ORIGINAL ARTICLE

Long-term clinical outcomes of imiquimod 5% cream vs. diclofenac 3% gel for actinic keratosis on the face or scalp: a pooled analysis of two randomized controlled trials

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Abstract

Background Actinic keratosis (AK) is an early *in situ* epidermal cancer which can progress to invasive squamous cell carcinoma (SCC). Imiquimod 5% cream (IMIQ) and diclofenac 3% gel (DIC) are frequently used to treat AK; however, their long-term effects following repeated treatment cycles have never been compared.

Objective To compare IMIQ and DIC in the treatment of AK with respect to the risk of change to grade III AK or invasive SCC, after 3 years.

Methods Data were pooled from two randomized, active-controlled, open-label, multicentre, multinational, phase IV studies (Clinicaltrials.gov NCT00777127/NCT01453179), with two parallel groups. Studies were conducted between 2008 and 2015 and were almost identical in design. Patients eligible for inclusion were immunocompetent adults with 5–10 visible AK lesions on the face/scalp and grade I/II AK. The primary endpoint was inhibition of histological change to grade III AK or invasive SCC in the study treatment area, observed until month 36. Patients applied either IMIQ or DIC for a maximum of six treatment cycles.

Results In total, 479 patients (IMIQ 242; DIC 237) were included in the full analysis set. Histological change to grade III AK or invasive SCC was observed until month 36 in 13 (5.4%) patients treated with IMIQ, compared with 26 (11.0%) patients treated with DIC (absolute risk difference −5.6% [95% confidence interval −10.7%, −0.7%]). Time to histological change was greater in the IMIQ group than the DIC group ($P = 0.0266$). Frequency of progression to invasive SCC was lower with IMIQ than with DIC at all time points. Initial clearance rate was higher in the IMIQ group compared with the DIC group, while recurrence rate was lower. Both treatments were well tolerated.

Conclusions Over 3 years, IMIQ was superior to DIC in clearing AK lesions and preventing histological change to grade III AK or invasive SCC and recurrence.

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Introduction

Actinic keratosis (AK) is an epidermal disease presenting as early *in situ* cancer of different grades (grades I–III), which can progress into invasive squamous cell carcinoma (SCC).[1–4] AK lesions are the initial clinical presentation, and recent research has shown that early stages of AK can directly evolve into invasive SCC.[1,2,5] The disease, which is typically caused by excessive exposure to sunlight, has a chronic course in which new or recurrent lesions often develop over time; the entire area of sun-exposed skin can be affected leading, in some cases, to field cancerization in which subclinical disease, clinical AK lesions and invasive SCC may co-exist.[6] Consequently, therapies need to clear both clinical and subclinical lesions across the entire affected field to reduce the likelihood of disease recurrence and minimize progression to invasive SCC.

Currently, the following forms for AK treatment exist: immunobiologics and ablative techniques such as electrodessication, cryotherapy, carbon dioxide laser or surgery. Immunobiologic therapies include imiquimod 5% cream (IMIQ, Aldara®), diclofenac 3% gel (DIC, Solaraze®) and ingenol mebutate 0.015% (Picato®). IMIQ is an immune response modifier, which acts as a toll-like receptor 7 agonist. This immune response is mediated through increased production of various pro-inflammatory cytokines such as interferon-α, tumour necrosis factor-α and interleukins 1, 6, 8, 10 and 12, through involvement of immune cells.[7–9] These cytokines stimulate both the innate and acquired immune pathways leading to enhancement of both antiviral and antitumour activity.[7] IMIQ also stimulates apoptosis in skin cancer cells.[10] IMIQ can also be used to treat subclinical lesions, as evidenced by an increase in lesion count during IMIQ treatment.[11,12] The effective detection and clearance of clinical and subclinical lesions translates into low disease recurrence rates.[13] DIC is a non-steroidal anti-inflammatory agent which acts through inhibition of cyclooxygenase-2, inhibition of angiogenesis and induction of apoptosis.[14–16] During treatment with DIC, there is no increase in lesion count[17] and, currently, no published evidence to suggest that subclinical lesions are detected and cleared.

