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REVIEW

New Vision in Photoprotection and Photorepair

Marie-Therese Leccia · Celeste Lebbe · Jean-Paul Claudel ·
Mridvika Narda · Nicole Basset-Seguin

ABSTRACT

Chronic exposure to solar radiation is associated with an increased incidence of skin cancer worldwide and more specifically with non-melanoma skin cancers and actinic keratosis. At the cellular level DNA damage is the main event following ultraviolet (UV) exposure. The kind of lesions produced depends on the wavelength and the energy profile of the radiation, with different photoproducts being formed as a result. Although endogenous DNA repair mechanisms are somewhat effective in repairing DNA, some DNA damage persists and can accumulate with chronic exposure. UV protection strategies, such as sunscreen use, are important in limiting further DNA damage. Several published studies have demonstrated the protective effect that regular use of sunscreen can have against the development of skin cancers. Newer options that aim to help repair damaged DNA may have an important role in reducing the incidence of chronic sun exposure-related photoaging and non-melanoma skin cancers. Photolyase, which is capable of repairing cyclobutane dimers formed as a result of DNA irradiation, is one such novel ingredient. In the first part of this paper we review the rationale for a combined treatment approach of photoprotection and photorepair with photolyase. In the second part we evaluate several published clinical studies, which suggest a beneficial effect in preventing new skin lesions in photodamaged skin. A strategy of photoprotection plus photorepair appears to be relevant for all persons with a high level of solar exposure and those at a higher risk for developing skin cancers.

M.-T. Leccia
Service de Dermatologie, Centre Hospitalier
Universitaire (CHU) de Grenoble, La Tronche,
France

C. Lebbe · N. Basset-Seguin (✉)
Policlinique de Dermatologie, Hôpital Saint Louis,
Paris, France
e-mail: nicole.basset-seguin@aphp.fr

J.-P. Claudel
Cabinet de Dermatologie, Tours, France

M. Narda
Innovation and Development, ISDIN, Barcelona,
Spain

INTRODUCTION

The omnipresent nature of ultraviolet (UV) radiation in our lives and increasing time spent outdoors has led to a rise in UV-exposure related

pathologies. In a 2006 report, the World Health Organization (WHO) estimated that around 1.5 million disability-adjusted life years were lost annually through the direct and indirect effects of excessive UV exposure worldwide [1]. Skin cancer is the predominant pathological manifestation resulting from overexposure to UV radiation, with non-melanoma skin cancers (NMSCs) representing more than 90% of all skin cancers. The WHO recently reported that up to 2–3 million NMSCs are diagnosed worldwide each year, with the USA reporting up to 200,000 new cases of squamous cell carcinoma (SCC) annually, representing 20% of all new skin cancers [1, 2]. Due to reporting requirements, precise figures for NMSCs in Europe are difficult to ascertain, but the literature includes estimates of 78,000 cases annually in the UK, and 41,000 in Germany [3]. New strategies to ameliorate the impact of chronic UV damage and thus skin cancers and photoaging are needed.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

UV-MEDIATED SKIN DAMAGE

Chronic exposure to solar radiation is the most important environmental factor involved in photoaging and in the pathogenesis of skin cancers, especially actinic keratosis (AK) and SCC. The role of UV radiation in the pathogenesis of basal cell carcinoma (BCC) and melanoma appears more complicated, but is probably related to acute exposure during childhood and adolescence.

Cellular DNA is the major cellular target in UV carcinogenesis, through the induction of photo-induced direct and indirect damage that can induce mutations [4]. The chemical nature and the formation of DNA lesions greatly depend on the wavelength of incident photons. UVB radiation, the most energetic and mutagenic component of solar radiations, is directly absorbed by DNA and induces dimeric photoproducts between adjacent pyrimidine bases, namely cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidone (6-4PP)

