Open-Label Study to Assess the Safety and Efficacy of Imiquimod 5% Cream Applied Once Daily Three Times per Week in Cycles for Treatment of Actinic Keratoses on the Head

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Background: **Local skin reactions are common during imiquimod treatment of actinic keratosis (AK). Cyclical application of imiquimod may improve tolerability while maintaining efficacy.**

Objective: **To assess the tolerability of imiquimod and clearance rate of AK lesions after imiquimod application.**

Methods: **Imiquimod 5% cream was administered three times per week for 4 weeks followed by 4 weeks of rest (cycle 1) to AK lesions on the head. If AK lesions remained visible at the end of cycle 1, a second treatment cycle was instituted.**

Results: **Fifty percent (30 of 60) of patients experienced complete clearance of AK lesions, and 75% (30 of 40) of patients experienced partial clearance of AK lesions after imiquimod treatment at the end of cycle 2. Moreover, 77% of patients who achieved complete clearance had no visible AK lesions 12 weeks post-treatment. Imiquimod was well tolerated.**

Conclusion: **Imiquimod cycle therapy may be a safe and effective treatment option for AK lesions.**

Antécédents: **Les réactions au niveau du site d'application sont fréquentes durant le traitement des kératoses actiniques (KA) à l'imiquimod. L'application cyclique de l'imiquimod pourrait améliorer la tolérance tout en maintenant l'efficacité du produit.**

Objectif: **Évaluer la tolérance à l'imiquimod et le taux d'épuration des lésions de KA après application d'imiquimod.**

Méthodes: **La crème d'imiquimod à 5 % a été appliquée sur les KA de la tête trois fois par semaine pendant 4 semaines, suivies de 4 semaines sans traitement (cycle 1). Si les KA étaient encore visibles à la fin du cycle 1, un autre cycle serait entamé.**

Résultats: **À la fin du cycle 2 du traitement cyclique à l'imiquimod, 50 % des patients (30/60) ont affiché une épuration totale de toutes les lésions de KA, et 75 % (30/40) des patients une épuration partielle. En outre, 77 % des patients dont l'épuration était totale ne présentaient aucune lésion visible de KA 12 semaines après le traitement. L'imiquimod a été très bien toléré.**

Conclusion: **Le traitement cyclique à l'imiquimod représenterait une option de traitement sécuritaire et efficace des lésions de KA.**

ACTINIC KERATOSES (AKs) frequently arise on sun-exposed areas of the skin and, if left untreated, may evolve into invasive squamous cell carcinoma (SCC).[1,2] The prevalence of AK in the Northern hemisphere ranges from 11 to 26%, and AK is most prevalent in men over the age of 30 years.[3] Risk factors include ultraviolet exposure, fair skin, male sex, advanced age, immunosuppression, smoking, and a high-fat diet.[4–6] The aim of AK treatment is to prevent the development of invasive SCC, to reduce the likelihood of new lesions, and to improve cosmesis.

Imiquimod is a topical immune response modifier approved for the treatment of AK, superficial basal cell carcinoma (BCC), and external anogenital warts.[7] Imiquimod, an agonist of Toll-like receptor 7, activates monocytes, macrophages, and dendritic cells and stimulates the secretion of cytokines, including interferon (IFN)-α, IFN-γ, interleukin-12, and tumor necrosis factor α.[8–10] These cytokines activate the type 1 T helper cell–mediated immune response.[8–10] In five recent phase III, randomized, vehicle-controlled trials (N = 1,214), administration of

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imiquimod 5% cream was safe and effective in the treatment of AKs on the face and balding scalp.[11–13] Moreover, the recurrence rate 16 months after imiquimod treatment was low.[11,12,14]

