ORIGINAL ARTICLE

Safety and efficacy of pimecrolimus in atopic dermatitis in children

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ABSTRACT

Atopic dermatitis (AD) (which is synonymous with atopic eczema) is a genetically determined, distinctive eczematous itchy, chronic relapsing, inflammatory skin condition. The present study is therefore undertaken to evaluates the efficacy and safety of pimecrolimus in the treatment of atopic dermatits in children and determine any side effects. A prospective case-control study was carried out in which the study population comprised atopic dermatitis patients. Clinical assessment was done at baseline, after one week and lastly at six weeks. Monitoring of side effects was done after one week and at six weeks by query of symptoms, physical examination. This case-control prospective study yielded to assess the efficacy and safety of use of steroid and pimecrolimus drugs for the treatment of atopic dermatitis in patient below 12 years of age. Assessment of outcome of treatment in the pimecrolimus group at entry and at 6 weeks revealed mean SCORAD as 64.68 ± 20.16 and 21.06 ± 4.6 respectively. Statistically significant SCORAD improvement was observed. Regarding side effects, in pimecrolimus group these were adequately minimized. Pimecrolimus is quite effective and safe in the treatment of atopic dermatitis in children as the efficacy stands valid in respect of low side effects.

KEYWORDS: Atopic dermatitis, pimecrolimus

INTRODUCTION

The word "atopy" means "out of place".[1] It is a collective term for a group of diseases, principally asthma and hay fever which occur spontaneously in individuals who have a family history of susceptibility. Atopic dermatitis (AD) (which is synonymous with atopic eczema) is a genetically determined, distinctive eczematous itchy, chronic relapsing, inflammatory skin condition. The eruption is frequently associated with other atopic conditions in the individual or other family members. Recent studies reported a prevalence ranging from 15% to 23%.[2, 3] Approximately 50% of atopic dermatitis patients develop this illness by the first year of life, and an additional 30% manifest atopic dermatitis between 1 and 5 years of age.

Initial treatments for atopic dermatitis include cutaneous hydration, topical glucocorticoids, identification and elimination of exacerbating factors and antipruritics. Until recently, antihistamines were a mainstay of therapy for the ever-present itchyness of atopic dermatitis. Although antihistamines are still prescribed by many dermatologists, allergists and pediatricians, evidence-based clinical studies have failed to demonstrate their efficacy.[4] Cyclosporine, tacrolimus and pimecrolimus (SDZ ASM 981) are steroid sparing immunosuppressive medications are new modalities of treatment for refractory atopic dermatitis. Pimecrolimus is more effective than steroid in the treatment of atopic dermatitis. It is associated with

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fewer side effects than steroid in the treatment of atopic dermatitis.[5, 6] The present study is therefore undertaken to evaluates the efficacy and safety of pimecrolimus in the treatment of atopic dermatits in children and determine any side effects.

PATIENTS AND METHODS

This is a prospective case-control study which was carried out from September 2003 to February 2005 for a total period of 18 months. In the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka. The study population includes atopic dermatitis patients attending the outpatient and inpatient Department of Dermatology and Venereology and referred from dermatologist. The age of the patient was 1 year to 12 years. Thirty One (31) patients were included in this study. Among them 16 were in the treatment group, treated with pimecrolimus and 15 were in the control group, treated with and topical corticosteroid (1% hydrocortlsone).

Random sampling method was followed and average five atopic dermatitis patients attended per month in out patient department of Dermatology of BSMMU were subjected to this study. Out of them randomly 31 patients were taken as study sample.

The inclusion criteria were i) Patients of both sexes. ii) Age up to 12 years old. iii) Patient having at least 1 year of intermittent or persistent symptom of atopic dermatitis, iv) SCORAD > 30. Exclusion criteria of the study were

i) Acute or chronic liver disease.
ii) Subjects unwilling to participate in the study.
iii) SCORAD < 30.