photoproducts (Fig. 1) [5]. A causal relationship has been established between UVB DNA lesions and photocarcinogenesis, as indicated by the high proportion of p53 mutations characterized by cytosine (C)–thymine (T) transitions at dipyrimidine sites and CC–TT tandem base substitutions detected at bipyrimidine sites in skin tumors [6]. Although less energetic than UVB, UVA is at least 20-fold more abundant in natural sunlight and is equally involved in skin carcinogenesis. The cytotoxic action of UVA radiation is strongly oxygen dependent and induces oxidative DNA lesions, mainly 8-oxo-7, 8-dihydro-2′-deoxyguanosine [7, 8]. However, UVA also induces large amount of CPDs in whole human skin through a mechanism which differs from that triggered by UVB [9]. In contrast to UVB, UVA preferentially induces the production of CPDs at TT sites without any detectable formation of 6-4PP photoproducts. Interestingly, the research group [9] showed in a subsequent study [10] that the rate of removal of UVA-induced CPDs was lower than those produced by UVB and that more UVA lesions were accumulated in whole skin, emphasizing the crucial role of UVA in skin carcinogenesis. UVA photons are partly absorbed by the upper layers of skin, yet they are also able to penetrate deep into the dermis, whereas UVB radiation is mostly absorbed by the epidermis. The limited capacity of human skin to repair UVA-induced
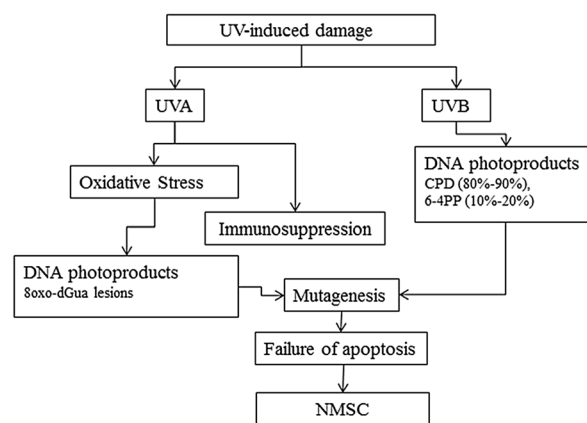

Fig. 1 Ultraviolet (*UV*) radiation-induced changes ultimately lead to non-melanoma skin cancers (*NMSC*). *CPD* Cyclobutane pyrimidine dimer, *6–4PP* pyrimidine (6–4) pyrimidone

DNA damage is responsible for the accumulation of UVA-induced DNA lesions in the whole human skin.

The role of unrepaired DNA lesions comes into play when these stereochemically unwieldy alterations lead to replication errors that result in mutations. Although the majority of spontaneously occurring mutations that accumulate in somatic cells throughout a person's lifetime may go unnoticed without having any major effects, some can alter key cellular functions, leading to cancer and aging [11]. Different mutations might evolve differently in sun-exposed skin depending on clonal expansion and the positive selection of the cells involved. At any given time sun-exposed skin has been described as a patchwork of thousands of evolving clones with over one-quarter of the cells carrying cancer-causing mutations while maintaining the physiological functions of the epidermis [11]. Loss of p53-induced protective mechanisms results in the accumulation of additional mutations and chromosome instability, culminating in abnormal keratinocyte proliferation and resulting in a gradual upregulation of the pre-tumorigenic (AK) and tumorigenic (SCC) lesions when compared to normal skin and non-tumorigenic lesions [12].

UV AND NMSC

Worldwide, NMSC incidence ranges from the highest rates in Australia (> 1000/100,000 person-years for BCC) to the lowest rates in parts of Africa (< 1/100,000 person-years for BCC). In Europe the highest incidence rates for BCC and SCC have been reported in the UK [13]. In France, BCC and AK represent 1 and 5% of dermatological consultations, respectively [14]. Sixty percent of SCC arise from a lesion diagnosed clinically as a solar keratosis in the previous year [15]. The relative risk of malignant transformation of a pre-existing AK lesion is 2.2-fold higher than the risk of SCC in normal skin [16]. SCCs are the most frequent (58%) skin neoplasm coexisting with AK, followed by BCC (30%) [17]. Up to 69% of SCCs and 53% of AK lesions are reported to be positive for p53 mutations [18]. There is an increase in mutation burden with the progression from normal UV-exposed skin to AK and then to SCC [19]. The development of skin SCCs involves a large number of chromosomal aberrations, with the most significant of mutated genes being *TP53*, *NOTCH1-2*, *FAT1*, *MLL2* and *KNSTRN* [20–24].

