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Recurrence rates and patient assessed outcomes of 0.5% 5-fluorouracil in combination with salicylic acid treating actinic keratoses

Background: Actinic keratoses (AK) have been classified as early *in situ* squamous cell carcinomas and should be treated. *Objectives:* To evaluate the clinical benefit of 5-fluorouracil 0.5%/salicylic acid 10.0% (5-FU/SA) versus 3% diclofenac/hyaluronic acid (HA) for the treatment of AK and report patients' assessments of efficacy, tolerability and practicability. *Methods:* Randomised, placebo-controlled, double-blind, parallel-group, multicentre trial. Patients received topical 0.5% 5-FU/SA once daily, its vehicle or diclofenac/HA twice daily for maximum of 12 weeks. Lesion recurrence rates were evaluated at 6 and 12 months after end of treatment (EOT). Patients' assessments were evaluated at 6 weeks, EOT, post-treatment (PT) visit, 6 and 12 months. *Results:* At 12 months 85.8% of lesions did not recur in the 5-FU/SA group compared to 79.8% (p=0.04419) in the vehicle and 81.0% (p=0.02476) in the diclofenac/HA groups. At PT visit 93.2% patients (n=163/175) in the 5-FU/SA group rated clinical improvement as "very good" or "good" compared to vehicle (66.7%, n=62/93, p<0.0001) and diclofenac/HA (81.6%, n=142/174, p<0.0001). Local side effects (inflammation and burning) were more common with 0.5% FU/SA but in general did not lead to discontinuation of therapy. Overall, patients were satisfied with the therapy. At 12 months, there were no differences in practicability and handling between treatments. *Conclusions:* Topical 0.5% 5-FU/SA demonstrated superior sustained clinical efficacy versus diclofenac/HA with acceptable tolerability. Patient satisfaction was high.

Key words: actinic keratoses, diclofenac HA, 5-fluorouracil, salicylic acid, patient assessment, recurrence rate

According to recent scientific findings and guidelines, actinic keratoses (AK) have been classified as early *in situ* squamous cell carcinomas, depending on the extent of atypical keratinocytes [1]. AK is usually diagnosed clinically, presenting with broad variations in size and thickness. Histologically, AK is characterised by the presence of atypical keratinocytes at the basal cell layer of the epidermis, which may extend into the entire epidermis in advanced lesions, showing signs of chronic UV-damage in the surrounding skin area. AK most commonly affects areas prone to increased sun exposure (*e.g.* face, scalp, backs of hands and forearms) in older populations, especially men. Most patients present with multiple AK, although single lesions do occur. Lesions are usually small (less than 1 cm in diameter), erythematous and scaly. They may enlarge, become tender or bleed [2].

Management of AK includes lesion or field directed approaches or a combination. A treatment algorithm has been developed by a European consensus group based on best practice [3]. It comprises recommendations for both lesion and field directed treatment and considers factors such as patient profile, medical history, and personal preference (*e.g.* cosmesis and pain).

A number of therapies with different levels of evidence exist, including physical ablation, topical chemotherapeutic agents, immunomodulators or diclofenac and photodynamic therapy. Therapeutic standards for topical treatment are diclofenac in hyaluronic acid (diclofenac/HA), 5-fluorouracil 5% cream and imiquimod 5% cream; diclofenac/HA is a possible product of choice for field treatment.

5-fluorouracil 0.5% in combination with salicylic acid 10.0% (5-FU/SA) is a novel lesion directed treatment option for especially hyperkeratotic AK. 5-FU/SA inhibits mitosis and leads to the breakdown of hyperkeratosis. It is available for the treatment of slightly palpable and/or moderately thick hyperkeratotic AK of clinical grade I/II in immunocompetent patients. The solution is applied topically with an integrated brush for precise application and to avoid contact with the drug, once daily, targeting up to 10 AK simultaneously as required [4].

Objectives. Recently, a Phase III study was conducted to evaluate the histological clearance rate of 0.5% 5-FU/SA compared to its vehicle (vehicle FU/SA) and the comparator 3% diclofenac/HA, measured by the histological clearance of one clinically pre-defined representative lesion.

