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A Pilot, Prospective, Open-Label Study on the Effects of a Topical Photorepair and Photoprotection Film-Forming Medical Device in Patients with Actinic Keratoses Evaluated by Means of Skin Analysis Camera Antera 3D

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Abstract

Background: Actinic keratosis (AK) is a very common precancerous skin lesion caused by chronic exposure to sunlight. UVA and UVB rays' exposure is considered as the main pathogenic mechanism of keratinocytes alterations and malignant transformations. UVB and UVA cause direct alterations of DNA molecules, such as the formation of cyclobutane-pyrimidine dimers (CPD) and cellular structures damage, in particular membranes, trough free radicals formation. Eryfotona AK-NMSC (Ery) is a film-forming medical device (MD) class II indicated for the prevention and treatment of cancerization field in subjects with AK or non-melanoma skin cancers (NMSC). Ery is characterized by a photorepair action, thanks to its content in photolyase, an enzyme able repairing DNA CPD, and by high broad-spectrum photoprotection (SPF 100+) (Repairsome). Controlled clinical studies have shown that this MD, both in the short and the long term, is able to induce in AK patients sub-clinical and clinical improvements at the cancerization field level.

Study aim: In this pilot, prospective study, we evaluated the effects of 3-month application of this product in 11 subjects with AK through an objective assessment by skin camera ANTERA 3D instrument. The primary endpoints of the study were to evaluate: a) the evolution of the skin haemoglobin content (parameter related to the level of "vascularization" and "inflammation" of the skin lesions) at the level of a target AK lesion, identified and defined at baseline visit and b) the evolution of AK lesion area.

Results: Ery treatment induced a statistically significant and clinically relevant reduction of AK target lesion area (a -75% reduction in comparison with baseline, range: -100%- 50%) and a significant haemoglobin content reduction as soon as after 1 month (-16%, p=0.01) and after 3 months of treatment (-34%, p=0.01) demonstrating an effect of "normalization" of this parameter at the AK target lesion level. The product was well tolerated.

Conclusion: Data from this pilot study suggest that the use of a photorepair and photoprotection film-forming MD in subjects with AK is able to change in the short-medium term, an objectively-assessed parameter such as AK lesion area and the haemoglobin content via spectral analysis suggesting that this strategy could improve the skin area affected by the AK process.

Keywords: Actinic keratosis; Photolyase; Photoprotection; Antera 3D

Introduction

Actinic keratosis (AK) is a precancerous lesion of the skin very frequently caused by chronic exposure to sunlight (UVB and UVA) [1]. AK is now considered a carcinoma in situ representing the initial phase of non-melanoma skin cancers (NMSC) such as squamous cell carcinoma and basal cell carcinoma [2].

The photo exposed areas (scalp, face, back of hands and forearms) are the classic sites of occurrence of such injuries [3]. Chronic exposure to UVA and UVB rays is considered as the main pathogenic mechanisms of keratinocytes alterations and transformations. UVB and UVA cause direct alterations of DNA molecules, such as the formation of cyclobutane-pyrimidine dimers (CPD) and alterations of cellular structures, in particular membranes mediated, by the formation of free radicals [4]. At the level of primary DNA damage caused by UVB is the formation of pyrimidine dimers (CPD) that altering the spatial structure of the DNA double helix are the main source of actinic mutagenic mechanisms [5].

Photolyase is an enzyme found in various organisms (plants, bacteria, animals are not placental) can fix quickly and efficiently the specific CPD which were formed after UV exposure [6]. The topical application of photolyase on human skin after exposure to UVB is able to quickly reduce by 55% the formation of CPD [7]. These data support the rational clinical use of topical product containing photolyase in order to reduce the damage to the DNA by exposure to UV [8,9].

Eryfotona AK-NMSC is a medical devices indicated for the treatment and prevention of field cancerization in patients with AK [10]. Controlled clinical studies have shown that treatment in both the short and the long term with such a product is accompanied by

improvements in the field of cancerization at both sub-clinic and clinical level [11,12].

The objective assessment of the texture of the skin and the concentration and uniformity of skin chromophores can provide important information on the response to medical treatment and are therefore of great importance for dermatological research.

Antera 3D (Miravex, Ireland) is an optical skin scanning device and it consists of a camera connected to a laptop computer via an USB cable and is complemented by proprietary software that runs on desktop computers or laptops with Windows operating system [13]. This device is able to evaluate the changes over the time of melanin, haemoglobin and skin profiles [14]. In more details Anther 3D is based on the acquisition of multiple images obtained with different lighting: diodes at different wavelengths illuminate the skin with the incident light at different illumination direction and the acquired data are used for spatial analysis and multi-spectrum for the reconstruction of the texture of the skin and the analysis of its chromophores. In particular the analysis via dermal ANTERA 3 D allows performing an analysis of the parameters profilometric skin is that of the colorimetric parameters of the skin and skin lesions [15]. This device employs a specific algorithm (Spot-On™) that automatically registers two or more images to one another, by correcting displacements due to different positions of the patient when capturing an image. This algorithm allows comparing "before-and-after" images in an objective manner.

