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ORIGINAL ARTICLE

Efficacy of a film-forming medical device containing sunscreen (50+) and piroxicam 0.8% in actinic keratosis and field cancerization: a multicenter, assessor-blinded, 3 month trial

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ABSTRACT

Introduction: Sunscreen protection in subjects with actinic keratosis (AK) is highly recommended to prevent clinical evolution of this *in situ* skin cancer condition. Use of topical anti-cyclooxygenase drugs such as diclofenac and piroxicam reduces the number of lesions and improves the cancerization field. A film-forming medical device in a cream formulation containing organic and inorganic sun-filters (50+ SPF) and piroxicam 0.8% (ACTX) has shown in a pilot, single-center, open trial to reduce AK lesions improving the cancerization field.

Aim: We evaluated in a multicenter, assessor-blinded, 3 month trial the efficacy of ACTX in AK.

Methods: A total of 70 subjects with at least three AK lesions on the scalp or face were enrolled after written informed consent. Primary outcomes of the study were the clinical evolution of number of AK lesions on a target zone area and the evolution of dermoscopy features of the target lesion, assessing erythema, scaling, pigmentation, and follicular plug, using a 5 point score (from 0 to 4; maximum score: 16). Lesion count and dermoscopy score were evaluated in a blind fashion assessing digital color high definition coded images. A secondary outcome was the Investigator Global Score (IGS) of clinical evolution of the target area using a 7 point scale from −2 (significantly worse) to +4 (completely cured). IGS was evaluated in an open fashion. Subjects were instructed to apply the cream twice daily on the target area, using one finger-tip unit for the treatment of a 35 cm^2 area.

Results: All but one subject (40 men and 30 women, mean age 73 years) concluded the study period. At baseline the mean (±SD) number of AK lesions in the target area were 7.0 (5.9) with a median value of 5 and the dermoscopy score of the target lesion was 7.0 (2.3) with a median value of 7.0. ACTX treatment reduced AK lesions to 3.2 (2.9), ($p = .0001$; Wilcoxon Test), representing a 55% relative reduction. Dermoscopy score was reduced to 3.3 (2.6) ($p = .0001$) (a reduction of 53%). The IGS after ACTX treatment was +1.9 (1.1), with a median of 2.0. A total of 86% of subjects showed a clinical improvement of IGS (≥1) with a very significant/complete clearance (score +3 or +4) in 42% subjects. No change or a worsening of AK lesions was observed in 14% of the subjects. The product was well tolerated. No serious adverse events were reported during the duration of the trial.

Conclusion: In this multicenter, assessor-blinded trial, the use of a film-forming medical device with sun protection and anti-inflammatory actions was effective in reducing AK lesions and improving the dermoscopy aspect of the target lesion in 86% of treated subjects. A head-to-head trial evaluating the efficacy of this medical device in comparison with diclofenac is warranted to establish whether this therapeutic approach could offer additional advantages in term of AK lesion reduction compared to an established topical treatment. (Trial ID: ISRCTN72020277).

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Introduction

Actinic keratosis is defined as an in situ non-melanoma skin cancer form caused by chronic sun exposure[1,2]. Actinic keratosis (AK) could be considered an in-situ carcinoma since many invasive squamous cell carcinomas derive from this kind of lesion. However, AK lesions could persist in the same stage or regress. Only a few can progress into squamous cell carcinoma[3]. The probability of a lesion undergoing malignant transformation to a squamous cell carcinoma is not clear, and it could range from 0.025% to 16% per year[4]. Therefore, the life time risk per patient is appreciable[5]. Because the progression of individual AKs cannot be predicted, it is advisable that all AKs, regardless of the grade, should be carefully monitored and treated in clinical practice[6]. Long-term sunscreen protection in subjects with AK is highly recommended in preventing clinical evolution of this condition into more aggressive cancer lesions such as basal cell carcinoma and squamous cell carcinoma[7]. In the pathogenesis of AK, an

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increased activity of cyclooxygenase enzymes (both COX-2 and COX-1) at the keratinocyte level plays a relevant role[8,9]. In addition, the use of topical anti-cyclooxygenase drugs, such as diclofenac[10] and more recently piroxicam[11], reduces number of lesions and improves the cancerization field in subjects with AK and actinic damage. A film-forming medical device in cream formulation containing organic and inorganic sun-filters (50+ SPF) and piroxicam 0.8% (ACTX) has recently become available. This medical device in a pilot open single-center trial has reduced AK lesions after a 6 month treatment period[12].