In contrast, BCCs arise with no established precursor and present with a high mutation rate. A high prevalence of UV signature. BCCs are driven by the Sonic Hedgehog (Hh) pathway, with a high frequency of mutations of *PTCH1* (73%), *SMO* (20%) and *SUFU* (8%). Other less frequently altered driver genes include *TP53*, *MYCN*, *PPP6C*, *STK19 LATS1*, *ERBB2*, *PIK3CA* and the *RAS* family [25–29].

Due to their high prevalence, NMSCs are altogether among the five most expensive cancer diseases according to the Medicare Beneficiary Survey 1992–1995 (Medicare being the health-insurance provider for Americans administered by the US government) [30]. Recent temporal trends investigated in Australia, Canada and the USA indicated a more than twofold increase in NMSC prevalence, as well as a higher frequency on sun-exposed areas, implicating long-term, repeated UV radiation exposure as a major causal factor. Some countries also report an association between increasing incidences of NMSCs with decreasing latitude, i.e. higher UV radiation levels [13].

When UV protection strategies are being developed, high-risk populations must be given special consideration. Risk factors include Fitzpatrick skin type I to III, baldness, male gender, older age, precancerous skin conditions (AK and Bowen's disease), immune deficiency and the frequent use of sunbeds [31]. A higher lifetime exposure to the sun or other sources of UV radiation is clearly associated with a higher incidence of SCCs and BCCs. Outdoor workers run a significantly increased risk for developing NMSCs [32]. A recent analysis of the European multi-center EPIDERM study showed a fourfold increased odds of developing AK among outdoor workers, with the risks increasing with increasing duration of outdoor exposure and health literacy [33].

PHOTOPROTECTION IN THE 21ST CENTURY

Long before epidemiological data on UV-related damage were available, protecting ourselves from the sun came naturally. Traditional practices, such as avoiding sun exposure at peak hours and using wide-brimmed hats or sun umbrellas, were the norm. Today sunscreens with the appropriate sun protection factor (SPF) and protection spectrum are the mainstay of our strategy for reducing UV damage. Typical sunscreen lotions or creams may contain physical and/or organic filters, antioxidant compounds and mixtures thereof. Technologies such as UV absorbers that are added to laundry detergents and potentially increase the UV protection factor by 400% [34] are an interesting approach to be explored further.

The efficacy of sunscreen use in preventing skin cancer is well documented. In 1993 Thompson showed that the regular use of sunscreen (SPF 17) by 588 Australians resulted in fewer new skin lesions and a decrease of solar keratosis compared to subjects who used a base cream minus the active ingredients of the sunscreen [35]. In a US study, the use of sunscreen (SPF 29) reduced the number of AK lesions over 2 years in individuals with lighter skin (skin types 1 and 2) and in those with more initial AK lesions [36]. In another study from Australia, the daily use of sunscreen (SPF 15) over 4.5 years lowered the incidence of SCC significantly versus those who did not apply sunscreen daily, although a similar reduction was not seen in BCC [37]. An Australian trial that compared daily sunscreen use to discretionary sunscreen use reported a decrease in the average rate of acquisition of solar keratoses in the daily sunscreen use group over a 2-year period [38]. In immune-compromised organ transplant recipients, daily use of sunscreen prevented the development of AK and SCC [39]. The WHO recommends the liberal use of a broad-spectrum sunscreen with at least SPF 15 to be re-applied every 2 h, or after sweating, swimming, working, playing or exercising outdoors. However, compliance in regular sunscreen use is a challenge, mainly due to the poor cosmetic qualities and cost of sunscreen products. More recently, concerns about the possible ill-effects of certain constituents of sunscreens have added to the confusion in the public mind regarding the use sunscreens. Additionally, it has been reported that chronic activation of the DNA damage response, mostly in P53 mutated mice model, could be deleterious [40]. However, no study conducted to date has shown that photolyase-induced repair could be harmful.

