

Comparison of efficacy of methotrexate and azathioprine in chronic resistant atopic eczema

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Abstract

Background Atopic dermatitis is a common dermatological problem in children and adults. It is associated with poor quality of life, significant financial burdens, and poor mental health. There are many topical and systemic treatment modalities for chronic atopic eczema. Systemic treatment like Methotrexate and azathioprine is indicated in chronic atopic eczema patients resistant to topical steroids.

Objective To assess the efficiency of methotrexate versus azathioprine in chronic resistant eczema.

Methods This study was conducted in the Department of Dermatology in Nishtar Hospital, Multan from January 2012 to July 2012. 270 patients with clinically resistant atopic eczema were included and detailed history and examinations were done. 135 patients were given weekly oral methotrexate and 135 were given oral azathioprine weekly. Patients were followed up for 12 weeks. All data were recorded in a predesigned proforma.

Results MTX treated group showed statistically significant better efficacy of (51%) when compared to AZA (36%) at 12 weeks.

Conclusion Methotrexate is more efficacious compared to azathioprine for the treatment of patients with chronic resistant atopic eczema.

Key words

Atopic eczema; Dermatitis; Methotrexate; Azathioprine.

Introduction

Eczema also called 'dermatitis' is a clinical and histological pattern of skin inflammation seen in a variety of dermatoses with many different aetiologies.¹ It is defined as an inflammatory response of the skin to endogenous and/or exogenous stimuli. Clinically, it is characterized by intense itching and soreness, variable degree of dryness, erythema, excoriation, exudation,

fissuring, hyperkeratosis, scaling, and vesiculation.¹ In chronic eczema, lichenification which is a thickening of the skin with accentuated skin lines, is also present.

Atopic dermatitis is eczema associated with atopy which is defined as a tendency to become sensitized and make IgE antibodies when exposed to allergens, usually in early life.² It is a common dermatological problem prevalence of approximately 20% in children and 10% in adults and this prevalence is increasing in industrialized countries.^{3,4} Atopic eczema is not only a result of poor quality of life and significant financial burden on the affected

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individuals and their families but is also associated with poor mental health.^{5,6}

There are many topical and systemic treatment modalities for chronic atopic eczema. Although topical glucocorticoids are very helpful.⁶ Sometimes patients with chronic atopic eczema are resistant to topical steroids, so systemic treatment is necessary for the Methotrexate and azathioprine are among the second-line treatment options in chronic resistant atopic eczema.^{7,8}

Methotrexate (MTX) is a folic acid antagonist that blocks DNA/RNA and protein synthesis leading to suppression of the immune cell functions.⁸ It is known to be effective in the treatment of several dermatological conditions like psoriasis, chronic eczema, chronic urticaria, and bullous pemphigoid.⁹ Azathioprine is a prodrug, activated to 6-mercaptopurine within the body, which blocks DNA synthesis and acts as an immunosuppressant.⁷

Both methotrexate and azathioprine are available in Pakistan and are economical systemic options for our patients. There has been one prospective Dutch trial, methotrexate versus azathioprine for severe atopic dermatitis (MAcAD) trial, which has concluded similar efficacy of both drugs,⁸ from is no such type of study has been done in our population. Our study was designed to compare the efficacy of methotrexate with azathioprine in chronic resistant atopic eczema so that the drug with better efficacy can be used when systemic therapy is indicated in our patients.

Materials and Methods

A randomized control trial was conducted in the Department of Dermatology in Nishtar Hospital, Multan from January 2012 to July 2012, to compare the efficacy of methotrexate with

azathioprine in chronic resistant atopic eczema.

After approval from the institutional review board, 270 male and female patients between 20-50 years were enrolled in the study. The enrolled patients had atopic eczema for more than 3 months diagnosed clinically and were not responding to topical steroid therapy. Individuals with co-morbid conditions or those in whom immunosuppressive therapy was contraindicated were excluded. Written informed consent was taken from the patients before the study.

Patients were randomized to Group A and Group B with 135 individuals in each group. Group A was given oral methotrexate 7.5mg–25 mg once weekly according to weight, while Group B was given oral azathioprine 2.5-3.5 mg/kg daily in 3 divided doses. Patients were followed up every 3-4 weeks and were assessed clinically. A final assessment was made at the end of the 12th week. Efficacy was considered as the clinical absence of 3 or more findings among erythema, induration, excoriation, and lichenification.

The data were analyzed using the software SPSS version 21. Effect modifiers like age, gender, weight, and duration of illness were controlled by stratification through the Chi-square test. p -value ≤ 0.05 was taken as significant.

Results

This study was conducted on 270 patients with chronic resistant atopic eczema. The mean age of the patients was 40 years while the mean weight was 61 Kg in both groups. Only a few subjects were aged between 21 to 30 years with 6 (4%) in Group A and 3 (2%) in Group B while most were either aged between 31 to 40 years: 67 (50%) and 71 (53%) in Group A and B respectively, or 41 to 50 years: 62 (46%) in Group A and 61 (45%) in Group B. There was a

slight male predominance with 80 (59%) males in Group A and 82 (61%) males in group B whereas 55 (41%) and 53 (39%) female subjects belonged to Group A and B respectively.

