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A 9-month, randomized, assessor-blinded, parallel-group study to evaluate clinical effects of film-forming medical devices containing photolyase and sun filters in the treatment of field cancerization compared with sunscreen in patients after successful photodynamic therapy for actinic keratosis

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Research letter

A 9-month, randomized, assessor-blinded, parallel-group study to evaluate clinical effects of film-forming medical devices containing photolyase and sun filters in the treatment of field cancerization compared with sunscreen in patients after successful photodynamic therapy for actinic keratosis

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Dear Editor, Actinic keratosis (AK) is a precancerous lesion caused by chronic exposure to sunlight.[1] Photodynamic therapy (PDT) is a well-established therapeutic approach for the treatment of AK.[2] PDT is effective in clearance of AK lesions and improving field cancerization.[3] However, > 20% of patients need a second procedure in the following months after the first treatment.[4] After PDT, sun protection strategies are important in order to reduce the risk of new lesions or the need for another session of PDT.[5] A film-forming medical class II device containing photolyase, a DNA-repairing enzyme with a broad photoprotection action (Eryfotona® AK-NMSC Fluid; Isdin, Barcelona, Spain), has been shown, in open clinical studies, to induce both subclinical and clinical improvements in patients with AK.[6,7] This product seems to be more effective than sunscreen products in improving clinical outcomes (clearance of AK lesions) and field cancerization.[8] So far, there are no published controlled data regarding the use of Eryfotona vs. sunscreen in patients with AK after successful PDT treatment. We assessed the efficacy of Eryfotona vs. sunscreen in the development of new AKs in patients with AK after successful PDT. In a prospective, two-arm, parallel-group, 9-month, assessor-blinded, comparative trial, immunocompetent patients between the age of 40 and 85 years with multiple AKs of the face and/or scalp suitable for PDT treatment, were enrolled. This study (clinical trial number: ISRCTN12347628) was conducted between January 2014 and June 2015. After obtaining institutional review board approval and written informed consent from the participants, 30 patients (22 men; mean age 69 years) with a total of 225 AK lesions (7·5 lesions per patient) were included. Exclusion criteria were age < 18 or > 75 years, presence of skin tumours, xeroderma pigmentosum and a history of skin conditions other than AK which might interfere with the study evaluations. Patients were randomized 1 : 1 to Eryfotona (n = 15) or to sunscreen (n = 15) Sunscreen SPF 50+ (Fotoprotector, ISDIN, Barcelona, Spain). The primary outcome of the study was the evolution of new AK lesions in the previous PDT-treated area or in another area. The secondary outcome of the study was the need to perform new PDT or other lesion-targeted or field-cancerization targeted therapies. Eryfotona or sunscreen were applied in the treatment evaluation area (scalp and face) for nine consecutive months, in the morning and 4–6 h later. For each application, patients were instructed to apply a total of 2·5 fingertip units for both products. All patients completed the trial. Table 1 summarizes the patient demographics and AK characteristics at baseline. At baseline, the mean ± SD number of AK lesions was 6·6 ± 2·8 in the Eryfotona group and 8·4 ± 3·0 in the sunscreen group. All patients underwent one standardized session of methylaminolaevulinate PDT using a 630-nm light-emitting diode lamp at 37 J cm^{-2}. Immediately after PDT (evaluation performed 2 weeks after the procedure) mean ± SD residual lesions were 2·0 ± 2·0 in the Eryfotona group and 0·6 ± 0·5 in the sunscreen group (nonsignificant). A progressive increase of AK lesions was observed in the sunscreen group, with a mean ± SD number of lesions of 3·6 ± 3·8 at the end of study period (month 9). In contrast, a significant reduction of AK lesions was observed at month 9 in patients in the Eryfotona group, with a mean ± SD number of lesions of 1·0 ± 1·1 in comparison with baseline and with the comparator group ($P < 0·01$). Evolution of new AK lesions after PDT is shown in Figure 1. In the sunscreen group, 13 of 15 patients (87%) presented new AK lesions during the study: in 10 patients new lesions appeared in the area previously treated

Table 1 Patient demographics and actinic keratosis (AK) characteristics

	Eryfotona group (n = 15)	Sunscreen group (n = 15)	P-value
Sex (female/male)	5/10	3/12	NS
Mean ± SD age (years)	71 ± 2·5	68 ± 3·0	NS
Skin type (n)			
I	0	0	NS
II	5	9	
III	10	6	
Baseline AK lesion count (mean ± SD)	6·6 ± 2·8	8·4 ± 3·0	NS
AK lesion after PDT	2·0 ± 2·0	0·6 ± 0·5	NS
Duration of AK years (mean ± SD)	7 ± 8	7 ± 9	NS

NS, nonsignificant; PDT, photodynamic therapy.

