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Research Article

The Relapse rate in patients with actinic keratosis treated with diclofenac sodium 3% gel

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Abstract: Actinic keratosis (AKs) are dysplastic lesions limited to epidermal keratinocytes and are considered squamous cell carcinomas in situ. AKs affect individuals who have had chronic exposure to sunlight, particularly those with skin types 1 or 2 on the Fitzpatrick phototype scale. In this clinical trial topical therapy with diclofenac gel was demonstrated to be safe and effective overall for the treatment of actinic keratosis. A resolution of at least 50% of lesions was observed in 78% of patients with a high level of satisfaction in 85% of cases.

Keywords: actinic kerstosis, diclofenac gel, non melanoma skin cancers.

Introduction

Non-melanoma skin cancer (NMSC) accounts for about 80% of all skin cancers, the most frequent being basal cell and squamous cell carcinomas.[1,2]

DNA mutations induced by UVB light cause the suppression of tumour suppressor proteins such as P53, whose mutation appears to be the main cause of clonal expansion of keratinocytes, which leads to AKs.[3]

Single or, more commonly, multiple actinic keratoses are slow-growing papules or plaques that are usually <1 cm in diameter, dry, of the same colour as the skin or erythematous, teleangectasic, with some covered in yellowish or brown scales.[4]

Despite the paucity of studies on the natural history of AKs, it is clear that up to 10% of lesions can degenerate at long term into invasive squamous cell carcinoma (SCC), that this risk increases over time, and that subclinical lesions in the photo-damaged area can also degenerate into SCC, in accordance with the concept of "field cancerisation".[4-6]

AKs are primarily treated to avoid progression to SCC, but also for cosmetic purposes and to eliminate symptoms such as itching and pain.

Although some SCC lesions are clinically indistinguishable from AKs lesions,[4] certain clinical features raise suspicion of SCC and warrant biopsy. These include bleeding, ulceration, hardening of the lesion, diameter >1 cm, rapid increase in volume and erythema.[7,8]

Treatments for AKs can be divided into self-applied topical therapies and surgical or ablation therapies. Surgical or ablation therapies are indicated for single lesions but are not effective on areas of field cancerisation.

Topical therapies, which treat an entire area of affected skin, currently include diclofenac sodium gel, 5-fluorouracil cream, 5-fluorouracil and acetylsalicylic solution, imiquimod cream and ingenol mebutate gel. Targeting the area of photo-damaged skin rather than individual lesions, topical therapies also have the advantage of treating subclinical lesions, after recent evidence showing that these also have the ability to degenerate into SCCs.[6,9,10]

The mechanism of action of diclofenac is complex and is still not fully understood. Some evidence shows that metabolites of arachidonic acid are involved in the response of keratinocytes to skin irritation and UV exposure[11,12] and that hyperactivation of cyclooxygenase enzymes (especially COX-2) is carcinogenic.[13] The action of diclofenac also seems to involve induction of apoptosis of neoplastic cells,[14] down-regulation of angiogenesis[15] and activation of PPAR-gamma receptors, which reduce the proliferation of neoplastic cells.[16]

A recent study involving reflectance confocal microscopy showed an improvement in epidermal atypia with the use of diclofenac in both clinical and subclinical lesions present in the field cancerisation area.[17]

Four systematic reviews of clinical studies conducted on treatment of actinic keratosis with diclofenac sodium gel highlighted its effectiveness and high safety profile, with complete response rates of up to 50%. The most common side effects, which in most cases were light to moderate, included itching, erythema, skin dryness and dermatitis.[18-21]

Purpose

The aim of this study was to assess the efficacy, safety and relapse rate of treatment with diclofenac sodium 3% gel in 2.5% hyaluronic acid in patients histologically diagnosed with actinic keratosis.

Patients and Methods

This study included patients histologically diagnosed with actinic keratosis[22] between January 2013 and July 2016, undergoing a course of treatment with diclofenac sodium 3% gel in 2.5% hyaluronic acid while attending the non-melanoma skin cancer clinic at the Department of Dermatology of the University of Pisa. Patients who had not received a histological diagnosis of actinic keratosis were excluded from the study. All patients before enrolment signed an informed consent form and the trial was approved by the local ethical committee. The course of therapy involved twice-daily application of diclofenac sodium gel in the morning and in the evening for 90 days, on the photo-damaged area of skin containing the AKs lesions. A treatment duration of 90 days has been shown to have the highest complete remission rate for AKs lesions.[18] The patients were assessed at baseline, immediately before the start of treatment, and after 90 days at the end of treatment. The same patients were monitored with a follow-up dermatologist consultation at 16 weeks from the end of the course of treatment, since it has been reported that the efficacy of topical treatment with diclofenac gel continues to increase up to a few weeks after the end of treatment.[13]

The patients were instructed to use daily a maximum level of a sunscreen protecting factor.