At the moment there are no data available concerning the effects of Ery treatment at actinic keratosis skin lesions levels evaluated with ANTERA 3D.

Patients and Methods

Patients with multiple AK after a baseline evaluation were treated with a topical medical device with very high (109 and SPF 39 UVA) photoprotection action and photorepair action through an enzyme (photolyase), which can repair UV-induced DNA damage, carried in liposomes (Repairsome®) (Eryfotona AK-NMSC, fluid Isdin, Spain). The treatment consisted in the application of the product at the level of the zones with the lesions (usually the face and scalp) twice daily (morning and afternoon). The patient was instructed to use 2 Finger Tip Unit (approximately equal to one gram of product) for each application (treatment of the face and scalp). The study was approved by the institutional review board of the investigator'center and complied with the provision of the Declaration of Helsinki, Good Clinical Practice guidelines and local law and regulations. All participants provided written informed consent to participate in the trial. ANTERA 3D images of a target lesion were performed as the primary outcome of the study evaluating and comparing the content of haemoglobin, expressed in Arbitrary Unit, considering this as a "vascularization" and "inflammation" parameter. To measure haemoglobin, we marked a representative (target lesion) area at baseline. Subsequently, the identical area was automatically marked in the follow-up image, and the concentration and distribution of haemoglobin were calculated by the software. Target lesion was identified at baseline visit as a well-defined AK lesion located in area of the face easy to access for picture documentation. Target lesion area evolution was evaluated calculating the size of the lesion at baseline and after treatment. Evolution of the size area was compared and calculated as % change in comparison with baseline. Treatment lasted 3 months. The clinical and instrumental evaluations were performed at baseline, after 1 and 3 months. Two-tailed Wilcoxon test was applied to compare baseline levels with values at month 1 and at the end of study period. A p value <0.05 was considered statistically significant. According to the characteristic of the study (pilot trial) no formal sample size calculation was performed.

Results

We recruited a total of 11 subjects with actinic lesions, single or multiple, localized to the face and/or head, aged between 50 and 75 years, 8 men and 3 women, mean age 68 years with a Fiztpatrick skin type II. The average number of clinically visible lesions per patient was 7. Target lesion area during application was reduced by 60% and 75% after 1 and 3 months of Ery application (Figure 1).

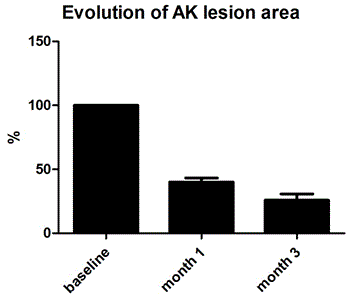

Figure 1: Evolution of AK target lesion area evaluated as % change in comparison with baseline. 1 month vs. Baseline: p<0.05; 3 months vs. Baseline: p<0.01; Wilcoxon Test. X-axis shows time points evaluation. Y-axis reports target lesion area in % (100% area of the lesions at baseline)

The results relating to the variation of the content of haemoglobin of a target lesion are reported in the graph of Figure 1. Application of Ery is accompanied by a statistically significant and clinically relevant reduction of the content of haemoglobin at level of the target lesion both at 1 month (-16%, p=0.001) and after 3 months of treatment (-34%, p=0.0125) (Figure 2).

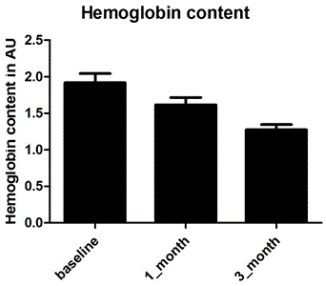

Figure 2: Evolution of hemoglobin content at level of AK target lesion level. 1 month vs. Baseline: p<0.01; 3 months vs. Baseline: p<0.01; Wilcoxon Test. X-axis shows time-point evaluation. Y-axis reports quantity of haemoglobin at the target lesion in Arbitrary Units

The product was well tolerated. There were no reported serious adverse events. Figure 3a and 3b shows two cases with assessment

before and after with ANTERA 3 D at baseline after 1 month and after 3 months of topical application of the product.