NEW STRATEGIES IN PHOTOPROTECTION

The future of photoprotection looks promising. The availability of new ingredients has led to considerable improvement in the texture, photostability, water resistance and efficacy of sunscreens. An increasing number of sunscreens offer a more complete protection by including additional ingredients, such as antioxidants, or natural molecules, such as herbal extracts, lichens and biomolecules, as photoprotection alternatives and enhancers [41]. Plankton extract, which contains DNA repair enzyme photolyase, is one such novel ingredient that is being incorporated into sunscreen to complement intrinsic DNA repair and thus expand the photoprotective abilities of sunscreens to photorepair.

The 2015 Nobel Prize in chemistry recognized the work of Aziz Sancar from the University of North Carolina for his work elucidating the mechanisms of DNA repair by photolyase [42]. Photolyase, a class of flavoproteins, repairs DNA photoproducts formed due to UVB exposure through the absorption of blue light [43–46]. Two different kinds of photolyases exist; these are classified as CPD photolyase and (6–4) photolyase based on the class of photoproducts they repair. Although structurally similar, the two photolyases are very specific in their action against one or the other type of photoproducts they repair. Photolyase isolated from the cyanobacterium *Anacystis nidulans* is specific for CPD photoproducts; this phytolyase breaks CPDs and restores the original monomeric state (Fig. 2). Photolyase is not innately present in humans, who possess other
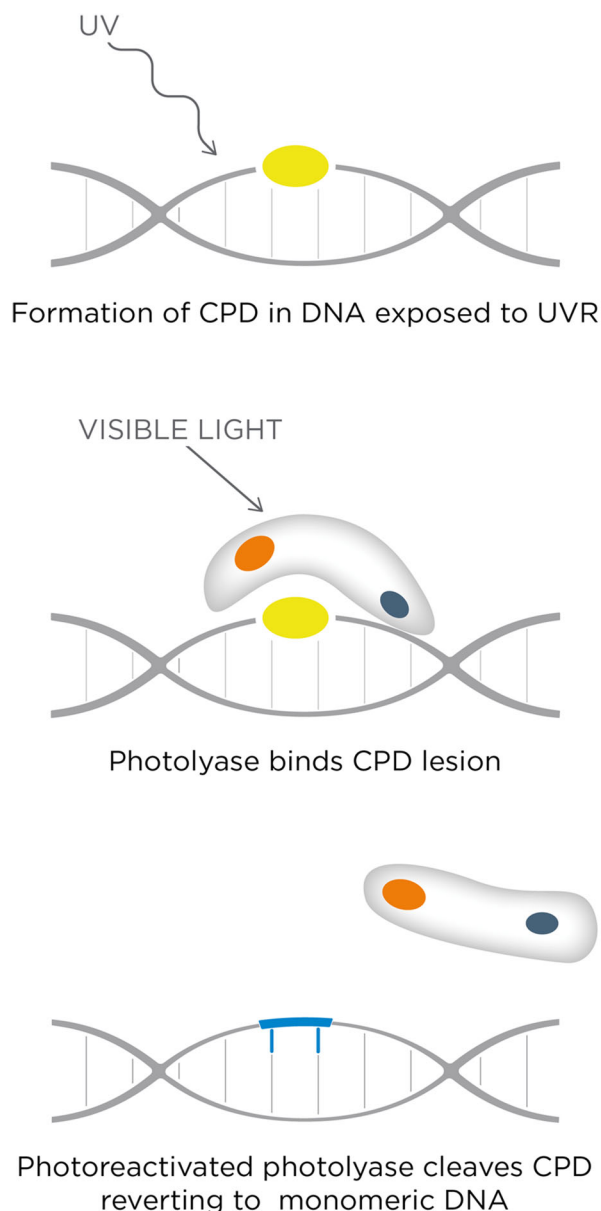
Formation of CPD in DNA exposed to UVR