Although IMIQ and DIC have been investigated in patients with AK over 1–5 years of follow-up,[13,17–21] the efficacy and safety of these treatments have only previously been directly compared in two short-term studies.[22,23] Therefore, the aim of this pooled analysis was to determine the long-term effects of repeated administrations of IMIQ vs. DIC in the treatment of AK, with respect to the risk of change to higher *in situ* grades or invasive SCC on the face or scalp, and to compare their safety profiles over a 3-year period.

Methods

We report on the pooled analysis of two randomized, active-controlled, open-label, multicentre, multinational, phase IV studies with two parallel groups with follow-up over 3 years after randomization (Study 3271 [ClinicalTrials.gov number NCT00777127] and 3284 [ClinicalTrials.gov number NCT01453179]). The trial designs of the studies were almost identical.

Study 3271 was conducted in 26 centres (17 in Germany, four in Austria and five in France) between November 2008 and November 2012, and Study 3284 was conducted in 17 centres (14 in Germany and three in Austria) between September 2011 and March 2015. The studies were approved by a leading ethics committee for each country involved in the studies. The pooled analysis was planned in the protocol of Study 3284, and the Statistical Meta-Analysis Plan (SMAP) was finalized while Study 3271 was still ongoing. The trials were carried out in accordance to the laws and guidelines current at that time: the German and Austrian drug laws (and French drug laws for Study 3271), the principles of the Declaration of Helsinki (Seoul 2008), the Guideline for Good Clinical Practice (GCP; ICH E6), and the EU GCP directives (2001/20/EC, 2005/28/EC, 2010/C 82/01) and their translations into national legislation. All patients provided written informed consent before participation in the studies.

Patients

In both studies, patients were eligible for inclusion if they were immunocompetent adults with 5–10 typical visible AK lesions in one contiguous area of up to 50 cm^2 on the face or scalp (the study treatment area [STA]), excluding the eyelids, the inside of the nostrils or ears and the lip inside the vermilion border. Patients also had to have grade I or II AK[4] determined by histological analysis of the pathological area from the most suspicious lesion in the STA, biopsied during the screening visit. This analysis was done by a central histopathological laboratory.

Exclusion criteria for the two studies were the same, with the exception of the exclusion of patients who had 'topical treatment with IMIQ or DIC anywhere else on the body within the last 2 months prior to randomization' for Study 3271. Patients were not eligible if they had received any topical or surgical AK treatment of the STA, had any systemic AK treatment or had been treated anywhere else with topical IMIQ or DIC within the 2 months prior to randomization.

Randomization and blinding

Patients were randomized in a 1:1 ratio to treatment with IMIQ or DIC via an interactive web-based randomization system in Study 3284 and via a central randomization system (TrialLine) in Study 3271 (co-ordinated by the Investigator). The study medication was not blinded or repackaged. Assessments were made by a blinded investigator in Study 3271, but this was not required according to EMA requirements in Study 3284. However, all professionals and all documentation at, and provided by, the central histopathological laboratory remained blinded to the study treatments administered throughout the study.

Interventions

IMIQ cream and DIC gel were administered as recommended by the Summary of Product Characteristics (SmPC).[24,25] During a treatment cycle, IMIQ was applied 3 nights per week, for 4 weeks followed by a 4-week treatment pause (Fig. 1).[24] If lesions in the STA had cleared following 4 weeks of treatment, the patient received no further treatment for the next 12 weeks. If the lesions had not cleared, the patient received a second 4-week course of treatment followed by an 8-week off-treatment phase. DIC was applied twice daily for 12 weeks followed by an 8-week off-treatment phase (Fig. 1).[25] A total treatment cycle for both regimens lasted 20 weeks (Fig. 1).

Efficacy was always assessed 20 weeks after the start of a treatment cycle. If the STA was not completely cleared at a regular half-yearly follow-up visit (i.e. months 6, 12, 18, 24 or 30), the patient received an additional treatment cycle using study medication as randomized, starting at that visit. If the STA was completely cleared at a regular half-yearly follow-up visit, then the patient had to come to the next half-yearly follow-up visit; the STA was not to be treated during this time. Patients could receive a maximum of five additional treatment cycles.

