Eur J Dermatol 2018; 28(3): 343-50

Ediléia BAGATIN[1]
Heitor de Sá GONÇALVES[2]
Maurício SATO[3]
Luiz Maurício Costa ALMEIDA[4]
Helio Amante MIOT[5]

[1] Professor, Department of Dermatology, Federal University of São Paulo, SP, Brazil. Thesis advisor, Translational Medicine Post-Graduation Program, Federal University of São Paulo, São Paulo, Brazil
[2] Director, Dona Libânia Dermatology center, Department of Health, Ceará, Brazil
[3] Dermatologist, Federal University of Paraná, Paraná, Brazil
[4] Professor; Department of Dermatology, Medical Sciences College, Minas Gerais, Brazil. Preceptor of the medical residency of the Santa Casa, Minas Gerais, Brazil
[5] Associate professor, Department of Dermatology, FMB-Unesp, São Paulo Brazil

Reprints: E. Bagatin
<edileia_bagatin@yahoo.com.br>

Article accepted on 10/06/2017

Comparable efficacy of adapalene 0.3% gel and tretinoin 0.05% cream as treatment for cutaneous photoaging

Background: Adapalene has been previously evaluated as a treatment for actinic keratosis (AK) and solar lentigines and shown to improve signs of photoaging. *Objectives:* To evaluate whether adapalene 0.3% gel is non-inferior to tretinoin 0.05% cream as treatment for photoaged skin. *Materials & Methods:* An investigator-blinded, parallel-group comparison study was conducted in Brazil. Subjects were randomised in a 1:1 ratio to receive, once daily, adapalene 0.3% gel or tretinoin 0.05% cream. Subjects were evaluated at Weeks 1, 4, 8, 12, 16, 20 and 24, based on clinical signs of cutaneous photoaging, histopathological and digital morphometric findings, as well as safety and tolerability. *Results:* A comparison of clinical efficacy showed that both treatments did not differ significantly regarding clinical evaluation of the following criteria: global cutaneous photoaging, periorbital wrinkles, ephelides/melanosis, forehead wrinkles, and AK. *Conclusion:* Adapalene 0.3% gel showed non-inferior efficacy to tretinoin 0.05% cream as treatment for photoaged skin, with a similar safety profile. Adapalene 0.3% gel may therefore be considered a safe and effective option for the treatment of mild or moderate photoaging.

Key words: adapalene, melanosis, photoaging, retinoid, tretinoin, wrinkles

Skin photoaging is premature skin aging, caused by chronic exposure to solar radiation [1-3]. In addition to intrinsic and chronological factors, it is part of a complex biological process. The extent of damage inflicted on the skin by sunlight is determined by the radiation a person is exposed to throughout life, affecting predominantly people with fair skin. The decay of cellular activities over time accelerates skin aging, resulting in the clinical appearance of fine and deep wrinkles, changes in pigmentation, laxity, pallor, and telangiectasia. At advanced stages of exposure, skin photoaging may lead to actinic keratosis (AK) and the development of skin cancer. The molecular and cellular mechanisms mediating damage caused by ultraviolet (UV) radiation, mainly UVA, in the connective tissue of human skin involve cell surface receptors, protein kinase transduction pathways, transcription factors, and enzymes which synthesize and degrade structural proteins that confer strength and resilience to the dermis [4].

Retinoids, which are commonly used for acne, have also been shown to be effective for the treatment of photoaging [5-9], being the most effective among anti-aging agents [5]. Tretinoin (all-trans retinoic acid), a topical retinoid, has been used for decades in dermatology, and is approved for the treatment of acne and photodamaged skin [9]. Tretinoin 0.025% or 0.05% cream is still considered the gold standard for the treatment of photoaged skin [5, 9]. Previous clinical studies comparing tazarotene 0.1% cream versus tretinoin 0.05% cream showed that tazarotene 0.1% was at least as effective as tretinoin 0.05% and provided faster clinical improvement [10].

Adapalene is a synthetic retinoid with specificity for RAR-β and RAR-γ. The formulation of 0.3% gel is approved for the treatment of acne with similar efficacy and a favourable tolerability profile compared to other retinoids [11, 12]. Adapalene 0.1% and 0.3% have been investigated as a treatment for AK and solar lentigines, and shown to improve signs of photoaging, such as fine and coarse wrinkles, and mottled hyperpigmentation [13]. There is clinical and non-invasive instrumental evidence that adapalene can be effective as treatment for photoaging [14].