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Secondary objectives included clinical lesion response and clearance of treated AK, as well as assessments of tolerability and safety. The histological and clinical study results, reported elsewhere, showed that 0.5% 5-FU/SA is an effective, topical, lesion directed treatment for AK, demonstrating higher histological and clinical clearance rates compared to diclofenac/HA or vehicle FU/SA [5]. 0.5% 5-FU/SA was superior to diclofenac/HA ($p<0.01$) and vehicle ($p<0.0001$) for histological clearance of one representative lesion 8 weeks post-treatment. In 72.0%, 59.1% and 44.8% of patients in the 0.5% 5-FU/SA, diclofenac/HA and vehicle groups, respectively, the week 20 biopsy revealed no AK. Significantly more lesions were cleared with 0.5% 5-FU/SA (74.5%), compared with diclofenac/HA (54.6%; $p<0.001$) or vehicle (35.5%; $p<0.001$). 0.5% 5-FU/SA was superior in terms of complete clinical clearance: 55.4%, compared with diclofenac/HA (32.0%, $p<0.001$) and vehicle (15.1% $p<0.001$). The objective of this publication is to show the long-term benefit of 0.5% 5-FU/SA for sustained clinical outcome over a 12-month follow-up period and to report additional outcomes and patients' assessments of efficacy, tolerability, practicability and handling of study treatments, as well as compliance.

AK is a chronic condition for which the UV-damage requires continuous observation. It is difficult to predict which AK will develop into squamous cell carcinomas; therefore sustained clinical benefit of treatment is of significant importance for successful management. Patient-reported outcomes are increasingly used to assess the effect of interventions from the patients' perspective, with both the EMEA and FDA having issued guidance on their use [6, 7]. Although no standardised method for patients' assessments was used in this study, patient acceptance of treatment, as well as long-term sustained clinical benefit, is the key to successful treatment of AK.

The study was conducted in accordance with the Declaration of Helsinki and its amendments, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice, and local regulatory requirements. The study protocol and all amendments were reviewed and approved by an independent ethics committee, and competent authorities. The study was registered under EudraCT No. 2007-003889-18 and NCT 00987246.

Materials and methods

Study design

This was a randomised, placebo-controlled, double-blind, three-armed, parallel-group, multicentre trial, conducted between 2008 and 2009 at 38 study centres in Germany. Patients aged 18-85 years, of skin type I to IV according to Fitzpatrick [8] (12 Type I (2.6%); 245 Type II (52.1%); 191 Type III (40.6%); 22 Type IV (4.7%)), with 4-10 AK lesions (clinical grade I or II according to Olsen [9]) on their face/forehead or bald scalp were randomised to receive either 0.5% 5-FU in combination with 10% SA solution, vehicle FU/SA (without active ingredients, not distinguishable from 5-FU/SA in colour, appearance or consistency, main excipient dimethyl sulfoxide) or 3% diclofenac sodium in 2.5% HA, respectively. 5-FU/SA and vehicle FU/SA were topically applied with a brush once daily to AK lesions and diclofenac/HA gel was topically applied twice daily (morning and evening). If severe adverse events (AEs) occurred, the frequency of application could be reduced to three times per week (5-FU/SA and vehicle FU/SA) or to once daily (diclofenac/HA).

Treatment was administered until lesions completely cleared or for a maximum of 12 weeks. A final evaluation of safety and efficacy parameters was documented 8 weeks after end of treatment (EOT) at the 20-week post-treatment (PT) visit. Patients were followed up 6 and 12 months after EOT.

Patients

Overall, 470 patients were randomised and received treatment with study medication (187 5-FU/SA; 98 vehicle FU/SA; 185 diclofenac/HA (randomisation 2:1:2)). 435 patients (92.6%) completed the 12-week treatment phase of the study and entered the follow-up period (173 5-FU/SA (92.5%); 93 vehicle FU/SA (94.9%); 169 diclofenac/HA (91.4%)).

