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Efficacy of different photoprotection strategies in preventing actinic keratosis new lesions after photodynamic therapy. The ATHENA study: a two-center, randomized, prospective, assessor-blinded pragmatic trial

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ABSTRACT

Background: Treatment of actinic keratosis (AK) and field cancerization with photodynamic therapy (PDT) is an effective therapeutic approach with a significant reduction in the number of AK lesions (–75% or more) associated with a significant cosmetic improvement of the photodamaged skin. Recently, also, the daylight PDT (DL-PDT) has proven to be as effective as the conventional PDT (C-PDT), but with a better tolerability. After C-PDT and DL-PDT it is advised to use photoprotection strategies to improve the clinical evolution and prevent the appearance of new AK lesions that usually appear 3–6 months after the last phototherapy session. However, there are no robust clinical data regarding the type of photoprotection to be used (SPF level, duration of treatment, etc.) after successful PDT.

Study aim: The present study (ATHENA trial) evaluated the efficacy and tolerability of a topical product based on 0.8% piroxicam and 50+ solar filters (ACTX), applied twice a day as sequential therapy after C-PDT or DL-PDT on the evolution of AK lesions number compared to the use of very high photoprotection products commonly used in this clinical setting (SPF50+ or SPF100+ associated with photolyase) (Standard Sunscreens: SS group). **Subjects and methods:** This was a multicenter, randomized, two-arm, prospective controlled, assessor-masked outcome evaluation, parallel group (1:1), pragmatic study of 6 months duration in patients with multiple AK lesions suitable for photodynamic therapy. The objectives of the study were the evaluation of the evolution of the number of AK lesions during the period of treatment/application of the study products, and the Investigator global clinical assessment score (IGA score; 4: marked improvement, 3: good, 2: moderate; 1 no improvement; 0: worsening) 2, 3, and 6 months after the last PDT session. A total of 68 subjects (50 men, 18 women; mean age 70 years), 34 assigned to treatment with ACTX and 34 to treatment with SS (17 treated with a SPF50+ and 17 with a photolyase-containing SPF100+ products), were enrolled in the study.

Results: The number of AK lesions present before C-PDT/DL-PDT was 11.8 ± 5.8 in the ACTX group and 12.4 ± 6.9 in the SS group. In both groups, there was a progressive reduction of AK lesions observed at baseline (–86% and –87% after 2 months and –88% and –83% at month 3 in ACTX and in the SS group, respectively). At month 6, AK mean lesion number was 1.8 ± 1.6 in the ACTX and 3.2 ± 2.3 in the SS group; this difference was statistically significant ($p = 0.03$). The IGA score at the end of the study was 3.2 in the ACTX and 2.7 in the SS group ($p = 0.05$). The percentage of subjects with an IGA score of 4/3 (very good or good) was 81% in the ACTX and 55% in the SS group ($p = 0.06$).

Conclusion: In subjects with AK treated with C-PDT or DL-PDT, a "medicalized" photoprotection treatment is associated with a favorable clinical outcome with progressive reduction of lesions. In contrast to a very high photoprotection (SPF50+ or SPF100+/photolyase), the use of piroxicam 0.8%/SPF 50+ is associated with a significantly greater improvement in clinical evolution of AK lesions.

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Background

Actinic keratosis (AK) is a very common *in situ* skin carcinoma originating from keratinocytes[1]. AK is commonly due to excessive non-protected chronic sun exposure[2]. Other risk factors are male gender, old age, and Fitzpatrick I or II photo-type skin[3]. AK lesions appear in general as patches of thick, scaly, or crusting skin in sun exposed area such as face, scalp, and the back of the hands[4]. The presence of AK lesions increases the risk of developing squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)[5]. In fact, the majority of cutaneous SCC arise from pre-existing AK lesions[6]. Around visible AK lesions there are sub-clinical, non-visible sun damage area which could be transformed into clinically visible or recurrent AK lesions and sun-related skin cancers. This process is known as field cancerization[7]. In the skin, field cancerization involves the cluster of alterations observed in a chronically photodamaged skin with several foci of non-melanocytic cutaneous cancers[8]. Treatment of actinic keratosis (AK) and field cancerization with

