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INVESTIGATIVE REPORT

A Statistical Model to Predict the Reduction of Lichenification in Atopic Dermatitis

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Acute symptoms of atopic dermatitis (AD), such as erythema, oedema/papulations and excoriations, respond quickly to topical corticosteroid treatment. Conversely, lichenification is regarded as a troublesome non-acute symptom of chronic AD which can take months of treatment before any improvement is seen. However, very little data actually support this opinion. Here, we analyse lichenification scores in 3 multicentre, short-term studies of nearly similar design. Two of these studies were active comparator dosage trials administered with either fluticasone propionate cream or ointment once or twice daily, the third study was a placebo control. In each of these 4-weeks studies lichenification was measured weekly. For the evaluation of the lichenification score over time a random-coefficients regression model was used. In all active treatments lichenification significantly improved ($p<0.005$) within one week. Improvement continued afterwards, with >80% of patients scoring no, very mild or mild lichenification after 4 weeks. We developed a model in which the lichenification score drops off linearly with the square root of time. The resulting convexly-shaped downward time trend of lichenification was significant during all treatments. This effect was significantly stronger during active treatment than with placebo. Fluticasone propionate can improve moderate to severe lichenification in a relative short period of time. ***Key words: atopic dermatitis; lichenfication; fluticasone propionate cream.***

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The efficacy of drugs in the treatment of atopic dermatitis (AD) is most often described in terms of reduction of intensity markers like erythema, oedema and excoriations, which constitute the Three Item Severity (TIS) score (1–4). The same markers are also part of scoring systems such as the SCORAD index or Objective SCORAD, EASI and others (1–3). Hence, there is a remarkably good correlation between TIS and the Objective SCORAD (5).

One of the other parameters of the overall scoring systems is lichenification, which is defined as thick, leathery skin, usually the result of constant scratching and rubbing. With prolonged rubbing or scratching, the epidermis becomes hypertrophied and this results in thickening of the skin and exaggeration of the normal skin markings, giving the skin a leathery bark-like appearance. Lichenification is a common consequence of AD and other pruritic (itchy) disorders. It may also arise on seemingly normal skin. This type of skin lesion is almost invariably present in long-lasting, chronic AD and it is not associated with acute AD. Most dermatologists consider a certain severity of lichenification as part of SCORAD and EASI, even when the acute exacerbation of AD is under control and erythema, oedema and/or excoriations have a score of 0. A lichenification score of 0, meaning that the lichenification has disappeared completely, is virtually unattainable in patients with chronic AD. Especially severe lichenification is seen as a more or less constant feature of AD and some trials/reports even state that no, or hardly any, sign of improvement was seen in case of lichenification (6, 7).

During the last years many studies were published in which the effects of the potent corticosteroid fluticasone propionate (FP) in patients with AD were investigated (8–10). A recent review summarises the activity, efficacy and safety profile of topical FP focussing on the treatment and prophylaxis of AD (11). In the vast majority of these studies acute effects were measured by looking at erythema, oedema and excoriations but little attention was paid to lichenification. Yet, lichenification, being part of the SCORAD index, was scored in many of these studies. These studies showed a remarkable reduction of mild lichenification within a few weeks. In addition, moderate to severe lichenification seemed to diminish, albeit not as fast as in the case of mild lichenification (reviewed in 11).

The decrease in lichenification severity appeared to develop according to a certain proces. Thus, the aim of this study was to collect lichenification data to establish a potential descriptive model for the reduction of lichenification.

MATERIALS AND METHODS

All 3 analysed studies were multicentre, randomised, double-blind studies. All of the patients included in the studies were suffering from moderate to severe eczema at entry (objective SCORAD > 15) and are representative of those who will be treated according to the SmPC. The study populations were well balanced in terms of age, sex and disease severity.

