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The effect of topical betamethasone valerate cream 0.1% and pimecrolimus cream 1% on serum levels of IL-4 and IL-13 in moderately severe atopic dermatitis. A comparative study.

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Abstract

Atopic dermatitis (AD) is a chronic inflammatory relapsing pruritic skin disease. T-helper 2 cytokines (e.g. IL-4, IL-13) play a cardinal role in the pathogenesis of AD. The aim of this study is to compare the effect of topical betamethasone valerate cream 0.1% and pimecrolimus cream 1% on the profile of IL-4 and IL-13 in patients with moderate atopic dermatitis. Twenty patients with atopic dermatitis and 10 apparently normal volunteers were included in the study. Ten patients were treated with topical betamethasone valerate cream 0.1%(group 1) and Ten patients with pimecrolimus cream 1 % (group 2) for 2 weeks. After 2 weeks of therapy eight cases in group 1 and six cases in group 2 showed clinical remission, up showed clinical remission . In both groups a significant decrease in serum IL-4 and IL-13 levels after treatment was observed , but the decrease in group1 (betamethasone valerate) was more than in group 2 (pimecrolimus cream). The IL-4 and IL-13 levels in serum after both drugs neatively correlated with the clinical severity as measured by SCORAD index.

Introduction

Atopic dermatitis is a chronic inflammatory skin disease associated with cutaneous hyperreactivity to environmental triggers that are innocuous to normal nonatopic individuals[1]. The clinical phenotype that characterizes atopic dermatitis is the product of interactions between susceptibility genes, the environment, defective skin barrier function, and immunologic response[2] .

Elevated levels of immunoglobulin E (IgE) have been demonstrated in 70-80 % of patients of atopic dermatitis[3] . The synthesis of IgE from B lymphocytes is regulated by several cytokines derived from T lymphocytes. One of the candidate cytokines is IL-4, which acts as switch factor for IgE synthesis from B cells[4] IL-13 is a pleiotropic cytokine produced by Th2-type lymphocytes and mast cells[5]. IL-13 resembles IL-4 at the amino acid level (20-25% homology), and both share common receptor components and biological activities[6]. IL-4, but not IL-13, induces expansion of Th2 cells and proliferation of T cells in both the mouse and human systems[7]. IL-4 acts on both mouse and human B cells in the same way, in that it induces class switching including IgE, and expression of CD23 and MHC class II. In contrast, IL-13 behaves on B cells differently in the mouse and human systems: human IL-13 induces class switching toward IgE and IgG4, as well as expression of CD23 and MHC class II on B cells, whereas mouse IL-13 does not exert such actions[8].

For almost half a century, therapy for AD has been based on the use of emollients to alleviate dry skin, coupled with short courses of topical corticosteroids to treat the disease flares. Topical corticosteroids, first introduced in the early 1950's have been the mainstay of therapy for atopic dermatitis for many years. This class of drugs is generally the standard to which other therapies are compared[9].

Topical corticosteroids are effective in the control of both acute and chronic skin inflammation. They mediate their anti-inflammatory effect through cytoplasmic glucocorticoid receptors (GCR) in target cells. Upon ligand binding, the corticosteroids / GCR complex translocates into the nucleus where it mediates its anti-inflammatory effect via binding transcription factors to inhibit genes encoding for production of proinflammatory cytokines such as IL-1, IL2, IL-4, IL-13[10]. .

Non-steroidal, topical, inflammatory-cytokine inhibitors have been developed for the treatment of AD such as tacrolimus ointment 0.03%-0.1% and pimecrolimus cream 1%. The basic mechanism of action is calcineurin inhibition[11] . They act by binding with high affinity to the 12 kDa macrophilin and inhibit the phosphatase activity of the calcium-dependent phosphatase, calcineurin. In the presence of this calcineurin inhibitor, the transcription factor, nuclear factor of activated T cell protein (NF-ATp), is not dephosphorylated and therefore cannot translocate into the nucleus to activate transcription of various Th1 and Th2 cytokine genes. Pimecrolimus inhibit the activation of a number of key effector cells involved in AD, including T cells and mast cells[2].