Given the available evidence, the hypothesis that efficacy of adapalene 0.3% gel may be non-inferior to tretinoin 0.05% cream, while providing a favourable tolerability profile, was the basis of the clinical study reported here. The primary objective was to evaluate the clinical efficacy of adapalene 0.3% gel versus tretinoin 0.05% cream regarding the reduction of cutaneous photoaging signs over 24 weeks of treatment. Secondary objectives included the evaluation of safety and tolerability, as well as the assessment of efficacy based on comparative histopathological and digital morphometric findings between the two treatment groups.

doi:10.1684/ejd.2018.3320

To cite this article: Bagatin E, Gonçalves HdS, Sato M, Almeida LMC, Miot HA. Comparable efficacy of adapalene 0.3% gel and tretinoin 0.05% cream as treatment for cutaneous photoaging. *Eur J Dermatol* 2018; 28(3): 343-50 doi:10.1684/ejd.2018.3320

Methods

Study design

This was a multicentre (comprising four clinical sites), randomised, investigator-blinded, parallel-group comparison study, conducted in Brazil. The study included subjects aged 35 to 55 years, with skin phototype I to IV, showing mild to moderate signs of photoaging (*i.e.* scores of 2 to 6 for overall assessment of skin photoaging, based on the Griffiths scale [15], and meeting specific eligibility criteria).
Study treatment duration was 24 weeks. The subjects were randomised in a 1:1 ratio to receive, once daily (evening application), adapalene 0.3% gel (Differin, Galderma Inc.) or tretinoin 0.05% cream (Vitanol, GSK Inc.). Subjects made hospital visits and were evaluated at Weeks 1, 4, 8, 12, 16, 20, and 24. All patients were required to clean their face with a lipid-free cleansing lotion (Cetaphil cleansing lotion, Galderma Inc.) and apply broad-spectrum sunscreen (Cetaphil Defense, Galderma Inc.) in the morning.
This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices, and in compliance with local regulatory requirements. The study was approved by institutional review boards, and all subjects provided written informed consent prior to study procedures. The project was registered at Clinicaltrialls.gov (NCT01406080).

Efficacy evaluation

The investigators assessed cutaneous photoaging assessment (ECPA) and global assessment based on the Griffiths scale for all visits throughout the study, and performed an evaluation of improvement at Weeks 12 and 24 (on a scale of -1 to 5: -1 = worse; 0 = no response; 1 = mild; 2 = moderate; 3 = marked; 4 = almost complete; 5 = complete). The evaluation of periorbital wrinkles (0-4), frontal wrinkles (0-4), ephelides/melanosis (0-4), and actinic keratosis (0-3) is included in the ECPA.
At Weeks 12 and 24, the questionnaire for subjects' assessment of improvement (scale of 0-4: 0 = difficult to notice; 1 = very mild; 2 = mild; 3 = moderate; and 4 = marked improvement) was completed by the participants. Biopsies of the temporal region using a 3-mm punch were performed at baseline and at Week 24 for histopathological and immunohistochemical assays. Digital photographs were taken at baseline and at Weeks 12, 16, 20, and 24.

Histopathology and immunohistochemistry

Skin samples were fixed in 10% buffered formalin for paraffin sections and subsequent haematoxylin-eosin (HE) and Fontana-Masson staining.
Immunostaining for p53 (clone D0-7, Dako, code M7001-1) and collagen type I (Abcam plc, cod AB34710) was performed using the EnvisonFLEX protocol, Dako, USA, at 1:20 and 1:1,200 dilution.
Gross histopathological quantification was performed by a group-blinded, boarded dermatopathologist. The analysis of p53 nuclear staining was performed by calculating the HSCORE [16] in the most intensely stained areas (hotspots) in the sample tissue.
Photographs were acquired according to a standardised procedure using a digital camera mounted on a Nikon Eclipse E200 light microscope under 1024 × 768 resolution, with 24-bit colour, ISO 80, TIFF, and speed of F4.5 1/2000. The photos represented interfollicular spaces and were captured in triplicate for each slide under 40x magnification.
The thicknesses of the stratum corneum, epithelium (measured from the basal layer to the upper granular layer), and granular layer (measured as the density of melanin and collagen in the upper dermis) was measured digitally using Image J software 1.46 [7, 17-19].

Safety and tolerability

Tolerability was assessed at all visits by taking into account specific criteria: erythema, burning sensation, pruritus, and dryness (scale of 0-3: 0 = absence; 3 = intense). Adverse event monitoring was performed throughout the study.

