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New local treatment for photoaging using a formulation containing piroxicam 0.8% and sunscreen

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Abstract

Objective: Skin aging is a complex process influenced by several factors that cause DNA damage and alter the extracellular matrix. The anti-inflammatory drug piroxicam can counteract photocarcinogenesis and photoaging by blocking cyclooxygenases-1 and 2, matrix metalloproteinases, and ornithine decarboxylase, and inducing apoptosis.

Methods: We conducted an open observational study in 50 adults with moderate to severe signs of photoaging treated with a new local formulation of piroxicam 0.8% plus sunscreen for 16 weeks. Photoaging was assessed using a validated dermoscopic photoaging scale. Each patient's own perception of their skin quality was assessed using a graphic scale.

Results: The new formulation demonstrated a reliable effect on photoaging after 16 weeks, based on improved median dermoscopic photoaging and skin-quality scores. No patients experienced any adverse effects.

Conclusions: To the best of our knowledge, this study provides the first evidence for the safe and effective use of a local piroxicam formulation for the treatment of moderate to severe photoaging.

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Introduction

Skin aging is a complex biological process influenced by a combination of endogenous (genetic, cellular, hormonal, and metabolic processes) and exogenous factors (chronic light exposure, pollution, ionizing radiation, chemicals, toxins). Chronic light exposure plays a key role in the pathogenesis of aging.[1] However, ultraviolet (UV) radiation, particularly UVB, is also important for human health by mediating the natural synthesis of vitamin D and endorphins in the skin. This beneficial role is well-established, and solar UV has been used to treat various diseases such as psoriasis and vitiligo.[1,2] Short-term UV exposure thus has indisputable beneficial effects, while its long-term consequences include photocarcinogenesis and photoaging. UV radiation induces a chronic inflammatory state related to the generation of reactive oxygen species and the activation of matrix metalloproteinases (MMPs). The effects of reactive oxygen species and MMPs result in the progressive destruction of collagen types I and III (in the papillary and reticular dermis) and collagen types IV and VII (in the dermo–epidermal junction).[1] These destructive events are followed by reshaping of the extracellular matrix. Finally, UV is also responsible for photocarcinogenesis, and the resulting direct and indirect DNA damage may lead to skin tumors via precursor lesions such as actinic keratoses (AKs) and the field of cancerization. This concept was formulated by Slaughter et al. in 1953, who examined histological abnormalities in the tissues surrounding oral squamous cell carcinomas.[3] The field of cancerization helps to explain the possibility of multifocal, contiguous, and coalescent tumors by the presence of an area of clinically normal, but histologically altered, skin around the primary lesion.[4] These alterations provide the basis for clonal expansion of molecularly abnormal neoplastic keratinocytes. Clinically, photo-damaged skin is characterized by xerosis, loss of elasticity, fine and deep wrinkles, thin or thick skin, shallowness, de- or hyper-pigmentation, freckles, comedones, angular cheilitis, guttate hypomelanosis, sebaceous hyperplasia, senile purpura, cherry angioma, and skin tumors. However, AKs are the only macroscopic feature in the field of cancerization.[5] New scientific research has demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) may exert their restorative action on skin carcinogenesis and aging by controlling earlier, reversible stages of inflammation. Among these NSAIDs, piroxicam (PXM) acts by blocking cyclooxygenases (COXs) 1 and 2, MMPs, and ornithine decarboxylase, of which the latter is a fundamental enzyme in the production of polyamines.[6] PXM also suppresses the synthesis of pro-inflammatory enzymes, reduces lipid mediators such as prostaglandins and thromboxane, and finally induces apoptosis, which is considered to be related to the anti-aging effect of the drug.[1,6,7] These properties suggest that PXM has important roles in limiting photocarcinogenesis and

photoaging. We therefore investigated the effects of a novel topical formulation of PXM plus sunscreen in patients with photoaging.

Patients and methods

Patients

We conducted an open observational study in adults with moderate to severe signs of photoaging. The inclusion criteria were age >18 years, clinical evidence of photoaging, and not receiving treatment for AKs or other non-melanoma skin cancers. Exclusion criteria were treatment of neoplasms with biological drugs and photosensitivity associated with autoimmunity. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and with written consent from the local ethics committee. All the participants provided written informed consent for participation in the study and for publication of the images.

