the inevitable effects of skin aging. The request for treatments that can speed up the pharmacological therapeutic response, without worsening a social life that has been already compromised by the disease, has always been encouraged by patients and, in some selected cases, is the essential complement for therapeutic success.

The international literature shows that the outpatient treatment with glycolic acid, both at low and high concentrations, is able to improve skin firmness, hydration and superficial roughness by means of a mechanism of corneolysis and neocollagenesis stimulation resulting in a global improvement of the quality of skin. In melasma, these mechanisms also include a progressive reduction in superficial melanic deposits, while in acne a comedolitic effect is produced to drain superficial pustules thus making it a coadjuvant treatment in the prevention of possible scarring outcomes. Moreover, in all cases, the corneolytic effect promotes a greater and more homogeneous absorption of topical agents to be used at home [15].

It is very often difficult to find a balance between treatment efficacy and patient compliance, because while patients recognize the chemo-exfoliating treatment as a valid support to maximize and speed up the outcomes, they are increasingly less willing to tolerate subjective annoying sensations and discomfort in their relationship life.

The proposed protocol was formulated with the specific aim of avoiding any issues related to compliance, still maintaining a high degree of efficacy and safety of the treatment.

These promising results shall be confirmed in the future on a larger patient population.

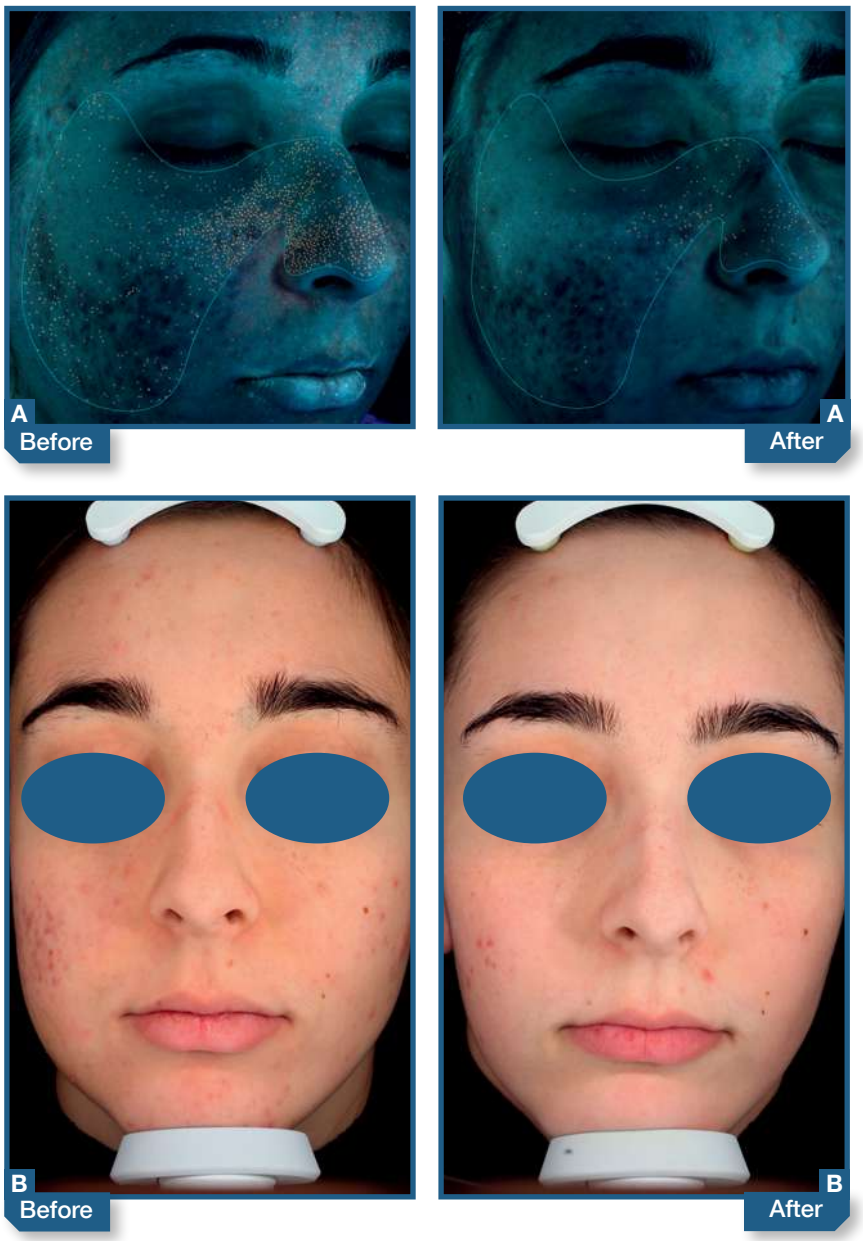

Figure 3.
Patient 3 with moderate papulo-pustular acne; ***A:*** *before and after VISIA Canfield Woodlight showing decreased levels of porphyrins (yellow fluorescent spots in the mask area);* ***B:*** *before and after VISIA Canfield Brown showing reduction of macules and papulo-pustular lesion in moderate acne.*

A previous therapeutic protocol that included outpatient treatment alone had already shown a high tolerability and safety [6, 7, 8, 9] that was confirmed by the combination of the pharmacological home therapies with treatment A.

Among the numerous outpatient therapeutic options for the management of these three diseases, this protocol has the characteristic of being especially tolerated and cost-effective, the latter being a considerable benefit if we consider that drop-outs are often due to the absence of these features and to the increasing patients' need to use socially presentable treatments.