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photodynamic therapy (PDT) is an effective therapeutic approach with a significant reduction in the number of AK lesions (–75% or more) associated with a significant cosmetic improvement of the photodamaged skin[9]. Recently, also the daylight PDT (DL-PDT) has proven to be as effective as the conventional lamp PDT, but with a better tolerability[10]. Both after conventional and DL-PDT it is necessary to use photoprotection strategies to improve the clinical evolution and prevent recurrence of new AK lesions that usually appear 3–6 months after the last phototherapy session[11]. However, there are no robust clinical data regarding the type of photoprotection to be used (SPF level, duration of treatment, etc.) after successful PDT[12]. A piroxicam-containing sunscreen filters (SPF 50+) cream (Actixicam, Cantabria Labs Difa Cooper, Caronno P, Italy) has demonstrated high efficacy in the treatment of AK lesions[13,14], also in high risk subjects such as solid transplant organ patients[15] and immunodeficient subjects[16]. Piroxicam is a potent cyclooxygenase 1 and 2 inhibitor[17]. This molecule is also able to inhibit the expression of metalloproteinase enzymes[18,19] (MMP2 and MMP9) and possesses anti-oxidant actions[20]. These effects could be relevant to block or counteract the invasion of tumor keratinocytes.

Study aim

In the present study (ATHENA study; trial number: ISRCTN16168548) we evaluated the efficacy and tolerability of a topical product based on 0.8% piroxicam and 50+ solar filters (ACTX), applied twice a day as sequential therapy after conventional or daylight PDT (C-PDT; DL-PDT) on the evolution of AK lesions number compared to the use of very high photoprotection products commonly used in this clinical setting (SPF50+ or SPF100+ associated with photolyase, a DNA-repairing enzyme; Defence Sun 50+, Bionike Italy; Eryfotona AK, Isdin Spain) (Standard Sunscreens: SS group).

Subjects and methods

Study design

We conducted a two-center, randomized, prospective, controlled, assessor-masked outcome evaluation, parallel group (1:1), study of 6 months duration in patients with multiple AK lesions suitable for photodynamic therapy (C-PDT or DL-PDT). To maximize applicability to primary care the trial was designed to be pragmatic, with eligibility criteria facilitating the enrollment of subjects. The local independent ethics committees approved study protocol. The study was designed in agreement to the principles of the Declaration of Helsinki[21] (2014 update). There was no change to the trial protocol after it commenced.

Subjects enrollment and treatment protocol

Eligible subjects were men or women, aged 18 years or more with at least six clinically typical, visible AK lesions on the scalp or face. Non-eligible criteria were history of skin conditions other than AK (i.e. eczema, psoriasis, or xeroderma pigmentosum) or specific AK treatments in the previous 6 months, a positive history of allergy to sunscreen or piroxicam, pregnancy, or breast feeding. A total of 68 subjects (50 men, 18 women; mean age 70 years), 34 assigned to treatment with ACTX and 34 to treatment with SS (17 treated with a SPF50+ and 17 with a photolyase-containing SPF100+ products), were enrolled in the study. Informed written consent was obtained from all patients before their treatment. For allocation of the participants, a computer-generated randomization list was used. C-PDT and DL-PDT sessions were performed according to the standard protocols[22,23] using methyl-aminolevulic acid (MAL) cream 16% (Metvix, Galderma, France) as a photosensitizing agent. For C-PDT sessions, red light source (Aktilite Photocure Oslo) was used, with a peak wavelength of 634 nm, light dose 37 J/cm^2, and irradiance 50 mW/cm^2 at 60 mm distance to the skin surface with a maximum variation over the target area of 10%. MAL cream was applied as a 1-mm thick layer to the entire treatment area under occlusion for 3 h after removal of overlying crusts and scales. DL-PDT sessions were performed according to standardized procedures such as daylight illumination performed between 11 a.m. and 3 p.m. on non-raining days. MAL cream was applied as a 1-mm thick layer to the entire treatment area and left uncovered for 30 min in a dark room, after removal of overlying crusts and scales. DL-PDT were performed in urban environments (latitude 46°North) between April and September. Patients were invited to expose themselves continuously to daylight for 2 h in the hospital garden close to the Clinic. The effective average light dose according to solar database was 50 Jeff/cm^2. At the end of daylight exposure, residual MAL cream was removed, followed by application of an emollient cream. Patients were instructed to avoid daylight for the following 24 h. At baseline AK lesions were counted and mapped and graded according to severity into grade I–III. Treatment with ACTX or SS started 2 weeks after the PDT sessions to ensure complete healing of treated AK lesions.