Study aim

We carried out a non-profit, 3 month, multicenter, assessor-blinded, prospective study in patients with AKs receiving ACTX twice a day to assess the efficacy and tolerability of this medical device in subjects with AK lesions.

Patients and methods

Participants

The study was performed in six dermatology clinics in Italy. The study was approved by the human research committee of each participating institution, and written informed consent was requested and received from all subjects in the study. The study was carried out between April 2016 and January 2017. Eligibility criteria included an age of at least 18 years and the presence of multiple AK lesions on the face, scalp, trunk or extremities. Patients were excluded from the study if they had recently received previous treatments interfering with the evaluation of the treatment area (topical medications, immunosuppressive or immunomodulating agents, phototherapy, oral retinoids, or other therapies for AKs). Pregnancy and breast-feeding were also exclusion criteria. A total of 70 subjects with at least three AK lesions on the scalp or face were enrolled. All patients were instructed to self-apply the product on the target AK lesions as well as on the perilesional field cancerization in a pre-specified 35 cm^2 area; patients were also advised to avoid sun exposure, although they didn't need to apply additional sunscreen in the morning because high protection and broad spectrum sunscreen was already contained in this medical device formulation.

Outcomes

The primary outcomes of the study were the clinical evolution of number of AK lesions on a target zone area defined as the area with the highest number of AK lesions and the evolution of dermoscopy features of the target lesion, assessing erythema, scaling, pigmentation, and follicular plug, using a 5 point score (from 0 to 4 for each item; maximum score: 16). Lesion count and dermoscopy score were assessed in a blind fashion evaluating digital color high definition images performed at each visit and coded in a blinded fashion. A secondary outcome was the Investigator Global Score (IGS), according to Nelson *et al.*[10], of clinical evolution of the target area using a 7 point scale from: -2 (significantly worse) to +4 (completely cured), with 0 score indicating no changes in comparison with baseline. IGS was evaluated in an open fashion. Subjects were instructed to apply the cream twice daily on the target area, using one finger-tip unit (0.5 g) for the treatment of a 35 cm^2 area.

Ethics

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with Good Clinical Practice Guidelines. All patients provided signed informed consent. (Trial ID: ISRCTN72020277).

Statistical analysis and sample size

Statistical analysis was performed using GraphPad statistical software version 13.0 (La Jolla, CA, USA). Continuous variables were expresses as mean ± standard deviation (SD). The primary endpoints of the trial were the evolution of AK mean number at the target area and the dermoscopy score from baseline and after treatment in the target lesion. The paired *t* test and the Wilcoxon test were used for the analysis of the study outcomes. We calculated the 95% confidence intervals of the difference in all the variables evaluated. Sample size calculation was performed calculating the difference in AK lesion number between baseline and end of the treatment. With an effect size (Cohen's *d* value) of 0.35, with an alpha value of 0.05 and a power of 90% a total of at least 70 subjects should be enrolled to detect this difference. The sample size was calculated using G-Power statistical software version 3.9 (Kiel, Germany). A *p*-value of $<.05$ was considered as significant.

Results

All but one subject (40 men and 30 women, mean age 72 years) concluded the study period. Subjects' characteristics are presented in Table 1. One subject was withdrawn prematurely due to non-compliance with the treatment. At baseline the mean (±SD) number of AK lesions in the target area was 7.0 (5.9) with a median value of 5 and the dermoscopy score of the target lesion was 7.0 (2.3) with a median value of 7.0. The Olsen grade[13] at baseline was: Grade 1: 29%; Grade 2: 61% and Grade 3: 10% of the lesions. ACTX treatment reduced AK lesions to 3.2 (2.9), ($p = .0001$; Wilcoxon Test), representing a 55% relative reduction (mean difference −3.8; 95% CI from −2.7 to −4.8) (Figure 1). Dermoscopy score was reduced to 3.3 (2.5) ($p = .0001$) (a reduction of 53%) (mean difference −3.7; 95% CI from −3.1 to −4.2) (Figure 2). The IGS after ACTX treatment was 1.9 (1.1), with a median of 2.0. A total of 86% of subjects showed a clinical improvement of IGS (≥1) at month 3. A very significant/complete clearance score (score +3 or +4) was reported in 42% subjects. Figure 3 shows three subjects and the respective target areas before and after treatment with the active cream. No change or a worsening of AK lesions was observed in 14% of the subjects. The product was well tolerated. No serious adverse events were reported during the

Table 1. Subjects' characteristics at baseline.