Statistical analysis

Sample size determination was based on non-inferiority of adapalene for efficacy, with significance level of 2.5%, power of 80%, standard deviation of 1 point for ECPA, and a margin of non-inferiority of 0.6. A total of 106 subjects (53 per treatment group) were determined to be required to meet the study objectives. For the histopathological evaluation, a sample size of 89 subjects maintains a power of at least 95% in order to detect a difference between treatment arms.
Primary efficacy analysis corresponded to intention-to-treat (ITT) analysis (LOCF) of the mean score variation of ECPA (average of scores of periorbital wrinkles, ephelides/melanosis, forehead wrinkles, and actinic keratosis) at the end of treatment compared to baseline. Confidence interval (CI) of 97.5% for the mean of the differences between treatments was calculated as -0.6.
Groups were compared using Cochran-Mantel-Haenszel (CMH) statistics. Changes were also transformed into dichotomous variables: "improvement" versus "no improvement or worsening" at each visit, and compared using Fisher's exact test (groups), the exact binomial test (vs baseline), and McNemar's test (Week 12 vs. Week 24). For histopathological measures and safety, the Student t test was used. The digital morphometric analyses were compared using a generalized linear mixed model.
Significance was set as two-tailed $p \leq 0.05$.
The software used for the statistical analysis was XLSTAT 2015 (Addinsoft, New York, USA) and IBM SPSS 22.

Results

Demographics

A total of 128 subjects (65 and 63 subjects in the adapalene 0.3% and tretinoin 0.05% groups, respectively) were evaluated (ITT population). Of those, 14 subjects did not complete the study (eight discontinuations due to loss of contact, five at the request of the patients, and one due to lack of adherence to the treatment), thus the per-protocol (PP) population consisted of 114 subjects (57 subjects per treatment group). The majority of subjects were females in both treatment groups (93.0% in the adapalene and 87.7% the

tretinoin group). Subjects were predominantly Caucasian. The mean age was approximately 47 years (adapalene group: 46.8; tretinoin group: 46.8) and the vast majority of subjects were female (adapalene group: 53 {93.0%]; tretinoin group: 50 {87.7%]).

Efficacy

Extent of cutaneous photoaging at Week 24

The results of the ECPA did not indicate any significant difference in efficacy between treatments for the ITT ($p = 0.458$) and PP ($p = 0.593$) populations. There was a significant reduction in the extent of photoaging ($p<0.001$) at the end of the study for both treatment groups. For the ITT population, the reported improvement was 20.4% vs. 20.8% (CI 97.5%: -0.125; 0.131) for adapalene 0.3% and tretinoin 0.05%, respectively. Similarly, for the PP population, the reported improvement was 22.4% vs. 22.6% (CI 97.5%: -0.133; 0.135), respectively. These CIs for the mean of differences between scores of treatments showed that adapalene 0.3% was non-inferior to tretinoin 0.05%.

Global assessment of cutaneous photoaging at each visit

Global assessment of photoaging did not show any significant differences between treatments in relation to the overall assessment at the end of the study ($p = 0.739$) (*figure 1A*).

Periorbital wrinkles

The treatments did not differ significantly in terms of the clinical evaluation of periorbital wrinkles at Weeks 12 and 24 ($p = 0.432$) (*figure 1B*). The percentage of subjects for whom improvement in periorbital wrinkles was reported at the end of the study was 59.6% (34 subjects) vs. 66.6% (38 subjects) ($p = 0.560$) for adapalene 0.3% and tretinoin 0.05%, respectively.

Ephelides/melanosis

There was a significant improvement in ephelides/melanosis in both treatment groups. There was no significant difference between the groups at Weeks 12 and 24 ($p = 0.460$) (*figure 1C*). The percentage of subjects for whom improvement in ephelides/melanosis was reported at the end of the study was 64.9% (37 subjects) vs. 71.9% (41 subjects) ($p = 0.546$) for adapalene 0.3% and tretinoin 0.05%, respectively.

Forehead wrinkles

Both treatments achieved similar results in terms of the clinical evaluation of forehead wrinkles at Weeks 12 and 24 ($p = 0.302$) (*figure 1D*). The percentage of subjects for whom improvement in forehead wrinkles was reported at the end of the study was equal; 50.8% (29 subjects) vs. 50.8% (29 subjects) ($p = 1.000$) for adapalene 0.3% and tretinoin 0.05%, respectively.

Actinic keratosis

No improvement was reported for either of the treatment groups, with no difference between groups. As almost all values were zero, an analysis was not performed.

Investigator assessment at Weeks 12 and 24

According to the investigators, the treatments did not differ in relation to improvement reported at Weeks 12 ($p = 0.785$) and 24 ($p = 0.298$). At Week 12, the percentage of subjects who showed improvement was 89.5% vs. 91.1% for adapalene 0.3% and tretinoin 0.05%, respectively. Of note, 82.4% vs. 85.7% showed mild or moderate improvement. At Week 24, the percentage of subjects who showed improvement was equal between treatments (96.5% in both groups). Also, 64.9% vs. 65% showed mild or moderate improvement, while 29.8% vs. 28.1% showed marked or almost complete improvement for adapalene 0.3% and tretinoin 0.05%, respectively (*figures 2, 3*).