35 patients (7.4%) dropped out of the study prematurely. 20 patients dropped out due to an application site treatment-related AE (7 5-FU/SA (3.7%); 3 vehicle FU/SA [3.1%]; 10 diclofenac/HA (5.4%)). Two patients (1.1%) in the diclofenac/HA group dropped out due to lack of tolerability, one (0.5%) in the 5-FU/SA group. Other reasons were "lost to follow-up" and *e.g.* "withdrew consent". *Table 1* shows the study population and the data sets for analyses.

Only one patient from the diclofenac/HA group discontinued the follow-up due to an AE. 397 patients (84.5%) completed the follow-up study at month 12 (165 5-FU/SA (88.2%), 88 vehicle FU/SA (89.8%), 144 diclofenac/HA (77.8%)).

Evaluations

To evaluate the long-term benefit of 0.5% 5-FU/SA for sustained clinical outcome, the status of successfully treated lesions in the treated area was evaluated at 6 and 12 months after EOT. Lesion recurrence rates, frequency of sustained cleared lesions and mean number of (pre-existing) lesions were reported for all subjects in the follow-up period.

Patients' self-assessed treatment outcomes were evaluated at EOT, PT visit and 6 and 12 months after EOT. Patient compliance, calculated as the difference in days between the days scheduled and the actual treatment days recorded via daily patient diaries, was reported at EOT. Patients' overall assessments of clinical improvement was performed at the PT visit. At follow-up 6 and 12 months after EOT, patients further assessed the compatibility of study treatments, with respect to side effects or negative symptoms and sense of inflammation, via a questionnaire also including a question on treatment satisfaction (*i.e.* recommendation of treatment). Patients assessed skin feeling, product appearance and ease of application at week 6, EOT and PT visit, using a five-point scale that ranged from "very good" to "minimal". Physicians assessed change in skin quality from the PT visit at 6 and 12 months after EOT using a four-point scale raging from "none" to "severe". Patients assessed the practicability and handling of study treatments at follow-up 12 months after EOT via a questionnaire.

Table 1. Study populations.

		Treatment groups			Overall
		0.5% 5-FU/SA	Vehicle FU/SA	Diclofenac/HA	
Patients treated	N	187	98	185	470
Patients completed	N (%)	173 (92.5)	93 (94.9)	169 (91.4)	435 (92.6)
Safety set (SS)	N (%)	187 (100)	98 (100)	185 (100)	470 (100)
Full analysis set (FAS)	N (%)	177 (94.7)	96 (98.0)	183 (98.9)	456 (97.0)
Per protocol set (PPS)	N (%)	168 (89.8)	87 (88.8)	164 (88.6)	419 (89.1)
All patients in follow-up	N (%)	173 (92.5)	93 (94.9)	169 (91.4)	435 (92.6)
Patients completed follow-up	N (%)	165 (88.2)	88 (89.8)	144 (77.8)	397 (84.5)

Statistical methods

Sustained clinical efficacy variables were compared exploratively (the main population was all subjects in the follow-up period). Frequencies of subjects for target variables were compared between treatment groups by Chi-square tests. At week 6, EOT, PT visit and follow-up 6 and 12 months after EOT patients' assessments were compared between treatment groups by Cochran-Armitage test for trend.

Results

Sustained clinical benefits

At follow-up 6 months after EOT, the frequency of sustained cleared lesions was higher in the 5-FU/SA group (91.6%, 680 of 742 lesions) compared to the vehicle FU/SA group (86.2%, 163 of 189 lesions) and the diclofenac/HA group (82.8%, 442 of 534 lesions) (p=0.02347 for 5-FU/SA *versus* vehicle FU/SA and p<0.00001 for 5-FU/SA *versus* diclofenac/HA). At follow-up 12 months after EOT, the frequency of sustained cleared lesions was again higher in the 5-FU/SA group (85.8%, 622 of 725 lesions) compared to the vehicle FU/SA group (79.8%, 146 of 183 lesions) and the diclofenac/HA group (81.0%, 400 of 494 lesions) (p=0.04419 for 5-FU/SA *versus* vehicle FU/SA and p=0.02476 for 5-FU/SA *versus* diclofenac/HA; considering only subjects with assessments at the 12-month visit) *(figure 1)*.

