The value of pimecrolimus in improving quality of life of children with severe eczema – an open non-randomised study

Kitchin O, MBChB, FCPaed(SA), Dip Allerg(SA)
Masekela R, MBBCh, MMed(Paed), Dip Allerg(SA), Cert Pulm(SA) Paed
Moodley T, MBChB, FCPaed, Dip Allerg(SA)
Green R, MB BCh, DCH, FCP(SA), DTM&H, MMed(Paed), FCCP, PhD, Dip Allerg(SA)
Department of Paediatrics and Child Health, Division of Paediatric Pulmonology, University of Pretoria
Correspondence to: Dr Omolemo Kitchin, e-mail: omolemo.kitchin@up.ac.za
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Abstract

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Background: Atopic eczema is a common skin condition. It has the potential to severely impair quality of life in affected children. Pimecrolimus is currently registered for mild-moderate eczema but in clinical practice children with more severe disease are often treated with this therapy in an attempt to find a safe addition to long-term topical corticosteroid usage. The aim of this study was to test the value of pimecrolimus in improving quality of life in children with severe atopic eczema.

Methods: This a single site, phase 4, non-randomised, open label trial of pimecrolimus use in children aged 4 months to 12 years living with moderate to very severe atopic eczema. The study was conducted at Steve Biko Academic Hospital. Patients with unsatisfactorily controlled disease despite conventional topical therapy, adequate use of emollients, allergen avoidance and non-pharmacological skin hygiene were enrolled. A Parent Index Quality of Life Questionnaire was completed by parents before and three months after using pimecrolimus.

Results: A total of 24 patients were recruited, 20 of whom completed the study. Ninety per cent of patients had co-morbid asthma and allergic rhinitis. The Parent Index Quality of Life demonstrated a mean 33% score improvement after the use of pimecrolimus. There was an attendant reduction in cost of therapy to these patients.

Conclusions: Pimecrolimus usage should be extended to patients with more severe atopic eczema as the improvement in quality of life is important and demonstrable.

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Introduction

Atopic eczema is a common skin condition. Most cases occur in young children (70% in children in the first year of life and 90% by the fifth year).[1,2] There is currently little data for atopic eczema prevalence in South Africa. However, the International Study of Asthma and Allergy in Children (ISAAC) phase 1 and phase III studies reported the prevalence of atopic eczema to be 11.8% and 19.4% respectively in Cape Town schoolchildren.[3,4] Worldwide the prevalence of atopic eczema has increased in recent times in line with other atopic diseases, that is asthma and allergic rhinitis. Atopic eczema is typically outgrown at puberty.[5]

It is a disease of exacerbations and remissions with associated trigger factors such as foods, infections and environmental factors. Risk factors for the atopic diathesis proposed, include rural to urban migration, increased use of antibiotics and western lifestyle. These are related to the hygiene hypothesis with a decrease in TH1 response and enhancement of TH2 responses.[5]

Clinically the diagnosis of atopic eczema is made when there is a pruritic skin rash, positive family history of atopy, early onset and typical localisation of skin lesions according to age, stigmata for atopy and/or IgE mediated sensitisation.[3] Atopic eczema's typical distribution is face, scalp and extensor surfaces in infants with sparing of the nappy area, and flexural surfaces and ankles in older children. For all age groups dry skin is common. Lichenification occurs if the rash is long standing.

The other important, and much neglected, component of atopic eczema is impaired quality of life. Direct effects such as misery, lethargy and depression are seen in affected children. However, this term may include parents' guilt on not being able to control the scratch/itch cycle, sibling rivalry due to attention shift to the affected sibling, loss of income due to repeated regular clinic visits for uncontrollable disease coupled with costs of both useful and useless interventions to control the disease. Psychological stress may occur in the whole family.

Conventional therapy includes avoidance of precipitating factors, attention to clothing and bathing, emollients and topical steroids. Other modalities include treatment of infections and newer therapies such as calcineurin inhibitors**.** A potential problem with topical steroids is side-effects which include skin atrophy, striae and potentially hypothalamic-pituitary-adrenal suppression and Cushing's syndrome due to systemic absorption. These side-effects, both real and perceived, can be worrying to parents and often result in poor adherence to therapy.

