International Journal of Research in Dermatology
Badad AS et al. Int J Res Dermatol. 2019 Aug;5(3):471-475
http://www.ijord.com

DOI: http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20192100

Original Research Article

Efficacy and safety of azathioprine in psoriasis

Ambresh S. Badad[1], Shruti A. Badad[2]*

[1]Department of Dermatology, Venereology and Leprosy, MRMC, Kalaburagi, Karnataka, India
[2]Department of Ophthalmology, GIMS, Kalaburagi, Karnataka, India

Received: 23 April 2019
Revised: 08 May 2019
Accepted: 09 May 2019

***Correspondence:**
Dr. Shruti A. Badad,
E-mail: drasbadad@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. In certain patients systemic therapy is required. Very little data about efficacy and safety of azathioprine in psoriasis is available in the Indian subpopulation.
Methods: In this study, a total of fifty consecutive patients of chronic plaque psoriasis comprising inpatients and outpatients of a tertiary care hospital in Kalaburagi, Karnataka, South India during the period of 01 January 2017 to 31 June 2018 were included to study the efficacy and safety profile of azathioprine in psoriasis. The response to therapy was evaluated in terms of improvement in the PASI score at 12 weeks and 24 weeks.
Results: Out of 50 patients being treated with azathioprine, 10 (20%) patients had to be dropped from the study group due to development of side effects. Of the remaining 40 patients, 11 (27.5%) showed good response, and 26 (65%) showed fair response. 3 patients (7.5%) showed poor response even after three months of therapy. The overall improvement in PASI was 65.94%.
Conclusions: Azathioprine is an effective drug in treatment of chronic plaque psoriasis in selected patients in whom standard drugs like methotrexate cannot be administered either due to development of side effects or in cases where other drugs are contraindicated.

Keywords: Azathioprine, Psoriasis, PASI

INTRODUCTION

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. Patients presents with characteristic lesions consist of red, scaly, well demarcated, indurated plaques, particularly over extensor surfaces and scalp.[1] It has genetic predisposition: the risk is 14% if one parent is affected, 41% if both parents are affected, and 6% if one sibling is affected, compared to 2% when no parent or sibling is affected.[2] The environmental risk factors include trauma, streptococcal infection of throat, drugs like lithium, NSAIDS, antimalarials, angiotensin converting enzyme inhibitors, the withdrawal of corticosteroids, hypocalcaemia, alcohol, smoking and HIV. Pathogenesis of psoriasis includes increased epidermal cell proliferation in which TGF-α plays an important role. Dermal capillary loops in lesional skin are dilated, elongated and twisted. Molecular genetics have an important role with at least nine chromosomal loci being linked to psoriasis (PSORS1-9).[3]

Management options usually include topical therapy in the form of coal tar, dithranol, corticosteroids, calcineurin inhibitors, calcipotriol, retinoids and phototherapy. In certain patients systemic therapy is required. The indications for systemic therapy are – chronic plaque type

psoriasis with extensive body surface area involvement, recalcitrant psoriasis, psoriatic arthritis, erythrodermic psoriasis and pustular psoriasis.[4] Presently available systemic therapies includes- methotrexate, hydroxyurea, acitretin, cyclosporine, azathioprine, fumarates and biologicals (infliximab, adalimumab, etanercept, ustekinumab).

Azathioprine is an immunosuppressive agent which has shown benefits in extensive psoriasis vulgaris. It is mainly used in extensive psoriasis in patients who do not tolerate methotrexate or develop side effects to it. Its metabolites (6-thioguanine monophosphate) are structurally similar to the endogenous purines, get incorporated into DNA and RNA inhibiting purine metabolism and cell division.[5]

Very little data about efficacy and safety of azathioprine in psoriasis is available in the Indian subpopulation.[6] A study on safety and efficacy of azathioprine will be useful in establishing whether azathioprine is as effective as methotrexate or if atleast it can be an effective alternative to methotrexate for patients with extensive plaque psoriasis.

METHODS

This is an observational study in which, a total of fifty consecutive patients of chronic plaque psoriasis comprising inpatients and outpatients of a tertiary care hospital in south India during the period of 01 January 2017 to 31 June 2018 were included to study the efficacy and safety profile of azathioprine in psoriasis.

Adult patients of chronic plaque psoriasis having the disease for at least 6 months, psoriasis area severity index (PASI) ≥10 and Body surface involvement (BSA) ≥10% were included in study. Patients less than 16 years of age, pregnant and lactating women, female patients who have not completed their family and associated with major systemic illness of respiratory, cardiac, renal, hepatic and gastrointestinal system are excluded from the study. Patients on immunosuppressive drugs within last 04 weeks, patient with known hypersensitivity to azathioprine. Withdrawal criteria includes any adverse effect of the drug warranting withdrawal of the treatment, PASI <50% improvement after 3 months of treatment and worsening or aggravation of the disease while on therapy.

The diagnosis of psoriasis was made clinically and in cases of doubt histopathological confirmation was obtained. Pretreatment evaluation including detailed history, clinical examination & baseline laboratory evaluation was carried out in every patient and recorded in a standard proforma. Following laboratory tests were done in all patients, complete blood count, liver function tests, blood urea, serum creatinine levels, chest X-ray, Mauntaux test and HBsAg.

Patients with normal baseline investigations were started on Tab azathioprine 50 mg BD for 6 months. All patients were given topical white soft paraffin and patients with pruritus were also given oral cetirizine for symptomatic control of the disease. The measurement of severity psoriasis was done using PASI score recorded in PASI form**.** The initial PASI score of all patients was calculated according to above formula. Follow up was done every 2 weeks for first month and every 4 weeks thereafter for the first 24 weeks wherein patients were clinically evaluated and relevant investigations were done. Treatment was stopped at 24 weeks and patients followed up every 4 weeks for a period of at least 3 months thereafter. The response to therapy was evaluated in terms of improvement in the PASI score at 12 weeks and 24 weeks. Clearance of PASI from the baseline levels was recorded and interpretation was done as follows; Patients showing ≥75% improvement in PASI=Good response, patient showing improvement between 50-74%=Fair response, patients showing less than 50% improvement =Poor response.