Subject assessment at Weeks 12 and 24

According to the subjects, the treatments did not differ in relation to improvement at Week 12 ($p = 0.925$) and 24 ($p = 0.904$). At Week 12, the percentage of subjects who showed improvement was equal between treatments; 94.8% vs. 94.7% for adapalene 0.3% and tretinoin 0.05%, respectively. Of note, 79% vs. 75% showed moderate or major improvement. At Week 24, the percentage of subjects who showed improvement was 94.8% vs. 93%, respectively. Of note, 89.5% vs. 85.9%, respectively, showed moderate or major improvement**.**

Morphometric analysis

Morphometric analysis (*table 1*) demonstrated significant epithelial hyperplasia: reduction in the thickness of the stratum corneum (*figure 4*) and reduced p53 expression and melanin density in the epidermis, as well as increased granular layer thickness and density of collagen type I in the papillary dermis (*figure 4*), between baseline and Week 24 for both treatment groups ($p<0.01$). However, no difference between the treatments was observed ($p>0.1$).

Histopathological analysis

Histopathological analysis (*table 1, figure 4*) demonstrated an increase in the frequency of compaction of the stratum corneum, reduced elastosis, and interstitial oedema, as well as homogenization of melanin distribution between baseline and Week 24 in both treatment groups ($p<0.01$). However, no difference between the treatments was observed ($p>0.1$).

Safety

A total of 622 adverse events (AEs) were reported in 117 subjects. There was no significant difference in AEs between groups, with 302 (48.6%) and 320 (51.4%) reported for adapalene 0.3% and tretinoin 0.05%, respectively (z test for a proportion; $p = 0.495$). The most commonly reported AEs were burning sensation (53 vs. 70), erythema (50 vs. 63), peeling (42 vs. 65), pruritus (43 vs. 41), and dryness (36 vs. 28), corresponding to 74.2% and 83.4% of the total number of AEs in the adapalene 0.3% and tretinoin 0.05% groups, respectively. The intensity of AEs was similar between treatments, with the vast majority of AEs (>90%) in both groups being mild or moderate. Moreover, causality of AEs was also similar ($p = 0.208$) between the groups. Of the 622 AEs, 164 were clearly related to treatment: 75 vs. 89 for adapalene 0.3% vs. tretinoin 0.05%, respectively.

