Reduction in lesions from Lmax: a new concept for assessing efficacy of field-directed therapy for actinic keratosis. Results with imiquimod 3.75%

Background: Current parameters for assessing the efficacy of actinic keratosis (AK) treatments compare clinical lesions at the start and end of a study. However, the sun-exposed field also contains subclinical lesions which may become detectable during treatment. Lmax, the maximum lesion count during treatment, is a new concept to better assess the efficacy of field-directed AK therapies. Measuring efficacy using the reduction in lesions from Lmax includes for the first time the clearance of both subclinical and clinical lesions. Objectives: To evaluate the reduction of lesions from Lmax to study end and compare the results with traditional efficacy endpoints using imiquimod 3.75% (IQ3.75%) as an example of field-directed AK therapy. Materials & Methods: Pooled analysis of data from two 14-week, vehicle-controlled, double-blind studies of IQ3.75%. Results: With IQ3.75%, the median number of lesions increased from 10 at baseline to an Lmax of 22. The median absolute reduction in lesions to study end was 18 from Lmax versus 7 from baseline. The median percentage reduction in AK lesions to study end was 92.2% from Lmax compared with 81.8% from baseline. Conclusions: The reduction in lesion count from Lmax is a novel efficacy parameter that should become the new way of evaluating field-directed AK therapies since it enables their efficacy against both clinical and subclinical lesions to be accurately determined. Together, the Lmax concept and IQ3.75% represent a new approach for the management of AK across a large sun-exposed field.

Key words: actinic keratosis, efficacy assessment, field-directed therapy, imiquimod 3.75%
and after treatment. Such assessments do not adequately reflect the latest understanding of the pathophysiology of disease in which the photodamaged skin contains both clinical and subclinical lesions and they therefore underestimate the actual benefit of a true field-directed treatment. Clearly there is a need to develop new and more appropriate efficacy parameters for field-directed AK treatments which can assess their ability to reduce not only clinically visible lesions, but also subclinical lesions across a large sun-exposed field, e.g., the full face or entire balding scalp. 

Lmax, defined as the maximum lesion count during treatment, is a new concept which is being introduced to fully assess the efficacy of field-directed AK therapy. Lmax takes into account, for the first time, the clearance of lesions which are clinically visible at baseline across a large sun-exposed area e.g., the full face or entire balding scalp, and also the subclinical lesions in the same field which are invisible at baseline and which become detectable upon treatment. For individual patients, Lmax can occur at any time point during the treatment period, up to and including the last treatment application, depending on the patient’s response to treatment. Efficacy is assessed by comparing Lmax with the final lesion count at study end, which is typically measured two months after the end of treatment. The theoretical advantage of this approach is that it represents a more complete measure of the efficacy of a field-directed AK therapy, in contrast to traditional efficacy parameters which compare the lesion count at study end with that at baseline and only assess the clearance of clinical lesions. The aim of the current investigation was to evaluate the reduction of lesions from Lmax to study end as a new concept for assessing the efficacy of field-directed AK therapy in comparison with traditional efficacy measures. The analysis used pooled data from two randomised, vehicle-controlled double-blind studies of imiquimod 3.75% (Zyclara®, Meda AB, Solna, Sweden) [17]. Imiquimod 3.75% is a Toll-like receptor-7 agonist which is being developed to treat a large sun-exposed field such as the full face or entire balding scalp, with studies indicating that imiquimod not only treats clinical AK lesions but that it can also “reveal” subclinical lesions that were previously not seen in the sun-exposed field [17-19]. Imiquimod is believed to reverse the immunosuppression in the skin caused by long-term ultraviolet light exposure by stimulating an immune response which destroys AK lesions in the treated area of the skin. This immune response is mediated through increased production of cytokines such as interferon-α, interferon-γ and interleukin-12, and through involvement of immune cells [20, 21]. Imiquimod also has the potential to directly induce apoptosis in skin cancer cells [22].

The study protocols and informed consents were approved by a central institutional review board or at specific institutions as required. Patients were eligible for participation in the studies if they had 5–20 AK lesions in an area greater than 25 cm² on either their face or balding scalp. All patients provided written informed consent before participating in the studies. Patients applied up to two sachets of study cream (250 mg cream/sachet) to either the full face or balding scalp each day for two weeks. Patients were advised to apply a second sachet of treatment if needed to completely cover the treatment area; however the amount of cream that patients applied to their treatment area was not standardised (the mean consumption of sachets per patient was 1.6 for imiquimod 3.75% and 1.7 for placebo). The first treatment period was followed by two weeks without treatment and then an obligatory second two-week treatment period. Rest periods from daily treatment were allowed by the investigator as needed to manage local skin reactions or application site reactions, with resumption of treatment when the condition had adequately resolved. End of study (EOS) was eight weeks after the end of the last treatment application, i.e., at week 14.

Efficacy evaluations

Lesions were to be counted by the same investigator at each visit and were considered to be AKs if they presented clinically as rough, crusted, flesh coloured to reddish brown papules or macules, with an adherent scale in a field of sun-damaged skin. Lesions were counted at baseline and at weeks 1, 2, 4, 5, 6, 10 and 14 during the double-blind studies. Lmax was defined as the highest or maximum lesion count during the entire treatment period (i.e., from baseline to end of treatment at week 6). Median absolute and percentage reductions in AK lesion count were calculated from Lmax to the lesion count at EOS.

Statistical analysis

The combined intent-to-treat population of all randomised patients from the two studies was used for all efficacy analyses. The original data for lesion counts at all study visits were used and missing or indeterminate lesion counts were not imputed. The Cochran-Mantel-Haenszel test stratified by study centre was used to evaluate the statistical significance of the difference in efficacy parameters between the two treatment groups.

Results

Patient population and treatment exposure

A total of 319 patients were included in the pooled analysis: 160 in the imiquimod 3.75% and 159 in the placebo group. The baseline characteristics of the two treatment groups were similar and have been published previously [17]. The mean age of the patients in the two groups was similar (imiquimod 3.75%: 64.5 years; placebo 64.3 years), most of the patients in each group were male (82.5% and 81.8%) and the median number of AK lesions at baseline in both

Materials and methods

Study design and patients

This pooled analysis included data from two identical 14-week multicentre, vehicle-controlled double-blind phase 3 studies of imiquimod 3.75%. The details of these studies have been previously published [17]. The studies were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and all relevant local regulations.