

Original Article

Comparison of methotrexate and azathioprine in the treatment of psoriasis: a randomized controlled trial

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Abstract *Background* Treatment of psoriasis requires a safe and effective drug which can be used on long term basis. Azathioprine is one such agent which was used in the past but has not been tested recently.

Patients and methods A randomized controlled trial was conducted at dermatology department, Combined Military Hospital, Kharian, to compare the efficacy and safety of azathioprine with that of methotrexate in patients with severe psoriasis requiring systemic therapy. Patients included in the study were randomized into two groups. Group A received tablet methotrexate 10 mg weekly for 8 weeks. Group B patients received tablet azathioprine in a dose of 1.5-3 mg/kg/day. In all the adult patients who were weighing more than 50 kg azathioprine was started at a dose of 50 mg tablet thrice daily for 8 weeks. PASI score was assessed at the start and end of treatment. Scores were compared in the two groups before and after and statistically analyzed using paired and independent sample t test.

Results 50 patients entered the study. Results were stratified into excellent, good, and poor response, based on improvement in PASI scores. Excellent response was seen in 73% patients in group A and 27% patients in group B ($p < 0.5$). Good response was seen in 45% patients in group A and 55% patients in group B ($p > 0.5$). Poor response was seen in one patient in each group ($p > 0.5$, paired sample t test).

Conclusion Azathioprine is less effective in systemic treatment of psoriasis. Nevertheless it can be a useful alternative in selected patients.

Key words

Psoriasis, methotrexate, azathioprine.

Introduction

Psoriasis is a genetically determined, inflammatory and proliferative chronic intractable disease of the skin affecting about 1 to 3% of world population.¹ Although the pathogenesis of psoriasis remains unknown it

has been hypothesized that an abnormality of immune system is involved.² The therapeutic tools available to combat this disease are numerous, as are their untoward effects.³ Systemic therapies for psoriasis which are in common use, include, psoralen-UVA (PUVA) therapy, retinoids, and immunosuppressants like methotrexate and cyclosporin.⁴ Of these the equipment required for PUVA therapy is generally available in only few centers in Pakistan. Moreover, there are some concerns

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about development of cutaneous malignancies after its prolonged use.⁵ Systemic retinoids are highly teratogenic and too expensive to be used in a third world country like ours.⁶ Methotrexate is effective in most of the cases, but its toxic effects on the liver limit its long-term use. Furthermore it is difficult to monitor its side effects.⁷ Cyclosporine is effective but its long-term safety is still to be determined as it is nephrotoxic when used for longer durations. Moreover, there is always a need for alternative drugs when primary cumulative toxicity affects other organs, when the profile of acute side effects is different and where there is comparable efficacy for the treatment of psoriasis.⁸ Therefore, a need for a drug is still felt which is cost-effective in comparison to retinoids, has no irreversible side-effects like those of methotrexate, easy to monitor and can be used on long-term basis.

The immunosuppressive agent azathioprine has a relatively good safety profile. There is vast experience of its use in various dermatological conditions, such as cutaneous bullous disorders. It differs from methotrexate in that it is easy to monitor and most of its side effects are reversible.⁹ Its major drawback is the risk of myelosuppression. This could be guarded against by regular blood counts of total leukocyte, total neutrophilic and platelet count.⁹ Moreover, susceptibility to bone marrow toxicity is due to a genetically determined metabolic defect occurring in a frequency of 1 in 300.¹⁰ Patients at risk of such toxicity may be identified by a thiopurine methyltransferase (TPMT) enzyme assay minimizing the risk of this side effect.¹⁰ Previously this drug was found to be effective in psoriasis but no large-scale controlled study was conducted.⁹ Most of the studies conducted consisted of very small number of patients and its efficacy was not

compared to that of methotrexate. This led us to conduct a large-scale trial of use of azathioprine in psoriasis, to determine its efficacy and safety and to compare it to that of methotrexate.

Patients and methods

The study was conducted on 50 adult patients of psoriasis from January 2008 to January 2009. They were selected from skin outpatient department of Combined Military Hospital, Kharian. The study was approved by the research and ethics committee of the hospital.