Treatment

All patients were treated with a new topical medical formulation containing PXM cream 0.8% and sunscreen (Cantabria Labs, Caronno Pertusella, Italy). Patients applied the product locally over the entire face twice daily for 16 weeks. The amount applied depended on the extent of the treated area, with a recommended dose of 1 g twice daily for an area of 30 cm^2 (more or less the extent of the scalp).

Assessment methods

Photoaging was assessed using a specially created chart with two parts. The first part included information on the patient's age, type and duration of work, history of chronic sun exposure, and use of sunscreen (if yes, for how long). The second part included a dermoscopic photoaging scale (DPAS) as a reliable and valid diagnostic tool for the quantitative evaluation of photoaged skin using objective criteria.[8] The DPAS divides the face into four areas (forehead, right malar, left malar, and chin), and each area is evaluated separately in terms of the following: i) yellowish discoloration, ii) white lines, iii) lentigo, iv) hypopigmented/hyperpigmented macules, v) teleangiectasia, vi) yellow papules, vii) AKs, viii) senile comedones, ix) superficial wrinkles, x) deep wrinkles, and xi) criss-cross wrinkles. We modified the original DPAS for this study by removing lentigo, hypopigmented/hyperpigmented macules, and teleangiectasia because these features show little regression with simple but effective medical therapy (DPAS-modified). The final scores thus ranged from 0–32 (rather than from 0–44 as in the original DPAS), with 0 indicating no dermoscopic signs of photoaging and 32 indicating severe signs of photoaging. DPAS-modified assessments and photographic documentation were performed in all patients at baseline and after 16 weeks of treatment. Patients were also required to indicate a score for their own skin quality based on a graphic scale of 0–100, with 0 corresponding to the worst quality and 100 to the best. Patients were clinically evaluated at the beginning and end (week 16) of the treatment period.

Statistical analysis

Data from the clinical laboratory analyses were entered into a Windows-based database (Excel 2007; Microsoft Corp., Redmond, WA, USA) and analyzed statistically using GraphPad Prism 5 statistical software (GraphPad Software, San Diego, CA, USA). The results were expressed as the mean $\pm$ standard deviation. The significance of differences in the mean values (age, sex, DPAS score, and self-assessed skin quality) between baseline and week 16

were assessed by paired Student's *t*-test s, with a significance level of $P<0.05$.

Results

We enrolled 50 patients with a median age of 74.43 years (range 42–89 years), including 36 men (72%) and 14 women (28%). Patients were also classified according to grade I (n=32) or grade II AKs (n=18). Each patient was evaluated using the DPAS-modified and by self-assessment at baseline and after 16 weeks. The median DPAS-modified was significantly reduced and the median self-evaluation score was significantly increased after treatment with the PXM/sunscreen preparation for 16 weeks (both $P<0.001$) (Figure 1). The enrolled patients showed a consistent improvement in median DPAS, which decreased from 19.01 at baseline to 9.33 at week 16. Changes in the components of the DPAS-modified are shown in Table 1. Embarrassment related to their perceived poor skin quality also improved, with an increase in score from 32.5/100 at baseline to 59.5/100 at week 16. The consistent score improvement may have continued with longer follow-up.

No patients developed any treatment-related adverse effects.

