

SHORT REPORT

The effect of topically applied corticosteroids on interleukin 1 β levels in patients with atopic dermatitis

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Abstract

Background Atopic dermatitis (AD) is a chronic recurrent disease of childhood. The therapeutics of AD needs to be more tailored given the new cytokine antibodies available. In this scenario we considered interleukin 1 beta (IL-1 β) levels before and after therapy with topical corticosteroids.

Objectives To measure the IL-1 β levels before and after treatment in patients with AD after 75% improvement in scoring for atopic dermatitis index.

Methods Forty-five subjects with AD were treated with betamethasone ointment and their IL-1 β level was measured prior to and following treatment.

Results The IL-1 β levels were raised during disease activity and following improvement they decreased in a statistically significant manner. Also the IL-1 β levels corresponded with the severity of disease activity.

Conclusions Newer modalities of therapy in the form of cytokine monoclonal antibodies should be studied in a larger scale in AD.

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Conflict of interest

There is no conflict of interest to report.

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Introduction

Atopic dermatitis (AD) is an inflammatory skin disease characterized by hyperactivity of the humoral immune system with an onset in infancy or early childhood. Prevalence is currently estimated to be in the range of 10%–15% in most parts of the world with increasing incidence in the recent times.^{1,2}

Cytokines involved in the pathogenesis of AD seem to be extremely complicated and inter related. Human AD involves upregulation of various cytokines expressed in the final pathway by infiltration of the inflammatory cells into the dermis, hyper proliferation of the epidermis and increase in the IgE levels.^{3–7} Interleukin 1 beta (IL-1 β) promotes the migration of activated langerhans cells to the regional lymph nodes⁸ which sets up the entire cascade of an antigen-derived inflammatory response. IL-1 β is hypothesized to be produced by the keratinocytes⁹ probably following an initiating event which in AD could be an exposure to an unknown antigen.

With the observations stated above we decided to follow the levels of IL-1 β prior to and following treatment of disease exacerbation. This could lead to potential use of IL 1 receptor

antagonists in the treatment of AD thus offering more directed management of this chronic disease.

Patients and methods

Forty-five AD patients with equal proportion of mild, moderate and severe cases attending the paediatric dermatology clinic of the Department of Dermatology, Venerology and Leprology at the Nehru Hospital attached to Post Graduate Institute of Chandigarh were enrolled for the study. Patients in the age group of 6 months to 16 years with diagnosis of AD satisfying the criteria by Hanifin and Rajka¹⁰ and who had not used corticosteroids in the past 3 months in any form were included.

Exclusion criteria were presence of concomitant serious skin disorders, clinically overt skin infection, patients with bronchial asthma, immune compromised states and systemic infections.

Investigations

Blood samples for plasma were collected in EDTA vials and stored at –20°C immediately after placing on ice. IL-1 β levels from the

plasma were measured using ELISA at week 0 and after 75% improvement in scoring for atopic dermatitis (SCORAD) index. Seventy-five per cent improvement in SCORAD index was achieved by application of topical Betamethasone Valerate IP 0.10% ointment. The limit of measurement for IL-1 β was 10.24 pg/L.

Disease activity

The severity of patients was recorded according to SCORAD index as mild, moderate or severe disease at week 0 i.e., at their first visit. Patients were assessed initially after 2 weeks and later every week with the SCORAD index for their disease activity until their SCORAD improved by 75% of the initial score. They were followed for a maximum period of 12 weeks. The study was designed to exclude the patients who did not respond to Betamethasone application. All patients did respond to the above therapy and in final analysis no one was excluded.

Statistical evaluation

Statistical analysis was performed using SPSS for Windows 1997 by Microsoft Corp. IL-1 β level correlation with severity of disease and with response to treatment was undertaken. The Wilcoxon signed ranks test which is a non-parametric test was used to analyse the difference in the levels of IL-1 β between the visits.

Results

Forty-five patients diagnosed with AD attending the paediatric dermatology clinic of Department of Dermatology, Venerology and Leprology were enrolled in the study. No patient was lost to follow-up. The age of the study population ranged from 6 months to 16 years with mean ($\pm$ SD) age of 6.95 years ($\pm$ 4.50 years). The study population comprised of 17 girls (37%) and 28 (62%) boys. The total duration of illness was 5.40 years ($\pm$ 3.97 years) with the exacerbation of the symptoms lasting for 1 month ($\pm$ 0.41 months). Family history of atopy was positive in 16 patients (36%) and negative in 29 patients (66%). History of other allergies was positive in 25 (54.8%) patients and was absent in 20 (45.2%) patients.

Disease activity

The mean ($\pm$ SD) SCORAD index of the mild group was 11.35 ($\pm$ 2.44) on the first visit which decreased to 6.33 ($\pm$ 2.13) 2 weeks after follow-up and in the final visit was 2.35 ($\pm$ 0.94). The moderate group patients had mean ($\pm$ SD) values of 23.95 ($\pm$ 3.25) on the first visit which following treatment decreased to 13.92 ($\pm$ 3.21) and finally was 5.11 ($\pm$ 1.44). The SCORAD index recorded by the severe group during the first visit was 44.27 ($\pm$ 5.60), second visit showed 23.07 ($\pm$ 6.37) and final visit showed 10.33 ($\pm$ 3.71) scores.