VISIBLE LIGHT

Photolyase binds CPD lesion

Photoreactivated photolyase cleaves CPD reverting to monomeric DNA

Fig. 2 Cyclobutane pyrimidine dimer (*CPD*) repair by photolyase action following photoreactivation. *UVR* UV radiation

DNA repair mechanisms, such as the nucleotide excision repair (NER) pathway, that are reported to repair UV-induced DNA damage. NER is, however, more effective in recognizing and repairing pyrimidine pyrimidones and relatively inefficient in repairing CPDs [47–50]. CPD repair efficiency further decreases with advancing age. The possibility of incorporating

photolyase—and with it the ability to repair UV-induced DNA damage—in a sunscreen adds an exciting new dimension to the strategic approach against UV damage.

Early work with the DNA repair enzyme T4 endonuclease V showed that topically applied T4N5 encapsulated in liposomes enhanced the removal of DNA photoproducts in human and mouse skin and reduced the incidence of skin cancer in mice [51]. Stege et al. demonstrated that topical treatment of human skin with liposomes containing biologically active photolyase and subsequent exposure to photoreactivating radiation was effective in partially removing UVB radiation-induced CPDs from the epidermis of treated skin areas. A 45% reduction in the number of CPDs was reported in 12 volunteers who used a topical application of a liposome formulation with CPD photolyase followed by exposure to sunlight [52, 53]. Compared to a previous clinical study in xeroderma pigmentosum (XP) patients in whom T4N5 treatment resulted in approximately 20% dimer removal in 6 h, photolyase treatment resulted in the removal of 40–45% of CPDs present in UVB-irradiated normal human skin immediately after photoreactivation, suggesting that photolyase may be more efficient than T4N5 in CPD repair activity [54]. In another study, the topical application of DNA repair enzymes to the sun-damaged skin of patients with XP lowered the rate of new AK lesions and BCCs compared to those using the placebo lotion by 68 and 30%, respectively, during 1 year of treatment [55].

In 2000, Stege et al. concluded their publication with these words "Exogenous application of photolyase differs from conventional photoprotection through its ability to remove damage that has already occurred. This enzyme therapy approach could thus be ideally combined as an after-sun strategy with conventional sunscreens to provide photoprotection and repair at the same time" [52]. At the time, it still remained to be seen whether such a product formulation was feasible, considering the inherent complications of combining UV filters and natural plankton extract, the source of photolyase enzyme. A product that combined plankton extract (source of photolyase) encapsulated in

liposomes to promote epidermal penetration with UV filters with very high SPF protection was ultimately developed and studied in several clinical trials (marketed in Europe as Eryfotona; ISDIN, Barcelona, Spain).

FROM PHOTOPROTECT TO PHOTOREPAIR?

Several clinical trials have been published on the use of a topical product containing the DNA repair enzyme photolyase encapsulated in liposomes and a very high SPF sunscreen, either alone or as an adjuvant therapy, in patients with AK (Table 1). As these studies were conducted with a small sample size and were sometimes lacking a control group, we consider them "proof of concept" studies that, nevertheless, report important results. Puviani et al. reported results from a six-patient trial in which all patients with visible AK lesions on the face and the scalp were treated with the topical product, either as an adjuvant or as sole treatment, applied twice daily as a cream or fluid formulation for 4–8 weeks. Clinical photographs of the skin lesions at baseline and after treatment showed an improvement of the field cancerization and a reduction in the number of AK lesions (Fig. 3) [56].

Another trial was conducted with eight XP patients [57] who were treated with the Eryfotona product for a period of 12 months. The rate of new skin lesions (AK, BCC and SCC) during active treatment and that during the 12 months prior to use of the topical product were compared. The number of new AK, BCC and SCC lesions during the 1-year treatment with the topical product were five, three and zero, respectively; in comparison, there were 14, 6.8 and three lesions, respectively, in the 12-month period prior. These results show a reduction of 65, 56 and 100% in the number of AK, BCC and SCC lesions, respectively, in the XP patients following use of the topical product.