Study outcomes

The primary objectives of the study were the evaluation of the evolution of the number of AK lesions during the period of treatment/application of the study products after 2, 3, and 6 months after the last PDT session and the Investigator global clinical assessment score (IGA score; 4: marked improvement, 3: good, 2: moderate; 1 no improvement; 0: worsening) evaluated at month 6 in comparison with baseline. AK lesion count and IGA score were evaluated by an investigator unaware of the treatment allocation (ACTX or SS). Secondary outcomes of the study were the percentage of subjects with an IGA score of 4/3 (very good or good) at the end of the trial and the evaluation of local tolerability assessing patient-reported side-effects.

Statistical analysis and sample size

Statistical analysis was performed using GraphPad statistical software ver. 13.0 (La Jolla, CA). Continuous variables were

expressed as mean ± SD. The primary endpoint of the trial was the evolution of AK mean number from baseline (last PDT session) and after treatment. The paired *T*-test, the Wilcoxon, and the Mann-Whitney tests were used for the analysis of the study outcomes (between and within groups). We calculated the 95% Confidence intervals of the difference in all the variables evaluated. This was a superiority trial. In a previous study, Eibenschutz[24] evaluated the efficacy of different sun protection strategies (50+ or 100+ SPF sunscreen) after successful C-PDT. At month 6 after the last C-PDT session AK new lesion number was 3 ± 1. We have hypothesized that AK lesion number at the end of the study period in the ACTX group would be lower in comparison with the control (i.e. 2.0 vs 3.0 with an effect size of 1). Sample size calculation was performed calculating the hypothetical difference in AK lesion number between the two group. With an effect size (Cohen's d value) of 0.4, with an alpha value of 0.05 and a power of 90%, a total of at least 60 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 <0.05 was considered as significant.

Results

Between March 2017 and February 2018, 68 subjects were enrolled and randomized in the trial, 34 to piroxicam/sunscreen (ACTX group) and 34 to standard sunscreen protection (SS group). Table 1 summarizes subjects' characteristics at baseline. The two groups were comparable for the main clinical variables considered. The two groups were also well balanced regarding the distribution of AK grade I/II/III. All but one subject concluded the 6-month trial period. The number of AK lesions present before C-PDT/DL-PDT was 11.8 ± 5.8 in the ACTX group and 12.4 ± 6.9 in the SS group, and there was a reduction to 1.5 ± 1 and to 1.3 ± 1, after the procedures, just before starting the ACTX or the SS treatments. In both ACTX and SS groups, there was a progressive reduction of AK lesions presented at baseline (–86% and –87% after 2 months and –88% and –83% at month 3 in the ACTX and SS group, respectively). At month 6, AK mean lesion number was 1.8 ± 1.6 in the ACTX and 3.2 ± 2.3 in the SS group; this difference was statistically significant ($p = 0.03$) (Figure 1 [f]insert Figure 1 near here[/f]). The IGA score at the end of the study was 3.2 in ACTX and 2.7 in the SS group ($p = 0.05$) (Figure 2 [f]insert Figure 2 near here[/f]). The percentage of subjects with an IGA score of 4/3 (very good or good) was 81% in the ACTX and 55% in the SS group ($p = 0.06$). All the products were well tolerated. One subject (ACTX) did not complete the trial due to the comparison of a moderate eczema and itching 3 months after the application of the product.

Discussion

In this study, we demonstrated that, in the medium term, a "medicalized" sunscreen cream containing piroxicam is more efficacious in reducing AK lesions number after successful PDT in comparison with standard sunscreen strategies

Table 1. Subjects' characteristics at baseline.

