

ORIGINAL ARTICLE

Moderate correlation between quality of life and disease activity in adult patients with atopic dermatitis

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Abstract

Background Studies assessing the relationship between disease activity and quality of life (QoL) in adults with atopic dermatitis (AD), before and after therapy are lacking. The relation between disease activity and QoL in AD patients was evaluated before ($t = 0$) and after 6 weeks ($t = 6$) of treatment with cyclosporin 5 mg/kg.

Methods In 54 patients with severe AD, disease activity was assessed using objective Scoring Atopic Dermatitis index (SCORAD), Six Area Six Sign Atopic Dermatitis (SASSAD), 'rule of nines' extent score and serum levels of thymus and activation-regulated chemokine (TARC). Patients filled out the Dermatology Life Quality Index (DLQI). To study the relation between disease activity and QoL, correlations were calculated and regression analysis was performed.

Results At $t = 0$ there was a small, non-significant correlation between the DLQI and the objective SCORAD, 'rule of nines' or serum TARC levels. At $t = 6$ the objective SCORAD, serum TARC and the 'rule of nines' score showed moderate and significant correlations with the DLQI ($r = 0.34$, $P = 0.02$; $r = 0.31$, $P = 0.03$; $r = 0.49$, $P < 0.001$). An individual's improvement in disease activity (objective SCORAD, SASSAD and 'rule of nines') with 10 points was associated with an improvement of 1.3, 1.5 and 1.1 points respectively in DLQI.

Conclusions Disease activity correlated better with QoL when disease activity was less severe and disease extent ('rule of nines') correlated better with QoL than disease severity. An individual's improvement of 10 points in disease activity was accompanied by only a small improvement in QoL. Other factors than disease activity may influence QoL in patients with AD.

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Conflict of interest

None declared.

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Introduction

Atopic dermatitis (AD) is a chronic skin disease, in which symptoms such as pruritus have a considerable impact on the quality of life (QoL). Clinical disease activity scores evaluate disease severity and extent but do not measure the impact of the skin disease. Health-related QoL measurement assesses burden of illness and can be used to evaluate outcomes of medical treatment.¹ QoL assessment has become an important endpoint in clinical trials. Moreover, in routine clinical practice, QoL assessment is increasingly being used.² The Dermatology Life Quality Index

(DLQI) was the first dermatology-specific QoL instrument and to date is the most commonly used.^{3,4} In this article, the DLQI has been used as QoL instrument because it has been extensively used in other randomized controlled trial (RCTs), is well validated and due to its' simplicity of use. An important issue is defining the clinically important change in DLQI scores. The minimal clinically important difference has been defined as 'the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate a change in the patient's management'.⁵ The minimal important

difference (MID) of the DLQI has been estimated in inflammatory diseases, hyperhidrosis and chronic idiopathic urticaria and has a range of 2.2–6.9.²

The most used disease activity scoring system in AD is the objective Scoring Atopic Dermatitis (SCORAD) index, which combines both disease extent and severity. The objective SCORAD is validated adequately on construct validity, interobserver reliability and sensitivity to change.^{6,7} The scoring of the extent in the objective SCORAD consists of grading the extent of body surface area (BSA) affected according to the 'rule of nines'. The scoring of the extent can also be performed independently using the 'rule of nines'. The Six Area Six Sign Atopic Dermatitis (SASSAD) severity score⁸ measures different severity signs on six different body parts, and has also been shown to have adequate inter-observer reliability.⁷ Both scoring systems have been used in RCTs assessing therapeutic interventions in AD.^{9–13} Visual analogue scales (VAS) are used for the evaluation of subjective symptoms, the VAS for pruritus and loss of sleep are used either isolated or as a component of the SCORAD.¹⁴