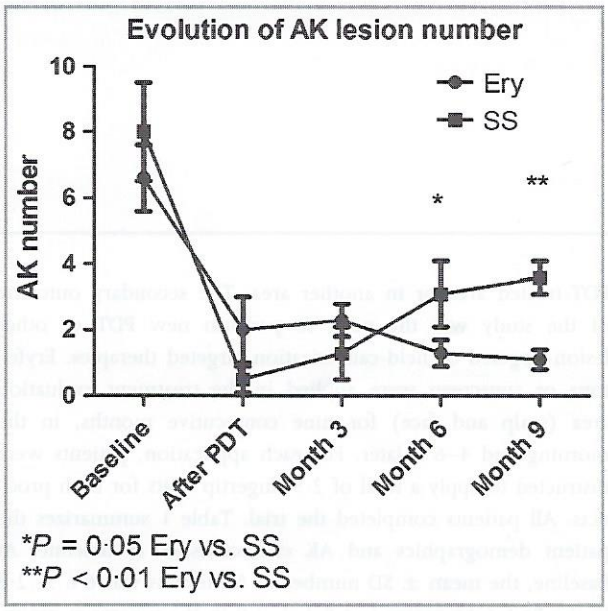

Fig 1. Evolution of actinic keratoses (AK) in Eryfotona (Ery) and sunscreen (SS) groups during the study period. PDT, photodynamic therapy.

with PDT and in three new areas. During the 9-month treatment period no patients in the Eryfotona group needed a new PDT session or another field-targeted treatment. In contrast, 10 (67%) patients in the sunscreen group needed a new PDT session ($n = 5$) or a field-targeted treatment [ingenol mebutate; $n = 5$ ($P < 0{\cdot}01$, Fisher's exact test)]. No adverse skin events related to the study products were observed during the trial in any of the groups. Sun protection is a mandatory strategy in all patients with AK, independent of the specific treatments chosen.[9] Photolyase is a very effective DNA repair enzyme.[10] It is able to repair rapidly specifically ultraviolet-induced DNA damage.[11] Photolyase specifically converts dimerized pyrimidines back into their original monomeric form.[12] In order to induce DNA repair in the epidermis of skin treated with photolyase, exposure to visible blue light (450–495 nm) is needed in order to photoreactivate the enzyme.[13] The long-term use of Eryfotona has been shown to be effective in patients with xeroderma pigmentosum, reducing the appearance of new AKs and nonmelanoma skin cancers.[14] In our study we found that, compared with sunscreen, Eryfotona improves the clinical outcomes in patients with AK after PDT treatment. In particular, no patients treated with Eryfotona needed a new PDT session or other field-targeted therapies in the 9-month observational period of the trial, whereas this was necessary in 66% of the sunscreen-treated group. A study limitation should be taken into account in evaluating the results of our study. The trial was not a double-blind study. The texture of Eryfotona (a fluid cream) is different to that of the majority of sunscreens available on the market; therefore, a double-dummy study design should have been adopted in order to carry out a double-blinded trial. In order to increase the internal validity of our trial, we overcame this limitation by adopting an assessor-blinded clinical evaluation approach with regard to the trial outcomes, that is, evolution of AK lesions and decision to perform a second PDT session or other field-targeted treatment. Our study shows that, compared with the use of sunscreen only, in patients with multiple AK lesions undergoing successful PDT, daily application of a medical device with photoprotection and photorepair actions is associated with a significant reduction in new AK lesions and no need for additional PDT or another field-targeted treatment.

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References

1 Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). *J Am Acad Dermatol* 2000; **42**: S11–17.
2 Dragieva G, Hafner J, Dummer R *et al.* Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation* 2004; **77**:115–21.
3 Vatve M, Ortonne JP, Birch-Machin MA *et al.* Management of field change in actinic keratosis. *Br J Dermatol* 2007; **157**(Suppl. 2): 21–4.
4 Szeimiesa RM, Karrera S, Radakovic-Fijanb S *et al.* Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol* 2002; **47**:258–62.
5 Ferrándiz C, Fonseca-Capdevila E, García-Diez A *et al.* Spanish adaptation of the European guidelines for the evaluation and treatment of actinic keratosis. *Actas Dermosifiliogr* 2014; **105**:378–93.
6 Puig-Butillé JA, Malvehy J, Potrony M *et al.* Role of CPI-17 in restoring skin homoeostasis in cutaneous field of cancerization: effects of topical application of a film-forming medical device containing photolyase and UV filters. *Exp Dermatol* 2013; **22**:494–6.
7 Laino L, Elia F, Desiderio F *et al.* The efficacy of a photolyase-based device on the cancerization field: a clinical and thermographic study. *J Exp Clin Cancer Res* 2015; **34**:1.
8 Piaserico S, Milani M. Efficacia clinica della fotoliasi topica dopo terapia fotodinamica in soggetti con cheratosi attiniche: studio prospettico randomizzato intrapaziente. *G Ital Dermatol Venereol* 2012; **147**(Suppl. 2):109.
9 Naylor MF, Boyd A, Smith DW *et al.* High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 1995; **131**:170–5.
10 Sancar A. Structure and function of DNA photolyase and cryptochrome blue-light photoreceptors. *Chem Rev* 2003; **103**:2203–38.
11 Thoma F. Light and dark in chromatin repair: repair of UV-induced DNA lesions by photolyase and nucleotide excision repair. *EMBO J* 1999; **18**:6585–98.

12 Kao YT, Saxena C, Wang L *et al.* Direct observation of thymine dimer repair in DNA by photolyase. *Proc Natl Acad Sci USA* 2005; **102**:16128–32.
13 Weber S. Light-driven enzymatic catalysis of DNA repair: a review of recent biophysical studies on photolyase. *Biochim Biophys Acta* 2005; **1707**:1–23.
14 Giustini S, Miraglia E, Berardesca E *et al.* Preventive long-term effects of a topical film-forming medical device with ultra-high UV protection filters and DNA repair enzyme in xeroderma pigmentosum: a retrospective study of eight cases. *Case Rep Dermatol* 2014; **6**:222–6.

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