Interleukin 1 β levels

The mild group recorded a mean IL-1 β level of 17.39 pg/L ($\pm$ 5.89 pg/L) on the first visit which decreased to a mean value of

8.68 pg/L ($\pm$ 3.53 pg/L) after a 75% improvement of disease activity. The moderate group recorded mean IL-1 β level of 35.33 pg/L ($\pm$ 8.76 pg/L) on the first visit which decreased to a mean value of 9.69 pg/L ($\pm$ 2.16 pg/L) after a 75% improvement of disease activity. The severe group recorded mean IL-1 β level of 127.68 pg/L ($\pm$ 17.87 pg/L) on the first visit which decreased to a mean value of 27.29 pg/L ($\pm$ 9.61 pg/L) after a 75% improvement of SCORAD index.

The decrease in the levels of IL-1 β levels was found to be statistically significant in all the three groups. Also the IL-1 β levels corresponded to the disease activity before therapy was instituted (Fig. 1).

Discussion

Atopic dermatitis is a chronic inflammatory disease in which the role of various cytokines has been studied on various animal models and in some studies in human patients. In our study of patients with mild, moderate and severe disease we found that the expression of IL-1 β was increased during disease exacerbation and decreased once the exacerbation was managed through topical corticosteroids. It was also interesting to observe that the level of IL-1 β also corresponded to the initial disease severity.

In a study, 23 children were assessed for serum interleukin 1 alpha (IL-1 α) and soluble IL 2 receptors: 11 with atopic dermatitis and 12 non-atopic normal controls. While no apparent relationship was found between cytokine concentration and disease severity or IgE concentrations, there was enhanced endogenous secretion of IL-1 α , and increased stimulation of IL 2 receptors, in children with atopic dermatitis. These findings suggest that these cytokines may contribute to the inflammatory process in atopic dermatitis.¹¹

In another study, the epidermal levels of cytokines were measured in patients with atopic dermatitis after patch test with house dust mite. In individuals who, prior to the application of house dust mite, exhibited a high level of IL-1 β mRNA in their epidermis, were more prone to developing a clinical response as

IL 1 β levels in AD patients during disease activity and post treatment

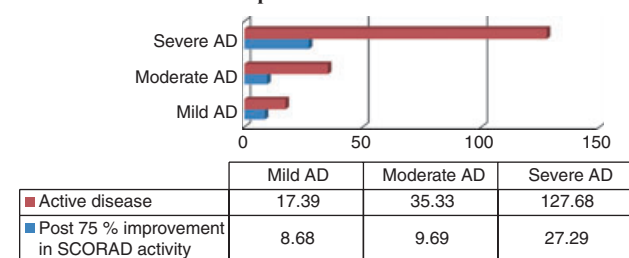


Figure 1 IL-1 β levels in pg/L in mild, moderate and severe AD patients prior to and after treatment. (IL-1 β , interleukin 1 beta; AD, atopic dermatitis).

evidenced by a positive patch test. This may indicate that the basic level of IL-1 β in normal appearing skin in individuals with AD reflects a certain activated state of langerhans cells.¹²

The role of IL-1 β on the levels of inflammatory mediators like CCL-17 and CCL-28 were studied in a culture of canine keratinocytes. IL-1 β was found to increase m-RNA expression of CCL-28 in the lesional keratinocytes thus furthering the proof of its role in inflammatory conditions like AD.¹³

The IL-8 has been elicited to be a specific cytokine in AD while IL-1 β has not found to be increased in mild, moderate or severe AD.¹⁴ In the same study it was noted that IL-1 β was elevated in contact dermatitis patients. They detected IL-1 β levels only in some patients (1/16 in mild, 3/18 in moderate and 4/18 in severe) with AD and limits of detection of IL-1 β were lower (30 ng/L). The study did not specify if the patients were having active disease or were in remission. They treated only severe AD patients but IL-1 β levels were not measured after therapy.

The tumour necrosis factor alpha (TNF- α), IL-1 β , IL 2 concentrations were measured in allergic patients. TNF- α levels were found to be increased in patients with AD and corresponding to the severity of AD while IL-1 β levels were increased only in patients with asthma and AD. IL 2 levels were not related to any inflammatory disorders.¹⁵

In an encompassing study on mice model of AD Chen *et al.*¹⁶ beautifully demonstrated that Th2-type and non-Th-type proinflammatory cytokines are involved primarily in disease induction, while Th1-type, Th2-type and non-Th-type proinflammatory cytokines are involved in disease maintenance. Thus, IL-1 β levels play a role in the induction of the disease and if they can be contained, disease progression can be prevented.

None of the above studies have been designed with paired levels of measurement of IL-1 β with disease severity. Our findings thus support for further studies into the use of IL-1 β antagonists or naturally occurring IL receptor antagonists in treatment of AD. These have already been in use for the treatment of various inflammatory disorders like rheumatoid arthritis, systemic juvenile rheumatoid arthritis.¹⁷

The limitations of our study include the small sample size. Having a normal control group would have validated our results further. Our study design was to delineate the levels between active

and controlled disease and in this sense our own patients acted as controls. Notwithstanding these short comings we feel it's an important observation in the face of new treatment options available.

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