The advantage of a laboratory marker is that it is independent of a physicians' judgement of the disease activity. Thymus and activation-regulated chemokine (TARC) has been used to evaluate disease activity in AD and has been described to correlate with clinical disease activity.^{15–17} Serum TARC levels are selectively elevated in patients with AD compared with healthy controls or patients with psoriasis.^{15,17} Furthermore, levels of serum TARC parallel disease severity during treatment with cyclosporin, topical corticosteroids and mycophenolate sodium.^{18,19}

Only a few studies have been performed on the relationship between disease activity and QoL in skin diseases.^{20,20–24} For example, in 359 psoriasis patients Mazzotti *et al.* found that the decrease of the Self-Administered Psoriasis Area and Severity Index was only moderately ($r = 0.24$) but significantly correlated to the decrease of the DLQI, before and after clinical admission.²¹ In 71 children with AD, the Children's Dermatology Life Quality Index (CDLQI) and the SCORAD was related at two occasions 6 months apart ($r = 0.52$, $P < 0.001$ and $r = 0.59$, $P < 0.001$ respectively), in an observational study.²² Additionally, in this study the change in SCORAD was related to the change in QoL. It might be important to know which improvement in QoL corresponds to a certain improvement in disease activity. This can be useful in clinical practice to set treatment goals or in defining a clinically relevant difference for sample size calculations in RCTs.

The aim of this investigation is to assess the relation between QoL and disease activity in adult AD patients before and after 6 weeks of treatment with cyclosporin 5 mg/kg. Additionally, we evaluated the improvement in DLQI when the disease activity scores (objective SCORAD, SASSAD and 'rule of nines') improved by 10 points.

Patients and methods

Patients

The patients and data used are obtained from a RCT comparing enteric-coated mycophenolate sodium to cyclosporin A (CsA) as long-term treatment in patients with severe AD.²⁵ In short, 55 patients were included from the Department of Dermatology of the University Medical Center Utrecht between November 2005 and November 2007. Before randomization patients were treated with CsA 5 mg/kg divided into two doses per day for 6 weeks as a run-in phase. Disease activity was assessed using the objective SCORAD, SASSAD severity score and 'rule of nines' extent score by a single trained investigator at inclusion, after 3 and 6 weeks. At these visits patients filled out the DLQI of Finlay²⁶ and the VAS for pruritus and loss of sleep, rating the severity of their symptoms in the preceding 7 days. In this study, the values at inclusion ($t = 0$) and after 6 weeks of treatment ($t = 6$) were evaluated. By using these two time points, we could assess the relation between disease activity and QoL in patients with high disease activity and moderate disease activity (after 6 weeks of treatment disease activity was considerably lower than at inclusion). The study was approved by the local ethics committee and patients gave their written informed consent.

Disease activity scorings systems

The objective SCORAD is a scoring system that takes into account both the affected BSA as well as the severity of the disease. In the objective SCORAD, the subjective items (pruritus and loss of sleep) have been eliminated and are assessed separately. The first part of the objective SCORAD consists of grading the extent of BSA affected by AD. This is done according to the rule of nines in which the total BSA is comprised of 9% for head and neck, each arm, the front and back of each leg and the four trunk quadrants, and 1% for the genital area. The second part of the objective SCORAD consists of scoring the intensity of six AD severity characteristics (erythema, oedema/papulation, oozing/crusts, excoriations, lichenification and dryness). Each item was graded 0–3 (0 = absent; 1 = mild; 2 = moderate and 3 = severe). Total objective SCORAD (maximum of 83) was obtained by the sum of BSA divided by five and total severity score multiplied by 3.5. For classification of the severity of the disease, the following cut-off points for the objective SCORAD have been made: score < 15 , mild AD; score 15–40, moderate AD; and score > 40 , severe AD.^{6,14} The SASSAD only measures the disease severity and comprises assignment of six signs (erythema, exudation, dryness, cracking and lichenification) at six sites (arms, hands, legs, feet, head and neck, trunk); each on a scale of 0 (absent); 1 (mild); 2 (moderate) and 3 (severe). Total SASSAD (maximum of 108) is calculated by adding all severity scores on each site.⁸ The 'rule of nines' disease extent index was also measured independently of the objective SCORAD. The level

of serum TARC was measured as an objective marker for disease activity.^{15,17} TARC was measured using the Quantikine Human TARC immunoassay according to the manufacturers' instructions (R&D Systems Inc., Minneapolis, MN, USA). Blood for TARC measurement was drawn shortly after disease severity was scored.