If one or more AK lesions remained in the STA after a complete treatment cycle (i.e. at week 20 of a given treatment cycle), the most suspicious lesion was biopsied and histologically characterized. If lesions remained after additional treatment cycles, these were treated by cryotherapy. Nevertheless, additional cycles could have been prescribed.

Outcomes

The primary efficacy endpoint was inhibition of histological change to grade III AK or invasive SCC in the STA, which was observed until month 36. Grade III AK was defined as atypical keratinocytes involving the full thickness of the epidermis, including the epithelia of the hair follicle, infundibula and acrosyringia. Time to histological change was an exploratory analysis.

Secondary efficacy endpoints included progression to invasive SCC in the STA, initial clearance rate (defined as the proportion of patients with all AK lesions cleared in the STA at week 20 of the initial treatment cycle), recurrence rate and time to recurrence. Patients were classified as recurrent if they had no AK lesions in the STA at week 20 and had a least one clinically diagnosed AK lesion in the STA later on. In addition, patients that withdrew from treatment before week 20 or were not cleared (patients with at least one AK lesion in the STA at week 20) were also classed as recurrent.

All adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities.

Statistical analyses

The pooled analysis was performed using the combined efficacy data from Study 3271 and Study 3284 (by pooling of the individual patient data), in accordance with the SMAP. Assuming a one-sided type I error level $\alpha = 2.5\%$ and 80% power, 183 patients per group would be required. Allowing for a drop-out rate of 30%, the required sample size was $476 = 2 \times 238$ randomized patients in total. Therefore, the target sample size of both studies together was set to 480 patients. The full analysis set (FAS) comprised all subjects who were exposed to study medication and who had efficacy data from at least one follow-up. The safety set comprised all patients who received at least one dose of study medication.

Descriptive statistics are presented for each variable. For the primary analysis, non-inferiority of IMIQ compared with DIC was concluded if the upper bound of the 2-sided 95% Newcombe–Wilson score confidence interval (CI) (corresponding to a 1-sided 97.5% CI) for the difference up until month 36 was $\leq \delta = 5\%$. Subsequently, superiority could be concluded if it was <0. Further analyses included Kaplan–Meier estimates and log-rank tests; and Newcombe–Wilson score CIs for difference in incidence between treatment groups.

Results

Patients

A total of 482 patients were randomized in both studies. Of these, 479 were included in the FAS and were eligible for this pooled analysis (242 patients in the IMIQ group; 237 patients in the DIC group; Fig. 2). Demographic and baseline characteristics were comparable between treatment groups (Table 1). The majority of patients in both treatment groups were male (IMIQ 83.9%; DIC 90.3%), and elderly, with the mean age being 70.8 and 71.1 years in the IMIQ and DIC groups, respectively.

One hundred and sixty-two (33.8%) patients withdrew from study treatment during the 3-year study period. Withdrawals were lower in the IMIQ group compared with the DIC group (IMIQ 28.9%; DIC 38.8%). The frequency of withdrawals due to lack of efficacy or adverse events was slightly lower for patients treated with IMIQ compared with DIC (5.4%, 7.9% vs. 12.7%,
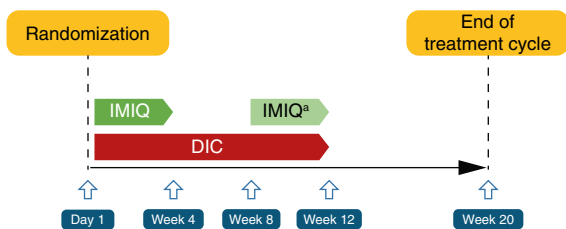