Patients and methods

This study was conducted on 20 patients with moderate atopic dermatitis and 10 normal persons as control. An oral consent was obtained from patients and controls.

The clinical severity of AD was evaluated by using the SCORAD index that developed by the European Task Force on atopic dermatitis (1993)[12] . It defines a score of three parameters: extent, intensity and subjective symptoms.

Extent is calculated with the rule of nines. Intensity items are erythema, edema/papulation, oozing/crust, excoriation, lichenification and dryness of non involved skin (0 to 3 points for each item). Subjective symptoms are pruritus and sleep loss for the last 3 days or nights (0 to 10 points for each item).

The final score is then calculated according to the following equation: A/5 + 7B + C, where A represents extent, B represents intensity and C represents subjective symptoms. It is considered mild moderate and severe AD forms in which SCORAD index was less than 25, between 25 and 50 and more than 50, respectively.

The studied persons were classified into three groups:
Group 1:
Included 10 patients with moderate atopic dermatitis (7 males and 3 females), their mean age was 8 +/- 6.5, the mean value of SCORAD index was 28.9+/- 1.8. They were treated with topical betamethasone valerate 0.1% twice daily.

Group 2:
Included 10 patients with moderate atopic dermatitis (5males and 5females) their mean age was 10.6 +/- 7.5. The mean value of SCORAD index was 32.1 +/- 2.2. They were treated with topical Pimecrolimus cream 1% twice daily.
Group 3:
Control group composed of 10 normal, apparently healthy volunteers matching in age and gender with patients in groups 1 and 2. None of them had any personal or family history of atopy.
Serum samples were obtained from patients before and 2 weeks after treatment and from controls .
Serum IL-4 level was measured using IL-4 ELISA Kit of Diaclone Research, France. It is a solid phase, sandwich ELISA, monoclonal antibody specific for IL-4.
Serum IL-13 was determined by using a competitive enzyme immunoassay (EIA) supplied from ACCUCYT R European patent EP6598 758 BI. The amount of IL-13 detected in each sample was compared to an IL-13 standard curve that demonstrated an inverse relationship between optical density and cytokine concentration.

Results

There was significant decrease in SCORAD index, IL-4, Il-13 after treatment in groups 1 and 2(table 1).

There was no significant difference in SCORAD index between groups 1 and 2 before treatment. The decrease in SCORAD index after treatment in group 1 was significantly more than that in group 2 (table 2).

In both groups of patients, IL-4 levels were higher than in control group. There was a statistically significant decrease in IL-4 level after treatment in both patient groups. There was no statistically significant deference between IL-4 level after treatment in group 1 and 2(table 3).

Higher IL-13 level was found in group 1and 2 than that in control group. The decrease in IL-13 level after treatment in both patient groups showed no statistically significant deference (table 4).

Table (1): Mean value +/- SD of age, SCORAD index, IL-4, and IL-13 in different groups

	Group 1 Before treatment	Group 1 2 weeks after treatment	Group 2 Before treatment	Group2 2 weeks after treatment	Control
Age	8 +/- 6.5		10.6+/-7.5		9.2+/- 6.7
SCORAD	28.9+/- 1.8	10.5+/- 3.5	32.1 +/- 2.2	16.5+/-2.5	
IL-4 (pg/ml)	24.9+/-5.5	11.8+/2.4	22.6+/- 3.6	14.8+/-4.6	4.8+/-1.3
IL-13 (ng/ml)	39.83+/-5.7	21.29+/-2.6	40.02+/- 6.2	22.9+/-2.9	14.23+/- 1.87

Table (2): Statistical comparison of SCORAD index in different groups.