Quality of life

The health-related QoL was assessed using the DLQI of Finlay.²⁶ It consists of 10 questions concerning patients' perception of the impact of skin disease on different aspects of their QoL over the last week. The items encompass aspects such as symptoms and feelings, daily activities, work, school or leisure, personal relationships and side-effects of treatment. Each item is scored on a four-point Likert scale: 0, not at all/not relevant; 1, a little; 2, a lot and 3, very much. Scores of individual items (0–3) are added to yield a total score (0–30); higher scores mean greater impairment of the patients' QoL.² A banding system has been designed to aid the interpretation of the DLQI scores, 0–1 means 'no effect on QoL'; 2–5, 'small effect'; 6–10, 'moderate effect'; 11–20, 'very large effect'; 21–30, 'extremely large effect'.²⁷ Additionally, a subjective measure for pruritus and loss of sleep, the VAS for pruritus and loss of sleep were used, and can be seen as a form of QoL measurement. The patients themselves indicated a point on a 10-cm VAS according to the intensity of itch and loss of sleep over the last week, with possible scores ranging from 0 (no pruritus/loss of sleep) to 10 (maximum pruritus/loss of sleep) points.²³

Statistical analysis

The objective SCORAD and the change in disease activity scores and DLQI were normally distributed. Pearson correlation coefficients were calculated for normally distributed variables, otherwise Spearman correlation coefficients were calculated. First, correlation coefficients were calculated between the disease activity scores (objective SCORAD, SASSAD, 'rule of nines' disease extent index and serum TARC) and the QoL scores (DLQI, VAS pruritus and VAS loss of sleep) at inclusion ($t = 0$) and after 6 weeks of treatment ($t = 6$). Second, correlation coefficients were calculated between the change from $t = 6$ to $t = 0$ in disease activity scores and the change in QoL scores to assess whether individual changes in disease activity were related to individual changes in QoL. A correlation coefficient of 0.10–0.29 indicates a small correlation, 0.30–0.49 a moderate correlation and 0.50–1.0 a high correlation. Third, to assess the change in QoL when disease activity scores were improved by 10 points, linear regression analysis was performed with change from $t = 6$ to $t = 0$ in disease activity scores divided by 10 as the independent variable and the change from $t = 6$ to $t = 0$ in DLQI as the dependent variable. Statistical analysis was performed using the program SPSS for Windows (version 15.0, 2006; SPSS Inc., Chicago, IL, USA).

Results

Patients

Of the 55 patients included in the study, one patient had not filled out the DLQI at inclusion and was excluded from the analysis. Five patients dropped out of the study during the first 6 weeks and were not included in some parts of the analysis. The average age of the patients at inclusion of the study was 37.3 ± 12.9 (mean $\pm$ SD). At inclusion the average objective SCORAD was 43.0 ± 10.1 (mean $\pm$ SD) indicating severe AD, average DLQI was 14.6 ± 6.4 (mean $\pm$ SD) indicating a large effect on QoL²⁷ and average serum TARC level was 4130 ± 5647 pg/L (mean $\pm$ SD). After 6 weeks of treatment with cyclosporin 5 mg/kg ($n = 49$) the average objective SCORAD was 22.0 ± 7.8 (mean $\pm$ SD) indicating moderate AD, average DLQI was 3.7 ± 4.0 (mean $\pm$ SD) indicating a small effect on QoL and average serum TARC level was 752 ± 1157 pg/L (mean $\pm$ SD).