Figure 1 Scheme for the first treatment cycle in studies 3271 and 3284. [a]Second course of IMIQ treatment was given if the study treatment area was not completely clear at week 8. DIC, diclofenac 3% gel; IMIQ, imiquimod 5% cream.
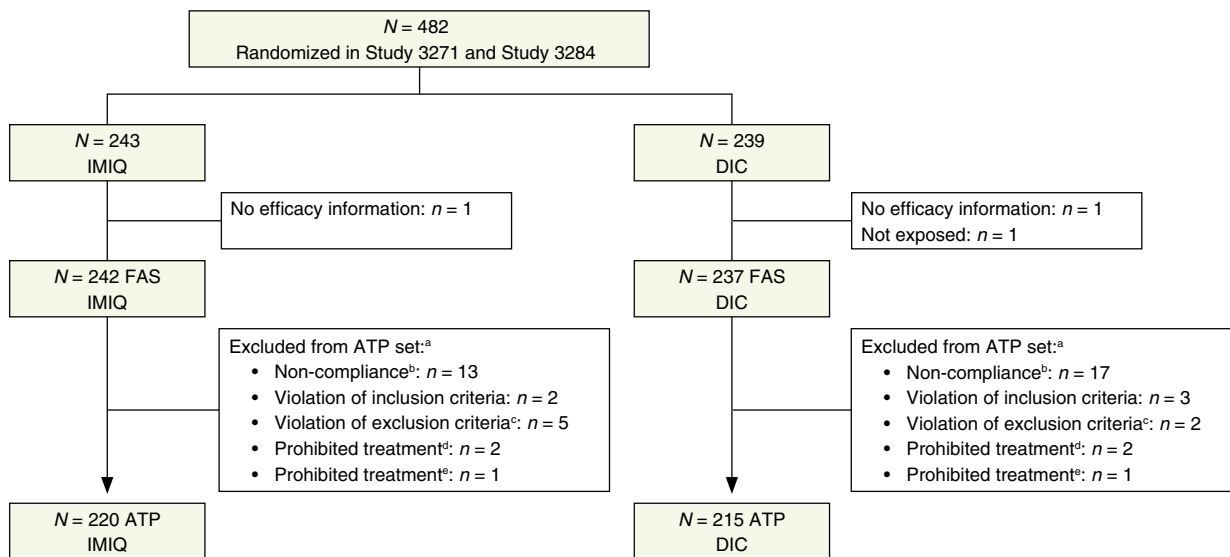
Figure 2 Patient disposition. [a]Multiple responses were possible. [b]Non-compliance (<70% of the intended medication was used during the first treatment cycle). [c]Violation of exclusion criteria in category ('Lack of suitability for the study'). [d]Sustained systemic immunomodulatory treatment before month 12 when recurrence had not yet occurred. [e]Treatment in the STA with psoralen-ultraviolet-A (PUVA), ultraviolet-B therapy or sustained treatment with topical steroids before month 12 when recurrence had not yet occurred. ATP, according-to-protocol; DIC, diclofenac; FAS, full analysis set; IMIQ, imiquimod

Table 1 Demographic and baseline characteristics, FAS

	FAS	
	IMIQ N = 242	DIC N = 237
Sex, n (%)		
Male	203 (83.9)	214 (90.3)
Female	39 (16.1)	23 (9.7)
Age, mean years (± SD)*	70.8 (7.9)	71.1 (7.9)
Ethnic origin		
Caucasian	242	237
Weight, mean kg (± SD)	80.3 (12.4)	81.0 (12.9)
BMI, mean kg/m^2 (± SD)	26.8 (3.5)	26.8 (3.6)

*At time of screening.
BMI, body mass index; DIC, diclofenac 3% gel; IMIQ, imiquimod 5% cream; FAS, full analysis set; SD, standard deviation.

11.4%, respectively). A total of 96 (20.0%) patients withdrew from follow-up.

Mean duration of study treatment (calculated as time from first exposure to last exposure of study medication) was longer for DIC compared with IMIQ (557.7 days vs. 440.6 days). Mean number of treatment cycles per patient was lower in the IMIQ group compared with the DIC group (2.4 vs. 2.9). Higher proportions of patients treated with DIC had treatment cycles at months 6, 12, 18, 24 and 30, compared with IMIQ.