Patients requiring systemic treatment for psoriasis were selected for the study. It included patients who had established diagnosis of moderate to severe plaque psoriasis. Patients were included on the basis of the following inclusion criteria: age 18 years or older and weight more than 50 kg; area involved should be more than 30 percent of total body area; psoriasis should be of stable plaque type; patients with no history or clinical evidence of dyspepsia, renal, hepatic or any hematological disease; written informed consent from the patient.

Patients were excluded on the basis of history of any current or previous malignancy. Patients having any associated systemic illness like vasculitis; arteritis; a history of pancreatitis or diabetes mellitus; known hypersensitivity to methotrexate and azathioprine; or epilepsy; uncontrolled infections specially history of suffering from hepatitis B or C infection; systemic therapy with steroids, immunomodulators and cytotoxic drugs in previous 2 months; PUVA in previous 4 weeks; specific topical treatment with formulations containing such active agents as steroids, tar or dithranol in previous 2 weeks; pregnant or lactating women; TLC less than $3 \times 10^9/l$,

platelets count less than 50,000/mm³ and hemoglobin less than 9 gm/dl.

Thorough medical history and complete physical examination was carried out at screening visit. All selected patients were examined for extent of cutaneous involvement as per Psoriasis Area and Severity Index (PASI). Following laboratory test were carried out at the start of trial, complete blood count, liver functions tests, blood urea and creatinine levels, ECG, and chest roentgenography. Screening for hepatitis B and C were also done.

Patients were randomized using block randomization method into either group A which received methotrexate in a dose of 10 mg weekly for 8 weeks. Group B received azathioprine in a dose of 1.5-3 mg/kg/day for 8 weeks.

The treatment trial was of 12 weeks duration. The study consisted of 8 weeks of hospitalized treatment and 4 weeks of outdoor follow up period. Adjuvant treatment with topical emollients like bland emulsifying ointments was allowed.

Severity of psoriasis was assessed by measurement scores according to PASI scale. It was done every week for the first 4 weeks and thereafter fortnightly for another 8 weeks. The PASI was, therefore, scored on following weeks, 0, 1, 2, 3, 4, 6, 8, 10 and 12th week. Clearance of PASI from the base line levels were taken as percentage of clearance and interpretation of the results was done as follows: excellent response = >80% clearance; good response = 70 to 79 % clearance; fair response = 50 to 69 % clearance; and poor response = less than 49 % clearance.

Monitoring of patients was done as follows. History and complete general physical

examination was conducted on every visit. Group A patients receiving methotrexate had their blood counts weekly for first two weeks and thereafter monthly. Liver function tests were done weekly for the first 4 weeks and then fortnightly thereafter until the completion of the study. In group B patients receiving azathioprine complete blood counts were done weekly for the first 4 weeks then fortnightly for another 4 weeks and thereafter monthly for patients who continued the drug. Liver function tests were done fortnightly for first month and then monthly.

Results

Out of 50 patients included in the study 44 were males and 6 were females. The age range was 19 to 66 years. Thirteen (73%) patients in group A and 5 (27%) patients in group B showed excellent response i.e. more than 80% clearance at 8th week ($p < 0.5$, paired samples t test). 5 (45%) patients in group A and 8 (55%) patients in group B showed good response i.e. more than 60% clearance at 8th week ($p < 0.5$, paired samples t test). One patient in each group showed poor response ($p > 0.5$, paired sample t test).

Table 1 shows PASI scores in two groups at the start of treatment ($p > 0.5$, paired samples t test).

Table 2 shows improvement in disease condition in the two groups as assessed by PASI scoring. There were 5 dropouts in group A. Two were due to deranged liver function tests while 3 were due to severe nausea and vomiting. There were 5 drop outs in group B, also. One was due to low platelet count (<100,000), two were due to deranged liver function tests, and two were due to severe gastrointestinal symptoms.

All statistical analyses were of the intent-to-treat population. The percentage change in the PASI

Table 1 Severity of disease at the time of presentation.

PASI score	Group A (Methotrexate)	Group B (Azathioprine)
1-10	2	3
11-20	13	13
21-30	4	3
31-40	5	4
>40	0	1

Table 2 Percentage of clearance of disease on 8th week of treatment.