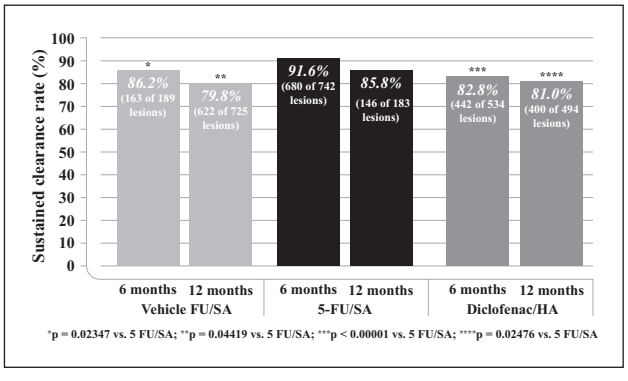

Figure 1. Patients with sustained clinical benefit 6 and 12 months after EOT.

At follow-up 6 months after EOT, the mean number of lesions per patient was lowest in the 5-FU/SA group (1.1 lesions) compared to the vehicle FU/SA group (2.4 lesions) and the diclofenac/HA group (2.0 lesions) (p<0.000001 for 5-FU/SA *versus* vehicle and p=0.0002 for 5-FU/SA *versus* diclofenac/HA). At follow-up 12 months after EOT, the number of lesions was again lowest in the 5-FU/SA group (1.1 lesions) compared to the vehicle FU/SA group (1.9 lesions) and the diclofenac/HA group (1.5 lesions) (p=0.00046 for 5-FU/SA *versus* vehicle and p=0.04198 for 5-FU/SA *versus* diclofenac/HA). In all three treatment arms the mean numbers decreased from EOT to 12-month follow-up.

Patient compliance

At EOT most patients had a good compliance of 80 to 120% (85.0% 5-FU/SA, n=159/187; 86.7% vehicle FU/SA, n=85/98; 81.1% diclofenac/HA, n=150/185). A compliance <80% was observed for very few patients only (4.8% 5-FU/SA, n=9; 0% vehicle FU/SA; 5.4% diclofenac/HA, n=10).

Patients' assessment of efficacy

In accordance with the results for clinical clearance and lesion-area reduction reported elsewhere [5], the patients' overall assessment of clinical improvement showed no clinically relevant difference between treatments by EOT. However, at the PT visit, more patients in the 5-FU/SA group (93.2%; n=163/175) rated their clinical improvement (efficacy) as "very good" or "good" compared to the vehicle FU/SA group (66.7%, n= 62/93) and the diclofenac/HA group (81.6%, n=142/174) (p<0.0001 for difference between the 5-FU/SA group and the other two treatment groups) *(figure 2)*.

Patients' assessment of tolerability

Overall, the study treatments were tolerated and accepted by patients. However, at week 6 of the treatment, inflammation (70.3% 5-FU/SA, n=124/176; 22.3% vehicle FU/SA, n=21/94; 28.9% diclofenac/HA, n=51/176) and burning (81.3% 5-FU/SA, n=143/176; 57.4% vehicle FU/SA, n=54/94; 25.0% diclofenac/HA, n=44/176) were reported by more patients in the 5-FU/SA group compared to the vehicle FU/SA group and the diclofenac/HA group (p<0.0001 for 5-FU/SA *versus* vehicle and diclofenac/HA for both inflammation and burning). At

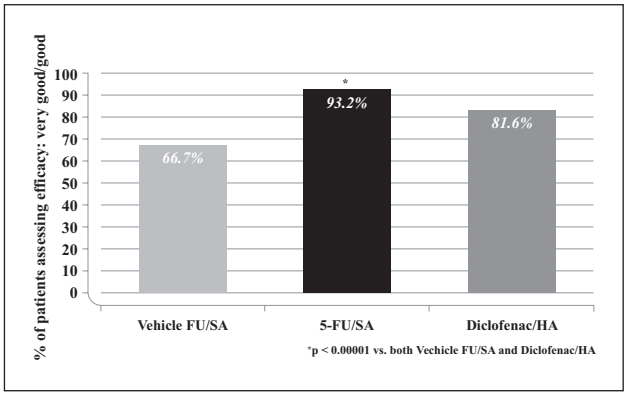

Figure 2. Patients' assessment of clinical improvement (FAS) at PT visit.

