Pharmacology and therapeutics

Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses

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Abstract

Background Actinic keratoses (AKs) are epidermal skin lesions with the potential to develop into invasive squamous cell carcinoma (SCC). Treatment at an early stage may prevent development of SCC. Current treatment options are highly destructive and associated with significant side-effects. Early studies with topical diclofenac were encouraging and led to its evaluation for the treatment of actininic keratosis. Previous studies have demonstrated that 3% diclofenac in 2.5% hyaluronan gel is effective and well tolerated in the treatment of AK. The present study was designed to further explore the therapeutic potential of this gel.

Methods This randomized, double-blind, placebo-controlled trial involved outpatients with a diagnosis of five or more AK lesions contained in one to three 5 cm^2 blocks. Patients received either active treatment (3% diclofenac gel in 2.5% hyaluronan gel) or inactive gel vehicle (hyaluronan) as placebo (0.5 g b.i.d. in each 5 cm^2 treatment area for 90 days). Assessments included the Target Lesion Number Score (TLNS), Cumulative Lesion Number Score (CLNS), and Global Improvement Indices rated separately by both the investigator (IGII) and patient (PGII).

Results Results obtained from 96 patients at follow up (30 days after end of treatment) indicated that a significantly higher proportion of patients who received active treatment had a TLNS = 0 compared to the placebo group (50% vs. 20%; $P < 0.001$). There was also a significant difference between the two groups in CLNS, with 47% of patients in the active treatment group having a CLNS = 0 compared with only 19% in the placebo group ($P < 0.001$). The proportion of patients with an IGII score of 4 (completely improved) at follow-up was 47% in the active treatment group compared with only 19% in the placebo group ($P < 0.001$); for PGII these values were 41% vs. 17%, $P < 0.001$. Both treatments were well tolerated, with most adverse events related to the skin.

Conclusions Topical 3% diclofenac in 2.5% hyaluronan gel was effective and well tolerated for the treatment of AK.

Introduction

Actinic keratoses (AKs) are premalignant intraepidermal skin lesions, caused by excessive exposure to solar radiation.[1] It is the third most common skin complaint treated by dermatologists in the USA and, according to the American Academy of Dermatology, 60% of predisposed individuals over 40 years of age have at least one lesion.[2,3] The prevalence of AK is higher in men than in women, increases with age and occurs more frequently in fair- than dark-skinned individuals.[1,4,5]

Epidemiological and histological features of AKs are similar to those of invasive squamous cell carcinoma (SCC), and the potential for AK to develop into SCC is a serious clinical concern.[3,4] In a recent study a high incidence of p53 mutations was reported in both AKs and SCC (53% and 69%, respectively).[6] The p53 gene encodes a protein responsible for, amongst others, DNA repair following UV-induced DNA damage. Consequently, AK may be viewed as the initial stage of a continuum beginning with UV-induced DNA damage, leading to neoplastic transformation and proliferation, invasion into deeper structures, and finally culminating in metastasis and death.[7] The presence of p53 mutation in AK lesions is consistent with this view. The rate of transformation is estimated between 0.1 and 20%, with a lifetime risk of progression of 6–10%.[8,9]

With currently available treatment modalities, the majority of AKs can be cured (cure rates as high as 90% have been obtained).[10] Liquid nitrogen freezing is the most frequently used method of treatment.[11] However, it is often highly destructive and the freezing method can leave unsightly hypopigmented marks on treated skin.[11] Less common destructive treatments include curettage, electrocautery, dermabrasion, laser and chemical peels, all with similar disadvantages including pigmentation problems.[5,10]

In terms of medical treatment for AK, topical 5-fluorouracil (5-FU) is also widely utilized. This method has the advantage of treating large areas and subclinical lesions, but a relatively long treatment period is required and it is only partially effective in removing deep or hyperkeratotic Aks.[10] It also causes unsightly and painful erosions.[12] Therefore, there is a definite need for an effective and well-tolerated treatment for AK that is acceptable to patients.