Local skin reactions are common during imiquimod treatment.[11,13,15,16] Although these reactions are generally innocuous, erythema and crusting are often disquieting to patients. In an open-label, dose-cycling study, imiquimod was applied three times per week for 4 weeks, followed by a rest period of 4 weeks (one cycle) for up to three cycles.[17] During the rest period, local inflammation subsided, whereas AK lesions continued to clear, and complete clearance of all AK lesions was noted in 82% of anatomic sites.[17] Therefore, application of imiquimod in a cyclical manner (termed ''cycle therapy'') may improve the tolerability profile while maintaining efficacy.[18]

The objective of the present study was to evaluate the efficacy and tolerability of imiquimod 5% cream in the treatment of AK lesions on the head. Efficacy was assessed by monitoring the clearance rate of AK lesions after the cyclical application of imiquimod 5% cream three times per week for 4 weeks in one or two cycles, separated by 4 weeks of rest. Adverse events (AEs) and local skin reactions were monitored throughout the treatment period to assess imiquimod tolerability.

Methods

Patients

Patients with clinically typical, discrete, nonhyperkeratotic AK lesions in a 25 cm^2 treatment area were enrolled in this Canadian multicenter, open-label, dose-cycling study. Eligible patients were $\geq$ 18 years of age, had four to eight discrete AK lesions on the balding scalp or face, and were willing to avoid natural or artificial tanning during the study period. Patients with evidence of clinically significant comorbidities, active chemical or alcohol dependency, a dermatologic disease or condition in the surrounding skin area that could cause difficulty with examination (eg, rosacea, psoriasis, atopic dermatitis), or confirmed SCC or BCC on the head were excluded from this study. Additional exclusion criteria were as follows: participation in another clinical trial; treatment for skin cancer, dermabrasion, or chemical peel in the 6 months before study entry; or use of any topical treatment for AK in the month before study entry. All patients provided written informed consent, and Institutional Review Board approval was obtained.

Study Design and Treatment

Imiquimod 5% cream (3M Pharmaceuticals, London, ON) was administered by the patient three times per week for 4 weeks followed by 4 weeks of rest (cycle 1). If AK lesions remained clinically visible at the end of cycle 1 (week 8), a second treatment cycle was instituted (cycle 2). Each dose of the study cream was applied to AK lesions at approximately the same time of day in a contiguous 25 cm^2 treatment area on the head. No patient received more than two cycles.

Efficacy Assessments

The primary efficacy end point was complete clearance rate, defined as the proportion of patients at the end of cycle 1 (week 8) or cycle 2 (week 16) with no clinically visible AK lesions in the treatment area. The secondary efficacy end points were partial clearance rate, defined as the proportion of patients at the end of cycle 2 with at least a 75% reduction from the baseline number of AK lesions and a sustained complete clearance rate at 8 weeks after treatment (week 16 for patients who completed cycle 1 only; week 24 for patients who completed cycles 1 and 2). The 25 cm^2 treatment area was mapped on a plastic template, and AK lesions in the treatment area were counted. Lesions were photographed and/or visually assessed at baseline and at each subsequent clinic visit to document treatment effects. The diagnosis of AK was made clinically. Patients were assessed at the initial visit (baseline), at week 8 in cycle 1, at week 16 in cycle 2, and at a follow-up visit after the last cycle (week 16, cycle 1 only; week 24, cycles 1 and 2).

Safety Assessments

Safety was monitored throughout the treatment cycles with AE assessments of the treatment site (head or face) and the surrounding area. AEs and local skin reactions (ie, erythema, edema, erosion, ulcerations, scabbing, crusting, weeping, exudate, vesicles, flaking, scaling, dryness) were described according to *MedDRA* (performed by investigators) or by descriptive characterization of the treatment site and surrounding area (mild, moderate, or severe reaction). Patients were asked about local skin reactions, and these reactions were noted by the physician if they were evident at the time of an assessment.

Statistical Methods

Descriptive statistics were used to summarize patient demographics and lesion counts, including mean and standard deviation. Complete clearance rates were calculated using the overall population (cycle 1 and cycle 2 population; intent-to-treat analysis), the cycle 1 population, and the cycle 2 population. Partial clearance rates were calculated using the cycle 2 population only. Sustained clearance rates were based on the total number of patients available for follow-up (per protocol analysis).