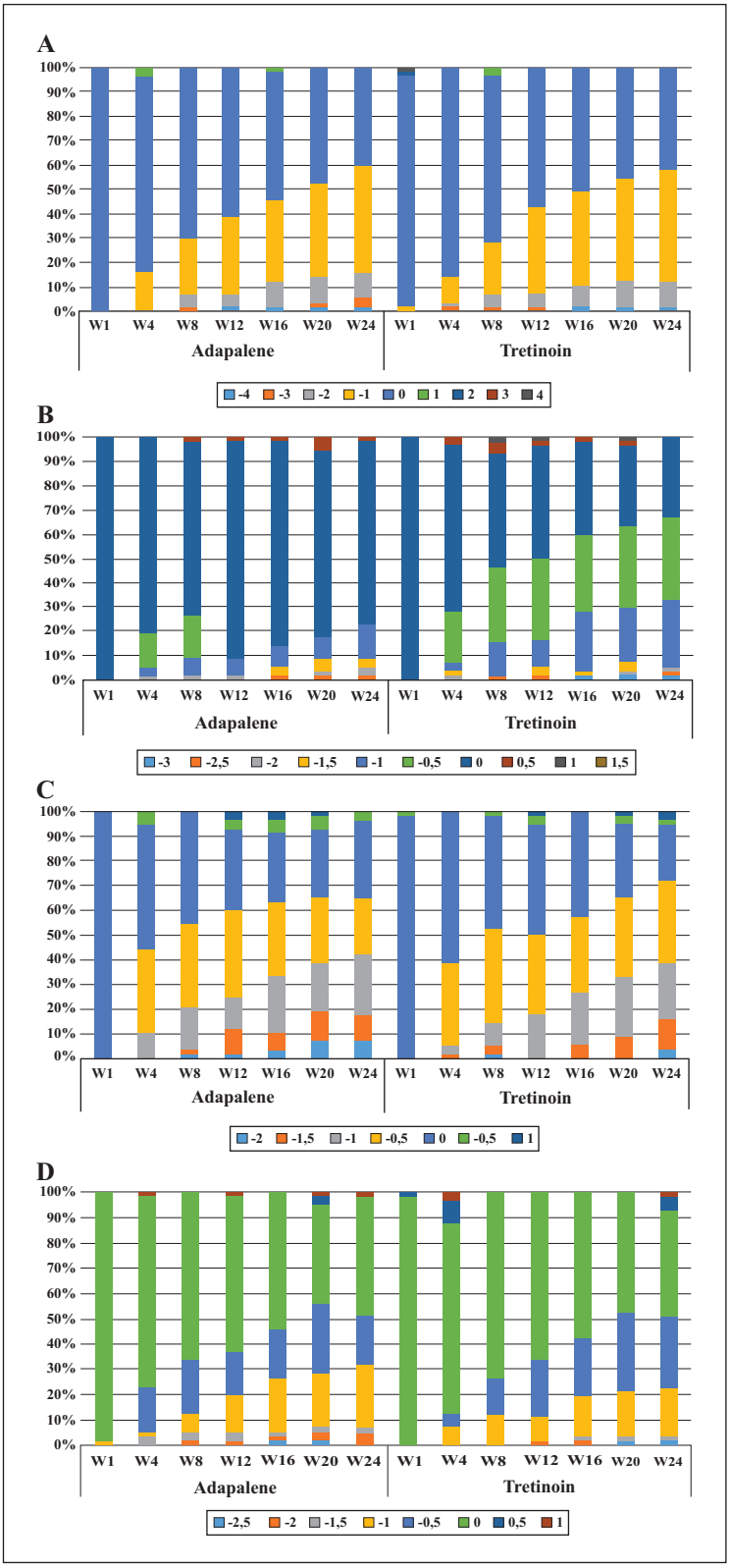

Figure 1. A) Difference in global assessment of photoaging at each visit compared to baseline. **B**) Difference in periorbital wrinkles at each visit compared to baseline. **C**) Difference in ephelides/melanosis at each visit compared to baseline. **D**) Difference in forehead wrinkles at each visit compared to baseline. The numbers (-4 to 4) in the legends represent the difference at each visit compared to baseline (0 = no difference, -1 = a one-point improvement, and 1 = a one-point worsening).

Figure 2. Improvement in overall skin pigmentation and fine wrinkles in an individual with adapalene treatment. **A**) Frontal view: Visit 1 (pre-treatment) and Visit 8 (24 weeks). **B**) Side view: Visit 1 (pre-treatment) and Visit 8 (24 weeks).

Discussion

There is clinical evidence for the effectiveness of topical adapalene in improving clinical features of facial photodamage (fine wrinkles and hyperpigmentation) and non-hypertrophic AK [13, 14]. In the present study, based on an evaluation of the clinical efficacy of adapalene 0.3% gel versus tretinoin 0.05% cream in reducing cutaneous photoaging signs over 24 weeks, we demonstrate non-inferior efficacy of adapalene 0.3% gel relative to tretinoin 0.05% cream, with a similar safety profile.

The global approach for photoaging should comprise prevention and targeted treatment, including topical treatments and medical devices. The use of broad-spectrum sunscreen reduces the production of reactive oxygen species (ROS) and the expression of p53 tumour suppressor protein [20]. Among topical treatment options, retinoids have been useful in reducing oxidative stress and photodamage, and improving epidermal renewal [21, 22]. Even though the complete mechanism is not thoroughly understood [23], the fact that retinoids influence different cellular pathways, from keratinocyte and melanocyte differentiation to collagen type I synthesis, may account for the improvement in photoaging observed after topical chronic use.

Topical retinoids work through activation of intranuclear retinoic acid receptors (RAR) [16]. Tretinoin activates all subtypes of retinoic acid receptors, while adapalene is a synthetic retinoid with a specificity for RAR-β and RAR-γ [24]. Since our comparison of clinical efficacy showed that adapalene 0.3% gel is non-inferior to tretinoin 0.05% cream in reducing mild or moderate signs of skin photoaging, one can infer that the activation of gamma subtype

