

ORIGINAL RESEARCH REPORT

Open-label evaluation of the skin-brightening efficacy of a skin-brightening system using decapeptide-12

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Abstract

This prospective study evaluated the safety and efficacy of decapeptide-12 in conjunction with an antioxidant cleanser, glycolic-acid containing facial moisturizer and broad-spectrum sunscreen in the treatment of facial hyperpigmentation associated with chronic photodamage. Fifteen female subjects with Fitzpatrick skin types I through IV and documented photodamage were entered into the study, of whom 13 completed the study. Results were obtained at weeks 4, 8, 12, 18 and 24 and were assessed by both volunteers and investigators based on standardised digital photography using the Global Assessment of Photodamage Severity Scale. At the conclusion of the study at 24 weeks, 38.5% of the volunteers achieved complete clearance from a moderate (grade 3) degree of photodamage at baseline to completely cleared (grade 1). Another 30.7% improved from a moderate (grade 3) degree of photodamage at baseline to a mild (grade 2) degree of photodamage. An additional 15.4% improved from a severe (grade 4) degree of photodamage at baseline to a moderate (grade 3) degree of photodamage while an equal 15.4% improved from a severe (grade 4) degree of photodamage at baseline to a designation of mild (grade 2) at 24 weeks. All study-related treatments were well tolerated. The mechanism of action of decapeptide-12 includes inhibition of melanin synthesis via inhibition of the tyrosinase enzyme. Advantages of decapeptide-12 over other skin-brightening agents include its low incidence of side effects, lack of cytotoxicity and safe use in ethnic skin as well as in patients who have failed other treatment regimens.

Key Words: *cosmeceuticals, topical agents*

Introduction

Facial hyperpigmentation remains one of the most common reasons for which patients seek cosmetic treatment. Patients are increasingly aware of the role chronic ultraviolet light exposure plays in the development of a photoaging. There are a number of medical interventions available to reverse this process (1,2). Besides the pigmentary changes associated with chronic photodamage such as solar lentigenes and ephelids, there are many other causes of facial hyperpigmentation, including melasma as well as drug-induced and post-inflammatory hyperpigmentation. Although the etiologies of facial hyperpigmentation are multiple, the underlying pathogenesis is the same, namely increased epidermal basal layer and/or dermal deposition of melanin (3). Increased epidermal or dermal melanin deposition often results from the increased activity of tyrosinase, which is the rate-limiting enzyme in the melanin biosynthetic

pathway (4). Depigmenting agents are therefore the most commonly prescribed medications for facial hyperpigmentation (1).

Decapeptide-12 (Lumixyl™, Envy Medical, Inc., Westlake Village, USA) is a novel cosmetic oligopeptide consisting of a sequence of ten amino acids with skin-lightening properties that can serve as an alternative to hydroquinone-based products.

Materials and methods

This study evaluated the safety and efficacy of combined topical decapeptide-12 cream, 0.01% in combination with an antioxidant cleanser, glycolic acid containing facial moisturizer and broadspectrum sunscreen in the treatment of facial photodamage.

Fifteen female subjects, Fitzpatrick skin types I through IV with documented photodamage, were entered into the study. Exclusion criteria included

pregnancy, a pre-existing dermatologic condition that would potentially interfere with the execution of the study as well as the use of oral or topical retinoids. Additional exclusion criteria were the use of prescription lightening products including hydroquinone as well as a chemical peel or microdermabrasion in the preceding 3 months prior to enrolment or corticosteroid or immunosuppressive therapy use in the preceding 6 months prior to enrolment. Written informed consent was obtained from each of the 15 study subjects prior to enrolment.

For the duration of the study, subjects were requested to refrain from using any topical products on the face other than the study products. Subjects used twice daily application of an antioxidant cleanser, twice daily application of a 0.01% decapeptide-12 cream, daily or alternate day application of a 20% glycolic acid exfoliating lotion as well as a daily broad-spectrum SPF 30 sunscreen.