Pimecrolimus 1% cream (Elidel®) is a calcineurin inhibitor and an anti-inflammatory ascomycin macrolactam derivative which selectively inhibits the production and release of pro-inflammatory cytokines and mediators in T cells and mast cells. Pimecrolimus binds with high affinity to macrophilin-12 and inhibits the calcium-dependent phosphatase

calcineurin. As a consequence, it inhibits T-cell activation by blocking the transcription of early cytokines. In particular, pimecrolimus inhibits, at nanomolar concentrations, interleukin-2, interferon gamma (Th1-type), interleukin-4 and interleukin-10 (Th2-type) cytokine synthesis in human T cells.

In addition, pimecrolimus prevents the release of cytokines and pro-inflammatory mediators from mast cells *in vitro* after stimulation by antigen and IgE. A major advantage of pimecrolimus is that it does not affect the growth of keratinocytes, fibroblasts or endothelial cell lines.[6]

Whalley D and colleagues[2] have demonstrated the ability of pimecrolimus to improve quality of life in children with atopic eczema. A double-blind, controlled study conducted in 251 infants aged 3 months to 23 months with atopic dermatitis, by Kapp A and colleagues,[7] demonstrated that the use of Elidel® reduced the incidence of flares, improved overall control, was safe and was well tolerated. Siegfried E and colleagues,[8] in a double-blind, multicentre, randomised, vehicle controlled trial of 275 children from 3 months to 11 years of age showed that early treatment of atopic dermatitis with pimecrolimus reduced the incidence of major flares, provided an effective steroid-sparing option and was efficacious and safe in the study subjects.

The current study was designed to address the value of pimecrolimus in improving quality of life of children with proven atopic eczema who have severe disease despite regular use of topical steroids.

Methods

This was a three-month, single site, phase 4, non-randomised, open label trial to investigate the use of pimecrolimus (Elidel® 1% cream) in children with severe or very severe atopic eczema. The severity was assessed using the Investigator Global Assessment and only patients scoring 4 (severe disease: severe erythema, severe papulation/infiltration) and 5 (very severe disease: severe erythema and papulation/infiltration with oozing/crusting) being enrolled.[9] All children, aged 4 months to 12 years, between August and October 2007, who were seen regularly at the Allergy Clinic of Steve Biko Academic Hospital and who met these criteria, were enrolled. In addition, for inclusion into the study these patients had to have at least four out of five of the following: pruritis, stigmata for atopy, personal or family history of atopy, early onset or typical localisation of skin lesions according to age and IgE mediated sensitisation. In addition these patients had to have been using emollients, topical steroids, allergen avoidance where necessary and adequate non-medical interventions for at least six months. All children required at least one course of oral steroids in this period.

Evidence from the literature suggests a controversial role for pimecrolimus in patients with severe atopic eczema.[10]

Following the control of the current flare, these children were started on Elidel® cream. This was applied twice daily, after bathing, to affected sites. All children and parents were taught the correct administration technique and given a package insert as a reminder. Usual therapy with emulsifying ointment was continued but topical corticosteroids were discontinued for the study period.

All subjects signed informed consent and assent if older than seven years of age.

PIQoL Assessment

The Parent Index Quality of Life (PIQoL) questionnaire was completed by parents on the first visit prior to using pimecrolimus. These were completed again at a follow-up visit at three months. The questionnaires were in English. At both visits those parents who had interpretation problems were assisted with translations into Sotho, Tswana or Zulu languages as needed. A total score out of 28 questions was given after each visit. PIQoL scores range from 0 to 28, the higher the score the poorer the quality of life.

Outcome measures

Comparison of quality of life scores before and after Elidel® use was performed. No clinical outcome measure was objectively made.

Statistical analysis

This study employed a paired T-test to assess the probability of the significance of using PIQoL before and after using Elidel cream as a variable. The null hypothesis is quality of life before Elidel® use – quality of life after Elidel® use = 0.

Approval to conduct this study was received from the University of Pretoria Ethics Committee.