Rstom et al. reported results from a clinical trial with 14 patients aged 45–65 years with Grade I and Grade II AK and other cutaneous signs of actinic damage. AK lesions were documented by clinical photography, optical polarized light dermoscopy and confocal microscopy in vivo. After treatment with the topical product containing photolyase encapsulated in liposomes and very high SPF sunscreen for 120 days, marked clinical improvement was reported, with a reduction of erythema and desquamation for grade I AK lesions [58].

Puig et al. compared the use of the same topical product containing photolyase encapsulated in liposomes to the use of a sunscreen product with comparable SPF protection. Thirteen patients with multiple AK lesions in a sun-exposed skin area were treated for 4 weeks. Clinical assessment, dermoscopy, confocal microscopy and histopathology evaluation showed an improvement in AK lesions after treatment with the Eryfotona product. Erythema, scaling, pigmentation and follicular plugs improved significantly in the Eryfotona-treated group. In contrast, no improvement was noted in the three patients that used the sunscreen. An absence of epidermal atypia and decreased proliferation markers Ki67 and proliferating cell nuclear antigen (PCNA) were reported in 50% of the samples following treatment with the topical cream. The investigators concluded that application of the product containing photolyase in liposomes and UV filters, twice a day for 4 weeks, led to an improvement in field cancerization in patients with AK lesions [59].

Laino et al. [60] assessed the effects of the photolyase product on thermographic parameters, as a secondary aim of their active telethermography study of field cancerization. Active telethermography is a technique used to observe the imaging of a hyperthermic halo (HH) surrounding the tumor. In this 9-month study with 30 patients (27 completed the study), these authors observed the presence of HHs in all patients, with a significant modification of the extension and thermal parameters of these areas after treatment. With treatment, they observed a reduction from a mean halo area of $3.46 \, cm^2$ at baseline to a mean halo area of $0.64 \, cm^2$ at 9 months, with the values of thermal recovery time progressively increasing

Table 1 Summary of clinical studies conducted to date with the finished product Eryfotona, which contains sun protection factor 50 plus photolyase

Study	Study design	Results
Puviani et al. (2013) [56]	6 patients Treated with product as adjuvant or as sole treatment, for 4-8 weeks Assessed with clinical photographs	Improvement of field cancerization, reduction in number of AK
Gaston et al. (2014) [57]	8 patients with XP Treated for 12 months Compared rate of new skin lesions (AK, BCC and SCC) during active treatment vs. the 12 months prior to use of the product	Number of new lesions of AK, BCC and SCC lesions during treatment period: AK, 5; BCC, 3; SCC, 0 Number of lesions before treatment: 14, 6.8 and 3, respectively (65, 56 and 100% reduction, respectively)
Rstom et al. (2014) [58]	14 patients, Grade I-II AK and other signs of actinic damage Treated for 3 months Assessed on clinical photography, optical polarized light dermoscopy and confocal microscopy in vivo	Marked clinical improvement with reduction of erythema and desquamation for grade I AK lesions
Puig et al. (2014) [59]	13 patients Treated for 4 weeks Compared the use of the product with a sunscreen product with comparable SPF Clinical assessment, dermoscopy, confocal microscopy and histopathology evaluation	Improvement in AK lesions after treatment with Eryfotona product. Erythema, scaling, pigmentation and follicular plugs improved significantly in Eryfotona-treated group No improvement in the 3 patients who used sunscreen alone 50% of the samples reported absence of epidermal atypia and decreased proliferation markers Ki67 and PCNA with treatment
Laino et al. (2015) [60]	30 patients (27 completed) Treated for 9 months Telethermography study of field cancerization Secondary aim was to assess effects of the photolyase product on thermographic parameters	Hyperthermic halos present in all patients. Significant modification of extension and thermal parameters after treatment Reduction in halo area with treatment Thermal recovery time increased toward healthy skin values Halo disappeared completely in 5 cases