Correlation between disease activity and quality of life

Table 1 presents the correlation coefficients between the disease activity scores (objective SCORAD, SASSAD, 'rule of nines' disease extent index and serum TARC) and the QoL scores (DLQI, VAS pruritus and VAS loss of sleep) at inclusion ($t = 0$), after 6 weeks of treatment ($t = 6$) and for the change between $t = 0$ and $t = 6$.

Table 1 Correlations between patient-assessed quality of life (DLQI, VAS pruritus, VAS loss of sleep) and doctor-assessed disease activity scores (objective SCORAD, SASSAD, 'rule of nines' extent score)/laboratory marker of disease activity (serum TARC), at inclusion ($t = 0$), after treatment ($t = 6$) and change over time ($t = 0$ to $t = 6$)

Correlation of patients quality of life scores and clinical/laboratory disease activity scores	At inclusion $n = 54$ ($t = 0$)		After 6 weeks of treatment $n = 49$ (T6)		Change from $t = 6$ to $t = 0$	
	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value
DLQI						
Objective SCORAD	0.17	0.23	0.34	0.02*	0.19	0.20
SASSAD	0.09	0.52	0.19	0.18	0.25	0.08
'Rule of nines'	0.25	0.07	0.49	< 0.001*	0.27	0.06
Serum TARC	0.16	0.24	0.31	0.03*	0.35	0.02*
VAS pruritus						
Objective SCORAD	0.18	0.21	0.33	0.02*	0.16	0.29
SASSAD	0.08	0.58	0.17	0.24	0.12	0.44
'Rule of nines'	0.09	0.54	0.36	0.01*	0.15	0.30
Serum TARC	0.05	0.75	0.38	0.01*	0.12	0.43
VAS loss of sleep						
Objective SCORAD	0.18	0.21	0.15	0.31	0.25	0.10
SASSAD	0.09	0.54	0.04	0.79	0.18	0.23
'Rule of nines'	0.08	0.56	0.18	0.21	0.23	0.13
Serum TARC	0.17	0.24	0.24	0.10	0.25	0.09

*Significant.

At the start of the study, there was a small, non-significant correlation between the DLQI and the objective SCORAD, 'rule of nines' and serum TARC, while the SASSAD did not correlate at all with the DLQI. There was also a small but non-significant correlation between the objective SCORAD and VAS pruritus and VAS loss of sleep. The SASSAD and the 'rule of nines' did not correlate with the VAS pruritus or the VAS loss of sleep. There was no correlation between serum TARC levels and VAS pruritus and a small non-significant correlation with VAS loss of sleep.

After 6 weeks of treatment, the objective SCORAD, 'rule of nines' and serum TARC showed moderate and significant correlations with the DLQI. The SASSAD severity index showed a small and non-significant correlation with the DLQI. The objective SCORAD, 'rule of nines' and serum TARC were also moderately correlated with the VAS pruritus but showed only small correlations with the VAS loss of sleep. The correlations between change from $t = 6$ and $t = 0$ in disease activity scores and change in QoL were all quite low except for the correlation between serum TARC and DLQI ($r = 0.347$, $P = 0.015$).

Clinical relevance of disease activity score

Table 2 shows an individual's improvement in QoL when disease activity scores are improved by 10 points. An improvement in objective SCORAD, SASSAD and 'rule of nines' of 10 points corresponded only to a slight improvement in the DLQI, 1.3, 1.5 and 1.1 points respectively.

Discussion

In this study, we observed that (i) disease activity correlated better with QoL when disease activity was less severe, (ii) disease extent ('rule of nines' score) correlated better with QoL than disease severity and (iii) an individual's improvement of 10 points in disease activity was accompanied by only a small improvement in QoL.