We should also highlight that in the management of melasma, outpatient therapy has the main aim of speeding up the removal of melanic deposits and of promoting the absorption of the molecules that regulate melanogenesis, the daily application of which is essential to achieve a positive result.

The absence of adverse events is another benefit that will obviously need to be confirmed on a larger number of subjects.

We think that the antioxidating and clarifying action of NAC and NAG [21, 22, 23], along with the progressive and uniform penetration of the compound in the skin layers, mediated by chitosan [24, 25], can be responsible for the encouraging results obtained in terms of safety, tolerability and efficacy profile.

N-acetyl-cysteine (NAC) acts as a depigmenting agent that inhibits tyrosinase, as well as elastase and hyaluronidase, thus helping maintain the functions of the extracellular matrix, which is important in the fight against photodamage processes [26].

Moreover, NAC stimulates the synthesis of glutathione, which is an important anti-oxidizing agent and a molecule capable of moving pigment synthesis from pheomelanins, dark pigments, to eumelanins, lighter pigments. Chitosan, in addition to regulating the speed of absorption of the compound by making it homogeneous and well-tolerated, generates N-acetyl-glucosamine (NAG), a precursor of hyaluronic acid, by enzymatic hydrolysis, thus promoting the hydrating and scavenger action of free radicals. Carnitine has a sebolytic and sebostatic action, useful in the acne disease [27].

The unexpected, still unexplained but thrilling observation of a reduction in the red component (erythema, vascular) shown in the VISIA

scans 60 days after the treatment end strengthens the belief that the proposed protocol deserves further studies, since today we give great importance to the vascular component especially in the pathogenesis of photoaging and melasma.

Conclusions

The ideal target patient for the proposed treatment is a patient with mild to moderate photo-damage, mild to moderate acne and melasma who is willing to undergo socially presentable or needle-free treatments.

Melasma and acne are extremely common skin diseases, often associated with photodamage, which are subject to environmental genetic components currently under study.

The doctors' request for effective and stable therapeutic options is due to the high reduction in patients' quality of life.

Today research is still ongoing due to the absence of an effective therapy to maintain stable results.

This study shows that this protocol can provide a safe, highly tolerated and effective therapeutic option, whose low cost and ease of use would represent an accessible opportunity for many doctors and patients to implement the results of home therapy alone. These protocols are suggested twice a year so as to maintain the results.