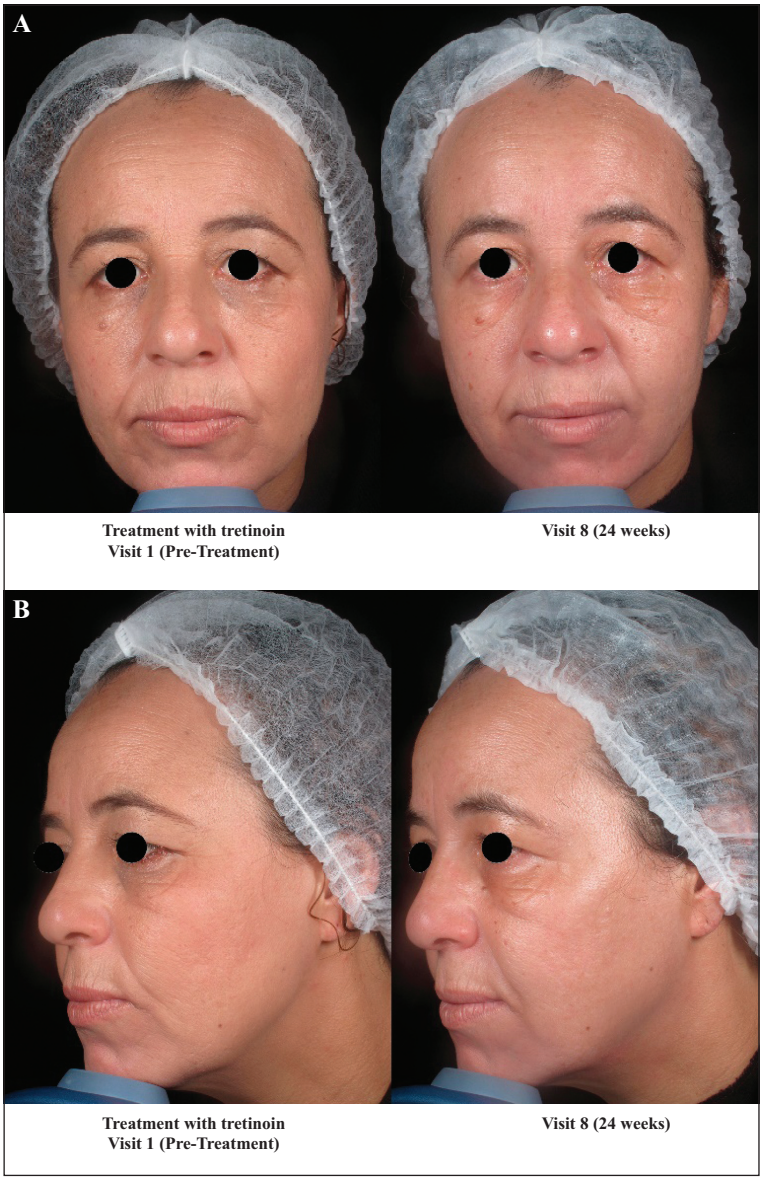

Figure 3. Improvement in overall skin pigmentation and fine wrinkles in an individual with tretinoin treatment. **A**) Frontal view: Visit 1 (pre-treatment) and Visit 8 (24 weeks). **B**) Side view: Visit 1 (pre-treatment) and Visit 8 (24 weeks).

by adapalene causes most of the cutaneous retinoid effects in the skin, as supported by our clinical and histological results and other trials with tazarotene [10, 25]. The effects of treatments investigated in this study did not differ significantly regarding the clinical evaluation of the following criteria: global cutaneous photoaging, periorbital wrinkles, ephelides/melanosis, forehead wrinkles, and AK.

Based on investigators' assessments, both treatments were efficacious for the vast majority of subjects and showed similar grades of improvement. These results were corroborated by subjects' assessments, reporting moderate or major improvement.

In addition, morphometric and histopathological analyses of an array of variables did not reveal any significant differences between the two treatments and corroborated the efficacy of the retinoid regimen in improving signs of photoaging. Observed alterations of the thickness of the stratum corneum, epidermal thickness, density of collagen, solar elastosis, frequency of stratum corneum compaction, and hypermelanosis were anticipated treatment effects, consistent with the use of retinoids in this clinical setting.

It is suggested that after UVR exposure, there is an increase in two transcription factors: AP-1 and NF-κB, leading to an increase in the production of matrix metalloproteinases, such as collagenase and gelatinase, which are responsible for the breakdown of dermal collagen and fibrillin [26]. The mechanism of action of adapalene, that involves the inhibition of transcription factor AP-1, deregulation of toll-like receptor 2, and anti-inflammatory actions through modulation of cytokines [27], may contribute to its favourable tolerability and anti-aging effect.

The two treatment regimens exhibited similar tolerability profiles, with the vast majority of AEs being of mild or moderate intensity. In general, discontinuations were not

Table 1. Main histopathological and morphometric results.

GROUP	Adapalene 0.3%		Tretinoin 0.05%		*p* value (time)	*p* value (time* group)
VISIT	T0	T24	T0	T24		
Stratum corneum (μm)[a]	27.9 (19.6-36.9)	15.7 (10.2-28.7)	24.0 (18.4-32.4)	14.9 (8.9-23.4)	<**0.01**	0.49
Epithelium (μm)[b]	54.3 (14.0)	63.8 (18.0)	54.1 (15.6)	69.0 (18.8)	<**0.01**	0.182
Granular layer (μm)[a]	6.9 (5.1-8.6)	9.2 (7.2-12.3)	6.9 (4.6-8.1)	8.6 (7.5-11.6)	<**0.01**	0.29
Melanin density (%)[a]	10.6 (7.8-13.8)	8.0 (5.9-11.8)	9.3 (6.1-16.3)	8.0 (2.6-3.7)	<**0.01**	0.78
Collagen type I density (%)[a]	8.5 (2.6-20.7)	32.9 (26.3-49.6)	10.0 (2.6-19.8)	32.1 (25.1-49.5)	<**0.01**	0.96
p53 (HSCORE)[a]	27.9 (12.4-47.8)	27.6 (5.7-41.0)	33.6 (15.7-43.3)	33.3 (6.7-53.2)	**0.01**	0.47
Compaction of stratum corneum[c]	7 (15)	24 (52)	3 (7)	23 (52)	<**0.01**	0.26
Areas of hypermelanosis[c]	17 (36)	8 (17)	15 (33)	12 (27)	0.06	0.34
Areas of hypomelanosis[c]	7 (15)	3 (7)	10 (22)	3 (7)	**0.04**	0.71
Interstitial oedema[c]	33 (70)	28 (61)	35 (78)	24 (55)	**0.01**	0.23
Solar elastosis[c]						
Mild	7 (16)	12 (27)	3 (7)	7 (16)	**0.01**	0.36
Moderate	22 (51)	23 (51)	25 (58)	24 (55)		
Severe	11 (26)	10 (22)	13 (30)	12 (27)		
Advanced	3 (7)	0 (-)	2 (5)	1 (2)		