	ACTX group	SS group
Number	34	34
Men	24	26
Women	10	8
Age years, mean (SD)	70 (10)	71 (11)
range	53–86	45–87
Skin Type %		
Type 1	0	0
Type 2	57	55
Type 3	43	45
> Type 3	0	0
Baseline AK lesion count, mean (SD)	11.8 (5.8)	12.4 (6.9)
Anatomical localization		
Total lesion	401	422
Scalp %	58	55
Face %	42	45
Duration of AK, years	7	6
Subjects previously treated for AK (%)	85	83
Olsen Grade AK lesion (% of subjects)		
Grade I/II	80	80
Grade III	20	20

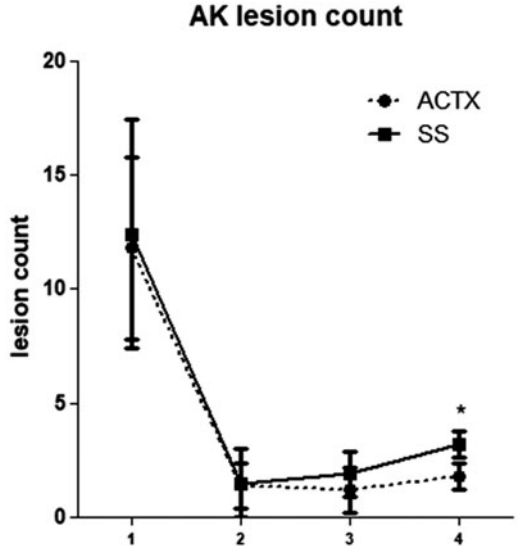

Figure 1. Evolution of AK lesion count at baseline (1) (before PDT) and after 2 (2), 3 (3), and 6 (4) months. At month 6 the difference between ACTX and SS groups is statistically significant (* $p = 0.03$; Mann-Whitney test).

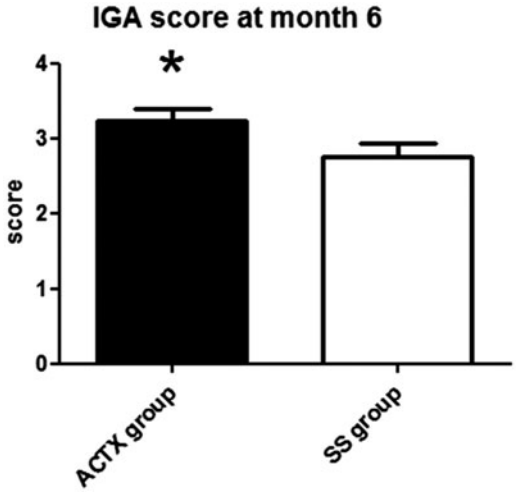

Figure 2. Investigator Global assessment Score (IGA) at month 6 in the ACTX and SS groups (* $p = 0.05$; Mann Whitney score). (IGA scores: 4: marked improvement, 3: good, 2: moderate; 1 no improvement; 0: worsening.)

commonly adopted in this clinical setting (50+ or 100+/photolyase sunscreens). Activation of cyclooxygenase 1 and 2 (COX) enzymes plays an important role in the pathogenesis of AK and skin cancers[25]. Piroxicam is a potent COX inhibitor[26]. In comparison with diclofenac, piroxicam is characterized by higher COX-1 inhibition activity[27]. In addition, piroxicam is a strong inhibitor of matrix metalloproteinase 2 (MMP-1) and 9 (MMP-9)[28], and it also promotes apoptosis. Several controlled trials have demonstrated that topical piroxicam in a sunscreen 50+ product is very effective in reducing AK lesions[13,14]. Clinical efficacy of this compound was also observed in high risk subjects, such as organ transplant patients who suffered from multiple AK and SCC[15]. Piroxicam 0.8% in sunscreen cream is now considered in the treatment algorithm of AK[29]. This product could also be suitable as a coadjuvant treatment after specific field-directed therapies such as PDT. Regular use of sunscreens in subjects with sun damage reduces the risk of AK[30]. International guidelines on AK treatments state that sun protection strategies are mandatory in subjects with AK, irrespective of the treatment adopted[12]. Our study should be considered a "pragmatic" trial for two reasons. First, the enrolled subjects could be treated with C-PDT or DL-PDT. We decided to adopt this approach because both procedures are now equally used in second level dermatology clinics in Italy[31]. C-PDT and DL-PDT are considered equally effective in the clearance of AK and in improving field cancerization. However, daylight therapy is better tolerated than conventional PDT[32]. In comparison with conventional PDT, DL-PDT shows similar efficacy for Grade 1 and 2 AK lesions, but less discomfort[33]. These two procedures have been shown to have the same level of efficacy also in respect of recurrence rate (13% and 10%, respectively) in the mid-term[34] (6 months). Another trial indicated that C-PDT could be more effective at 12 months[35]. However, more recent data show there are no differences in RR between DL-PDT and c-PDT at 6, 12, and 18 months (Calzavara Pinton, personal communication). Some authors have stated that DL-PDT is an effective alternative to conventional PDT, with equivalent efficacy for thin and moderate-thickness actinic keratoses (AKs) on the face and scalp[36]. DL-PDT seems to obtain better clearance for lesions located in the scalp compared with facial ones. However, in the northern part of Italy (i.e. latitude >45°N), DL-PDT should not be performed during late autumn and winter seasons. From a pragmatic point of view both C-PDT and DL-PDT could be considered equivalent, especially if a 6-month observational period is considered. The second pragmatic aspect of the present trial was that we decided that the comparator chosen should be the product routinely used in the participating centers. The current guidelines for the management of AK state that sun block applied twice daily for 7 months may protects against AK development (strength of recommendation A)[37]. However, there is no clear statement regarding the SPF level of protection to be used in this clinical setting (30, 50, 50+, or 100+). Therefore, we decided to adopt a pragmatic approach allowing the participating centers to use the sun blocker product they routinely utilize. The main limitation of the present study was that the study design was not double blind. However, to improve the internal validity of our results, we adopted the assessor-blinded evaluation methods for the primary outcomes assessment.