Results

Patients

Sixty-three patients were enrolled in this study (center 1, $n = 21$; center 2, $n = 22$; center 3, $n = 20$). Twenty (32%) patients completed one cycle of treatment, 40 (63%) patients completed two cycles, and 3 (5%) patients decided to withdraw from the study before completion of cycle 1. Most patients were men (83%), and the mean age was 67 years.

Efficacy Assessments

The total overall clearance rate was 50% (30 of 60) (Figure 1). Twelve (60%) patients who completed only one cycle of imiquimod and 18 (45%) patients who required two cycles of imiquimod achieved complete clearance at the end of the study. Thirty of forty (75%) patients achieved partial clearance of their AK lesions. Finally, of the 30 patients who completely cleared their AK lesions, 23 (77%) achieved sustained clearance, with 12 patients in the cycle 1 population and 11 patients in the cycle 1 and cycle 2 population having no visible AK lesions at the 8-week follow-up.

Overall, patients had a mean of 5.8 AK lesions at baseline, 2.9 lesions at week 8, and 1.1 lesions at week 16 (Figure 2). Patients who received only one cycle of imiquimod treatment (ie, patients who had complete clearance after the first cycle, patients who withdrew because of AEs, and patients who were lost to follow-up) had a mean of 5.1 lesions at baseline and 1.2 lesions at the end of cycle 1. Patients who received two cycles of imiquimod treatment had a mean of 6.2 lesions at baseline and 1.2 lesions at the end of cycle 2. At follow-up for cycle 1 (week 16), 1.1 lesions remained, whereas at follow-up for cycle 2 (week 24), 1.4 lesions remained.

Safety Assessments

Only two of the three treatment centers reported AEs. Imiquimod therapy was generally well tolerated, and only three patients discontinued the study because of AEs. One patient discontinued the study at week 3 because of inflammation and pruritus, and one patient discontinued the study at week 12 because of erythema. Although AEs were not recorded at the third treatment center (owing to data loss), none of the patients withdrew from the study because of a severe reaction to imiquimod treatment. The most common AEs in both treatment centers were erythema (95%), crusting (81%), and flaking, scaling, or dryness (55%) (Table 1). The majority ($\geq$ 93%) of AEs were mild to moderate in severity. Severe local skin reactions included scabbing or crusting (8.8%), weeping or exudate (7.1%), erosions or ulceration (5.3%), erythema

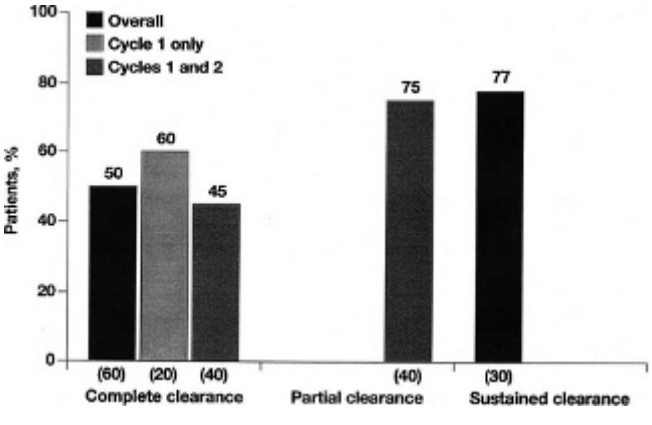

Figure 1. Complete, partial, and sustained clearance rates after imiquimod treatment. The numbers in parentheses represent the number of patients who completed cycle 1, cycles 1 and 2, or follow-up.