The following clinical parameters were assessed:

- the degree of healing of actinic keratoses;
- the side effects of therapy;
- relapse of lesions at 16-week follow-up;
- the degree of patient satisfaction.

To determine the degree of healing in patients with actinic keratosis, the number of lesions present were counted at baseline, before the start of treatment, and again at the end of the course of treatment. Four response levels answer were identified:

- 100% healing: complete clearance of actinic lesions present at baseline.
- >50% healing: more than 50% clearance of actinic lesions present at baseline.
- <50% healing: less than 50% clearance of actinic lesions present at baseline.
- no improvement: no change in actinic lesions number from baseline.

With regard to the side effects of the course of treatment with diclofenac 3% gel in 2.5% hyaluronic acid, we considered the most frequent, in accordance with the findings reported in previous studies[13,18,23] divided as follows into three levels of seriousness:

- no side effect;
- mild side effect: erythema, itching;
- serious side effect: photodermatitis, allergic contact dermatitis, intense pain.

At the follow-up visit 16 weeks after the end of treatment, the patients were assessed for relapse of the disease in the areas of treated skin.

Lastly, we assessed the degree of patient satisfaction, according to a four level score:

- very satisfied
- satisfied
- not very satisfied
- dissatisfied

The assessment of the patients' perception of the treatment was made more simple than the Patient Global Impression of Improvement tool (PGII) which involves a seven-level scale.[13,23]

Statistical analysis

Categorical data were represented as frequencies. We analysed the qualitative variables using the chi-square test correlating the risk factors and the level of healing. The level of healing was divided into two subgroups > or <50%.

All descriptive and inferential analyses were obtained using SPSS technology v.24. The only risk factor that is significantly related to healing is phototype ($p<0.0001$).

We also correlated the level of healing > or < 50% with a high level of satisfaction (moderate and high satisfaction) or a low level of satisfaction (poor satisfaction or dissatisfaction).

Results

This study included 82 patients with biopsy proven actinic keratosis who followed a course of treatment with diclofenac sodium 3% gel in 2.5% hyaluronic acid applied twice daily in the morning and in the evening for a total of 90 days. Out of a total of 82 patients aged between 42 and 95, with a mean age of 75, 55 were male and 27 were female. We divided patients into 3 groups according to the Fitzpatrick scale:

- phototype 1 – 6 patients (7.3%);
- phototype 2 – 72 patients (87.8%);
- phototype 3 – 4 patients (4.8%);

Of the total, 65 patients were smokers or former smokers and 72 had a history of chronic sunlight exposure for work or recreational reasons. 27 patients (2.9%) had a family history of non-melanoma skin cancer (NMSC) and 16 patients (19.5%) had a previous history of NMSC (Table 1).

Table 1: Patients demographics

Sex	Male 55 (67%)	Female 27 (32.9%)
Age	42-95	Mean 75
Smoking	Yes 65 (79.2%)	No 17 (20.8%)
Chronic sun exposure	Yes 72 (87.8%)	No 10 (12.2%)
Previous non-melanoma	Yes 16 (19.5%)	No 66 (80.5%)
Relapses and previous treatments	Yes 65 (79.2%)	No 17 (20.8%)
Family history of NMSC	Yes 27 (32.9%)	No 55 (67.1%)

The initial number of actinic keratoses and the affected part of the body were considered. The actinic keratoses were located in the head/neck region in 59 patients (72%), the trunk in 9 patients (11%) and the limbs in 14 patients (17%).

Degree of healing

12 patients (14.6%) had achieved total clearance by the end of treatment, with a total of zero lesions still present; 52 patients (63.4%) had achieved more than 50% clearance of the lesions present at the time zero; 10 patients (12.2%) had achieved less than 50% clearance and 8 patients (9.7%) showed no improvement in the lesions, with the same number of actinic keratoses as at time zero (Table 2).

Table 2: Level of healing

Level of healing	Number of patients (82 total)
100%	12
>50%	52
<50%	10
No improvement	8

Phototype 1 was associated with a <50% level of healing in all cases (n=6), phototype 2 with a >50% level of healing in 83.3% of cases (60/72) and phototype 3 was associated in all cases (n=4) with >50% level of healing (Table 5).