Discussion

Several drugs (such as retinoids) and procedures (including chemical peeling,

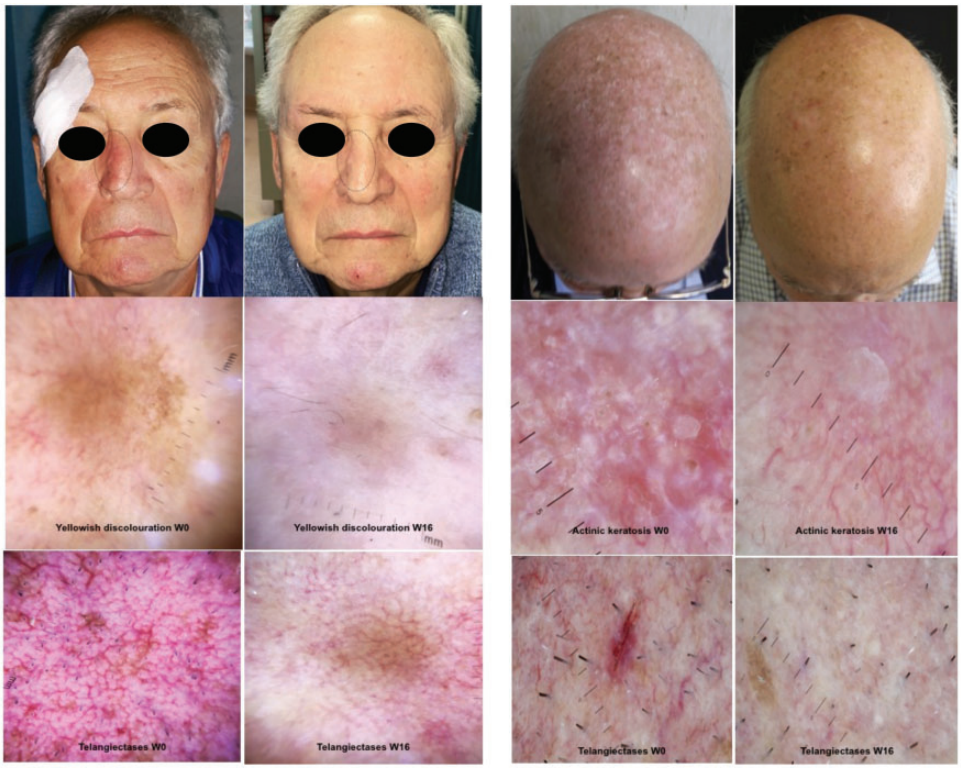

Figure 1. Effects on photoaging of treatment with piroxicam/sunscreen twice a day for 16 weeks. Clinical aspect and dermoscopic findings are shown at baseline (W0) and after 16 weeks of treatment (W16) in two patients (A and B).

Table 1. Changes in DPAS-modified components after treatment with PXM/sunscreen.

DPAS-modified component	Baseline (Week 0)	Week 16
Yellowish discoloration	34	14
White lines	10	4
Yellow papules	8	4
Actinic keratoses	25	4
Senile comedones	12	5
Superficial wrinkles	32	16
Deep wrinkles	29	26
Criss-cross wrinkles	3	2
Total	19.01	9.33

All numbers represent median values.
DPAS: Dermoscopic photoaging scale; PXM: piroxicam.

radiofrequency, or ablative and non-ablative laser treatment) have been explored for treating the signs of skin aging, and many have shown histological and clinical improvements. Bosch et al. used acetylsalicylic acid and other NSAIDs[9] and showed that indomethacin, PXM, sulindac, and diclofenac reduced the incidence of skin tumors and improved AKs. Other controlled clinical trials have demonstrated similar findings.[6] However, there have been no previous reports of the effects of NSAIDs, particularly PXM, on photoaging. PXM acts by blocking COX-1 and 2, MMPs, and ornithine decarboxylase, suppressing the synthesis of pro-inflammatory enzymes, reducing lipid mediators such as prostaglandins and thromboxane, and inducing apoptosis.[6,7]

The current results demonstrated the efficacy of PXM in association with sunscreen for treating photoaging. Furthermore, no patients in the current cohort developed any adverse effects. In addition to improving photodamaged skin, the PXM/sunscreen treatment also resulted in progressive resolution of grade I and II AKs and the field of cancerization. Although the current study did not aim to investigate the effects of PXM on photocarcinogenesis, these improvements in patients with multiple AKs and in the cancer field were important observations. PXM treatment should thus be considered not only in patients with advanced photoaging signs, but also in individuals aiming to prevent photoaging and photocarcinogenesis.[10–12] Notably, PXM was previously shown to be effective as a non-field-directed therapy for the treatment of AKs.[13] However, further studies are needed to compare the efficacies of field and non-field-directed therapies.

The current results were based on a small cohort of patients evaluated over a short period of time; nevertheless, the results provide important information in relation to the treatment/prevention of photoaging and photocarcinogenesis. However, further studies based on larger sample sizes and longer treatment and follow-up periods are required to confirm the suitability of the treatment.

To the best of our knowledge, this represents the first study to explore clinical benefit of PXM as a local treatment for moderate to severe photoaging. Topical application of PXM with sunscreen proved safe and effective for this indication. Although the study did not aim to evaluate the effects of PXM on photocarcinogenesis, the novel formulation resulted in improvements in patients with multiple AKs or an extended field of cancerization, in accordance with previous studies.[10–13]

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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