All the patients were given an explanation of the study and informed verbal consent was taken before entry into the study. The study did not involve any significant risk. Routine investigations TC, DC, Hb%, ESR, circulating eosinophil, serum IgE were performed.

A detailed history was taken from the parents of the patient specially about the family history, whether there were any atopic or allergic diseases like asthma, hay fever, rhinitis etc. Clinical assessment was done at baseline, after one week and lastly at 6 weeks later. Clinical assessment includes the major and minor criteria of atopic dermatitis. A general physical examination and systemic examination was done. Laboratory assessment was done at baseline. Monitoring of side effects was done after one week and at 6 weeks by query of symptoms, physical examination. Information obtained from history, physical examination and laboratory investigation were recorded in patient data sheet. Due to lack of available facility histopathology could not be done.

Consecutive 31 patients were included in this study using random number table. Sixteen patients (16) were enrolled into pimecrolimus group (P group) and fifteen (15) patients were enrolled into control group (C group).

Dose of pimecrolimus (Elidel) was 1% pimecrolimus (Elidel cream) apply topically twice daily for 6wks on the lesions. Manufactured by: Novartis Pharma AG, Basel, Switzerland.

Dose of Control group

Treated by topical glucocorticoid (1% hydrocortisone) twice daily for 6 weeks.

Severity scoring of atopic dermatitis

The SCORAD Index 7 (Scoring Atopic Dermatitis) is a scoring index for measuring the severity

of atopic dermatitis. It is intended to standardize the assessment of therapeutic studies. It was designed to be easy to use in the outpatient setting (European Task Force, 1993).[8] In order to evaluate the severity of atopic dermatitis as objectively as possible, the European Task force on atopic dermatitis has developed a method allowing consistent assessment by means of severity index called SCORAD.

Statistical analysis

Data was collected in a predesigned data sheet and analysis was performed by using SPSS (V-12) for windows. All the variables, except sex, are expressed as mean +SD. Sex is expressed as male-female ratio. Comparison between more than two groups was done by ANOVA and comparison between two groups was done by paired T-Test. P <0.05 was considered as a level of significance. Categorical data was tested by x, 2- test for comparison.

RESULTS AND OBSERVATIONS

This case-control prospective study yielded to assess the efficacy and safety of use of steroid and pimecrolimus drugs for the treatment of atopic dermatitis in patient below 12 years of age. All individuals under this study belonging to P group (pimecrolimus) and C group (control) were clinically examined and diagnosed confidently by dermatologist revealed the following result. The age of pimecrolimus group (P group) ranges from 1 year to 12 years with a mean of 5.6 (±3.49) years and the age of control group (C group) ranges from 1 year to 12 years with a mean of 7.1 (+2.8) years. Table 1 represents a comparative baseline Clinical characteristics of the two groups (n=31).

It was evidenced that pruritus is present in all individuals of the control group, where as crustation was observed in 14 controls, excoriation, asthma and allergy in all 13 controls. Comparatively in pimecrolimus group pruritus was found in 15 patients, excoriation in 13, crustation in 13 patients, Asthma and allergy were present in 14 patients.

Table 2 represents a comparative baseline clinical characteristics post-treatment of the two groups (n=31).

The result represented in Table 2 shows that in control group. None of the individual had irritation. However, skin atrophy was seen present in 5

Table 1 Baseline clinical characteristics of two groups of individuals pretreatment (n=31)

Characteristics		Group of individuals under study			
		Control (n = 15)	Pimecrolimus (n = 16)	T-value	P-value
Pruritus	Absent	0	0	0.000	1.000
	Present	15	15		
Excoriation	Absent	2	3	0.168	0.682
	Present	13	13		
Crustation	Absent	1	3	1.00	0.31
	Present	14	13		
Asthma	Absent	2	2	1.00	0.31
	Present	13	14		
Allergy	Absent	2	2	0.005	0.94
	Present	13	14		

Table 2 Characteristic of side effect post treatment in control and patient group