Assessment of degree of photodamage

Baseline degree of photodamage was assessed using standardized digital photography. Volunteer self-assessed grading of photodamage was performed at baseline, week 4, week 8, week 12, week 18 and week 24 and consisted of the designations of completely cleared, nearly cleared and significant hyperpigmentation present according to the Volunteer Global Assessment of Photodamage Scale as outlined in Table I. Investigator-assessed grading of photodamage was performed at baseline, week 4, week 8, week 12, week 18 and week 24 and consisted of the designations of cleared, mild, moderate and severe according to the Investigator Global Assessment of Photodamage Severity Scale as outlined in Table II.

Study subjects and investigators utilized the same standardized grading scale to evaluate the tolerability of the study products with respect to stinging and/or burning sensation, erythema, dryness and pruritis.

Results

At baseline, all study subjects (15/15) assessed their photodamage severity at Grade 3. At the week 4 follow-up visit, none of the study subject noticed any improvement in their photodamage severity. At week 8 follow-up visit, 1 study subject (1/15) noticed improvement from Grade 3 to 2 in her photodamage severity. At week 12, 3 study subjects (3/15) noticed improvement from Grade 3 to 2 in their photodamage

Table I. Volunteer global assessment of photodamage scale.

Grade	Appearance of photodamage
1	Completely cleared
2	Nearly cleared
3	Significant hyperpigmentation present

Table II. Investigator global assessment of photodamage severity.

Grade	Severity	Hyperpigmentation status
1	Cleared	Colour of photodamaged areas approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation
2	Mild	Colour slightly darker than the surrounding normal skin
3	Moderate	Colour moderately darker than the surrounding normal skin
4	Severe	Colour markedly darker than the surrounding normal skin

severity. By week 18, 8 study subjects (8/15) noticed improvement from Grade 3 to 2, while 1 study subject noticed improvement from Grade 3 to 1 in her photodamage severity. Finally, by week 24, 10 study subjects (10/13) noticed improvement from Grade 3 to 2, while 3 study subjects (3/13) noticed improvement from Grade 3 to 1 in their photodamage severity. One study subject (1/15) felt she was not improved. Table III.

At baseline, investigators determined 10/15 study subjects' photodamage severity to be grade 3 (moderate), while 5/15 study subjects were graded as 4 (severe). At week 4, no improvement was noticed in photodamage severity for any of the study subjects. At week 8, 1 study subject (1/15) showed improvement in her photodamage severity from Grade 3 to 2. At week 12, 5 study subjects (5/15) showed improvement in their photodamage severity from Grade 3 to 2 and 3 study subjects (3/15) showed improvement from Grade 4 to 3. At week 18, 6 study subjects (6/15) showed improvement in their photodamage severity from Grade 3 to 2, while 1 study subject (1/15) showed improvement from Grade 3 to 1. Two study subjects (2/15) showed improvement in their photodamage severity from Grade 4 to 3, while another two subjects (2/15) showed improvement from Grade 4 to 2. At week 24, 4 study subjects (4/13) showed improvement in their photodamage severity from Grade 3 to 2, while 5 study subjects (5/13) showed improvement from Grade 3 to 1. Finally, 2 study subjects (2/13) showed improvement from Grade 4 to 3, while 2 study subjects (2/13) showed improvement from Grade 4 to 2 (Table IV and Figures 1–4). Side effects were minimal and consisted solely of rare mild erythema, dryness and pruritis.

Table III. Change in volunteer global assessment of photodamage from baseline to week 24.

Baseline	Week 24	Percentage (no/total no)
Significant hyperpigmentation present	Nearly cleared	76.9 (10/13)
Significant hyperpigmentation present	Completely cleared	23.1 (3/13)

Table IV. Change in investigator global assessment of photodamage from baseline to 24 weeks.

Baseline	Week 24	Percentage (no/total no)
Severe photodamage	Moderate photodamage	15.4% (2/13)
Severe photodamage	Mild photodamage	15.4% (2/13)
Severe photodamage	Cleared	0.0% (0/13)
Moderate photodamage	Mild photodamage	30.8% (4/13)
Moderate photodamage	Cleared	38.4% (5/13)

Two subjects were dropped from the study due to non-compliance with the topical treatment regimen.