Outcomes

Primary efficacy variable Histological change to grade III AK or invasive SCC in the STA was observed up to month 36 in 13 (5.4%) patients in the IMIQ group and 26 (11.0%) patients in the DIC group (absolute risk difference: −5.6%; 95% CI −10.7%, −0.7%). The treatment difference observed for histological change at month 36 was also apparent at month 12 (absolute risk difference: −3.9%; 95% CI −8.2%, 0.2%) and 24 (absolute risk difference: −4.7%; 95% CI −9.2%, −0.5%). Time to histological change was greater in the IMIQ group than in the DIC group ($P = 0.0266$) (Fig. 3; exploratory analysis).

Secondary efficacy variables The proportion of patients with progression to invasive SCC in the STA was greater in the DIC group than in the IMIQ group at all time points (months 12, 24 and 36, until last treatment cycle, and until last follow-up) (Table 2).

At week 20, the initial clearance rate was higher in the IMIQ group (52.1%) than in the DIC group (35.4%; absolute risk difference of 16.6%; 95% CI 7.7%, 25.1%).

The recurrence rate was higher in the DIC group than in the IMIQ group at all time points (Table 3). When subjects without initial clearance were excluded from the analysis, the recurrence rate at month 36 was 66.7% in the IMIQ group and 73.8% in the DIC group (absolute risk difference: −7.1%; 95% CI
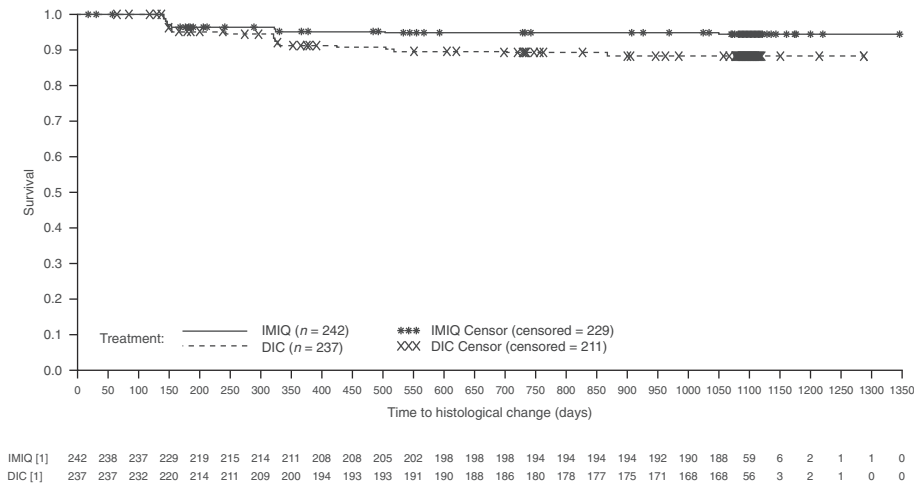
Figure 3 Time to histological change, FAS. DIC, diclofenac; FAS, full analysis set; IMIQ, imiquimod

−19.0%, 5.7%). Analysis of time to recurrence showed that the treatment effect was maintained after week 20 with the probability of recurrence being higher in the DIC group than in the IMIQ group at all time points until end of follow-up (*P* = 0.0025) (Fig. 4). When the time to recurrence analysis was restricted to a subgroup of patients who had initial clearance at week 20, the log-rank test resulted in a *P*-value of 0.1646.

Safety

Combined data from Studies 3271 and 3284 show that treatment-emergent adverse events (TEAEs) occurred in 86% of patients on IMIQ and 82% on DIC, of which 21% and 18% were assessed as treatment-related, respectively. The majority of TEAEs were mild or moderate in intensity. TEAEs of special interest and of any cause are listed in Table 4. As expected, local skin reactions occurred in both groups; application site pain was more frequent in the IMIQ group while dermatitis- and rash-like events were more frequent in the DIC group. Overall, severe TEAEs occurred in 17% of patients on IMIQ and 23% on DIC. From both studies, seven (2.9%) patients in the IMIQ group and three (1.3%) patients in the DIC group died. None of the serious adverse events (including deaths) were treatment-related, apart from one serious TEAE (application site dermatitis) reported in the DIC group.