Table 5: Correlation between risk factors and level of healing > and < 50%

Risk factor	Healing		p-value
	>50%	<50%	
Age (years)			0.907
<75	31	9	
>75	33	9	
Sex			0.097
F	24	3	
M	40	15	
Phototype			<0.0001
1	0	6	
2	60	12	
3	4	0	
Site			0.469
Limbs	12	2	
Trunk	8	1	
Head-Neck	44	15	
Chronic sun exposure			0.874
Yes	56	16	
No	8	2	
Family history			0.967
Yes	21	6	
No	43	12	
Previous non-melanoma cancer			0.309
Yes	14	2	
No	50	16	
Smoking			0.365
Yes	51	14	
No	15	2	
Relapse and previous treatments			0.072
Yes	48	17	
No	16	1	

Side effects

Out of a total of 82 patients, 73 (89%) had no side effects; 9 (11%) had a mild side effect and no patients had an important side effect. (Table 3)

Table 3: Side effects

Side effects	Number of patients
No side effect	73
Mild side effect	9
Serious side effect	0

Relapse

At the follow-up visit 16 weeks after the end of therapy, 25 patients (30.5% of the total) had experienced a relapse of the disease.

Level of patient satisfaction

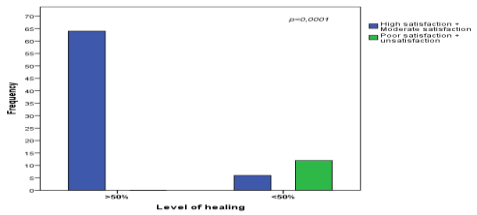
25 patients (30.5% of the total) gave a response of "very satisfied"; 45 (55.9%) said they were "satisfied"; 3 (3.1%) of patients said they were "not very satisfied" and 9 (10.5%) said they were "dissatisfied". (Table 4).

Table 4: Level of patient satisfaction

Level of patient satisfaction	Number of patients (82)
Very satisfied	25
Satisfied	45
Not very satisfied	3
Dissatisfied	9

There was a significant correlation between healing >50% and high patient satisfaction (p<0.0001) (Figure 1).

Figure 1: Correlation between level of healing < or > 50% and patient satisfaction (high or poor)



Discussion

In this clinical trial topical therapy with diclofenac gel was demonstrated to be safe and effective overall for the treatment of actinic keratosis.

A resolution of at least 50% of lesions was observed in 78% of patients with a high level of satisfaction in 85% of cases. The statistical analysis showed a statistically significant correlation between >50% healing and a high patient satisfaction (p<0.0001). The only risk factor significantly correlated to healing was phototype (p<0.0001). Phototype 1 (100% cases) was correlated to a low level of healing (<50%) whereas phototypes 2 (83.3% of cases) and 3 (100% of cases) were correlated to a high level of healing (>50%).

No side effects were found in 89% of patients. Those cases of side effects reported were all mild and in no case the treatment was discontinued as a result of adverse reactions. Diclofenac sodium is one of the topical products for the treatment of actinic keratosis with the lowest incidence of side effects, despite the difficulty involved for direct comparison of the adverse effects in the various studies.[24,25]

This study, with its short-term follow-up, though comparable to many in the literature, might nevertheless underestimate the efficacy of diclofenac gel therapy. This is shown in a study which demonstrates that efficacy continues to increase slightly for up to a year, with a further reduction in AKs lesions one year after the end of treatment as compared to the follow-up visit 30 days after the end of treatment.[26]

Considering the limited number of studies on the various topical therapies for actinic keratosis with a follow-up of more than 30 days, it is vital to conduct further phase 2/3 studies on the efficacy and possible side effects of diclofenac gel with a follow-up duration greater than one year.

The numerosity of the sample in our study is in line with most studies found in the literature. To our knowledge, only a few studies have included more than 100 patients.[20,21,27]

Exclusion from our study of patients with no histological diagnosis of actinic keratosis may have led to the inclusion of a high number of patients with advanced AK lesions which had undergone biopsy as part of the differential diagnosis for SCC. This might explain the 20% lower complete response rate in our study compared to others in the literature.

This study currently confirms that the high safety, efficacy and tolerability demonstrated by diclofenac sodium 3% gel make it an important resource among the treatment options for actinic keratosis.

Disclosure

The author reports no conflicts of interest in this work.

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