The characterisation of the analysed studies were as follows: (*i*) FLT001 was a 4-week multicentre double-blind study to compare safety and efficacy between once daily (OD) and twice daily (BD) administration of FP 0.05% cream in the treatment of AD. Patients should suffer from active AD of at least moderate severity and lichenification was scored every week. Study FLT001 had 2 arms: a 1:1 randomisation to either FP cream OD or FP cream BD with 137 and 133 patients, respectively. Patients in this study were aged between 4 months and 62 years. (*ii*) FLT002 was a 4-week multicentre double-blind study to compare safety and efficacy with an OD and BD administration of FP 0.005% ointment in the treatment of AD. Patients should suffer from active AD of at least moderate severity and lichenification was scored every week. Study FLT002 also had 2 arms: a 1:1 randomisation to either FP ointment OD or FP ointment BD with 118 and 122 patients, respectively. Patients in this study were aged between 8 months and 63 years. (*iii*) FLT401 was a 4-week multicentre double-blind study to compare safety and efficacy between either OD or BD administration of FP 0.005% ointment, or placebo ointment in the treatment of AD. Patients should suffer from active AD of at least moderate severity and lichenification was scored every week. Study FLT401 had 3 arms: a 1:1:1 randomisation to either FP ointment OD, FP ointment BD, or placebo ointment, with 79, 79, and 76 patients, respectively. Patients in this study were aged between 13 and 87 years.

These studies were comparable in so far that in each of these studies all SCORAD parameters were scored in an identical way. These parameters pertain to the objective parameters erythema, oedema/papulations, excoriations, oozing/crusts, lichenification and dry skin and the subjective parameters itch and sleeplessness. Lichenification, one of the chronic parameters of AD, was therefore one of the outcome variables. All parameters including lichenification were scored weekly according to the following criteria (0: absent, 0.5: very mild, 1.0: mild, 1.5: mild to moderate, 2.0: moderate, 2.5: severe, 3.0: very severe).

Statistical analysis

In these 3 studies lichenification was an ordinal 7-points scaled variable ranging from 0 (lichenification absent) to 3 (very severe lichenification) in steps of 0.5. Firstly, each of these studies was analysed separately, followed by a pooled analysis of the 3 studies. Linear mixed modelling was used to analyse the lichenification score as the dependent variable. The following independent variables were entered in the model: the square root of time (weeks 0–4) and its interaction with the treatment group (3 treatments: OD, BD and placebo). In a pooled analysis of the 3 studies, study was also entered in the model as explanatory factor (3 levels). Because of the randomisation at week 0, treatment was not entered as main factor in the model as there can be no effect of treatment at week 0. In the analysis each subject was supposed to have his/her own regression curve of lichenification with time. This was effectuated by assuming that the intercept and slope of the regression model had a bivariate normal distribution across the subjects, representing the between-subjects variability of the regression curves ("random coefficients"). The residual term, representing the within-subject random deviations from the subject's regression curve, was assumed to have a normal distribution and to be serially correlated between successive weeks according to a first order autoregressive structure that was the same across the subjects. The following model estimates (with standard errors) were obtained from the analyses: the mean of the intercepts and slopes across subjects, mean differences in slope of OD treatment with BD and placebo treatment. For the between-subject variability of the regression curves we presented the estimated standard deviations and correlation of the intercept and slope. For the within-subject variability we presented the estimated standard deviation (SD) and first-order autocorrelation coefficient of the residuals. Data was analysed using SAS version 9.2.

RESULTS

In total, 749 patients were randomised and analysed, distributed over 3 studies. Only 16 (2.2%) of these patients, suffering from active, moderate to (very) severe AD, showed no signs of lichenification at the start of acute treatment of their disease (lichenification score = 0), as is shown in Table SI[1]. The vast majority of patients, viz. 537 (72.2%), had a score of ≥ 2 at study start, indicating moderate to very severe lichenification. Table SII[1] shows the distribution characteristics of lichenification by study, by treatment and by week.

In all FP treatment arms lichenification significantly improved ($p < 0.005$) within one week. Depending on the study, improvement continued afterwards in > 60% to > 80% of patients, resulting in a lichenification score of ≤ 1 after 4 weeks (see Figs S1–3[1]). Compared to active treatment, placebo treatment showed a far lesser decrease in the lichenification scores (see Fig. S3[1]).