EOT the number of patients reporting inflammation (50.9% 5-FU/SA, n=89/175; 22.6% vehicle FU/SA, n=21/93; 21.7% diclofenac/HA, n=38/175) and burning (62.2% 5-FU/SA, n=109/175; 38.7% vehicle FU/SA, n=36/93; 16.6% diclofenac/HA, n=29/175) had decreased in all three treatment groups but was still highest in the 5-FU/SA group ($p<0.0001$ for 5-FU/SA *versus* vehicle and diclofenac/HA for both inflammation and burning). At the PT visit the number of patients reporting inflammation and burning had further decreased in all three treatment groups as the treatment was stopped and there was no statistically significant difference between the treatment groups any more.
Itching was reported in all three treatment groups by a similar percentage of patients. No clinically relevant differences were seen between the treatment groups at week 6, EOT or PT visit. At week 6, pain was reported more frequently by patients in the 5-FU/SA group (20.5% (n=36/176) compared to 5.4% (n=5/94) and 5.7% (n=10/176) in the vehicle FU/SA and diclofenac/HA groups, respectively, $p<0.025$). These differences decreased until the EOT. At the PT visit nearly all patients were without pain (98.9-100%).

Patients' assessment of compatibility

At follow-up 6 months after EOT, compatibility of the medication was considered as "good" or "very good" in fewer patients in the 5-FU/SA group (80.6%, n=137/170) compared to the vehicle FU/SA group (91.0%, n=81/89) and the diclofenac/HA group (90.5%, n=144/159) ($p=0.003$ for 5-FU/SA *versus* vehicle FU/SA and $p<0.0001$ for 5-FU/SA *versus* diclofenac/HA). Nearly all patients (94.7%, n=161/170), however, in the 5-FU/SA group would recommend the treatment, compared to 79.5% of patients (n=72/88) in the vehicle FU/SA group and 88.7% of patients (n=141/159) in the diclofenac/HA group ($p<0.0001$ for 5-FU/SA *versus* vehicle and $p=0.0233$ for 5-FU/SA *versus* diclofenac/HA).

Patients' assessment of skin feeling, product appearance and ease of application

At EOT, skin feeling was rated as "very good" or "good" by 62.8% patients (n=110/175) in the 5-FU/SA group compared to 78.5% (n=73/93) in the vehicle FU/SA group and 89.2% (n=156/175) in the diclofenac/HA group ($p<0.025$ for 5-FU/SA *versus* vehicle FU/SA and diclofenac/HA). The majority of patients in all three treatment groups rated the product appearance as "very good" or "good" and the ease of application of the treatment as "very good" or "good". 87.5% of patients (n=154/176) applying the 0.5% 5-FU/SA solution by brush rated this application procedure as "very good" or "good" at week 6.

Skin quality

There were no large differences for skin quality assessed at follow-up 6 and 12 months after EOT between the three treatment groups. Compared to the PT visit, most patients showed no change or an improvement.

Patients' assessment of practicability and handling

At follow-up 12 months after EOT there were no differences between the treatments with respect to practicability and problems with handling of the study medication assessed. Most patients applied the medication themselves (67.5% 5-FU/SA, n=77/114; 72.9% vehicle FU/SA, n=43/59; 69.6% diclofenac/HA, n=71/102, no statistically significant difference). In 23.7% of patients (n=14) using 5-FU/SA and in 19.6% (n=20) using diclofenac/HA, a partner or nurse applied the medication (no statistically significant difference). Treatment of lesions on the scalp could be performed precisely by the majority of patients (88.5% 5-FU/SA, n=100/113; 86.0% vehicle FU/SA, n=49/57; 90.9% diclofenac/HA, n=90/99, no statistically significant difference). All patients who were to apply study medication on hairy areas reported that they had no problems, except for 2 patients in the 5-FU/SA group. These data are in accordance with the outcomes at EOT. At that visit, the treatment administration was rated as "very good" or "good" by 84.6% of patients (n=148/175) using 5-FU/SA, 90.4% (n=84/93) using the vehicle FU/SA and 98.8% (n=173/175) using diclofenac/HA.

