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The Benefit of Pimecrolimus (Elidel, SDZ ASM 981) on Parents' Quality of Life in the Treatment of Pediatric Atopic Dermatitis

Diane Whalley, BSc*; Jasper Huels, PhD‡; Stephen P. McKenna, PhD*; and Daniel van Assche, PhD‡

ABSTRACT. *Objective.* Two 26-week US clinical trials of identical design were conducted to evaluate the efficacy and safety of pimecrolimus (Elidel, SDZ ASM 981) cream 1% in pediatric atopic dermatitis (AD). A secondary aim of both trials, and the focus of this article, was to evaluate the quality-of-life (QoL) impact of pimecrolimus compared with its vehicle.

Methods. A 6-week randomized, double-blind treatment phase was followed by a 20-week open-label phase during which all patients received pimecrolimus (403 patients 2 to 17 years old with mild to moderate AD; 267 randomized to pimecrolimus and 136 to vehicle). QoL analyses were conducted on the intention-to-treat data and included patients 8 years old or younger. QoL was evaluated with the Parent's Index of Quality of Life in Atopic Dermatitis (PIQoL-AD) at baseline, 6 weeks, and 6 months. The PIQoL-AD is a 28-item measure completed by the parents of children with AD (0 to 8 years old).

Results. PIQoL-AD scores were available for 241 cases at baseline (158 pimecrolimus, 83 vehicle), 193 at 6 weeks (132 pimecrolimus, 61 vehicle), and 161 at 6 months (113 pimecrolimus, 48 vehicle). Improvement in parents' QoL was seen for both groups between baseline and 6 weeks and 6 months. Analysis of covariance on PIQoL-AD scores at 6 weeks showed statistically significant superiority of pimecrolimus compared with vehicle. After all patients were switched to receive pimecrolimus at week 6, mean PIQoL-AD scores were the same across both groups at 6 months. Positive but low levels of association were observed between changes in PIQoL-AD scores and changes in severity of AD (Investigator's Global Assessment and parent-perceived severity of pruritus).

Conclusion. The results showed that pimecrolimus had a beneficial effect on parents' QoL in pediatric AD. *Pediatrics* 2002;110:1133-1136; *clinical trials, atopic dermatitis, eczema, child, quality of life, SDZ ASM 981, PIQoL-AD.*

ABBREVIATIONS. AD, atopic dermatitis; QoL, quality of life; PIQoL-AD, Parent's Index of Quality of Life-Atopic Dermatitis; IGA, Investigator's Global Assessment.

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Atopic dermatitis (AD) is a common skin condition that affects 12% to 15% of all children in early childhood.¹ Approximately 70% of cases begin within the first year of life² and up to 90% within the first 5 years.³ Remission by 15 years of age is usual for 75% of children, although some of these may relapse later in life.

The prevalence of AD is reported to have increased over the last 3 decades.^{4,5} The condition is ~1.7 times more common in females than males,⁶ and Nevot et al⁷ report a higher prevalence of AD for British schoolchildren from higher social classes than for those from lower classes. Evidence indicates that there is a clear genetic component to the condition.⁸ Approximately 70% of patients have been identified as having a personal or family history of atopic diseases such as asthma, allergic rhinoconjunctivitis, and AD.¹

Although generally regarded as an acute, sub-acute, or chronic pruritic inflammation of the skin, there are no primary or distinctive cutaneous lesions that characterize AD. Furthermore, symptoms may vary across individuals and from infancy to adulthood. It is an itchy, chronic or chronically relapsing, inflammatory skin condition characterized by itchy papules, which become excoriated and lichenified. Distribution is variable and age dependent, typically involving the face, antecubital and popliteal spaces, wrists, and hands. Severe forms may present with oozing, crusting, or impetiginized skin lesions, which may involve the entire integument. AD often precedes or is associated with other atopic diseases, such as hay fever, asthma, food allergies, or anaphylactic reactions (eg, to insect stings). This condition, called atopy, is characterized by a positive family history and elevated serum immunoglobulin E levels in a majority of patients.