Percentage of reduction in PASI	Group A (Methotrexate)	Group B (Azathioprine)
91-100%	3	1
81-90%	10	4
71-80%	5	6
61-70%	0	2
51-60%	1	6
41-50%	0	0
31-40%	0	0
21-30%	0	0
11-20%	1	1

from baseline was analyzed by the Wilcoxon signed ranks test after 6, 8 and 12 weeks. The main target parameter was the percentage change in the PASI after 8 weeks. As no adjustment was performed, *p* values for the percentage change at weeks 6 and 8 are of a descriptive nature only. T test application on individual groups and on both the groups showed *p* value less than 0.5.

Discussion

Azathioprine was used in this study in comparison to methotrexate, an established therapy for chronic plaque psoriasis, for a number of reasons. There is a vast clinical experience of its use in the treatment of immunobullous diseases and as an adjuvant therapy to steroids. It is easily available, less expensive and has mostly reversible side effects. Moreover, since the discovery of the enzyme TPMT deficiency, one can safely predict patients at risk and prevent one of the most

important adverse effects of this drug that is bone marrow suppression, it is hoped that the use of this drug will increase in the days to come.

There had been a few clinical trials of azathioprine in plaque psoriasis. We could not find any recent study comparing the efficacy of azathioprine with methotrexate in stable plaque psoriasis. Hence, this study brings forth a forgotten aspect of azathioprine use in dermatology.

The study population consisted of troops and families stationed around Kharian. Age difference between two groups was not significant. The age range was from 19 years to 66 years but most of the patients were between 25 to 35 years of age. Most of the study population was male hence minimizing the chance of difference in clinical response if any in the two sexes.

Improvement with respect to the percentage change in the PASI relative to baseline was observed in both treatment groups at the end of week 2, 3, 4, 6 and 8. There was no significant difference in percentage reduction in the PASI score at the end of week 2. The use of emollients by the patients may have contributed to the placebo effect as the removal of hyperkeratotic scales that contain pro-inflammatory mediators can lead to disease improvement. At the end of week 8, the methotrexate-treated group had a significantly greater percentage reduction in the PASI compared with that of the azathioprine-treated group (*p*<0.05).

Comparing with the study done by Greeves and Dawber,¹¹ they showed improvement of only 25% in PASI clearance in half of the patients. Their study lasted only for 6 weeks and as azathioprine needs about six to eight weeks for

its maximum anti-proliferative effects on dermatological lesions the results were not significantly good.

Mezzadara *et al.*¹² in their study gave azathioprine in very high doses to their patients i.e. 6 gram over a period of 18 days and then followed their patients for further ten weeks. They found azathioprine to be comparable to methotrexate in psoriasis. There were two dropouts due to diarrhea and GI bleeding and five of their 20 patients stopped treatment due to other side effects. Intolerance to high levels of azathioprine dosage made them suggest it should not be prescribed except under very strict clinical control.

Du Vivier *et al.*¹³ did their trial on azathioprine in 29 patients of psoriasis. It was the biggest controlled study until now. The dosage given to every patient was not discussed. They only mention azathioprine up to a dose 300mg for six months before concluding no response. 66% of their patients showed improvement. In their study, incidence of hepatic fibrosis was very high, almost fifty percent. Perhaps because their study lasted in few patients for up to 6 months; whereas only one patient in our study showed deranged LFTs necessitating discontinuation of treatment. Leukopenia occurred in about half of the patients in their study as compared to only 2 patients in ours. However, our study was of shorter duration and we employed lower dosages.

Throughout the study the tolerance to the two drugs was comparable. The incidence of adverse events was similar in the two groups, serious side effects occurring in 5 patients in both the groups needing patients to stop the treatment.

As expected the principal toxicity of azathioprine was myelosuppression.

Thrombocytopenia was most frequent. However, incidence of thrombocytopenia was less common in our study than in previous reports.¹⁴ This finding may be attributable to normal TPMT enzyme levels in our population.

Our study was of short duration employing only 4 weeks follow up. We suggest further controlled trials on larger patient groups with a longer follow up period so that long term efficacy of azathioprine can be assessed.

Azathioprine appears to be effective in the treatment of severe recalcitrant plaque-type psoriasis but its efficacy is less when compared with methotrexate. Although myelosuppression is most important risk in patients given azathioprine, it can be monitored easily with the help of routine blood counts. Most of the other adverse effects associated with azathioprine are causally related, mild to moderate in severity, and usually resolve without a reduction in dosage. It is, therefore, suggested that azathioprine should be considered as an alternative treatment in selected patients of chronic recalcitrant psoriasis when methotrexate cannot be used.

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