Discussion

There are several topical skin-lightening agents available for the treatment of facial hyperpigmentation, such as hydroquinone and hydroquinone-based preparations, azelaic acid, glycolic acid, arbutin, catechins, flavonoids, kojic acid and vitamins C and E derivatives (1,4,5). Additional treatment modalities include exfoliants, chemical peels, lasers and other light sources, which may be employed concurrently with or sequential to topical skin-lightening treatment regimens. The gold standard and the most commonly prescribed remedy for the treatment of facial hyperpigmentation has historically been hydroquinone (6).

Although hydroquinone remains the number one physician-prescribed topical lightening agent around the world, its demonstrated efficacy has been sub-optimal, with response rates between 60–90% depending on the study cited (5,6). The mechanism of action of hydroquinone, a phenolic compound, is via the inhibition of tyrosinase, although it has been proposed that interference with DNA and RNA synthesis as well as the degradation of melanosomes and destruction of melanocytes may also play a role (1,3,7,8). Side effects of hydroquinone include erythema, irritation, burning sensation, scaling and the development of contact dermatitis (9). More serious adverse events include the development of exogenous ochronosis and a possible drug hypersensitivity reaction in patients with a sulphite allergy (10). Exogenous ochronosis is a paradoxical and often treatment-resistant hyperpigmentation of the skin following prolonged use of topical hydroquinone and has been reported at concentrations as low as 4% (1,11). Because of the risk of exogenous ochronosis, long-term use of hydroquinone beyond 4- to 6-month treatment periods is discouraged (1). Despite recommendations to stop hydroquinone after 4–6 months of continued use, discontinuing hydroquinone has been known to result in rebound hyperpigmentation, which would potentially negate any positive benefits achieved by hydroquinone treatment (6). In addition, patients must carefully apply hydroquinone topical formulations strictly to the hyperpigmented areas on



Figure 1. Subject before treatment.



Figure 2. Subject 24 weeks after treatment.



Figure 3. Subject before treatment.



Figure 4. Subject 24 weeks after treatment.

their skin, which may only be a few millimetres in diameter in certain patients, as application of hydroquinone to unaffected areas may result in unintended bleaching of normal skin. Furthermore, as a result of hydroquinone's risk of cytotoxicity and potential for mutagenicity, it has been banned in Europe for general cosmetic purposes since 2000 (4).

In order to improve the efficacy and reduce the side effect profile of hydroquinone, a combination therapy consisting of hydroquinone, 4%, fluocinonide, 0.01% and tretinoin, 0.05% cream has been employed. The perceived benefit of adding a topical retinoid such as tretinoin is that it can assist in increasing the rate of epidermal cell turnover, inhibit tyrosinase transcription and interfere with melanin synthesis (3). However, a common side effect of both hydroquinone and tretinoin is irritation and erythema, which may potentiate facial dyschromia by leading to post-inflammatory hyperpigmentation in predisposed individuals (6).

Decapeptide-12 is a novel, efficacious and well-tolerated skin lightening agent with a favourable side effect profile that could serve as an alternative or complement to other commonly available skin lightening agents. The mechanism of action of decapeptide-12 includes inhibition of melanin synthesis via inhibition of the tyrosinase enzyme, without having any cytotoxic effects against melanocytes. Recently, Abu Ubeid et al. demonstrated that at similar concentrations, decapeptide-12 produced more potent inhibition of human and mushroom tyrosinase com-

pared to hydroquinone and was able to reduce the intracellular melanin content in human melanocytes to a greater degree compared to hydroquinone. In addition, decapeptide-12 was found to be non-cytotoxic to melanocytes, whereas cytotoxicity, as measured by reduced melanocyte proliferation and cell counts, was considerable for hydroquinone even at low concentrations (8).