At the start of each of these 3 studies almost all subjects had a lichenification score exceeding zero. In all treatment groups there was a similar pattern that the mean lichenification score dropped off convexly in time. After careful model selection it appeared that in all 3 studies the best choice was a model that specifies a decrement in time that is linear to the square root of week number. This model also appeared to result in very robust estimates of the slopes across the 3 studies.

In the model a random intercept and a random slope between subjects were specified. The model allowed no difference in the distribution of intercepts between the treatment groups (due to the randomisation), but it did allow a difference in mean slope between the treatment groups. This mean difference in slopes is the effect of interest and it was specified as a fixed effect. The within-subject residuals were assumed to serially correlate with the same variance and first-order autocorrelation across patients and weeks. A separate analysis was first done for each of the 3 studies, when after the pooled data of the 3 studies were analysed with study as explanatory factor, the BD treatment was taken as reference in each

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analysis. Table I presents the estimated parameters of the mean regression lines (mean intercepts and slopes across subjects). Table SIII[1] presents the elements of the random disturbances around the mean regression lines. These disturbances have a between-subjects component and a within-subjects component, as mentioned earlier. The between-subjects component is a result of the variability of the subject's intercepts and slopes across the subjects, represented by the SDs of slopes and of intercepts and by the correlation between intercepts and slopes in Table SIII[1]. The within-subjects component is formed by the within-subject serially correlated residuals around the subject's own regression line, represented in Table SIII[1] by the SD of the residuals and by the 1st order autocorrelation coefficient between successive residuals.

The variation of mean intercepts between the studies denote the between-study differences in mean levels. A striking result is that the mean linear decrement of the latent lichenification response with the square root of time (the slope) during FP treatment is about the same between studies and between OD and BD treatments: –0.66 during OD treatment and –0.68 during BD treatment. Of course, this decrement is not only due to treatment with FP alone. There may be other time effects, such as a placebo effect and the regression-to-the mean artefact due to the selection of patients with a high score entering the studies. In order to correct for all these other time effects, one may consider the results of study FLT401 where also a placebo arm is involved. The mean decrement in time is in the placebo group much less marked than in the actively treated group: the slope is 0.386 (SE = 0.054, hence highly significant) points nearer to zero than the slope of –0.673 in the BD-treated group.

In summary, the model in which mean lichenification at a certain time-point can be predicted from the mean lichenification at the start of treatment can be described as:

$LCT = LS - slope\sqrt{week}$[1].

[1]LCT = mean Lichenification at Certain Time-point; LS = mean Lichenification at Start; slope = number, dependent of treatment.

DISCUSSION

By careful statistical interpretation of the data of 3 comparable studies we developed a formula to predict mean lichenification score in AD at a certain time-point. This predicted mean score is dependent on 3 parameters, namely the mean lichenification at the start of the treatment, the treatment itself (expressed as mean decrement of the latent lichenification response with the square root of time, giving a slope between –1 and 0) and the duration of treatment (in weeks). For FP this mean decrement of the latent lichenification response with the square root of time was strikingly comparable over the analysed studies and varied between –0.68 and –0.66, based on 4 measurements in time.

As estimated from the model the mean decrement in lichenfication score after 4 weeks of twice daily treatments was 1.34 points which was 0.78 points more than the mean decrement during placebo treatment. Only a small mean difference of 0.05 points after 4 weeks was estimated between once- and twice-daily treatment. However, an individual patient may behave in time very differently from the mean. Each patient may follow his or her own time path of lichenification score with serially correlated random fluctuations around that path.

As a consequence the decompostion of total variance in a between-subjects and a within-subject component as well as the total variance itself of lichenification score may vary in time in a complicated way. Therefore, 5 parameters in the model were specified to take into account the (co)variance structure of lichenification score (see Table SIII[1]).