Conclusion

In subjects with AK treated with conventional or daylight PDT, a "medicalized" photoprotection treatment is associated with a favorable clinical outcome with progressive reduction of lesions. In contrast to a very high photoprotection (SPF50+ or SPF100+ and photolyase), the use of piroxicam 0.8% and SPF50+ is associated with a significantly greater improvement in clinical evolution of AK lesions.

Transparency

Declaration of funding

Difa Cooper Spa, Cantabria Labs Group, supported this trial with an unrestricted grant.

Declaration of financial/other relationships

MM is an employee of Cantabria Lab, Difa Cooper. The other authors report no conflicts of interest in this work. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work, but have no other relevant financial relationships to disclose.

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References

1. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000;42:S4-S7
2. Kennedy C, Willemze R, de Gruijl FR, et al. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. J Invest Dermatol 2003;120:1087-93
3. Flohil SC, Van Der Leest RJ, Dowlatshahi EA, et al. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam study. J Invest Dermatol 2013;133:1971-8
4. Moy RL. Clinical presentation of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000;42:S8-S10
5. Ratushny V, Gober MD, Hick R, et al. From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma. J Clin Invest 2012;122:464-72
6. Mittelbronn MA, Mullins DL, Ramos-Caro FA, et al. Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. Int J Dermatol 1998;37:677-81
7. Slaughter DP, Southwick HW, Smejkal W. "Field cancerization" in oral stratified squamous epithelium. Clinical implications of multicentric origin. Cancer 1953;6:963-8