Pediatric AD can affect children's physical abilities, emotions and behavior, social skills, self-esteem, and overall psychological development.^{2,9} The impact is not limited to the child but extends to the entire family.¹⁰⁻¹² Factors such as constant itching, skin infections, lack of sleep, discipline problems, lowered self-esteem, and growth and developmental problems can be debilitating for both the child and the family.¹³ Daud et al¹⁰ reported that parents of children with AD were more likely to feel distressed, tired, and fed up than other parents. It was also found that having a child with AD could have a detrimental effect on the parent's intimate and social relationships, as parents' social lives often tend to

revolve around the child's treatment or care needs. As a result, social contacts can be lost, leading to social isolation. Such problems are compounded by financial burdens caused by time away from work and the cost involved in travel to clinics, treatments and additional bedding, clothes, and special foods.¹¹ Elliot¹⁴ also found that parents of children with AD experienced stress, feelings of guilt, and powerlessness caused by their inability to relieve their child's pain or stop the scratching and bleeding.

In addition to the time needed to deal with special dietary needs and treatment regimens, the financial and psychosocial pressures placed on parents can have a widespread and devastating impact on the whole family. Parents often are unable to attend to the needs of their other children, and this can lead to sibling rivalry. Furthermore, other family members may also experience sleep deprivation and are subjected to family limitations in lifestyle, altered social and holiday plans, and adverse effects on family relationships.¹⁵

The current standard of care for pediatric AD is skin care with emollients and short-term, reactive use of topical corticosteroids. Topical corticosteroids are effective short-term treatments, but their prolonged use should be avoided because of the associated adverse effects (eg, skin atrophy and hypothalamic-pituitary-adrenal axis suppression).¹⁶ Pimecrolimus (Elidel, SDZ ASM 981) cream 1% is a selective inflammatory cytokine inhibitor and has been shown to be tolerable and effective in adults.¹⁷

Two clinical trials of identical design (6-week randomized, double-blind followed by a 20-week open-label phase in which all patients received pimecrolimus) were conducted in the United States to compare the efficacy and safety of pimecrolimus with those of its vehicle in children with AD. A secondary aim of both trials, and the primary focus of the results presented, was to evaluate the impact on quality of life (QoL) of pimecrolimus compared with vehicle.

METHODS

Study Design

As part of the 2 trials, 403 patients 2 to 17 years old were recruited from 11 centers across the United States. Patients were included if they had a clear diagnosis of AD (fulfilling the diagnostic criteria of Williams¹⁸), had 5% or more of their body surface area affected, and were considered to have mild or moderate disease (as indicated by an Investigator's Global Assessment [IGA] score of 2 or 3).

Patients were randomized to receive pimecrolimus or its vehicle for a period of 6 weeks. At week 6, the control group was switched to active treatment, and all patients received pimecrolimus for an additional 20 weeks. This formed the open-label phase of the trial. QoL and severity of AD were assessed at baseline, 6 weeks, and 6 months.

Assessment of QoL

QoL was assessed with the Parent's Index of Quality of Life-Atopic Dermatitis (PIQoL-AD). The measure has 28 items that take the form of statements to which respondents are asked to indicate whether they are true or not true for them. It is designed to be completed by the parents of children with AD 8 years old or younger and thus measures the impact of AD on the parents' QoL.

The theoretical basis of the measure was the needs-based model of QoL.¹⁹ This model states that life's quality is at its highest when

most needs are met and at its lowest when fewest needs are fulfilled. The content of the measure was derived through in-depth qualitative interviews with parents of children with AD in the United Kingdom, the Netherlands, and Italy.²⁰ Each item in the PIQoL-AD relates to a need that could be influenced by the child's AD. Because the items in the measure all relate to need fulfillment, an index of QoL is produced. Versions of the measure were also produced for the United States, France, and Germany. All 6 language versions have been shown to be highly relevant and acceptable to patients and to have good psychometric properties.²¹

Assessments of Disease Severity

Assessments of the severity of AD included IGA and perceived severity of pruritus. Six possible IGA scores can be assigned based on certain signs of AD (erythema and papulation or infiltration): 0, clear (no signs of AD); 1, almost clear (signs just perceptible); 2, mild disease; 3, moderate disease; 4, severe disease; and 5, very severe disease (severe signs with oozing or crusting). Severity of pruritus over the 24 hours before the trial visit was rated by the primary caregiver (in discussion with the child if possible) as 0, none; 1, mild; 2, moderate; or 3, severe.

