Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles

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Background: The approved imiquimod 5% cream regimen for treating actinic keratoses requires a long treatment time and is limited to a small area of skin.

Objective: We sought to evaluate imiquimod 2.5% and 3.75% for short-course treatment of the full face or balding scalp.

Methods: In two identical studies, adults with 5 to 20 lesions were randomized to placebo, imiquimod 2.5%, or imiquimod 3.75% (1:1:1). Up to two packets (250 mg each) were applied per dose once daily for two 2-week treatment cycles, with a 2-week, no-treatment interval between cycles. Efficacy was assessed at 8 weeks posttreatment.

Results: A total of 479 patients were randomized to placebo, or imiquimod 2.5% or 3.75%. Complete and partial clearance ($\geq$75% lesion reduction) rates were 6.3% and 22.6% for placebo, 30.6% and 48.1% for imiquimod 2.5%, and 35.6% and 59.4% for imiquimod 3.75%, respectively ($P < .001$ vs placebo, each; $P = .047$, 3.75% vs 2.5% for partial clearance). Median reductions from baseline in lesion counts were 25.0% for placebo, 71.8% for imiquimod 2.5%, and 81.8% for imiquimod 3.75% ($P < .001$, each active vs placebo; $P = .048$ 3.75% vs 2.5%). There were few treatment-related discontinuations. Patient rest period rates were 0% for placebo, 6.9% for imiquimod 2.5%, and 10.6% for imiquimod 3.75%.

Limitations: Local pharmacologic effects of imiquimod, including erythema, may have limited concealment of treatment assignment in some patients.

Conclusions: Both imiquimod 2.5% and 3.75% creams were more effective than placebo and were well tolerated when administered daily as a 2-week on/off/on regimen to treat actinic keratoses. (J Am Acad Dermatol 2010;62:582-90.)

Key words: actinic keratosis; clinical trial; dose optimization; imiquimod.

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Actinic keratoses (AKs) are common cutaneous lesions associated with chronic ultraviolet radiation exposure. Because of the similar genetic and histologic features, AKs are considered by some as incipient squamous cell carcinomas.[1,2] If left untreated, up to 25% of AKs spontaneously regress within a year.[3] However, patients with multiple AKs typically have them for long periods of time; the 10-year risk for developing an invasive squamous cell carcinoma has been estimated to be 6.1% to 10% for a patient with 7.7 AKs.[4] As it is not possible to determine which individual AK lesions will progress to invasive squamous cell carcinoma, treatment of AKs combined with routine surveillance is recommended, especially in patients with evidence of photodamaged skin.[5,6]

Imiquimod is a toll-like receptor-7 agonist that has been shown to boost the cutaneous immune response.[7] Originally approved in 1997 for the treatment of external anogenital warts, imiquimod 5% cream was subsequently approved in 2004 as a topical treatment for AKs. The approved dosing regimen was application of 250 mg of cream, 2×/wk for a full 16 weeks, to a 25-cm^2 area on the face or balding scalp.[8,9] Subsequently, a treatment regimen of 3×/wk for 4 weeks followed by a 4-week "therapeutic" no-treatment interval, and then by a second 4-week treatment cycle was approved in Europe.[10-12]

Although patient compliance to the approved dosing regimens was good in the clinical studies, the long duration of dosing may be inconvenient for some patients and affect compliance. One way to shorten treatment duration is to increase the frequency of treatment. However, in a dose-response study evaluating imiquimod 5% cream, daily dosing was not well tolerated.[13] Therefore, to evaluate an imiquimod product that could be applied daily for AK for a short duration, and to expand treatment area to the full face/scalp, lower concentrations were assessed. Two identical, randomized, multicenter, placebo-controlled studies were conducted to evaluate the safety and efficacy of two new formulations of imiquimod cream, 2.5% and 3.75%. The creams were applied once daily to the entire face or balding scalp for two 2-week treatment cycles, separated by a 2-week, no-treatment interval. The results of a pair of identical studies evaluating two 3-week treatment cycles are reported in an accompanying article.[14]

CAPSULE SUMMARY

- Short-course daily therapy with imiquimod 2.5% and 3.75% creams were both more efficacious than placebo cream in clearing actinic keratoses.
- Both imiquimod creams were well tolerated when applied to the full face or scalp using a regimen of two 2-week cycles of daily dosing with a 2-week, no-treatment interval.
- Lesion reduction was greater with imiquimod 3.75% than imiquimod 2.5%.
- Investigator-assessed photodamage improved more with the imiquimod creams than placebo cream.

METHODS

Study population

Adults in general good health with 5 to 20 visible or palpable AKs, as determined by clinical assessment by the investigator, in an area greater than 25 cm^2 on either the face or the balding scalp, but not both, were eligible for participation in the studies. A study patient could not have any significant condition in the treatment area that might impair evaluation, have atypical AKs (eg, AK > 1 cm^2), be pregnant or lactating, have a chemical or alcohol dependency, or have an allergy to imiquimod or study cream excipients. Earlier therapy exclusions included: within 1 year before treatment initiation—imiquimod 5% cream on the head; within 90 days—interferon, interferon inducers, cytotoxic drugs, immunomodulators, immunosuppressants, oral or parenteral corticosteroids, topical corticosteroids greater than 2 g/d, investigational drug or device use outside of the treatment area, dermatologic procedures or surgeries in the treatment area, and any AK therapy in the target treatment area; and within 30 days—imiquimod outside of the head, and topical prescription drugs and investigational drug or device use within treatment area. Use of any of the aforementioned treatments was also excluded throughout the study.

The studies were conducted in compliance with the Code of Federal Regulations of the US Food and Drug Administration (21 Code of Federal Regulations Parts 50 and 56), and International Conference on Harmonization Guideline E6 (Good Clinical Practice). The study protocols and informed consents were reviewed and approved by a central institutional review board or at specific institutions when required. All patients provided written informed consent before any study procedures. Enrollment for both studies began in January 2008, and all study procedures were completed by June 2008. The studies were registered on Clinicaltrials.gov on January 16, 2008, registration identifier NCT00605176.

Study design and study cream dosing

Patients were enrolled at 25 study centers in the United States in two identical designed studies