Comparison	P value	Significance
Group (1) before treatment – Group (1) after treatment	< 0.05	Significant
Group (2) before treatment – Group (2) after treatment	< 0.05	Significant
Group (1) before treatment – Group (2) before treatment	> 0.05	Not significant
Group (1) after treatment – Group (2) after treatment	< 0.05	Significant

Table (3): Statistical comparison of IL-4 in different groups.		
Comparison	P value	Significance
Group (1) before treatment – Group (1) after treatment	< 0.05	Significant
Group (1) before treatment – Control	< 0.05	Significant
Group (2) before treatment – Group (2) after treatment	< 0.05	Significant
Group (2) before treatment – Control	< 0.05	Significant
Group (1) before treatment – Group (2) before treatment	>0.05	Not significant
Group (1) after treatment – Group (1) after treatment	>0.05	Not significant

Table (4): Statistical comparison of IL-13 in different groups.		
Comparison	P value	Significance
Group (1) before treatment – Group (1) after treatment	< 0.05	Significant
Group (1) before treatment – Control	< 0.05	Significant
Group (2) before treatment – Group (2) after treatment	< 0.05	Significant
Group (2) before treatment – Control	< 0.05	Significant
Group (1) before treatment – Group (2) before treatment	>0.05	Not significant
Group (1) after treatment – Group (1) after treatment	>0.05	Not significant

Figure (1)

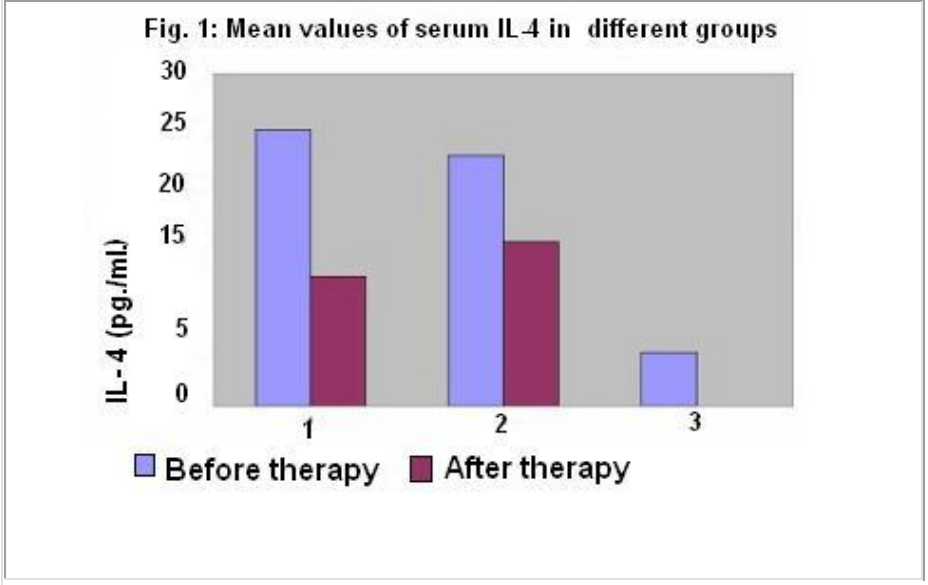


Figure (2)