Table 1 continued

Study	Study design	Results
Eibenshutz et al. (2016) [61]	30 patients Treated for 9 months Randomized, assessor-blinded, controlled clinical trial Compared effects of product vs. SPF 50 + in field cancerization, after PDT	One session PDT reduced mean number of AK lesions to 2.0 in Eryfotona group, 0.6 in sunscreen group Sunscreen group showed increase in number of AK lesions (mean 3.6 lesions),vs. 1 in Eryfotona group No patient in Eryfotona group needed further PDT or other field-targeted treatment; 66% of sunscreen group needed further PDT
Vaño-Galvan et al. (2016) [62]	41 patients, skin phototype II Treated for 6 months Prospective observational study assessing topical product plus cryotherapy	84% reduction in mean number of AK lesions vs. baseline Mean 0.27 new AK lesions present after1 month, 0.76 after 6 months No new lesions in patients who had not required additional cryotherapy sessions More effective in thin AK lesions than in hypertrophic AK lesions 1/3 patients showed complete response; all others, partial response
Navarette-Dechent et al. (2016) [63]	Case series, 9 patients with field cancerization and AK Treated for 3 months, no concomitant treatments, no treatment 3 months prior	All patients had partial response All had at $\geq$ 50% reduction in lesion number Lesion count decreased from 13.4 to 3.1
Moscarella et al. (2017) [64]	36 patients Randomized, double-blind, parallel-group pilot study of the product vs. SPF50 + sunscreen as comparator 6 months Assessed on clinical evaluation, dermoscopy and reflectance confocal microscopy	Both groups significantly improved vs. baseline Mild AK subgroup ($\leq$ 10 lesions) had greater improvement with Eryfotona than did the sunscreen-alone group ($-$ 3.8 vs. $-$ 2.7 lesions, respectively) and fewer new lesions ($+$ 0.01 and $+$ 1.5, respectively)

AK actinic keratosis, *BCC* basal cell carcinoma, *PCNA* proliferating cell nuclear antigen, *PDT* photodynamic therapy, *SCC* squamous cell carcinoma, *SPF* sun protection factor, *XP* xeroderma pigmentosum

toward the perilesional values of healthy skin; in five cases, the halo disappeared completely.

A recent randomized, assessor-blinded, controlled clinical trial compared the effects of the topical product in the treatment of field

Fig. 3 Clinical improvement in the appearance of the actinic keratosis lesions in a 65-year old man after 6 weeks of treatment with a medical device with very high sun protection factor and photolyase. Pictures are reproduced courtesy of Dr. Mario Puviani, Unit of Dermatology and Surgical Dermatology, Sassuolo Hospital, Sassuolo, Modena, Italy. Informed consent was obtained from the patient for being included in the paper

cancerization in comparison with sunscreen (SPF 50+) in patients who had undergone successful photodynamic therapy (PDT) for AK [61]. PDT is a well-established therapeutic approach for the treatment of AK which clears the lesions and improves field cancerization. However more than 20% of patients need a follow-up procedure in following months following PDT treatment as the lesions tend to reappear. Thirty patients with multiple skin lesions who underwent successful PDT were randomized 1:1 into an Eryfotona (Ery) group or sunscreen SPF 50+ (SS) group. All patients underwent one standardized session of methylaminolaevulinate PDT, which reduced the mean number of AK lesions to 2.0 lesions in the Ery group and to 0.6 lesions in the SS group. However, at the 9-month evaluation following PDT, the SS group showed a progressive increase in the number of AK lesions (mean 3.6 lesions); in contrast, the mean number of AK lesions in the Ery group at 9 months was 1. During the 9-month observational period no patient in the Ery group needed an additional PDT session or another field-targeted treatment, whereas 66% of the SS group needed an additional PDT

session [61]. Ery improved, in comparison with sunscreen, the clinical outcomes in AK subjects after PDT treatment. These results suggest that DNA photorepair mechanisms, such as that provided by photolyase, in combination with UV filters may provide a benefit over simple sunscreens.