Results

A total of 24 patients (12 females), meeting the enrolment criteria, were recruited. Four patients were lost to follow-up and did not complete the PIQoL questionnaire after study completion. These patients were excluded from the final analysis. Therefore, 20 subjects (11 female) completed the study. The subjects ranged in age from 4 months to 12 years. One hundred per cent of patients had their eczema develop before the age of 5 years with 40% having an onset before 3 months of age, 25% had onset between 3 months and 1 year and 30% before age 5. Slightly more than half the patients (55%) presented for medical help for the first time before age 5. Of the 20 patients who completed the study, 12 (60%) had severe disease and 8 (40%) had very severe disease.

Fifty per cent of subjects had been using topical steroids daily for six months and 25% of patients had been using topical steroids daily for more than a year. Twenty five per cent of the subjects who had been on long-term topical steroids had developed striae and skin atrophy. All of these signs improved on the institution of pimecrolimus. No study drug side-effects were reported by the patients.

Skin prick testing was performed in all children (see Table I). Ninety per cent of subjects had co-existing asthma and/or allergic rhinitis.

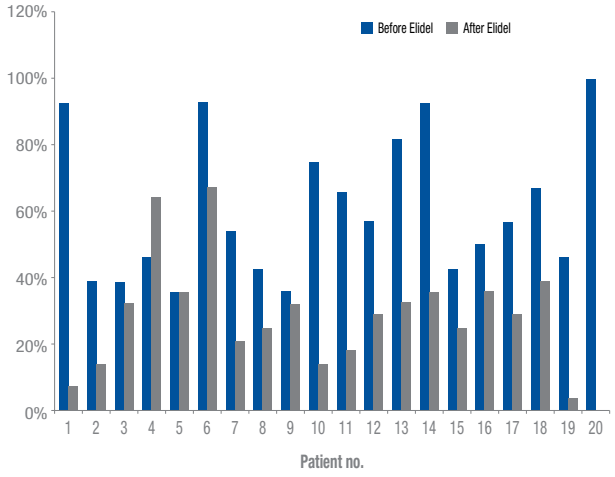
Table I: Allergy test results for subjects. Skin prick test (n = 20)

Allergen	N (%)
House dust mite	8(40)
Peanut	8(40)
Grass mix	7(35)
Eggs	4(20)
Cockroach	4(20)
Cat	3(15)
Dog	2(10)
Cow's milk protein	2(10)
Negative test	2(10)

Some patients had more than one positive test.

Figure 1 demonstrates the before and after intervention PIQoL scores for each individual. The average score before pimecrolimus was 61% (95% confidence interval 50.67338–70.82662). After therapy this improved to 28% (95% confidence interval 20.06153–36.09847). A 33% improvement was noted. ($p < 0.0001$). There was both a subjective and clinical improvement in eczema lesions after intervention.

Figure 1: Comparison of PIQoL before and after use of pimecrolimus



Patient no 20 had a score of 0, after Elidel® use

Discussion

Atopic eczema has a devastating impact on children and parents. On one hand, there is guilt and helplessness from parents when they are unable to control the scratch-itch cycle, poor quality of sleep, and adverse effects of treatment given to their children. On the other hand, direct and indirect costs for medications, investigations and transport are economically taxing especially to patients from a poor socio-economic background. Other indirect costs such as loss of income due to absence from work coupled with reduced productivity as well as intangible costs including loss of quality of life, pain and suffering and psychological maladjustments are also borne.

Subjects enrolled in this study demonstrated an improvement in quality of life as assessed by the PIQoL questionnaire and clearing, or reduced, severity of skin lesions, after the use of the study medication. This quality of life improvement should be judged in these children on so-called 'maximal' therapy for a severe disease.

Pimecrolimus use has been associated with clinical and quality of life improvement in children with mild to moderate atopic eczema but studies in cases of severe disease are limited. This study suggests that children with more severe eczema will also benefit from this intervention. Certainly this form of therapy is a safe addition to other more adverse pharmacological therapies.

Study limitations

The main study limitation is the small number of enrolled subjects. In addition, due to disease severity, it was deemed unethical to subject this group of patients to placebo therapy, hence each patient had to suffice as his/her own control with scores assessed prior to and after therapy.

Conclusions

While cost-effectiveness by direct measurement could not be calculated, it must be remembered that direct cost is but one of the actual 'cost' determinants. Improved quality of life translates into cost-saving but is, in its own right, one of the most important measures in any chronic condition. We cannot and should not judge a therapy by its up-front direct monetary cost. The principle of cost-effectiveness is at stake.

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