Discussion

AK is a common and chronic disease of the elderly, and long-term management is needed. The studies included in this pooled

Table 2 Progression to invasive SCC, FAS

Time point	IMIQ (*N* = 242) n (%)	DIC (*N* = 237) n (%)	Difference (95% CI)*
Month 12	3 (1.2)	5 (2.1)	−0.9 (−3.7, 1.8)
Month 24	3 (1.2)	6 (2.5)	−1.3 (−4.3, 1.4)
Month 36	4 (1.7)	7 (3.0)	−1.3 (−4.5, 1.6)
Until last follow-up	4 (1.7)	7 (3.0)	−1.3 (−4.5, 1.6)
Until last treatment cycle	1 (0.4)	2 (0.8)	−0.4 (−2.6, 1.6)

*Newcombe–Wilson score confidence interval for the absolute risk difference (IMIQ − DIC) for recurrence rate by visit.
Progression to invasive SCC was defined as the histological finding of an invasive SCC in the STA after the start of treatment. Data are the cumulative number of patients. Missing data and withdrawals were classed as no progression to invasive SCC.
CI, confidence interval; DIC, diclofenac; FAS, full analysis set; IMIQ, imiquimod; SCC, squamous cell carcinoma; STA, study treatment area.

Table 3 Recurrence rate by visit, FAS

Time point	IMIQ (*N* = 242) n (%)	DIC (*N* = 237) n (%)	Difference (95% CI)*
Month 12	166 (68.6)	195 (82.3)	−13.7 (−21.2, −6.0)
Month 18	182 (75.2)	203 (85.7)	−10.4 (−17.4, −3.3)
Month 24	190 (78.5)	211 (89.0)	−10.5 (−17.1, −3.9)
Month 30	197 (81.4)	215 (90.7)	−9.3 (−15.5, −3.1)
Month 36	200 (82.6)	215 (90.7)	−8.1 (−14.2, −2.0)

*Newcombe–Wilson score confidence interval for the absolute risk difference (IMIQ − DIC) for progression to invasive SCC.
Patients were classified as recurrent if they had no AK lesions in the STA at week 20 and had a least one clinically diagnosed AK lesion in the STA later on. In addition, patients that withdrew from treatment before week 20 or were not cleared (patients with at least one AK lesion in the STA at week 20) were also classed as recurrent.
AK, actinic keratosis; CI, confidence interval; DIC, diclofenac; FAS, full analysis set; IMIQ, imiquimod; SCC, squamous cell carcinoma; STA, study treatment area.
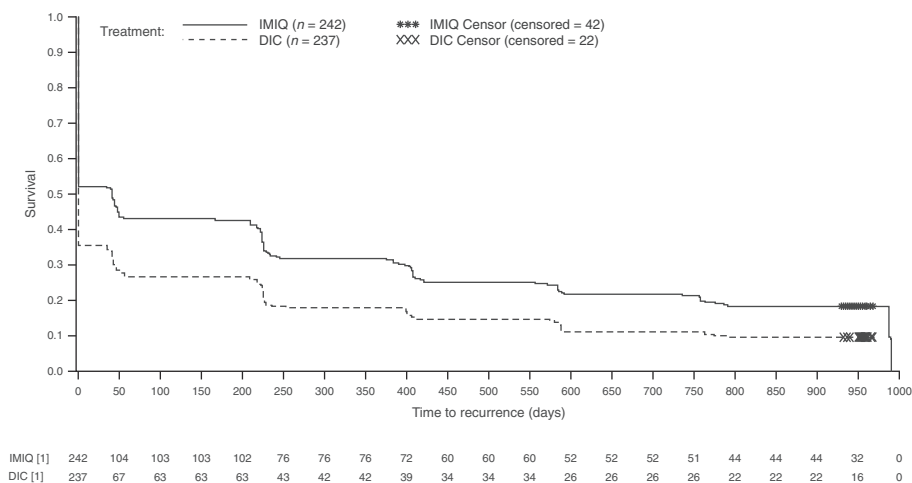
Figure 4 Time to recurrence, FAS. DIC, diclofenac; FAS, full analysis set; IMIQ, imiquimod

analysis are the first studies of field-directed AK therapy to compare the long-term efficacy of IMIQ and DIC with repeated treatment cycles over 3 years. The design of the studies allowed patients to receive repeated treatment cycles (a maximum of six), if the STA was not completely cleared. This is considered to