Vaño-Galvan et al. [62] conducted a prospective observational study in 2016 in which they assessed the performance of the topical product plus cryotherapy in 41 patients with AK and with skin phototype II. Patients who had received PDT in the 6 months prior to study initiation or any AK treatment in the 3 months prior to study initiation were excluded. The product was applied twice daily, starting the day after the first cryotherapy session. At visits at baseline and at 1, 3 and 6 months after treatment initiation, a dermatologist evaluated the need for further cryotherapy. The investigators looked at the number, location and severity of existing lesions and occurrence of new AK lesions or SCCs. After 6 months of treatment they found an 84% reduction in mean number of AK lesions compared with baseline. Regarding the occurrence of new AK lesions, they found a mean number of 0.27 new lesions present after 1 month and 0.76 new lesions after 6 months, with no new lesions in those patients who had not required additional cryotherapy sessions beyond the baseline visit. The treatment was found to be more effective in patients with thin AK lesions than in those with hypertrophic AK lesions. Overall, approximately one-third of the patients showed complete response; all others showed partial response.

The same year, Navarette-Dechent et al. [63] reported a case series of nine South American patients with field cancerization and AK, who were treated for 3 months, with no concomitant treatments; there had also been no treatment in the 3 months prior to study initiation. All patients had partial response and had a minimum 50% reduction in lesion number, with the lesion count decreasing from 13.4 to 3.1, a 76.6% absolute reduction.

In 2017, Moscarella et al. [64] conducted a randomized, double-blind, parallel-group pilot study of the product in which they used a

commercially available SPF50 + sunscreen as a comparator, in 36 patients. After 6 months, both groups showed significant improvement in the endpoints of clinical evaluation, dermoscopy and reflectance confocal microscopy, while in the "mild" AK subgroup ($\leq$ 10 AK lesions in target area at baseline), the Eryfotona group showed a greater improvement than the sunscreen alone group ($-$ 3.8 lesions vs. $-$ 2.7 lesions, respectively) and fewer new lesions ($+$ 0.01 and $+$ 1.5, respectively).

Although it would be desirable to have a randomized, controlled, double-blinded, multicenter clinical trial to better demonstrate the role of photolyase in the product Eryfotona, the authors recognize that conducting such a trial is faced with challenges. However, we do believe that there is sufficient existing clinical data, as discussed above, to suggest that the topical application of a product containing the DNA repair enzyme photolyase in the form of a plankton extract and UV filters with very high SPF may offer a clinically perceptible benefit compared to a classical sunscreen product.

PHOTOREPAIR IN DAILY CARE REGIMEN

Photoprotection with photorepair incorporated in the same product is at the frontier of new strategies in photoprotection today. The difference from conventional photoprotection lies in the fact that photolyase is capable of repairing UV-induced DNA damage that has already occurred, whereas a sunscreen, at best, protects against accruing further damage. In addition, while sunscreens are recommended for use when excessive solar exposure is expected, typically in summer months, a photorepair product should be used all year around to achieve ideal results in reverting CPD-mediated damage. Patients need to be reminded that photolyase is a photoreactive enzyme and needs some light for its activity (though a few minutes of light is sufficient) and that the product should be applied on clean skin before other skincare products are applied. The Eibenshutz study [61] is an example of how it can be combined with PDT treatment for multiple actinic lesions.

Further studies are needed to demonstrate efficacy when used in combination with other AK treatments.

Krutmann et al. in their review of the literature on a topical product containing photolyase and very high SPF UV filters suggested an algorithm for adjuvant photoprotection that recommends the use this product for persons at moderate to high risk, i.e., those with a history of AK, BCC/SCC, organ transplant recipients or other immunosuppressed individuals, and those with clinically relevant photodamage [65]. However, if we consider photocarcinogenesis to be a result of actinic damage accumulated over years of UV exposure, it seems that all at-risk populations for developing NMSC or AK, such as outdoor workers, outdoor sports persons, those with Fitzpatrick skin type < III and/or those with a family history of NMSC and/or risky behavior, such as previous sunburn history or sunbed use, would benefit from a photoprotection and photorepair strategy. Good texture and feel of the product are keys to achieve patient compliance for long-term topical treatments. Improved aesthetic quality with good sensory and tactile profiles should ensure the use of these products as recommended [66].

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