Characteristics		Group of individuals under study			
		Control (n = 15)	Pimecrolimus (n = 16)	T-value	P-value
Pruritus	Absent	15	14	2.00	0.15
	Present	0	2		
Skin atrophy	Absent	5	0	6.35	0.01
	Present	11	16		
Telangiectasia	Absent	1	3	4.89	0.02
	Present	4	0		
Thinning of skin	Absent	12	16	3.54	0.06
	Present	3	0		
Infection	Absent	12	14	0.008	0.93
	Present	3	3		

persons but absent in the rest. Telangiectasia was recorded in 4 individuals, but this was not found in 11 individuals. Other characteristics such as thinning of skin were exhibited in 3 people but there was occurrence of infection only in 3 controls. The phenomena in pimecrolimus group are some what different from control group where irritation was observed only in 2 patients and absent in 14 patients. It is interesting to note that skin atrophy was absent in all 16 patients. There was telangiectasia in 4 patients but not evident in 11 patients. Thinning of skin was absolutely present in all 16 patients. Regarding the occurrence of infection only 3 patients exhibited infection but was completely absent in 13 patients.

The statistical analysis revealed the fact that the side effects like skin atrophy and telangiectasia were statistically significant. The treatment with pimecrolimus had much less side effect than steroid ($p<0.05$).

Table 3 shows that the patient on steroid had the SCORAD (mean ± SD) 63.5 ± 17.8 at start of the study. After treatment of 6 weeks the SCORAD had reduced to 21.6 ± 4.1 (mean ± SD). There was statistically highly significant difference in clinical outcome with medication with steroid (P- value 0.001). Patient having the treatment with pimecrolimus had the SCORAD (mean ± SD) 64.68 ± 20.16 at beginning of the study. After treatment of 6 weeks the SCORAD had reduced to 21.06 ± 4.6 (mean ± SD). The study found statistically significant difference in the outcome of pimecrolimus ($p < 0.05$). Thus it is clear that the patient in the steroid group and pimecrolimus group, after treatment of 6 weeks had no statistically significant difference in clinical outcome with medication ($P > 0.05$). Both the groups had similar efficacy in treatment.

Table 3 Assessment of SCORAD Index at baseline and after 6 weeks treatment with pimecrolimus.

Variables	Outcome of treatment in the group		T-value	P-value
	At entry	At 6 weeks		
Total SCORAD (mean ± SD) Control group (n = 15)	63.5 ± 17.8	21.6 ± 4.1	8.313	0.000
Total SCORAD (mean ± SD) Pimecrolium group (n = 16)	64.68 ± 20.16	21.06 ± 4.6	8.508	0.002

DISCUSSION

Pimecrolimus (SDZ ASM 981) is one of the new class of novel ascomycin immunonodulating macrolactams. It was developed for the treatment of inflammatory skin diseases. Ascomycin was first isolated as a fermentation product of Streptomycin hygroscopicus var. ascomycetus in the early 1960s and was initially documented as primarily for its antifungal properties. However, it was more than 20 years later ascomycin was further investigated for its structural and immunomodulatory properties.[9, 10, 11] In view of this fact and antimicrobial properties the present study was undertaken to determine the efficacy and safety of pimecrolimus in the treatment of atopic dermatitis. Since there is no published or any recorded study in Bangladesh, it is believed that this is happened to be the first study of its kind in Bangladesh.

Standard treatment of atopic dermatitis is still recognized as not satisfactory, therefore there are numerous research works has been under trial to search for an effective and satisfactory treatment of atopic dermatitis.[10] The present study was destined to assess the effectiveness and safety of pimecrolimus in the treatment of atopic dermatitis.

The study was employed in 31 patients with atopic dermatitis. Sixteen (16) patients were treated with pimecrolimus for 6 weeks and comparatively fifteen (15) patients were treated with topical corticosteroid (1% hydrocortisone) for a period of 6 weeks. SCORAD index system was used to calculate the efficacy at baseline and 6 weeks after treatment. Statistically significant SCORAD improvement was analyzed in both pimecrolimus group ($P < 0.001$) and steroid group ($P < 0.001$).