Duration of disease was 1-5 years in 101 (75%) and 121 (90%) patients in Group A and B respectively while 34 (25%) subjects in Group A and 13 (10%) in Group B had been suffered from the disease since 6-10 years. Only 1 patient in Group B and none in Group B had atopic eczema for 11-15 years. The mean duration of disease was 3.92 ± 0.15 years in Group A compared to 3.42 ± 0.15 years in Group B.

The outcomes of our study are shown in **Table 1**. Methotrexate treated group showed statistically significant better efficacy when compared to Azathioprine. There was no significant effect of age, gender, duration of disease, or weight of patients in the Methotrexate group. Similarly, in the Azathioprine group gender and weight had no statistically significant effect although males responded better (35 out of 82) compared to females (14 out of 53). However, patients with the age range of 31 to 40 years and duration of disease between 6 and 10 years had significantly better responses in Azathioprine (p-value 0.023 and 0.04, respectively) as compared to the other subgroups.

Discussion

Atopic eczema is 1 of the most frequent skin disease and often has a chronically relapsing course with a poor prognosis.^{3,4} It is a multifactorial disease that has enormous socio-

economic consequences and a massive impact on a patient's quality of life.^{5,6,10} Zoller *et al.*, also observed complete remission in 66% of their patients on MTX.¹¹ This study compared the efficacy of MTX with AZA in the treatment of 270 patients with chronic resistant atopic eczema. The mean age of the patients was 40 years and there was a slight male predominance in both study groups. This mean age and male predominance in our patients are similar to the trial by Schram *et al.* that compared MTX and AZA efficacy.¹⁰ The duration of the disease was 1-5 years in most of our patients. In contrast, the mean age of participants in the comparative study by Schram *et al.* was 36 years.¹⁰ This difference can be due to the tendency of our patients with resistant eczema to opt for systemic therapy at an earlier stage.

In our patients, MTX treated group showed statistically significant better efficacy when compared to AZA (51% efficacy of MTX vs. 36% efficacy of AZA). Schram *et al.*, however, observed 42% efficacy with MTX compared to 39% efficacy in the AZA group with no statistically significant difference between the 2 (p=0.52).¹⁰ We had a larger cohort of patients with equal numbers in both groups (135 MTX, 135 AZA), in contrast to the much smaller and unequal group (20 MTX+22 AZA) studied by Schram which might account for the difference in statistical findings.

In a retrospective review by Hughes and colleagues from Ireland, 41% of chronic atopic eczema patients treated with AZA achieved remission.¹² Similarly, Meggitt *et al.* observed a significant improvement in disease activity when AZA was compared to placebo (37% vs. 20%).¹³

The treatment of chronic atopic eczema depends upon various factors like the sites of involvement, duration, and severity of the disease, and the triggering and exacerbating factors. Patients with severe atopic eczema

Table 1 Efficacy of drugs in patients with chronic resistant atopic eczema.

Efficacy	No. of Patients		p-value
	Group A	Group B	
Yes	69 (51.1%)	49 (36.3%)	0.014
No	66 (48.9%)	86 (63.7%)	
Total	135(100%)	135(100%)	

require prolonged treatment with large amounts of highly potent topical corticosteroids, systemic treatment, or both. Frequently used systemic treatment options include cyclosporine, systemic corticosteroids, methotrexate (MTX), and azathioprine (AZA). Many studies have been performed on the use of AZA in the treatment of atopic eczema.¹⁴⁻¹⁶

Epidemiological studies show varying gender prevalence with some eliciting a higher female ratio in atopic adult eczema while others show a male majority.¹⁷

Goujon and co-workers observed even better results in their study where MTX was beneficial in 75% of patients.¹⁸ Shaffrali *et al.* used methotrexate in elderly patients with eczema and recorded a successful response in 80%.¹⁹ Shah *et al.* observed even better results with 93% of subjects achieving targeted clearance.²⁰ Syed AR and colleagues from Pakistan recorded a 50% improvement in all of their subjects on MTX for eczema.²¹ The different efficacy results observed among these various studies on MTX can be due to the differences in the end-points of each study and the small number of patients observed in most studies.

These results are comparable to the 36% AZA efficacy we have observed in our study. However, another study undertaken by Berth-Jones and co-workers showed a lower efficacy of AZA (26%) in patients with atopic eczema.²² The number of observed subjects was only 35 which might explain the different response ratio compared to other studies.

Our study has some limitations as the outcomes were observed after only 3 months of therapy and follow-up visits were not recorded. The study did not focus on the safety profile of the 2 drugs which is an important consideration for long-term therapy. Multicentre randomized

controlled trials of longer duration are needed to further compare the efficacy and safety of MTX and AZA in the treatment of chronic resistant atopic eczema in our population.

Conclusion

Our study demonstrated that Methotrexate has significantly more efficacy ($p=0.014$) as compared to azathioprine in the treatment for chronic resistant atopic eczema in our patients.

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