8. Vatve M, Ortonne JP, Birch-Machin MA, et al. Management of field change in actinic keratosis. Br J Dermatol 2007;157(s2):21-4
9. 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
10. Wiegell SR, Wulf HC, Szeimies RM, et al. Daylight photodynamic therapy for actinic keratosis: an international consensus. J Eur Acad Dermatol Venereol 2012;26:673-9
11. Werner RN, Stockfleth E, Connolly SM, et al. Evidence-and consensus-based (S3) guidelines for the Treatment of Actinic Keratosis–International League of Dermatological Societies in cooperation with the European Dermatology Forum–Short version. J Eur Acad Dermatol Venereol 2015;29:2069-79
12. De Berker D, McGregor JM, Hughes BR, et al. Guidelines for the management of actinic keratoses. Br J Dermatol 2007;156:222-30
13. Babino G, Diluvio L, Bianchi L, et al. Long-term use of a new topical formulation containing piroxicam 0.8% and sunscreen: efficacy and tolerability on actinic keratosis. A proof of concept study. Curr Med Res Opin 2016;32:1345-9
14. Puviani M, Galloni C, Marchetti S, et al. 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. Curr Med Res Opin 2017;33:1255-9
15. Garofalo V, Ventura A, Mazzilli S, et al. Treatment of multiple actinic keratosis and field of cancerization with topical piroxicam 0.8% and sunscreen 50+ in organ transplant recipients: a series of 10 cases. Case Rep Dermatol 2017;9:211-16
16. Scotti E, Deledda S, Milani M. Efficacy of a film-forming medical device containing piroxicam and sun filters in the treatment of multiple actinic keratosis lesions in a subject with a history of kaposi sarcoma. Case Rep Dermatol 2016;8:254-61
17. Brogden RN, Heel RC, Speight TM, et al. Piroxicam: a review of its pharmacological properties and therapeutic efficacy. Drugs 1981; 22:165-87
18. Mirshafiey A, Vaezzadeh F, Khorramizadeh MR, et al. Effect of piroxicam on matrix metalloproteinase 2 and apoptosis. Int J Tissue React 2004;26:1-7
19. Mazumder MK, Bhattacharya P, Borah A. Inhibition of matrix metalloproteinase-2 and 9 by Piroxicam confer neuroprotection in cerebral ischemia: an in silico evaluation of the hypothesis. Med Hypoth 2014;83:697-701
20. Cini R, Pogni R, Basosi R, et al. Oxygen radical scavenger activity, EPR, NMR, molecular mechanics and extended-Hückel molecular orbital investigation of the bis (piroxicam) copper (II) complex. Metal-based Drugs 1995;2:43-56
21. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent 2014; 81:14
22. Freeman M, Vinciullo C, Francis D, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix®) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatol Treat 2003;14:99-106
23. Lacour JP, Ulrich C, Gilaberte Y, et al. Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses: a randomised, investigator-blinded, controlled, phase III study throughout Europe. J Eur Acad Dermatol Venereol 2015;29:2342-8
24. Elbenschutz L, Silipo V, De Simone P, et al. 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. Br J Derm 2016;175(6):1391–1393
25. Buckman SY, Gresham A, Hale P, et al. COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. Carcinogenesis 1998;19:723-9
26. Brogden RN, Heel RC, Speight TM, et al. Piroxicam. Drugs 1984;28: 292-323
27. Blanco FJ, Guitian R, Moreno J, et al. Effect of antiinflammatory drugs on COX-1 and COX-2 activity in human articular chondrocytes. J Rheumatol 1999;26:1366-73
28. Ahrens D, Koch AE, Pope RM, et al. Expression of matrix metalloproteinase 9 (96-kd gelatinase B) in human rheumatoid arthritis. Arthrit Rheum 1996;39:1576-87
29. Jetter N, Chandan N, Wang S, et al. Field cancerization therapies for management of actinic keratosis: a narrative review. Am J Clin Dermatol 2018;19:543-557
30. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 1993;329:1147-51
31. Zane C, Facchinetti E, Rossi MT, et al. A randomized clinical trial of photodynamic therapy with methyl aminolaevulinate vs. diclofenac 3% plus hyaluronic acid gel for the treatment of multiple actinic keratoses of the face and scalp. Br J Dermatol 2014;170: 1143-50
32. Rubel DM, Spelman L, Murrell DF, et al. Daylight photodynamic therapy with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial. Br J Dermatol 2014;171:1164-71
33. Wiegell SR, Fabricius S, Gniadecka M, et al. Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study. Br J Dermatol 2012;166:1327-32
34. Rubel DM, Spelman L, Murrell DF, et al. Daylight photodynamic therapy with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial. Br J Dermatol 2014;171:1164-71
35. Fargnoli MC, Piccioni A, Neri L, et al. Conventional vs. daylight methyl aminolevulinate photodynamic therapy for actinic keratosis of the face and scalp: an intra-patient, prospective, comparison study in Italy. J Eur Acad Dermatol Venereol 2015;29:1926-32
36. Morton CA, Wulf HC, Szeimies RM, et al. Practical approach to the use of daylight photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: a European consensus. J Eur Acad Dermatol Venereol 2015;29:1718-23
37. Stockfleth E, Ferrandiz C, Grob JJ, et al. Development of a treatment algorithm for actinic keratoses: a European Consensus. Eur J Dermatol 2008;18:651-9