Table 4 All treatment-emergent adverse events of special interest, any causality

Adverse event*	IMIQ (N = 243) n (%)	DIC (N = 238) n (%)
Number of patients with ≥ 1 event		
Mild	24 (9.9)	19 (8.0)
Moderate	24 (9.9)	24 (10.1)
Severe	3 (1.2)	9 (3.8)
Application site pruritus	13 (5.3)	16 (6.7)
Application site pain	6 (2.5)	2 (0.8)
Application site dermatitis	0	6 (2.5)
Application site reaction	5 (2.1)	5 (2.1)
Application site irritation	5 (2.1)	4 (1.7)
Application site inflammation	2 (0.8)	3 (1.3)
Application site rash	0	3 (1.3)
Application site infection	2 (0.8)	0
Alopecia	3 (1.2)	3 (1.3)
Anaemia	3 (1.2)	2 (0.8)
Psoriasis	2 (0.8)	0

*Adverse event data given when experienced by ≥2 patients in either treatment group.
Adverse events of special interest were defined as haematological adverse events including (immune) thrombocytopenia; stimulation or exacerbation of (auto) immune conditions; alopecia; local skin reactions; other adverse events in the study treatment area; angio-oedema/capillary leak syndrome (hypersensitivity); lichen planus plus related terms.
DIC, diclofenac; IMIQ, imiquimod.

be representative of current clinical practice. In contrast, previous long-term studies of IMIQ or DIC only investigated the effects of a single treatment cycle.[17–19] The results from this pooled analysis show that IMIQ was superior to DIC in preventing histological change to grade III AK or invasive SCC over a 3-year period, with such histological change occurring in 50% fewer patients in the IMIQ group, relative to DIC (5.4% vs. 11.0%). Furthermore, time to histological change was significantly longer in the IMIQ group than in the DIC group.

While the primary endpoint of this pooled analysis was based on histological change of AK lesions, it must be noted that, at present, it is difficult to predict the progression risk of individual AK lesions. An established histological classification system was described by Röwert-Huber et al.,[26] which grades the extent of atypical keratinocytes throughout the epidermis. In early in situ SCC grade I AK (mild), atypical keratinocytes are confined to the basal and suprabasal layer of the lower one-third of the epidermis. In early in situ SCC grade II AK (moderate), atypical keratinocytes extend to the lower two-thirds of the epidermis, whereas in in situ SCC grade III AK (severe), atypical keratinocytes extend to more than two-thirds of the full thickness of the epidermis.[26] According to current knowledge, within this grading system, every single AK lesion has the tendency to progress into invasive SCC and subsequently metastasize.[27,28] Furthermore, two recent studies have identified grade I AK lesions as the lesions most commonly associated with invasive SCC.[5,29] As such, the clinical relevance of inhibiting histological change to grade III AK is currently uncertain.

While the results relating to histological change to higher grades of AK are difficult to interpret, the finding that the frequency of progression to invasive SCC was numerically lower in the IMIQ group than in the DIC group provides evidence for a

beneficial effect of IMIQ on disease progression compared with DIC. An explanation could be that IMIQ clears not only clinical AK lesions but also sub-clinical lesions.[30]

Recurrence was measured as a composite of the proportion of patients who were recurrent after week 20, together with those who were not cleared or were withdrawn from the study by week 20. The probability of recurrence over time was significantly higher in the DIC group than in the IMIQ group ($P = 0.0025$). When this analysis was repeated including only patients who had clearance at week 20 of the initial treatment cycle, the log-rank test resulted in a P-value of 0.1646. This could be attributed to a reduced sample size in this subgroup. Alternatively, it could indicate that there is no difference in time to recurrence if a patient responds exceptionally well to either treatment.