Statistical Analyses

The 2 trials, being of identical design, were pooled for analysis. Analyses were conducted on all randomized intention-to-treat patients 8 years old or younger. PIQoL-AD scores can range from 0 to 28, with a high score indicating poor QoL. Scores were calculated for cases with up to 20% (that is, 5 or fewer) missing responses. Change scores were calculated relative to baseline, such that a positive change score represented an improvement in QoL. Change over time within treatment groups were evaluated using repeated-measures *t* tests. An analysis of covariance was conducted to estimate treatment differences. The statistical fixed-effects model considered center and treatment as main effects, with the respective baseline values used as covariate. The levels of association between changes in PIQoL-AD and IGA and severity of pruritus were estimated using Spearman rank correlation coefficients.

RESULTS

Sample Characteristics

Of the 403 patients who were randomized, 278 were 8 years old or younger. PIQoL-AD scores were available for 241 of these patients at baseline (158 pimecrolimus and 83 vehicle), 193 cases at 6 weeks (132 pimecrolimus and 61 vehicle), and 161 cases at 6 months (113 pimecrolimus and 48 vehicle).

Table 1 shows the demographic characteristics of the 241 patients at baseline. No statistically significant baseline differences between treatment groups were found for sex and age.

Summary Statistics

Table 2 shows the summary statistics (mean, standard deviation, median, and interquartile range) for PIQoL-AD scores at baseline, 6 weeks, and 6 months in each treatment group.

Change in QoL

Figure 1 illustrates how PIQoL-AD scores changed over the 6-month trial period in each of the treatment arms. It shows that the baseline scores for the parents of children in the pimecrolimus group were slightly higher (indicating poorer QoL) than those for the parents of children in the vehicle group. However, these differences did not achieve statistical significance.

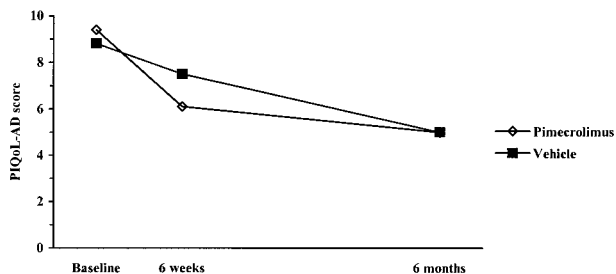
PIQoL-AD scores for the parents of children in both treatment groups significantly improved over

TABLE 1. Demographic Details of the Clinical Trial Sample

	Pimecrolimus Group (<i>n</i> = 158)	Vehicle Group (<i>n</i> = 83)	All (<i>n</i> = 241)
Sex			
Male (%)	84 (53.2)	41 (49.4)	125 (51.9)
Female (%)	74 (46.8)	42 (50.6)	116 (48.1)
Age			
Mean (standard deviation)	4.0 (1.75)	3.8 (1.82)	3.9 (1.77)
Median (interquartile range)	4.0 (2.0–5.0)	4.0 (2.0–5.0)	4.0 (2.0–5.0)
Range	1.0–7.0	1.0–7.0	1.0–7.0

TABLE 2. Summary Statistics for PIQoL-AD Scores

Treatment Group	Baseline	6 Weeks	6 Months
Pimecrolimus			
<i>n</i>	158	132	113
Mean	9.4	6.1	5.0
Standard deviation	6.04	5.89	5.03
Median	8.0	4.5	4.0
Q1–Q3	5.0–13.0	2.0–9.0	1.0–8.0
Vehicle			
<i>n</i>	83	61	48
Mean	8.8	7.5	5.0
Standard deviation	6.91	7.82	6.51
Median	7.0	5.0	2.0
Q1–Q3	3.0–13.0	1.0–12.0	1.0–8.0



Note: All patients were switched to receive pimecrolimus at week 6.

Fig 1. Mean PIQoL-AD scores over the trial period.

the initial 6-week double-blind part of the trial ($P < .001$ for pimecrolimus and $P = .019$ for vehicle). A reduction (indicating improvement) of 10% or more in PIQoL-AD score was found in 74.2% of parents of children in the pimecrolimus group, 62.3% of parents of children in the vehicle group, and 70.5% of all parents. The correlations between change in PIQoL-AD and changes in IGA and pruritus severity were .33 and .22, respectively.

At 6 weeks, an analysis of covariance on the PIQoL-AD scores showed statistically significant superiority of pimecrolimus when compared with vehicle treatment. ($P = .023$). The least-square mean change was 3.20 for the pimecrolimus group and 1.63 for the vehicle group, with an estimated treatment difference of 1.57 and corresponding 95% confidence interval of 0.22–2.92. Changes in parents' QoL and the observed differences between groups were found to be independent of the children's age.