[a]*median (p25-p75);* [b]*mean (standard deviation);* [c]*n (%); *adapalene x tretinoin.*

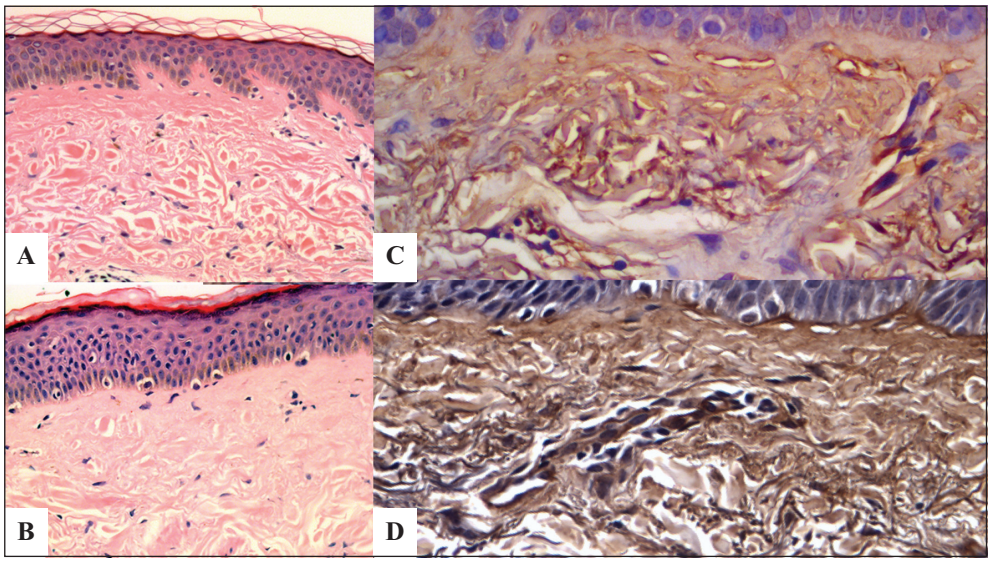

Figure 4. **A**, **B**) Histology (H&E; magnification: 40×) showing compaction and reduction of the thickness of the stratum corneum and increase in the thickness of the epithelium: **A**) pre-treatment; **B**) after 24 weeks of adapalene 0.3%. **C**, **D**) Immunostaining for collagen type I showing an increase in the density of collagen type I at the papillary dermis: **C**) pre-treatment; **D**) after 24 weeks of adapalene 0.3% (magnification: ×100).

directly related to AEs from the treatments. The limitations of the study include the low representation of men which precludes stratification of the analysis.

In conclusion, adapalene 0.3% gel showed comparable efficacy and safety to tretinoin 0.05% cream, and may thus be considered a safe and effective option for the treatment of mild or moderate cutaneous photoaging. Further studies are needed to explore adapalene for other retinoid responsive disorders beyond acne, such as melasma, striae distensae, the field of cancerization, pseudoacantosis nigricans, and keratosis pilaris.

Acknowledgments. The authors thank Camila Cazerta MD, Cristhine Kamamoto PhD, Danielle Shitara PhD, and Sotirios Georgantopoulos for editorial assistance, and Ananda Q. Campos, Manager of Clinical Research and Sci-

entific Information, and Meirenice Silva, Senior Clinical Research Analyst, at Galderma Brazil for clinical study assistance. ■

Disclosure. *Financial support: This study was sponsored by Galderma. Conflict of interest: Dr Almeida is a speaker for Bayer, Vichy, and Glenmark. Dr Sato is a speaker for Merz. Dr Bagatin is a speaker for Vichy, Avon, and GSK. Dr. Miot discloses no conflicts of interest.*

References

1. Fisher GJ, Kang S, Varani J, *et al*. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol* 2002; 138: 1462-70.

2. Rabe JH, Mamelak AJ, McElgunn PJ, Morison WL, Sauder DN. Photoaging: mechanisms and repair. *J Am Acad Dermatol* 2006; 55: 1-19.