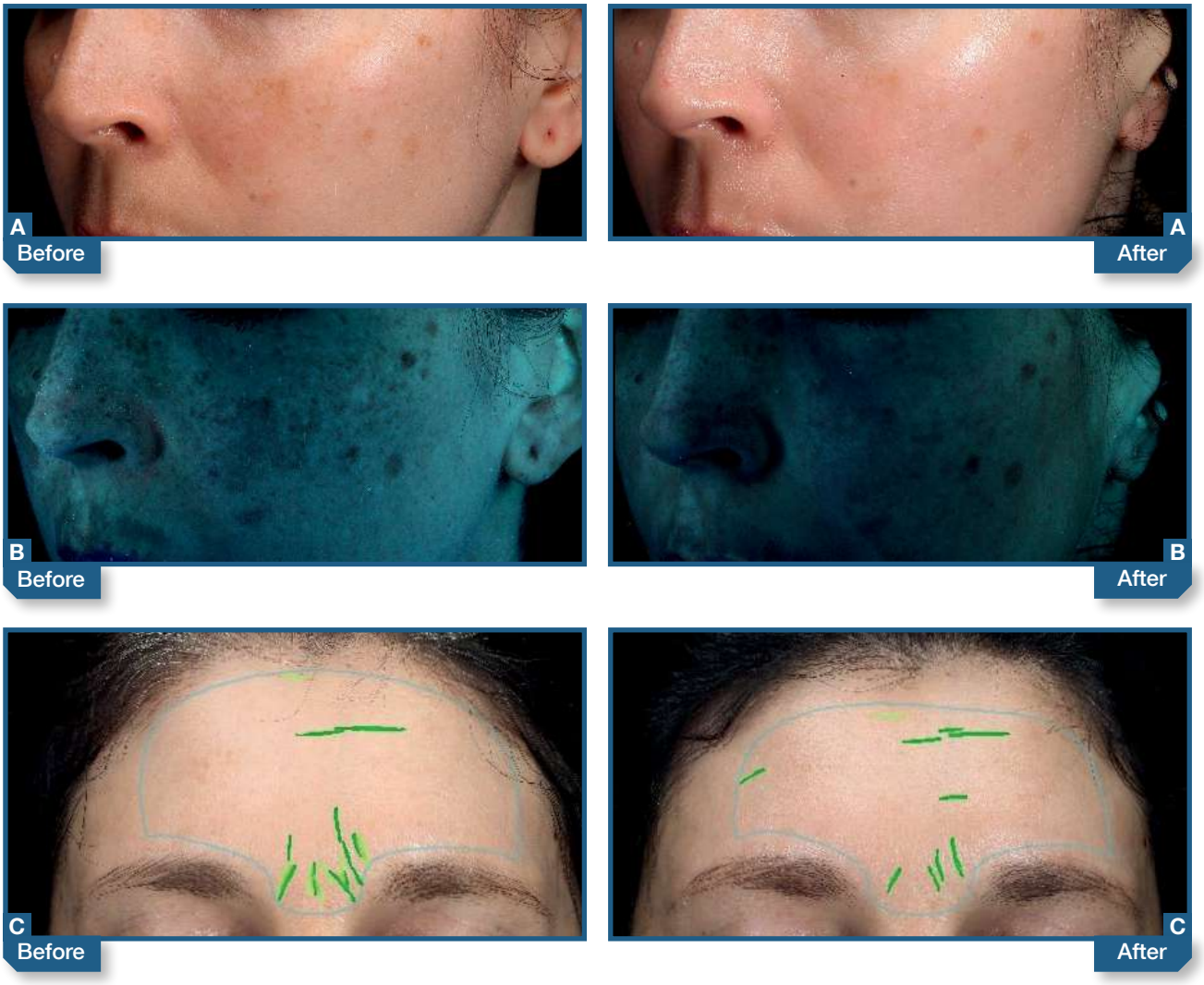

Figure 4.
Patient 4 – Patient with melasma and aging; ***A:*** *Improved temporal-zygomatic texture (VISIA Canfield – wrinkle);* ***B:*** *reduction of melanic pigmentation in the melasma area and pigment uniformity (VISIA Canfield – Woodlight);* ***C:*** *wrinkle reduction in the glabellar area (VISIA Canfield – wrinkle mask).*