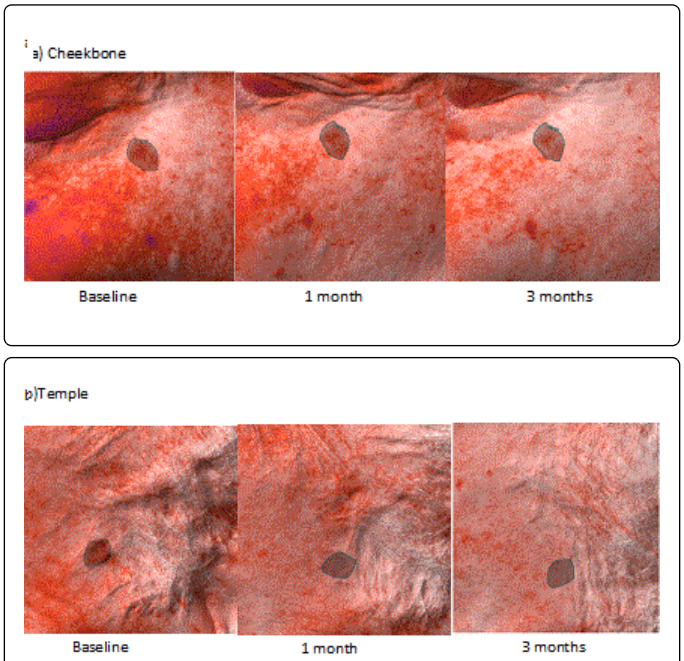

Figure 3: a) Antera 3D assessed target lesions evolution b) Target lesions are marked by the circle

Discussion

Actinic keratosis (AK) is a skin disease very common especially in the elderly population. AK is a condition that increases the risk of developing cancer lesions true as squamous cell cancer and basal cell cancer. For this reason it is important to treat this type of skin lesions. The main pathogenic mechanism of AK is the chronic exposure to UV rays [16]. The actinic damage accumulated due to an alteration in the DNA of keratinocytes either directly (UVB) and indirectly (UVA). The DNA damage induced by UVB radiation sees the formation of cyclobutane-pyrimidine dimers as the main mechanism of genetic damage [17]. The accumulation of these alterations contributes to the appearance of altered keratinocytes that can give rise to cell clones that proliferate in an uncontrolled manner with the formation of lesions of actinic keratosis that may later develop into cancer completely changes such as squamous cell carcinoma and basal cell carcinoma. The photoprotection is an important tool for prevention in patients at risk for actinic damage [18]. Since not much time available topical products that can associate with the photoprotection "passive" an action of photorepair "active" able to help the correction of the actinic damage that gradually accumulates at the level of cheratinociti. Photolyase in particular is an enzyme able to correct in an effective and specific CPD which are formed at the level of the epidermis as a result of UV exposure [19]. Photolyase is not present in mammals [20]. However, the application of the topically photolyase both in experimental animals and in humans has shown that this enzyme is able to repair up to 50% of the CPD which are formed after exposure to UVB [21]. Eryfotona AK-NMSC is a medical device indicated for prevention and treatment of field cancerization in patients with actinic keratosis and non-melanoma skin cancers [22]. This product exerts a photorepair action, through the presence of Anacistis nidulans photolyase formulated in liposomes, and a photo protection action due to the content of very high and broad spectrum (SPF 109 and UVA protection 39) sun-filters. Several controlled trials, and not, have shown that the use of Eryfotona is accompanied by improvements in the field of cancerization evaluated by histology, confocal microscopy, and genetic expression of proteins involved in the regulation of keratinocytes. This product is in the medium and long term has been shown to improve the field of cancerization and to reduce the formation of new lesions in actinic subjects undergoing PDT. To date there were available data on the effects of this topical treatment assessed using objective analysis and spectrophotometric 3D. Some limitations should be taken in account in evaluating the results of the present study. First this was an open non controlled pilot trial. However the primary outcome (change in haemoglobin content at target lesion level) was assessed by operator-independent imaging analysis, therefore the observed changes reflect a real modification of this parameter. A second aspect to be considered is the lack of a controlled treatment. The use of a simple photoprotection product could have induced similar modification we observed. However previous controlled trials comparing the use of Ery in AK patients with simple photoprotection have been demonstrated that photorepair and photoprotection improves at sub-clinical and clinical level AK lesions better than sunscreens. After 3 months of Ery application, the change in haemoglobin concentration we documented was quite relevant (>30%). This result could be interpreted as a reduction in the vascularization level that is increased in AK lesions as documented by histological and microscopy confocal evaluations [23,24]. In fact especially in hypertrophic and clinical visible AK lesions there is an increased vascular density and vasodilation. These data suggest that photorepair and photoprotection combined could have a relevant effect at skin level in AK lesion.

Conclusion

The data from our pilot study show that the use of a product with photorepair and photoprotection actions in subjects with AK is able to change in the short-medium-term average levels of a parameter objectively evaluated by spectral analysis, such as the content of hemoglobin (considered as a marker of “vascularization” and "inflammation") suggesting that the use of this product tends to improve the skin area affected by actinic process. The use was also associated with a relevant clinical improvement with a reduction in the mean number of visible lesions.

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