3. Kang S, Fisher GJ, Voorhees JJ. Photoaging: pathogenesis, prevention, and treatment. *Clin Geriatr Med* 2001; 17: 643-59.

4. Poon F, Kang S, Chien AL. Mechanisms and treatments of photoaging. *Photodermatol Photoimmunol Photomed* 2015; 31: 65-74.

5. Ascenso A, Ribeiro H, Marques HC, Oliveira H, Santos C, Simoes S. Is tretinoin still a key agent for photoaging management? *Mini Rev Med Chem* 2014; 4: 629-41.

6. Kircik LH. Histologic improvement in photodamage after 12 months of treatment with tretinoin emollient cream (0.02%). *J Drugs Dermatol* 2012; 11: 1036-40.

7. Bagatin E, Guadanhim LR, Enokihara MM, *et al*. Low-dose oral isotretinoin versus topical retinoic acid for photoaging: a randomized, comparative study. *Int J Dermatol* 2014; 53: 114-22.

8. Phillips TJ, Gottlieb AB, Leyden JJ, *et al*. Efficacy of 0.1% tazarotene cream for the treatment of photodamage: a 12-month multicenter, randomized trial. *Arch Dermatol* 2002; 138: 1486-93.

9. Baldwin HE, Nighland M, Kendall C, Mays DA, Grossman R, Newburger J. 40 years of topical tretinoin use in review. *J Drugs Dermatol* 2013; 12: 638-42.

10. Kang S, Leyden JJ, Lowe NJ, *et al*. Tazarotene cream for the treatment of facial photodamage: a multicenter, investigator-masked, randomized, vehicle-controlled, parallel comparison of 0.01%, 0.025%, 0.05%, and 0.1% tazarotene creams with 0.05% tretinoin emollient cream applied once daily for 24 weeks. *Arch Dermatol* 2001; 137: 1597-604.

11. Thiboutot D, Pariser DM, Egan N, *et al*. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. *J Am Acad Dermatol* 2006; 54: 242-50.

12. Pariser DM, Thiboutot DM, Clark SD, *et al*. The efficacy and safety of adapalene gel 0.3% in the treatment of acne vulgaris: a randomized, multicenter, investigator-blinded, controlled comparison study versus adapalene gel 0.1% and vehicle. *Cutis* 2005; 76: 145-51.

13. Kang S, Goldfarb MT, Weiss JS, *et al*. Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: a randomized trial. *J Am Acad Dermatol* 2003; 49: 83-90.

14. Herane MI, Orlandi C, Zegpi E, Valdes P, Ancic X. Clinical efficacy of adapalene (differin(®)) 0.3% gel in Chilean women with cutaneous photoaging. *J Dermatolog Treat* 2012; 23: 57-64.

15. Griffiths CE, Wang TS, Hamilton TA, Voorhees JJ, Ellis CN. A photonumeric scale for the assessment of cutaneous photodamage. *Arch Dermatol* 1992; 128: 347-51.

16. Ishibashi H, Suzuki T, Suzuki S, *et al*. Sex steroid hormone receptors in human thymoma. *J Clin Endocrinol Metab* 2003; 88: 2309-17.

17. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods* 2012; 9: 671-5.

18. Miot HA, Brianezi G, Tamega Ade A, Miot LD. Techniques of digital image analysis for histological quantification of melanin. *An Bras Dermatol* 2012; 87: 608-11.

19. Brianezi G, Grandi F, Bagatin E, Enokihara MM, Miot HA. Dermal type I collagen assessment by digital image analysis. *An Bras Dermatol* 2015; 90: 723-7.

20. Antoniou C, Kosmadaki MG, Stratigos AJ, Katsambas AD. Sunscreens-what's important to know. *J Eur Acad Dermatol Venereol* 2008; 22: 1110-8.

21. Kligman AM, Grove GL, Hirose R, Leyden JJ. Topical tretinoin for photoaged skin. *J Am Acad Dermatol* 1986; 15: 836-59.

22. Sorg O, Antille C, Kaya G, Saurat JH. Retinoids in cosmeceuticals. *Dermatol Ther* 2006; 19: 289-96.

23. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; 65: 1061-72.

24. Shroot B, Michel S. Pharmacology and chemistry of adapalene. *J Am Acad Dermatol* 1997; 36: S96-103.

25. Lowe N, Gifford M, Tanghetti E, *et al*. Tazarotene 0.1% cream versus tretinoin 0.05% emollient cream in the treatment of photodamaged facial skin: a multicenter, double-blind, randomized, parallel-group study. *J Cosmet Laser Ther* 2004; 6: 79-85.

26. Fisher GJ, Datta SC, Talwar HS, *et al*. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature* 1996; 379: 335-9.

27. Czernielewski J, Michel S, Bouclier M, Baker M, Hensby JC. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. *J Eur Acad Dermatol Venereol* 2001; 15: 5-12.