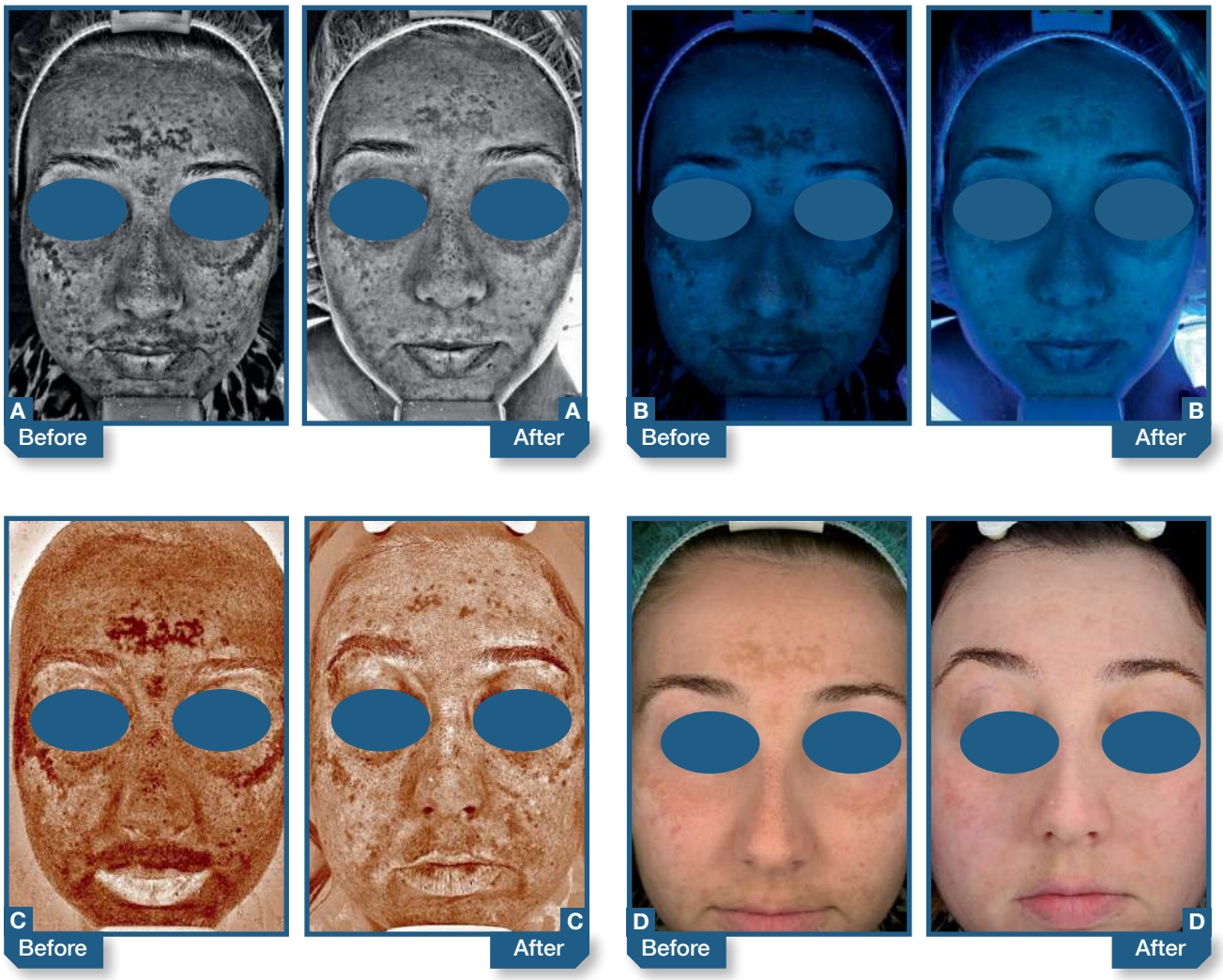

Figure 5.
Patient 5 with melasma. Result: improvement of melasma pigmentation with quite complete resolution; ***A:*** *VISIA Canfield – UV light;* ***B:*** *VISIA Canfield - Woodlight;* ***C:*** *VISIA Canfield - Brown;* ***D:*** *VISIA Canfield - unprocessed Brown.*