Gender	
Men, *n* (%)	40 (57)
Women, *n* (%)	30 (43)
Age, years	
Mean	72
Range	48–90
AK duration, months	
Mean	15.57
Range	5–24
Baseline number of AK lesions	
Mean	7.0
Range	3–27
Olsen grade	
Grade 1, *n* (%)	140 (29)
Grade 2, *n* (%)	296 (61)
Grade 3, *n* (%)	49 (10)
Anatomical site (of a total of 485 lesions)	
Face	251 (51)
Scalp	130 (27)
Trunk	59 (12)
Upper extremities	10 (3)
Lower extremities	35 (7)

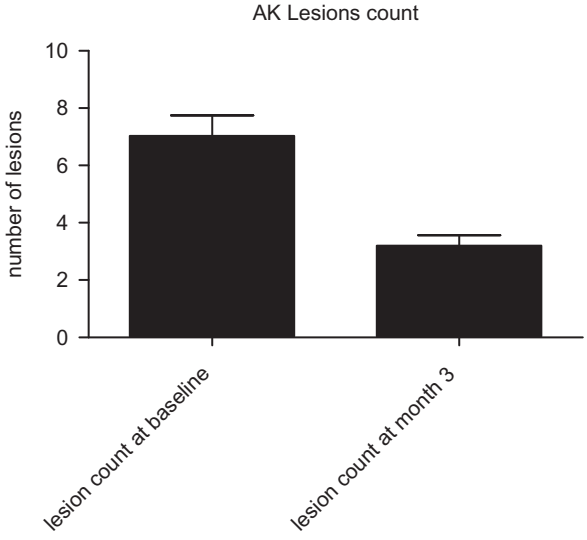

Figure 1. Evolution of mean number of AK lesions in the target area ($p = .0001$ vs. baseline; paired *t* test).

duration of the trial. In particular, no dry skin in the application site was reported. Three subjects reported mild to moderate transient skin rash after application of the cream.

Discussion

AK treatment is based on many different therapy options[14]. A major distinction is made regarding lesion-targeted (i.e. cryotherapy, curettage) and field-targeted treatments (i.e. photodynamic therapy)[15]. Topical therapy is a suitable and effective approach when multiple AKs should be managed due to the field cancerization effect[16]. In addition, topical treatments are effective in treating both clinical and subclinical lesions[17]. The chemo-preventive effect of Nonsteroidal anti-inflammatory drugs (NSAIDs) on non-melanoma skin cancers has been well demonstrated[18]. NSAID efficacy is related to their inhibitory effect on the increased activity of COX-1 and COX-2 enzymes in skin tumor tissue, induced by UVB exposure, causing skin inflammation[19]. The use of topical diclofenac reduces AK lesions[20]. Piroxicam is an enolic

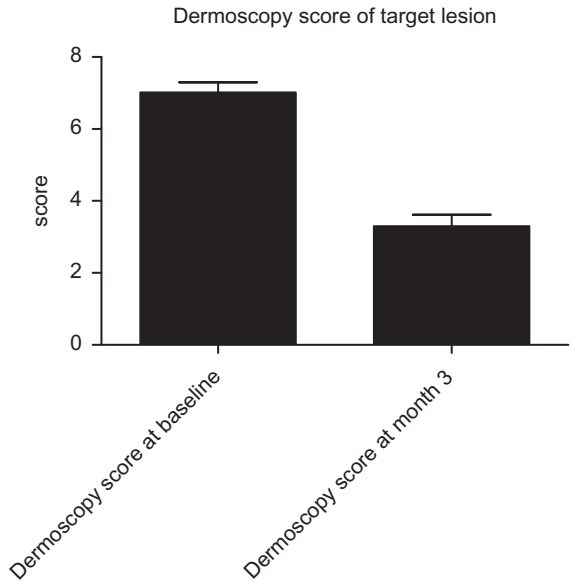

Figure 2. Evolution of dermoscopy score of the target lesion in the target area ($p = .0001$; vs. baseline; paired *t* test).

benzothiazine and a potent member of the oxicam series, structurally different from diclofenac[21]. In contrast with diclofenac, piroxicam is characterized by a potent COX-1 inhibitory action[22]. The agent suppresses the synthesis of pro-inflammatory enzymes as prostaglandins and tromboxanes, and inhibits polyamine production by blocking ornithine decarboxylase induction[23]; these pathways are involved in skin carcinogenesis[24].