The total number of 749 patients entering the studies dropped off to 532 at week 4. In the linear mixed model analysis all 749 patients had been involved, with missing values appropriately imputed through the restricted maximum likelihood estimation method.

The model cannot only be used to predict disappearance of lichenification, it also can be used to predict how lichenification will develop after a certain period of treatment. Again taking FP with a slope of 0.67 as example, it can be predicted that after 4 weeks of treatment a very severe lichenification (score 3) will have been diminished to $3–0.67 \times \sqrt{4} = 1.66$. A score of this magnitude is classified as mild to moderate lichenifica-

Table I. *Results of the analysis of the random-effects regression models of the lichenification score*

Study	Intercept (SE)	Slope BD (SE)	Slope OD – BD (SE)	Slope Plac – BD (SE)
FLT001	1.919 (0.038)	–0.666 (0.034)	0.034 (0.044)	NA
FLT002	2.226 (0.032)	–0.666 (0.036)	0.019 (0.050)	NA
FLT401	1.657 (0.055)	–0.673 (0.042)	0.019 (0.052)	0.386 (0.054)
3 studies	FLT001: 1.926 (0.037) FLT002: 2.225 (0.039) FLT401: 1.652 (0.040)	–0.668 (0.021)	0.025 (0.028)	0.382 (0.048)

Intercept: the estimated mean intercept across subjects; Slope BD: the estimated mean slope across subjects with the square root of week in the twice daily (BD) group; Slope OD-BD: the estimated difference between the mean slopes in the once daily (OD) and BD treatment groups; Slope Plac-BD: the estimated difference between the mean slopes in the placebo and BD treatment groups.

tion. This calculation shows a good correlation from what is seen (Fig. S1–S3[1)].

The value of the slope is the most important factor in the lichenification diminishing process. The potency of the steroid is probably some kind of prediction instrument for the value of the slope.

Until a few years ago when long-term treatment of chronic AD patients consisted of an advice to use emollients and bath oil, hardly any patient was treated with a corticosteroid for more than 4 weeks. Although the use of emollients and bath oil will result in less exacerbations than doing nothing at all (and this is in fact the real placebo treatment), it is unlikely that under such circumstances no exacerbation will happen in a time period of more than 2 years. Our model is based upon the assumption that no exacerbations of AD will occur during the reduction period, a chronic AD patient will undoubtedly suffer from an exacerbation in such a long time-period. An optimal treatment with emollients and bath oils will diminish the number of exacerbations compared to doing nothing at all, but results from long-term studies have shown that a treatment with only emollients and bath oil is inferior to the same treatment where FP is added twice weekly (8–10, 12).

A few studies with a long-term treatment during such a time period were performed with FP (8–10, 12). In these studies treatment consisted of an acute treatment period of daily application of FP during 4 weeks (as in the studies used for the development of the prediction model described in this manuscript) followed by a maintenance phase of 16 weeks where FP was applied twice weekly to the areas that were usually affected. The majority of patients on active maintenance treatment indeed reached the 20 weeks total treatment endpoint without an exacerbation and most of these had a lichenification score of 0, indicating that no exacerbations during a certain time-period will for the greater part of patients lead to a non-lichenified skin. Applying our model on these long-term studies showed a good correlation between our predictive model and the actual results of these long-term studies. However, it should be remembered that our predictive model is based upon daily treatment with FP while in these long-term studies patients were treated twice weekly during 16 out of 20 weeks. Theoretically it would be very interesting to conduct a study where daily application for 20 weeks is compared with OD application for 4 weeks in combination with twice weekly application for 16 weeks to find out if differences consist regarding the values of the slope between these 2 treatments.

Currently we only have slope values of FP and placebo. It would be very interesting to find out how other molecules compare to values of 0.67 viz. 0.29 and what the consequences might be for the long-term treatment of lichenification using these molecules. Based upon our predictive model and based upon the long-term results of other studies, FP is a suitable candidate to use as treatment of acute as well as chronic parameters of AD.

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