Discussion

In this controlled study we evaluated, in addition to outcomes of the treatment phase, the long-term sustained clinical benefit of topical 5-fluorouracil 0.5% in combination with salicylic acid 10.0% as a novel lesion-directed treatment for mild to moderate hyperkeratotic AK. At follow-up 6 and 12 months after end of treatment (EOT), 5-FU/SA demonstrated superiority to the standard therapy, diclofenac 3.0% in hyaluronic acid 2.5%, when measuring AK lesion recurrence rates. The frequency of sustained cleared lesions was significantly higher following treatment with 5-FU/SA than with its vehicle or diclofenac/HA. These data indicate a clear clinical benefit in lesion sustained clearance of 5-FU/SA over its vehicle and diclofenac/HA. The long-term sustained clinical efficacy of 5-FU/SA (85.8%) demonstrated in this study is underpinned by evidence of high histological clearance at the primary study endpoint (8 weeks post-treatment) as previously reported [5]. The histological clearance rate of 72.0% of 0.5% 5-FU/SA was statistically superior compared with its vehicle (44.8%, $p<0.0001$) and diclofenac/HA (59.1%, $p<0.01$). The clinical lesion response in relation to the grade of severity

(mild or moderate hyperkeratotic AK) was statistically significant for 0.5% 5-FU/SA and diclofenac/HA *versus* vehicle ($p<0.001$). Mild AK were reduced by 80.2%, AKII by 73.6% treated with 5-FU/SA ($p>0.001$ *versus* vehicle for both groups).

These data are of specific value as there are few evidence-based reports available for long-term treatment regimens in AK. Smaller populations and primarily mono-centre studies report sustained clearance rates of 28% for cryosurgery, 54% for 5-FU 5% cream and 73% for imiquimod 5% [10]. Patients' assessments of clinical improvement 8 weeks post-treatment confirmed the results of the clinical outcomes of the study. According to patients, 5-FU/SA provided a better clinical outcome than treatment with its vehicle or diclofenac/HA. Although local side effects, such as inflammation and burning, were common in the 0.5% 5-FU/SA group, they were mainly of mild to moderate intensity and were accepted by patients at the time of onset. Physician overall tolerability was rated in 77.2% of patients as "very good" or "good". Overall, patients tolerated the treatment well and nearly all patients (94.7%) treated with 5-FU/SA would recommend the treatment, compared to 79.5% and 88.7% of patients, respectively, treated with vehicle FU/SA and diclofenac/HA, reflecting the high rate of 93.2% of patients rating efficacy as "very good" or "good". A high level of compliance was also observed across all treatment groups. This is important as a review of patient adherence to topical dermatologic medications found that suboptimal adherence is a common cause of minimal or lack of response to treatment and is linked with poor dermatologic outcomes [11].

Treatment efficacy depends also on the patients' product acceptance. In this study we reached a compliance rate acceptance of the product of around 85%. Only 7 patients in the 0.5% FU/SA treatment group (3.7%) dropped out due to application side effects. Most patients rated the product appearance and ease of application of the study treatments as "very good" or "good", however, the ratings were highest in the diclofenac/HA group. Patients rated the skin feeling of diclofenac/HA treatment better than 5-FU/SA or its vehicle. At follow-up, patients' assessment of practicability and problems with the handling of study medications gave no indications for any differences between the treatments.

In conclusion, 0.5% 5-fluorouracil combined with 10% salicylic acid once daily represents a highly effective lesion directed treatment for mild to moderate hyperkeratotic AK, offering an efficacious alternative to existing therapies with acceptable tolerability, practicability and handling. Targeted topical application of 5-FU/SA solution with an integrated brush device demonstrates high efficacy, documented by histological clearance at 8 weeks post-treatment and long-term sustained clinical efficacy after 12 months. ■

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