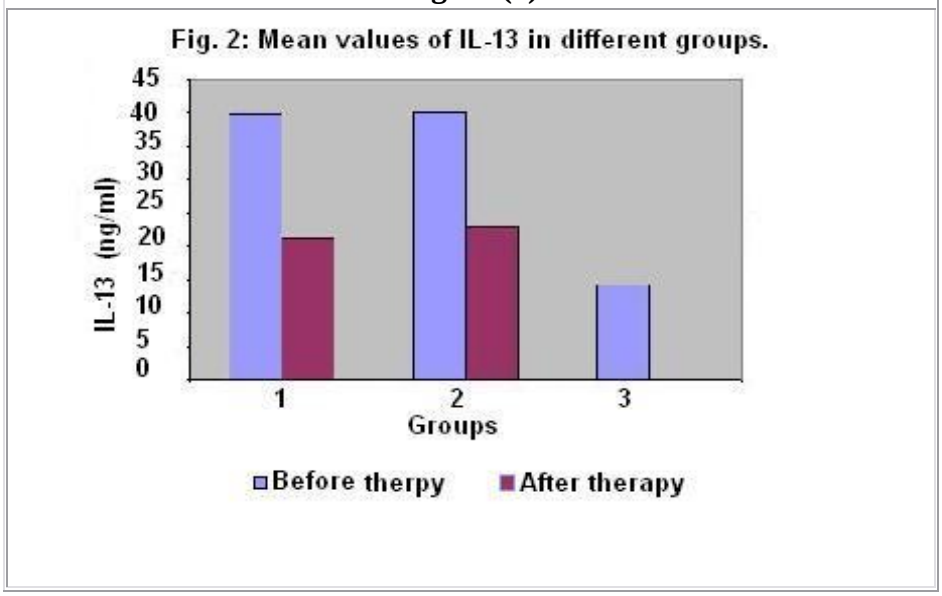


Figure (3)

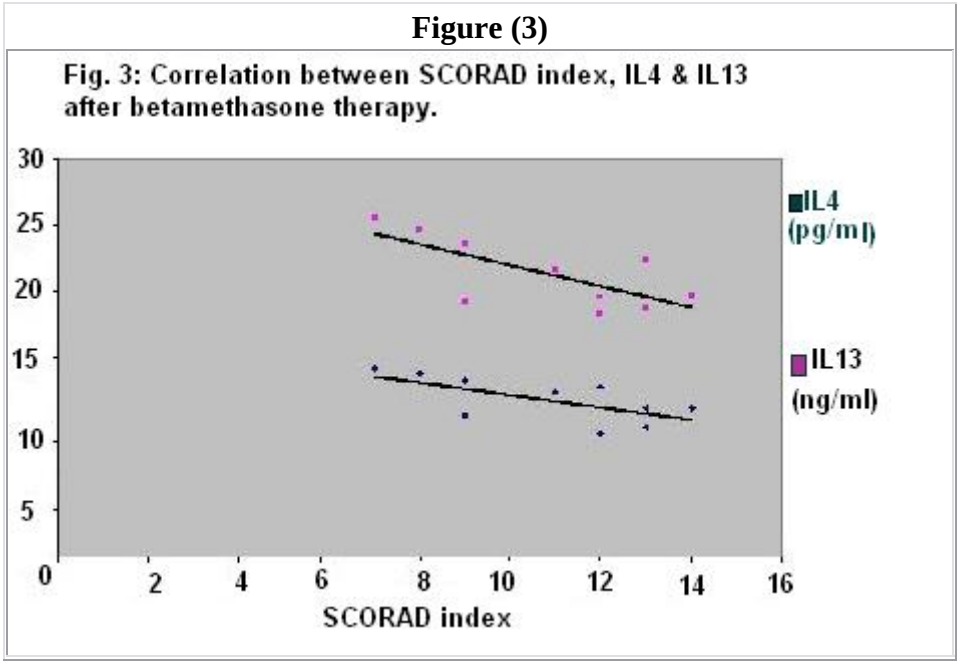
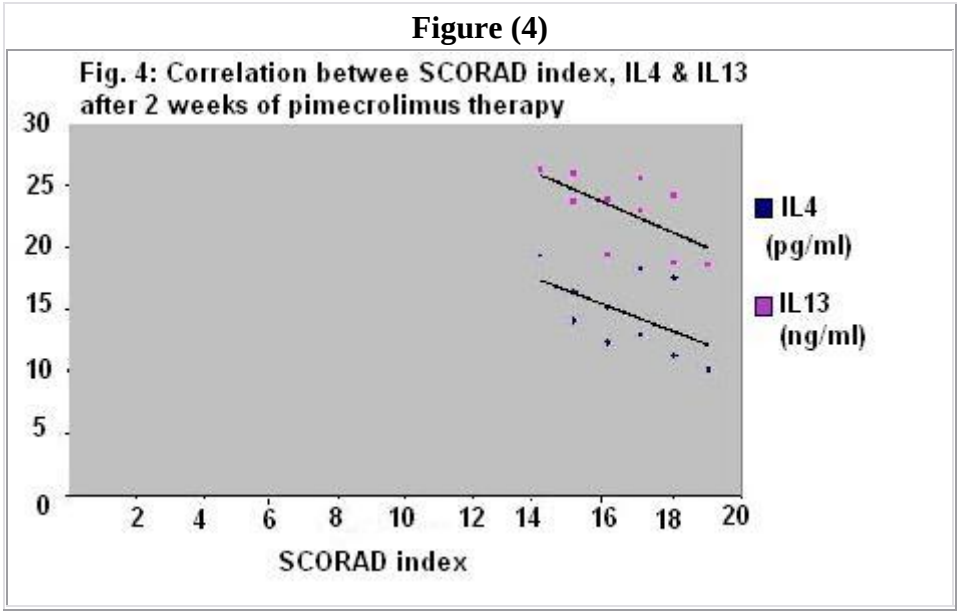