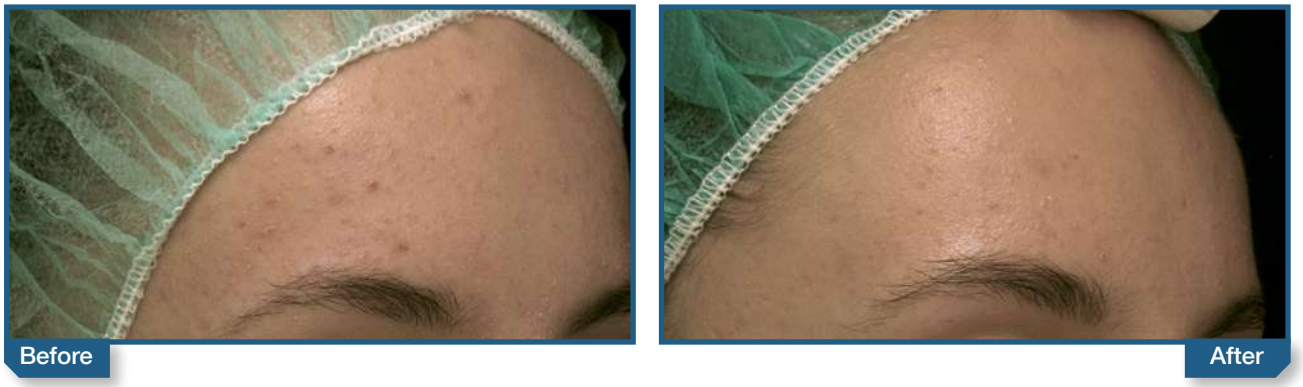

Figure 6.
Patient 6: comedonic acne showing improvement in comedons (VISIA Canfield).

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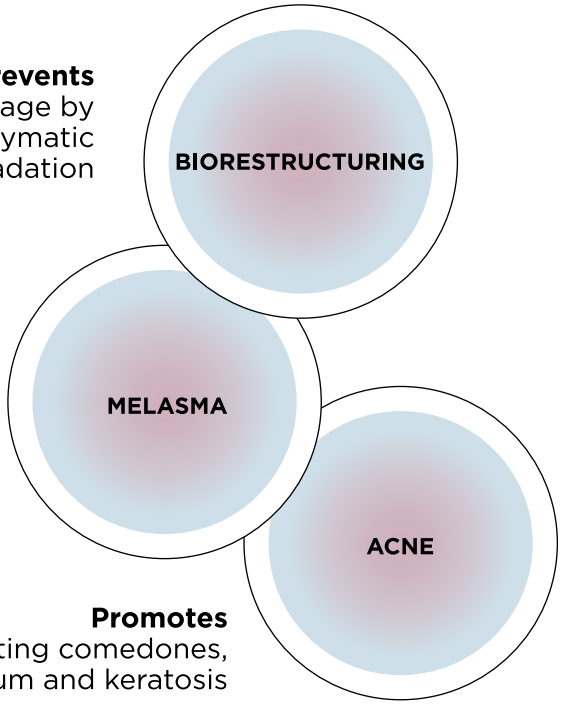

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