In contrast to diclofenac, piroxicam induces apoptosis and suppresses metalloproteinase 2 and 9 activities[25,26], the most prominent proteinase families associated with tumorigenesis[27]. Piroxicam also blocks the UVB-induced AP-1 production[28] with mechanisms independents of cyclooxygenase-2 inhibition. Sun protection strategies are considered mandatory in subjects with AK or more generally with documented actinic damage[29]. Controlled clinical trials have shown that sun filters in AK subjects prevent the appearance of new AK lesions[30,31]. Commonly in trials evaluating the efficacy of diclofenac in AK, subjects are advised to also use sunscreen and to avoid excessive exposure to the sun[32]. The medical device evaluated in this study, containing piroxicam and sun filters, could have the advantage of improving subject adherence to the therapy. In a long-term, single-center study in patients with AKs treated with a 6 month course of sunscreen (50+) and piroxicam 0.8% gel a complete response was achieved on 38 of the 69 treated lesions (55%)[8]. Clearance of AK lesions was maintained at the end of the 12 month follow-up period in completely healed patients. This medical device was very effective in a subject with a history of Kaposi sarcoma and multiple AK lesions unresponsive to previous ablative treatments[33].

In our study, we observed that after 3 months of therapy a significant reduction of AK lesions in the target area was achieved (−55%). Forty-two percent of treated subjects had a very significant/complete clearance score (score +3 or +4). The results we observed in the present study seem in line with or better in comparison with the data available for diclofenac 3%. The use of diclofenac 3% in 2.5% hyaluronic