An early study of the therapeutic efficacy of topical diclofenac in a hyaluronan gel vehicle in patients with AK provided encouraging results and led to the evaluation of this formulation for the treatment of AK.[13] The present study was performed to investigate the therapeutic potential of 3% diclofenac in 2.5% hyaluronan gel in the topical treatment of AK.

Methods

Study design

This randomized, double-blind, placebo-controlled trial was conducted in four centers in the USA. The study consisted of three parts: Screening (Visit 1, 6 days before the administration of study medication began), Treatment (Visits 2–5, up to 30–90 days) and follow-up (Visit 6, 30 days after the end of treatment [EOT]). All patients provided written informed consent before being enrolled into the study. The study was conducted in accordance with the Declaration of Helsinki and North American Good Clinical Practices, and appropriate local Review Boards approved the protocol.

Patients

Outpatients aged 18 years or over with a diagnosis of five or more AK lesions were eligible to participate in the study. The lesions had to be contained in one to three 5 cm^2 designated treatment blocks in one or more of the selected Major Body Areas (forehead, central face, scalp, arms, hands). In addition, the lesions were scored according to the investigators' impression of their severity at baseline using the Baseline Severity Index (BSI). The scale used for determining BSI was as follows: 0 = no AKS visible, 1 = clearly visible lesions, 2 = many visible, small, moderately thick lesions or a few large, thick, rough scaly lesions, 3 = many thick, hypertrophic lesions which are clearly visible and palpable with well defined borders.

Patients had to be in good general health, with no other clinically significant medical problems, and women had to be using reliable contraception. Patients were excluded from the study if they had a known allergy to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), had a dermatological condition (including psoriasis) in the designated site which might interfere with the absorption, accumulation or metabolism of the study medication, or were being treated with a disallowed concomitant medication (including masoprocol, 5-FU, etretinate, cyclosporine, retinoids, trichloroacetic acid peel or glycolic acid).

Treatment schedule

One week after the Screening Visit, patients were randomized to receive either the active treatment, 3% diclofenac in 2.5% hyaluronan gel (Solaraze™ Bioglan) or placebo, which consisted of the inactive gel vehicle, hyaluronan only. The dose instructions were 0.5 g b.i.d. in each 5 cm^2 treatment area for 90 days. All patients were also advised to use sunscreen and to avoid excessive exposure to the sun.

Efficacy assessments

In order to assess the efficacy of the treatment, four variables were measured, two quantitative and two qualitative. These were measured at each visit; from visit 2 through to follow-up.

The quantitative variables were the Target Lesion Number Score (TLNS) and Cumulative Lesion Number Score (CLNS). The TLNS refers to the number of lesions identified in the designated treatment blocks at baseline. Any remaining target lesions, plus new lesions not present in the treatment blocks at baseline, constituted the CLNS.

Qualitative assessments were made independently by both the investigators and patients indicating their perception of the change in the severity of the lesions throughout treatment. The assessments, recorded as Investigator and Patient Global Improvement Indices (IGII and PGII, respectively), were made using the following 7-point scale: −2 = Significantly worse, −1 = Slightly worse, 0 = No change, 1 = Slightly improved, 2 = Moderately improved, 3 = Significantly improved and 4 = Completely improved.

Primary endpoints were the proportion of patients at follow-up with TNLS, CLNS = 0 and IGII, PGII = 4. The follow-up results were chosen as previous studies have shown that the optimal response to treatment is obtained after a slight delay following EOT.[13]

Safety assessments

Adverse events

Patients were given a diary to take home, in which to record all applications of study medication, concomitant medications and adverse events. The physician also assessed and recorded adverse events for duration, intensity and causality.

Laboratory analyzes

Standard laboratory analyzes (hematology, biochemistry, urinalysis) were performed on all patients at screening and EOT.

Serology

In order to study the potential sensitization of patients to diclofenac, patients' serum samples obtained at Screening and EOT were assessed for the presence of antidiclofenac antibodies. Serum samples were also obtained at the onset of any clinically significant skin reaction.

Statistical analysis

The sample size calculation was based on the effect on lesion numbers, and determined that 54 patients per group would be sufficient to detect (with 80% power) an effect size of 0.54. All efficacy analyzes were performed on the Intend To Treat (ITT) cohort. All statistical tests used two-sided *P*-values rounded to three decimal places. The treatment group differences were assessed using ANOVA.