At 6 months, at the end of the open-label phase when all patients had been receiving pimecrolimus for a minimum of 20 weeks, both treatment groups showed a significant within-group improvement

($P < .001$) compared with baseline. Figure 1 illustrates that mean PIQoL-AD scores were the same across treatment groups at the end of the open-label period. A reduction of 10% or more in PIQoL-AD score between baseline and 6 months was found in 76.1% of parents of children who had been initiated with pimecrolimus and 77.1% of parents of children who had started with vehicle. A total of 76.4% of all parents had shown improvement. The correlation coefficients between PIQoL-AD change scores and changes in IGA and pruritus scores were .112 and .313, respectively. Once again, changes in parents' QoL were found to be independent of the age of their child.

DISCUSSION

Like many other chronic diseases in childhood, AD has a substantial effect on the whole family. Therefore, in addition to the distress caused to the child, such conditions influence the parents' mental, physical, and emotional well-being. In the case of AD, this impact in turn has an adverse effect on QoL, with parents less able to fulfill the needs of their child, their family, or themselves.²⁰ Few instruments are available to assess outcome in pediatric dermatology. Those that do exist, such as the Children's Dermatology Quality of Life Index,²² focus on the direct symptomatic and functional impact of the condition. The PIQoL-AD differs from these measures in that it assesses the impact of such influences on the QoL of those concerned. Furthermore, many of the existing measures cannot be used for young children. For example, the Children's Dermatology Quality of Life Index can be used only for children 5 years of age and older. In contrast, the PIQoL-AD allows the QoL impact of AD and its treatment to be assessed from the first few months of a child's life because the

instrument goes beyond assessing symptoms and functioning.

The content of the PIQoL-AD reflects the areas of concern that have been reported in many studies of the impact of childhood AD on the family. For example, the stress experienced by parents¹⁴ is illustrated by their inability to relax during the day or sleep well at night. As a result, parents feel tired all the time and are unable to alleviate tension in the family. Feelings of powerlessness¹⁴ result from the chronic nature of the disease, leaving parents with the perception that they have little control over the eczema. Authors have also described parents' general feelings of distress and stress,^{10,14} and in the PIQoL-AD these are reflected in questions relating to the constant worry, time, and attention that the child needs. The fact that the content of the instrument was derived directly from interviews with parents meant that the issues of particular relevance and concern were included. As a result, the measure is better able to detect improvements in QoL brought about by effective treatment.

The purpose of this article was to present the results of an investigation into the QoL benefits of treating pediatric patients with pimecrolimus (Elidel, SDZ ASM 981) cream 1%. This treatment offers tolerable and effective therapy in the long-term management of childhood AD. Evidence to date suggests that its systemic absorption in children is low, even with extensive application.²³ In the first 6 weeks of the present trials, an improvement in QoL was seen in the parents of children in the pimecrolimus group, and this improvement was statistically greater than that observed in the parents of children in the vehicle group. After the next 20 weeks of the trial, in which all patients were treated with pimecrolimus, the parents of children in both groups reported the same QoL.

When the clinical effectiveness of an intervention is seen soon after treatment initiation, it does not necessarily follow that QoL benefits will be evident at the same time, or indeed at all. This is because clinical symptoms and functioning are mediators of QoL in that they influence rather than constitute the construct.²⁴ Therefore, there can be a delay before the full impact of improved symptoms and functioning on QoL is realized. Furthermore, it is possible that this delay is more pronounced where QoL measurement is not confined to the person experiencing the clinical benefit, as has to be the case for young children. This was reflected in the low levels of association observed between parent's QoL and the severity of pruritus as perceived by the parent and the investigator's assessment of the severity of the child's AD. Nevertheless, improvements in QoL associated with pimecrolimus were apparent after a short time; indeed, the PIQoL-AD was able to detect a QoL benefit over vehicle after only 6 weeks.

QoL information generally is collected to evaluate aspects of disease and its treatment that are not reflected in clinical outcomes. The method used to

develop the PIQoL-AD ensures that every item (and thus each incremental score) is relevant to parents of children with AD. The relationship between the PIQoL-AD and clinical parameters is likely to depend on many factors, including the nature of the disease and the clinical variables of interest. This also applies to the relationship between the PIQoL-AD and economic outcomes such as utility. Additional research is needed to explore the relationship between QoL and clinical and economic outcomes.

The results presented from the 2 trials provide evidence that pimecrolimus is effective in improving the QoL of the family of the children treated.

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