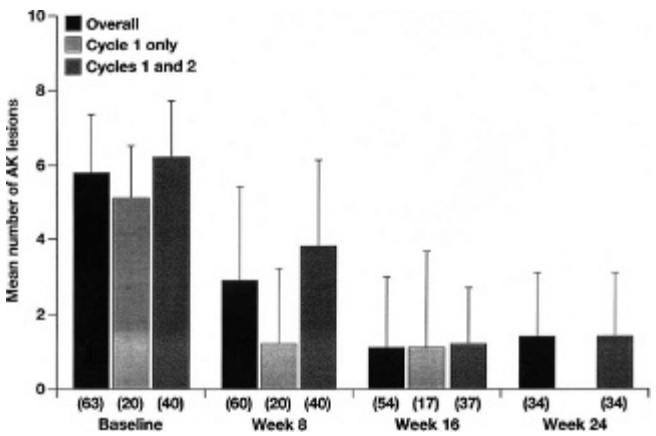

Figure 2. Actinic keratosis (AK) lesions after imiquimod treatment for all centers. The numbers in parentheses represent the number of patients.

Table 1. Adverse Events Reported by Two Study Centers ($N = 42$)

Adverse Event	*Patients,* n *(%)*
Erythema	40 (95)
Crusting	34 (81)
Flaking/scaling/dryness	23 (55)
Erosion/ulceration	19 (45)
Weeping/exudation	14 (33)
Edema	10 (24)
Vesicles	7 (17)
Upper respiratory infection (common cold)	6 (14)
Pruritus	3 (7)
Lymphadenopathy	2 (5)
Headache	2 (5)
Malaise, general	2 (5)
Back pain	1 (2)
Basal cell carcinoma	1 (2)
Bladder carcinoma	1 (2)
Chills	1 (2)
Depression	1 (2)
Environmental allergies	1 (2)
Fatigue	1 (2)
Finger laceration	1 (2)
Herpes simplex virus	1 (2)
Muscle ache	1 (2)
Osteoarthritis	1 (2)
Tingling	1 (2)

(5.0%), and flaking, scaling, or dryness (4.3%). Approximately 76% of local skin reactions and 67% of AEs that excluded local skin reactions occurred in patients who received one cycle of treatment. One serious AE was reported (worsening of congestive heart failure) but was not considered to be related to the study drug treatment.

Discussion

AKs represent an early stage in the continuum of changes that may culminate in the development of invasive SCC.[19] Although not all AK lesions progress to invasive SCC (estimates range from 0.025 to 16% per year),[20] it is difficult to determine which lesions will progress to invasive disease.[3] Therefore, it is reasonable to treat both clinical and subclinical AK lesions, which imiquimod is able to achieve through modulation of cutaneous immunity. However, imiquimod therapy is frequently associated with local skin reactions, including erythema and crusting, that can be explained by local immune upregulation.[11,13,15,16] Although these reactions are innocuous, they are cosmetically unpleasant, and this can lead to treatment noncompliance. A dosing regimen that is effective as well as tolerable to patients would be ideal for the treatment of AK lesions.

Imiquimod 5% cream administered by cycle therapy was very well tolerated, with only three patients discontinuing because of AEs. Severe local skin reactions included scabbing or crusting (8.8%), weeping or exudate (7.1%), erosions or ulcerations (5.3%), erythema (5.0%), and flaking, scaling, or dryness (4.3%). From published trials, the incidence of severe local skin reactions in patients who received imiquimod as cycle therapy was lower than in patients who received continuous therapy. Severe erythema was reported by 17.7% of participants who were treated with imiquimod once daily, 2 days per week, for 16 weeks.[11] Szeimies and colleagues reported that the incidences of severe erythema, scabbing or crusting, and erosions or ulcerations were 30.6%, 29.9%, and 10.2%, respectively, in patients treated with imiquimod once daily, 3 days per week, for 16 weeks.[13] However, AEs need to be interpreted with caution in the current study because only two of three centers reported AE results.