In this study, we found that disease activity correlates better with QoL when disease activity is less severe. This has not been investigated or reported before. There are two previous studies in patients with AD that compared QoL with disease activity, one in

children²² and one in adults and children.²⁰ Additionally, there is one study that compared VAS pruritus with disease activity.²³ In the children's study, the CDLQI significantly correlated with the objective SCORAD at the first and second visits; this correlation was in the same range as that between the DLQI and the 'rule of nines' at $t = 6$ in our study.²² A possible explanation for the difference with our data at inclusion is a difference in the severity of AD. The children included in the study had in general, a mild AD with most patients having an objective SCORAD ≤ 15 , whereas the patients in our study had severe AD (average SCORAD of 43) at inclusion. After 6 weeks of treatment, the objective SCORAD decreased to 22 (moderate AD) and this resulted in correlation coefficients nearing those in the study with children with mild AD. In adults and children with AD, Holm *et al.* assessed health-related QoL (using the DLQI and CDLQI), VAS pruritus and disease activity (objective SCORAD) in 101 patients with moderate AD at two visits at a 6-monthly interval. Although no correlation coefficient is given, the authors report that convergent validity was found for scores of DLQI, CDLQI and VAS pruritus which were significantly related with the objective SCORAD.²⁰ Moreover, in this study disease activity at both time points were in the same range as in our study at $t = 6$. Hachisuka *et al.* related objective SCORAD to the VAS pruritus in 22 adult AD patients and found these two to be highly correlated ($r = 0.692$, $P < 0.001$).²³ In comparison with our study, this correlation is higher. However, the range of objective SCORAD in their study was 5–55, suggesting heterogeneity in disease activity, which make these results difficult to compare with our data. We do not know how to explain the finding that the correlation between disease activity and QoL was lower in severe AD than in mild AD. Further research is needed to replicate and explain this finding.

We observed that disease extent ('rule of nines' score) correlates better with QoL than disease severity measured with the SASSAD, both at $t = 0$ and $t = 6$. This suggests that the extent of the BSA affected has more impact on QoL than disease severity. This may be attributed to the visibility of the disease for others. Another possible explanation is that measurement of disease severity is less reliable than the measurement of disease extent. In this study, as in most studies disease activity scoring was performed by a single investigator at each time point. As objective disease parameter, we also measured serum TARC levels. At $t = 0$ the correlation between serum TARC and DLQI paralleled the correlations between the clinical scores and DLQI. At $t = 6$ the moderate and significant correlation between serum TARC and DLQI and the correlation between serum TARC and VAS pruritus confirmed the correlations found between the objective SCORAD and DLQI. The relation between disease extent and QoL has not been reported before in patients with AD. Maroti *et al.* assessed QoL in patients with AD before and 6 weeks after an outpatient treatment and additionally interviewed nine of these patients about factors that might influence their QoL. They indicated important areas of concern such as withdrawal from public places, adoption of special clothing habits and concern

Table 2 Linear regression analysis [regression coefficient and 95% confidence interval (CI)], for change in DLQI when the disease activity scores (objective SCORAD, SASSAD and 'rule of nines') improve by 10 points

	Regression coefficient (95% CI)
Improvement in DLQI per 10 points improvement in objective SCORAD	1.3 (–0.7; 3.4)
Improvement in DLQI per 10 points improvement in SASSAD	1.5 (–0.2; 3.2)
Improvement in DLQI per 10 points improvement in 'rule of nines'	1.1 (–0.03; 2.2)

about personal relationships.²⁸ These factors may be more important when disease activity is extensive and may be less important when disease is severe but not extensive.