Results

Patients

A total of 120 patients enrolled for the study, 118 started the treatment and 96 patients completed the study. There were 22 withdrawals from the study. Of these, 14 were from the active treatment group (eight due to adverse events and six due to noncompliance) and eight from the placebo group (four due to adverse events, two due to non compliance and two withdrew consent).

The patients were well matched across the treatment groups. Of the comparisons made between the two groups for baseline demographic characteristics, none were statistically significant except for hair color. There was a greater proportion of patients with blonde hair in the active treatment group; however, this was not deemed to present any kind of favorable bias. The distribution and severity (classified according to the BSI) of the lesions across major body areas were also similar in both groups.

There was a high degree of comparability of medical history and concomitant medication between the two groups. Their current medical conditions were also comparable and did not change significantly from baseline to end of treatment. Compliance was deemed excellent.

Efficacy (primary outcome measures)

At follow-up, 50% of patients in the active treatment group had TLNS = 0 (indicating complete resolution of all target lesions in a designated area) whereas in the placebo group this value was only 20%, a statistically significant difference ($P < 0.001$). With regards to CLNS, a significant difference was also observed between the two groups with 47% of patients using active treatment having CLNS = 0 (indicating complete resolution of target and new lesions in a designated area) compared to 19% in the placebo group ($P < 0.001$) (Fig. 1).

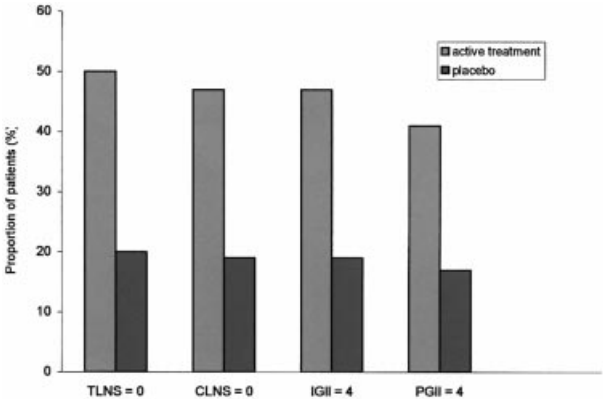

Figure 1 Comparison of the results obtained for the four primary outcome variables for both treatment groups at follow-up (30 days after end of treatment). All comparisons are statistically significant ($P < 0.05$). For abbreviations refer to text

The Global Improvement Indices followed the trend in the lesion number scores. At follow-up, a significantly greater proportion of patients using active treatment had IGII = 4 (complete lesion improvement) compared to placebo group (47% vs. 19%; $P < 0.001$). Furthermore, a combined 79% of patients in the active treatment group had achieved complete (IGII = 4) or significant (IGII = 3) lesion improvement compared to 45% in the placebo group. With regards to PGII, 41% in the active treatment group had a score = 4 compared to 17% in the placebo group ($P < 0.001$). Once again, a combined 77% of patients in the active treatment group had achieved complete (PGII = 4) or significant (PGII = 3) lesion improvement compared to only 33% in the placebo group.

Although not part of the primary outcome measures, it was also noted that no post-treatment hypopigmentation or adverse textural changes in the skin of patients were observed in either group.

Safety and tolerability

Overall, both treatments were well tolerated. At least one adverse event was reported in 90 and 81% of patients in the active treatment and placebo groups, respectively. The majority of adverse events were related to the skin, the most commonly reported (in descending order of frequency) being pruritus, application site reactions, dry skin, rash and erythema. The active treatment was associated with a higher proportion of skin-related adverse events than the placebo group (79% compared with 64%), and in