The lower recurrence with IMIQ may be due to its mode of action, which can detect and treat both clinical and subclinical lesions.[11,31] In addition, IMIQ may provide long-term disease control by stimulating immune memory via cell-mediated anti-tumour pathways.[10,32,33] A comparative study with a 1-year follow-up showed non-recurrence rates of initially cleared lesions were higher with IMIQ (86%), compared with 5-fluorouracil (57%) and cryotherapy (41%).[13] A further study of IMIQ showed that only 25% of patients, treated three times per week for 16 weeks, had AK recurrence during an 18-month follow-up;[19] this was similar to an additional study that showed only 20% of patients developed new AKs or were lost to follow-up 2 years after treatment.[18] These studies support the findings of this pooled analysis. In a 1-year follow-up of patients treated with DIC twice daily for 90 days and who did not receive any additional AK treatment in the designated areas, 100% clearance of cumulative lesions was only achieved in 30% of patients.[17]

Initial clearance rate was higher in the IMIQ group than in the DIC group (52.1% vs. 35.4%) with an absolute risk difference of 16.6% (95% CI: 7.7%, 25.1%). Clearance may lead to increased patient adherence, which is an important factor in chronic disease management. A previous study showed that initial clearance rates with IMIQ were high, with 89.6% of patients being clear by 12 weeks post-treatment.[21] In a long-term follow-up of this study, 162 patients were analysed in the estimate for the sustained clearance rate, and of these, only 18 patients had a clinical recurrence at the end of the 60-month period.[20] This high sustained clearance rate 5 years following IMIQ treatment is encouraging and supported by the results of this pooled analysis.

The frequency of withdrawals due to lack of efficacy was lower in the IMIQ group, compared with the DIC group. There was also a marked difference in the mean duration of study treatment between the two treatment groups (IMIQ: 440.6 days; DIC: 557.7 days), which could have been because a lower number of patients received additional IMIQ treatment cycles compared with DIC. The reduced number of treatment cycles required with IMIQ highlights its efficacy compared with DIC, which had to be used more frequently. Two previous short-term comparative studies of IMIQ and DIC reported that these treatments have similar efficacy; however, these studies only evaluated the effect of a single treatment cycle and used different regimens to those in the current study.[22,23]

Safety data showed that both treatments were well tolerated during the first and subsequent treatment cycles, similar to the findings of previous short-term comparative studies,[22,23] thus supporting the use of additional treatment cycles in daily practice. As expected, due to the mode of action of IMIQ, local skin reactions were common with this treatment.[12] These skin reactions indicate that the immune system has been activated; however, reactions usually decrease in intensity during therapy, indicating a beneficial effect.[24] The skin reactions usually resolve following cessation of therapy.[24]

One limitation of the studies in this pooled analysis was the open-label study design. Blinding of study medication was not possible due to the different administration schemes. However, it is unlikely the absence of a blinded investigator would have had a major impact on results as histological assessments were performed by blinded histological examinations of biopsy specimens in both studies. A further limitation of these studies could be the high number of withdrawals. This could have been due to the long-term study designs, with a 3-year follow-up causing some subjects in this group of elderly patients to withdraw. Regular biopsies could have also influenced the high withdrawal rate. An additional limitation was that the most suspicious lesions were biopsied, both for the enrolment of patients in the study and in cases where lesions remained after a complete treatment cycle. However, there is no established relationship between the clinical appearance and histology of a given lesion.[34,35] Finally, it must be acknowledged that performing biopsies of different lesions before and after treatment in order to assess histological changes has limitations, since this does not allow a lesion to be investigated in a longitudinal manner. Although the second biopsy was taken in the zone immediately adjacent to the first biopsy to minimize this limitation, the AK field is histologically quite diverse. Despite these limitations, biopsies are still a standard and other (non-invasive) procedures have not been demonstrated to differentiate histological variability of AK.

In conclusion, AK lesions require a long-term disease management approach that encourages patient adherence, in order to improve disease outcomes. The results presented here show that, over the long-term, IMIQ is more effective than DIC at treating AK lesions, with superior lesion clearance, fewer recurrences and less histological change to grade III AK or invasive SCC.

Acknowledgments

Data availability statement

Requests for datasets generated and/or analysed during the current study should be sent to the corresponding author (Harald Gollnick).

Authors' contributions

All authors provided substantial contribution to the design, acquisition of data, analysis and interpretation of data. Authors critically reviewed the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 CONSORT 2010 checklist of information to include when reporting a randomised trial.