Figure (4)



Discussion

Atopic dermatitis is an inflammatory chronically relapsing pruritic skin disease. AD is associated with elevated skin production of Th2 cytokines and low levels of proinflammatory cytokines such as TNF-α, IFN-γ, and IL-1. Th2 cytokines include IL-4 and IL-13, which are known to induce isotype switching to IgE synthesis, as well as IL-5, which plays an important role in eosinophil development and survival [13]). Both IL-4 and IL-13 may play some important role in the development of AD [6].

Topical corticosteroids were originally introduced in 1952 as an effective means of treating atopic dermatitis. During the past 50 years, research has focused on strategies to optimize potency and efficacy while minimizing both local and systemic side effects. In general, halogenated corticosteroids have been associated with more local adverse events and a higher risk of systemic absorption [14].

Topical corticosteroids are the standard of care to which other treatments are compared [15].

Topical application of pimecrolimus cream 1% suppresses the production of inflammatory cytokines associated with AD by selectively inhibiting T-cell activation [16]. Through binding to specific receptors on T cells leading to an increase in intracellular calcium that, in turn, causes a series of reactions inhibiting the transcription of several genes, mainly the cytokines (IL-2, IL-4, and IL-5) [15].

of IL-13 by peripheral blood monocytes was suppressed by use of topical calcineurin inhibitor (tacrolimus).

In this study, 20 patients with moderate atopic dermatitis and 10 normal volunteers were included. Ten patients treated with topical betamethasone valerate cream 0.1% twice daily and Ten patients with pimecrolimus cream 1 % twice daily for 2 weeks. Clinical remission were noticed in 8 cases after 2 weeks of betamethasone valerate therapy while 6 cases showed clinical remission 2 weeks after pimecrolimus treatment cream. There was significant decrease in IL-4 and IL-13 levels in serum after treatment in both drugs, but the decrease with betamethasone valerate was more than that with pimecrolimus cream. The IL-4 and IL-13 levels in serum after both drugs were negatively correlated with SCORAD index that evaluate the clinical severity of AD.

Our results showed that both betamethasone valerate cream 0.1% and pimecrolimus cream 1 % are effective in treatment of moderate AD as regard clinical improvement (SCORAD index) and change in the cytokine pattern (IL-13 and IL-4).

Although, the decrease in the level of IL-4 and IL-13 was nearly similar in both groups, the decrease in SCORAD index (clinical improvement) was more in the group treated with betamethasone valerate cream 0.1%.

Although both treatments can induce remission in a relatively short time, maintenance anti-inflammatory therapy may be required to prevent relapse. Due to the concern about potential side effects associated with chronic use of corticosteroids such as skin atrophy and stria, topical corticosteroids have not been used for maintenance therapy. Nevertheless, the use of long-term intermittent application of corticosteroids appears helpful and safe in two randomized controlled studies [17, 18].

There are situations in which topical pimecrolimus may be advantageous over topical corticosteroids and can be used as first line therapy Such as treatment of the face and neck dermatitis. Pimecrolimus can be used as maintenance therapy however, the cost benefit relation may limit its uses. Further studies for the possible combination of topical corticosteroids and pimecrolimus are recommended to gain effective less costly treatment and decrease possible side effects of both drugs.

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