Table 1 Frequency of adverse events occuring in different body systems

Patients with one or more adverse event by body system		
Body system	**Treatment group**	
	Diclofenac ***n*** **= 58** ***n*** **(%)**	**Placebo** ***n*** **= 59** ***n*** **(%)**
Skin and appendages	46 (79)	38 (64)
Nervous system	18 (31)	20 (34)
Body as a whole	13 (22)	12 (20)
Metabolic and nutritional disorders	10 (17)	2 (3)
Digestive system	5 (9)	6 (10)
Respiratory system	4 (7)	5 (8)
Urogenital system	2 (3)	6 (10)
Musculoskeletal system	2 (3)	3 (5)
Special senses	4 (7)	1 (2)
Cardiovascular system	3 (5)	1 (2)
Hemic and lymphatic system	1 (2)	1 (2)
Unknown	1 (2)	2 (3)
Most common skin-related adverse events		
Pruritus	32 (55)	29 (49)
Application site reaction	20 (34)	12 (20)
Dry skin	21 (36)	10 (17)
Rash	19 (33)	9 (15)
Erythema	15 (26)	4 (7)
Rash vesiculobullous	3 (5)	0 (0)
Skin exfoliation	3 (5)	0 (0)
Ulcerated skin	3 (5)	0 (0)

96% of these cases, the events were classified as mild or moderate. Adverse events reported in the nervous system were all local effects related to application site (paraesthesia, hyperesthesia and tingling) and are unlikely to be clinically significant. In general, there were a comparable number of adverse events categorized as mild or moderate between the active treatment and placebo arms. The majority of adverse events resolved spontaneously and did not require treatment. There were no treatment-related serious adverse events and no deaths in this study. A summary of the adverse events is presented in Table 1.

Laboratory parameters (hematology, biochemistry, urinalysis) were comparable between groups and no clinically relevant findings were recorded. The serology test results were negative.

Discussion

The use of 3% diclofenac in 2.5% hyaluronan gel was effective and well tolerated for the treatment of AK.

The application of topical diclofenac resulted in a greater rate of lesion resolution in the designated treatment areas. This was indicated by a greater proportion of patients using diclofenac obtaining TNLS and CLNS = 0 compared to those using hyaluronan alone. The Global Improvement Indices ratings also supported the trends observed in the lesion number scores. The perceived effect however, appears to be slightly lower when rated by patients; this may be due to the fact that even though lesions completely respond to treatment, the skin may still have a slight pink coloration. This can be confused with an incomplete response by the patient.

Overall, diclofenac gel was well tolerated in this study. As expected, the most common adverse events were skin-related and localized to the designated treatment areas. The majority of these events were assessed as being related to treatment, with a slightly greater number occuring in the active treatment arm. The exception was pruritus, which had a similar incidence in both groups; this may be due to antipruritic effects of diclofenac.[14,15] Most non skin-related adverse effects were rated mild or moderate and were not considered to be due to treatment. They were comparable between the two groups and most resolved spontaneously.

The mechanism of action of diclofenac with regards to the treatment of AK is not clearly understood. However, like other NSAIDs, diclofenac has been shown to have antitumorigenic effects, an observation that is currently under investigation. As a NSAID, diclofenac inhibits the cyclooxygenase enzymes (COX-I and COX II), which are involved in arachidonic acid metabolism. It is thought that by inhibiting the metabolism of arachidonic acid, NSAIDs curtail the numerous and potent tumorigenic effects of its metabolites. Such effects include the conversion of procarcinogens to carcinogens, inhibition of immune surveillance, inhibition of apoptosis, stimulation of angiogenesis and increasing the invasiveness of tumor cells.[16–19] As a result, NSAIDs are emerging as potentially powerful agents in the prevention of cancer, particularly those of epithelial origin.

Recent publications suggest that AK is an early step in the development of SCC and should therefore be treated aggressively to stop the progression to SCC.[3,4,7,20] However, not all AKs will progress to SCC, some, especially small lesions, will even spontaneously involute. At present there are no reliable methods to assess the progression rate of AK. Although it is important to diagnose and treat AK, not all patients will require destructive treatment on their first visit; each case must be tailored to suit the needs of the patient.[5,9] The availability of a new topical 3% diclofenac in 2.5% hyaluronan gel provides a new therapeutic option that is effective, well-tolerated, easy to administer and most importantly nondestructive. Consequently, it is more likely to be accepted by patients and allow early treatment of AKs without resorting to invasive methods.

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Solaraze™ will be marketed by Bioglan Pharma Inc.

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