The AK clearance rates reported in the current cycling study are lower than those reported by Salasche and colleagues.[17] However, the clearance rates in the current study are comparable with those reported in five recent phase III AK trials.[11–13] In each of these studies, imiquimod 5% cream was administered two to three times per week for 16 weeks; the complete clearance rates ranged from 45 to 57%, and the partial clearance rates ranged from 59 to 72%. In the present study, 50% of patients achieved complete clearance (60% of patients receiving one treatment cycle only, 45% of patients receiving two treatment cycles), and 75% of patients achieved partial clearance of their AK lesions after the second rest period. Moreover, 77% of patients remained clear, with no (zero) clinically visible AK lesions 12 weeks after imiquimod treatment. It is important to note that, in phase III trials, the rate of AK recurrence was quite low (25 to 43%, depending on the dosing frequency) even 1.5 years after active therapy.[14] Furthermore, in patients who did experience a recurrence, only a few lesions were present in the original treatment area.[14] The fact that 77% of patients in the present study remained lesion free 12 weeks after treatment (8 weeks after last cycle) suggests that cycle therapy does not appear to affect the short-term AK recurrence rate, although long-term follow-up will be required.

In conclusion, although further randomized, vehicle-controlled trials are needed, cycle therapy with imiquimod

may be a safe and effective alternative to continuous therapy for the treatment of AK lesions.

References

1. Yantsos VA, Conrad N, Zabawski E, et al. Incipient intraepidermal cutaneous squamous cell carcinoma: a proposal for reclassifying and grading solar (actinic) keratoses. Semin Cutan Med Surg 1999; 18:3–14.
2. Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). J Am Acad Dermatol 2000;42:11–7.
3. Frost CA, Green AC. Epidemiology of solar keratoses. Br J Dermatol 1994;131:455–64.
4. Lebwohl M. Actinic keratosis: epidemiology and progression to squamous cell carcinoma. Br J Dermatol 2003;149 Suppl 66:31–3.
5. Black HS, Herd JA, Goldberg LH, et al. Effect of a low-fat diet on the incidence of actinic keratosis. N Engl J Med 1994;330:1272–5.
6. De Hertog SA, Wensveen CA, Bastiaens MT, et al. Relation between smoking and skin cancer. J Clin Oncol 2001;19:231–8.
7. Gupta AK, Cherman AM, Tyring SK. Viral and nonviral uses of imiquimod: a review. J Cutan Med Surg 2004;8:338–52.
8. Stanley MA. Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential. Clin Exp Dermatol 2002;27: 571–7.
9. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. J Am Acad Dermatol 2000;43 (Suppl):S6–11.
10. Navi D, Huntley A. Imiquimod 5 percent cream and the treatment of cutaneous malignancy. Dermatol Online J 2004;10:4.
11. Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. J Am Acad Dermatol 2004;50:714–21.
12. Korman N, Moy R, Ling M, et al. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. Arch Dermatol 2005;141:467–73.
13. Szeimies RM, Gerritsen MJ, Gupta G, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. J Am Acad Dermatol 2004;51:547–55.
14. Lee PK, Harwell WB, Loven KH, et al. Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. Dermatol Surg 2005;31:659–64.
15. Perras C. Imiquimod 5% cream for actinic keratosis. Issues Emerg Health Technol 2004;Sep:1–4.
16. Harrison LI, Skinner SL, Marbury TC, et al. Pharmacokinetics and safety of imiquimod 5% cream in the treatment of actinic keratoses of the face, scalp, or hands and arms. Arch Dermatol Res 2004;296: 6–11.
17. Salasche SJ, Levine N, Morrison L. Cycle therapy of actinic keratoses of the face and scalp with 5% topical imiquimod cream: an open-label trial. J Am Acad Dermatol 2002;47:571–7.
18. Tran H, Chen K, Shumack S. Summary of actinic keratosis studies with imiquimod 5% cream. Br J Dermatol 2003;149 Suppl 66:37–9.
19. Lang PG Jr. Management of actinic keratoses. Compr Ther 2003; 29:108–14.
20. Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol 2000;42:23–4.