The result of the study revealed that the patient in the steroid group and pimecrolimus group, after treatment of 6 weeks had the SCORAD (mean ± SD) 21.6 ± 4.15 and 21 ± 4.1 respectively. There was not statistically significant difference in clinical outcome with medication with steroid and pimecrolimus ($P > 0.05$). Both drugs had similar efficacy in treatment. Regarding the side effect, the study searched for irritation, atrophy of skin, telangiectesia, thinning of skin and infection. Irritation was absent in the patient having steroid therapy. The outcome of the result was found statistically significant. The treatment with pimecrolimus had much less side effect than steroid ($p<0.05$). The present research finding is very much in agreement with other researches.

Whalley et al. (2002)[12] studied the quality of life after use of pimecrolimus in atopic dermatitis they showed that children with atopic dermatitis had improved significantly. The investigators used 1% pimecrolimus cream in patient of age from 2 years to 17 years. The result yielded functional and symptomatic improvement. It is consistent with our study. In another research study conducted by Vincent et al. (2003)[13] revealed the safety and efficacy of pimecrolimus in the treatment of atopic dermatitis in infants. The investigators found that the treatment with pimecrolimus was highly effective and safe for the treatment of the mild to moderate atopic dermatitis. They also demonstrated that pimecrolimus was well tolerated. It was suggested that twice-daily application of pimecrolimus 1% cream could provide rapid and sustained clinical benefit in infants. Furthermore the pruritus was rapidly and significantly ameliorated by pimecrolimus. It is remarkable that the present study analogously obtains the same findings. In those receiving pimecrolimus 1% cream alone, 65% reported resolution of pruritus within one week and 75% reported marked or complete clearance of the eruption within the first 2-4 weeks. In the present study similar complete clearance of eruption occurred but within 4 to 6 weeks was observed. Although initial combination therapy was used by some researches and 80% experienced resolution of pruritus within 1 week and market or complete clearance of the eruption within 2-4 weeks, but no such combination therapy was employed in this syudy.

Like many other chronic disease in childhood, atopic dermatitis 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. This impact in turn has a bearing on the adverse effect of quality of life with parents who are less able to fulfill the needs of their child their family.

Whalley et al (2002)[12, 13, 14] studied the benefit of pimecrolimus (Elidel, SDZ ASM 981) on parents quality of life in the treatment of pediatric atopic dermatitis, that, this treatment offers tolerable and effective therapy in the long term management of childhood. In the first 6 weeks of the present trials an improvement in quality of life was seen in the parents of children belonging to pimecro-

limus group, and this improvement was statistically significant than that observed in the parents of children in the vehicle group. In this study also it has been demonstrated that there was relief of mental stress in the parents of atopic dermatitis patients and this improved the quality of life. It is noteworthy that pimecrolimus had better tolerance than that of steroid.

CONCLUSION

The present prospective case-control study was carried out to determine the efficacy and safety of pimecrolimus in atopic dermatitis in children. Assessment of outcome of treatment in the pimecrolimus group at entry and at 6 weeks revealed mean SCORAD as 64.68 ± 20.16 and 21.06 ± 4.6 respectively. Assessment of outcome of treatment in steroid group at entry and at 6 wks evidenced mean SCORAD was 63.5 ± 17.8 and 21.6 ± 4.1 respectively. Statistically significant SCORAD improvement was observed in both groups. Regarding side effects, in pimecrolimus group these were adequately minimized. In conclusion it can be stated that pimecrolimus is quite effective and safe in the treatment of atopic dermatitis in children. Although pimecrolimus and steroids are equally effective in the treatment of atopic dermatitis, but the side effects are less in pimecrolimus group. This demonstrates the fact that hypothesis of efficacy stands valid in respect of low side effects.

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