We found that an individual's improvement of 10 points in disease activity is accompanied by only a small improvement in QoL (1.3, 1.5 and 1.1 points for objective SCORAD, SASSAD and 'rule of nines' respectively). Although the improvement of the whole group ($t = 0$ to $t = 6$) in DLQI and objective SCORAD is on average 11 and 21 points respectively, this is not the case on an individual basis: not every individual who improves considerably in objective SCORAD also improves considerably in DLQI. Ten points is often used as a relevant difference in disease activity. In patients with psoriasis, the rules of tens has been proposed to define the severity of psoriasis (current severe psoriasis is defined when BSA involved > 10% or PASI > 10 or DLQI > 10).²⁹ However, in this study, we observed that 10 points improvement in disease activity only corresponds to a small improvement in QoL. In the AD children's study,²² it was found that each unit change in the SCORAD was associated with a 0.12 (95% CI 0.04–0.19, $P = 0.004$) unit change in the CDLQI. This is comparable with our study, each unit change in the objective SCORAD was associated with 0.13 units change in DLQI (95% CI –0.07 to 0.34). This suggests that other factors than disease activity predict QoL in patients with AD. Potocka *et al.* showed that there were statistically significant differences in self-assessment of QoL depending on one's level of self-acceptance. Patients with a negative self-image (compared with those with a positive self-image) deem their QoL to be poor.³⁰ In patients with acne, it was also found that other factors than the severity (such as age and self-perception of acne) influenced QoL.^{24,31} Another possibility is that DLQI does not encompass all aspects of QoL that affect AD patients. From the literature, it is known that patients with AD experience a greater degree of anger,^{32,33} depression³⁴ and anxiety^{32,35,36} than control groups. These aspects, anger, depression and anxiety are not specifically addressed in the DLQI. In studies in other skin diseases such as psoriasis and vitiligo, this issue has also been raised and it is opted that there is an under representation of the emotional aspects of the patients' life in the DLQI.^{4,37} Wittkowski *et al.* assessed illness perception in patients with AD and their study suggests that participants' beliefs and emotional response are more strongly associated with the meaning they ascribe to their condition rather than its severity.³⁸ These factors may explain that a substantial improvement in disease activity is accompanied by only a small improvement of QoL in patients with AD.

Several authors have attempted to establish which MID of the DLQI are clinically relevant.² In patients with chronic plaque psoriasis treated with adalimumab, the MID was reported to range between 2.3 and 4.0 (mean of 3.2).³⁹ In patients with chronic urticaria, the MID ranged between 2.2 and 3.1.⁴⁰ Khilji *et al.* reported that a minimum change of five points in DLQI is clinically relevant for AD patients.⁴¹ Hongbo *et al.* indicated that a 10-point improvement in DLQI gives a shift in category in the banding

system according to Hongbo *et al.* This author also showed that DLQI score > 10 points meant that the skin disease had a very large effect on the patient's life and was strong supportive evidence for the need for active patient intervention.²⁷ The main aim of this banding system set down by Hongbo was to achieve harmonization of treatment strategy between clinicians and allow DLQI scores to inform clinical decisions. Limitation of the MID values in the previously mentioned studies is that they are based on the QoL assessment and are not related to disease activity. We found that 10 points improvement in disease activity for each individual corresponded with 1.1–1.5 points improvement in QoL. This would mean that an improvement of 38.5, 33.3 and 45.5 points in objective SCORAD, SASSAD and 'rule of nines' corresponded with an improvement of five points on the DLQI. Our data do not give a realistic relation between the MID of DLQI and disease activity, confirming our conclusion that other factors besides disease activity alone influence QoL. Further studies will be necessary to evaluate which MID in QoL scores are relevant to use in RCTs and in daily clinical practice.

A limitation of this study is the small number of patients. Furthermore, as the correlation coefficients between disease activity and QoL were not high, the regression coefficients we found have to be interpreted with caution and should be replicated by other studies. Possibly disease activity correlates better with other QoL instruments as other questions are asked than in the DLQI; however, we did not investigate this and might therefore be an interesting question for further research.

In conclusion, we found that disease activity correlated better with QoL when disease activity was less severe, that disease extent ('rule of nines' score) correlated better with QoL than disease severity and that an individual's improvement of 10 points in disease activity was accompanied by only a small improvement in QoL. Therefore, there must be other factors besides disease activity that influence QoL in AD such as anger, anxiety and self-image. To better assess the influence of AD on QoL, these items may have to be incorporated in the assessment of QoL in AD. When assessing QoL in research or clinical settings, it is important to bear in mind that disease activity and QoL do not perfectly correspond.

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