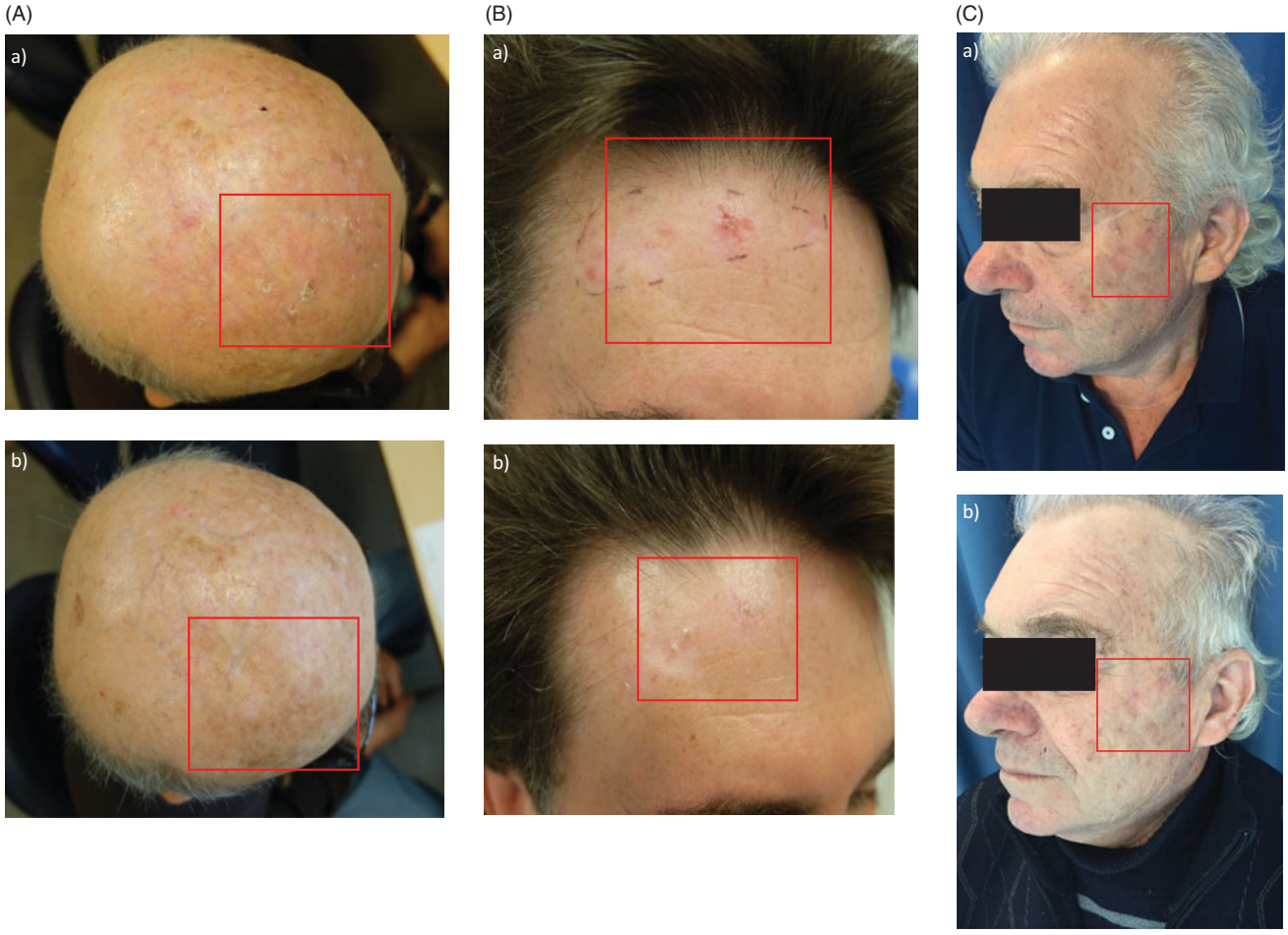

Figure 3. (A) Subject 1: before (a) and after treatment (b). (B) Subject 2: before (a) and after treatment (b). (C) Subject 3: before (a) and after treatment (b). Target areas delimited by red squares.

acid (HA) gel in a vehicle controlled trial has shown, after 3 months of treatment, a reduction of 37% of the number of AK lesions (from 9.8 at baseline to 6.2) at the end of the follow up treatment[34]. The protocol of our study was designed with the final evaluation at month 3, just at the end of the treatment period. This time endpoint evaluation could underestimate the real efficacy of the tested product regarding lesion clearance. In diclofenac treated patients (Solaraze SPC*) it is stated that the usual duration of therapy is from 60 to 90 days. The complete healing of the lesion may not be evident for up to 30 days following cessation of therapy[35]. In comparison with diclofenac and hyaluronic acid gel, the medical device used in the present study has two main components: sunscreen and the COX-1/COX-2 inhibitor piroxicam. It is well known that the use of sunscreen could be associated with a reduction in AK lesions[36]. As underlined previously, patients during treatment with diclofenac 3% should avoided direct sunlight, including solariums[32] and this was not the case with this medical device due to the presence of sun filters. However, so far no head-to-head trials are available to evaluate and compare the efficacy of these two topical strategies for the treatment of AK.

Some study limitations should be taken in account in evaluating the study results. First, this was not a double-blind trial. However, to increase the internal validity of the trial we performed an assessor-blinded evaluation of the primary outcomes. A second aspect was the relative short period of study treatment (3 months). However, the goal of our study was to evaluate in the short term the clinical efficacy of this medical device. Finally, this was not a comparative trial. Therefore, it is not possible to state whether this medical device containing piroxicam and sunscreen has superior, equal or inferior clinical efficacy in comparison with simple sunscreens or topical diclofenac. Specific comparative trials should be performed in this regard.

Conclusion

In this multicenter, assessor-blinded trial, the use of a film-forming medical device with sun detection and anti-inflammatory action shows efficacy in reducing AK lesions and improving the dermoscopy aspect of the target lesion in 86% of treated subjects. Our experience confirms that 3 month treatment with this medical device is efficacious and well tolerated in clearing AK lesions and improving field cancerization. A head-to-head trial evaluating the efficacy of this medical device in comparison with diclofenac is warranted to establish whether this therapeutic approach could offer additional advantages in terms of AK lesion reduction compared to an established topical treatment.

Note

*Solaraze is a registered trade name of Almirall S.A, Barcelona, Spain.

Transparency

Declaration of funding

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Author contributions: All authors participated in study design, data collection, data interpretation, development, review, and final approval of the manuscript. M.P. and M.M. performed the assessor-blinded evaluation of coded pictures for the calculation and scoring of primary outcomes.

Declaration of financial/other relationships

M.P., C.G., S.M., P.S.P., S.L., G.P., V.C., G.T., G.S., E.C., L.D., and M.M. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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