Physician assessment, at 24 weeks, showed that all 13 volunteers who completed the study experienced some degree of improvement in the appearance of their hyperpigmentation, thus supporting the tyrosinase-inhibiting activity of decapeptide-12 as reported by Abu Ubeid et al. 38.5%, or 5/13 study subjects, showed complete clearance from a moderate (grade 3) of photodamage at baseline to completely cleared (grade 1), at 24 weeks. Similarly, 30.7%, or 4/13 of study subjects, showed an improvement from moderate (grade 3) of photodamage at baseline to a mild (grade 2) of photodamage at 24 weeks. A total of 15.4% or 2/13 study subjects improved from a severe (grade 4) degree of photodamage at baseline to a moderate (grade 3) of photodamage while another 15.4%, or 2/13 study subjects achieved an improvement from severe (grade 4) photodamage at baseline to a designation of mild (grade 2) at 24 weeks.

Not only does decapeptide-12 have demonstrable *in vitro* and *in vivo* efficacy, it may also serve as an alternative for patients who have failed other skin-lightening topical regimens. In a split-face, double-blind,

randomized, placebo-controlled study of decapeptide-12 in treatment-resistant melasma, the decapeptide-12 treated side of the face revealed a greater than 50% improvement in melasma in patients who had previously failed a 6-month treatment course with combination topical hydroquinone–retinoid–steroid cream (12).

Additional benefits of decapeptide-12 over other topical skin-lightening agents such as hydroquinone are its lack of cytotoxicity and relatively benign side effects profile. The decapeptide-12 cream, 0.01% formulation is water-soluble, unscented, non-mutagenic, readily metabolized by the skin and produces no cytotoxic metabolites (13). In addition, it is relatively non-irritating and non-sensitizing as repeated insult patch testing at concentrations 10 times the recommended dose and in-use clinical trials demonstrated no allergic or irritant contact dermatitis (5,6,13,14). Hantash et al.'s pilot study resulted in no occurrence of visible signs of irritation or cutaneous allergy and side effects observed in our study were limited to the rare occurrence of mild erythema, dryness and pruritus (12).

Decapeptide-12 is considered safe for all skin types, as opposed to hydroquinone–tretinoin–steroid containing topical products (5). Because of its little propensity for producing any signs of clinical inflammation as evidenced by the rare occurrence of erythema and pruritus, decapeptide-12 is unlikely to result in post-inflammatory hyperpigmentation, to which patients with higher skin phototypes are more predisposed. Unlike hydroquinone, decapeptide-12 is safe for long-term daily use and is not associated with any known rebound hyperpigmentation upon discontinuation. Moreover, decapeptide-12 cream, 0.01% is intended for whole face application, as opposed to hydroquinone, which necessitates localized spot treatment as application to normal skin may result in unintended bleaching of the skin. Decapeptide-12 can therefore be implemented as a substitute for other skin lightening-agents, or complementary to hydroquinone-based products for patients to use in between hydroquinone treatments in order to reduce the risk of hydroquinone-associated rebound hyperpigmentation and exogenous ochronosis (6). Furthermore, as opposed to hydroquinone–tretinoin–steroid containing topical products, decapeptide-12 does not carry the risk of photosensitivity, steroid-induced acne or a drug hypersensitivity reaction in patients with sulphite allergies.

Collectively, the combination regimen of decapeptide-12 cream, 0.01% with an antioxidant wash, glycolic acid lotion, 20% and broad-spectrum SPF 30 sunscreen, provides additional benefits over a single skin-lightening agent alone. The antioxidants in the cleanser help regulate melanin production while glycolic acid aids in exfoliation, acceleration of epidermal cell turnover and the penetration of decapeptide-12 (1,6). Finally, the broad-spectrum SPF 30 sunscreen limits the production of new melanin in

response to UV radiation. All in all, all four components of the decapeptide-12 skin-brightening system act synergistically to eliminate existing hyperpigmentation and prevent its recurrence (6).

Although decapeptide-12 has been studied in terms of efficacy and safety in the past, this is the first study to show the efficacy and safety of combination topical glycolic acid, sunscreen and decapeptide-12 in the treatment of photodamage. Possible confounding factors in our study include uncontrolled baseline markers of photoaging such as rhytides, sallow or mottled pigmentation, loss of elasticity and telangiectasias. While the results obtained in this study appear promising, further research is needed to evaluate the tolerability and efficacy of decapeptide-12 in larger and more diverse study populations.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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