Monitoring of patients was done as follows. Complete history and clinical examination was done at every visit. Patients had their complete blood count done fortnightly for the first 2 months, monthly for the next 2 months and every 2 months thereafter. LFTs were done monthly for the first 3 months, then every 2 months thereafter.

RESULTS

Out of 50 patients included in the study 35 were males and 15 were females. By using 2 sample proportion test, p value was >0.05. The age range was 17 to 73 years. The mean age was 39.87 years.

Out of 50 patients being treated with azathioprine, 10 (20%) patients had to be dropped from the study group due to development of side effects. Of the remaining 40 patients, 11 (27.5%) showed good response, and 26 (65%) showed fair response. 3 patients (7.5%) showed poor response even after three months of therapy and therefore was withdrawn from the study.

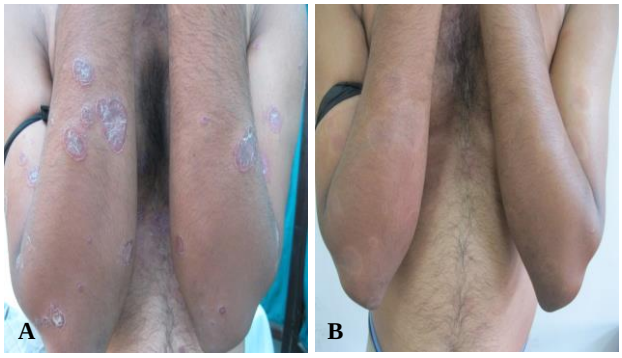

Figure 1: Improvement after 12 weeks of therapy with azathioprine; (A) before, (B) after.

Table 1: Therapeutic response.

Improvement in PASI	<50% (poor response)	(50%–74%) (fair response)	≥75% (good response)	P value
Patients on Azathioprine	03	26	11	< 0.001

The overall improvement in PASI was 65.94%. The response was slow for initial 06 weeks of starting therapy and maximum response was observed between 8 to 12 weeks. After three months, there was no further improvement in the PASI score till the end of study duration (Table 1) (Figure 1).

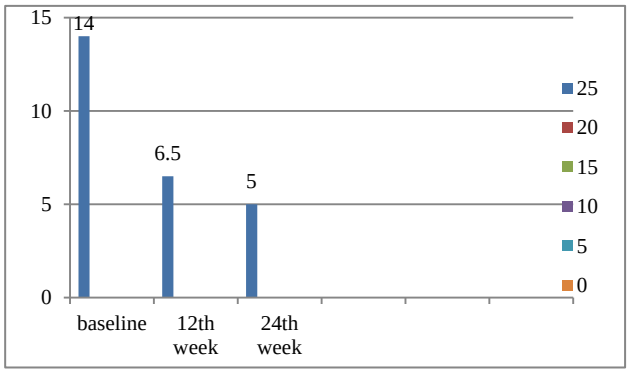

Figure 2: Comparison of PASI at baseline, 12th week and 24th week.

Table 2: Distribution of patients with respect to occurrence of various adverse effects.

Adverse effects	Patients on azathioprine
No adverse effects	34
Deranged LFT'S	2
Exacerbation	10
Nausea and vomiting	4
Total	50

Figure 2 compares the PASI at baseline, 12th week and 24th week. The mean baseline PASI in the azathioprine treated patients was 14. At 12 weeks it had reduced to 6.5 and subsequently at 24 week PASI further reduced to 5 (Mann-Whitney U test p value was <0.05). Out of 50 patients in azathioprine group, 10 (20%) patients had exacerbation of lesions after two weeks of starting therapy and the drug was withdrawn. 4 (8%) patients experienced nausea and vomiting initially which subsided after 2 days while continuing the drug. 2 (4%) patient had mild derangement of liver function tests with maximum serum bilirubin of 1.4 mg/dl and raised enzyme levels which was less than 3 times the normal values. However the drug was not stopped and the levels returned to normal within 2 weeks (Table 2).

DISCUSSION

Chronic plaque psoriasis affects approximately 2 percent of the world's population and results in social, economical and psychosexual problems. Azathioprine was used in this study for treating chronic plaque psoriasis. Role of azathioprine as an adjuvant therapy in the treatment of immunobullous diseases is well established.[7] It is relatively cheap, easily available and well tolerated with few side effects, most of which are reversible. One of the most important adverse effects of azathioprine is bone marrow suppression. However, one can predict the patients at risk and prevent this adverse effect, subject to availability of enzyme TPMT level estimation. Only few clinical trials have been carried out using azathioprine in patients suffering from chronic stable plaque psoriasis.[8,9] Hence, this study aims to describe the role of azathioprine in psoriatic therapy.

Age and sex distribution

In literature, psoriasis is found to be less common in very young and elderly.[10,11] Peak incidences have been reported as 22.5 years and 27 years in various studies.[12] In our study average age of patients was 42 years. The age range was from 17 years to 73 years but most of the patients were between 35 to 49 years of age.

Earlier studies have shown an equal incidence between males and females, though females tend to develop psoriasis early.[13,14] In our study male: female ratio was 2:1.

Response to therapy

In this study out of 50 patients of psoriasis treated with azathioprine, 40 patients showed positive response to therapy. 11 (27.5%) patients showed good response, 26 (65%) showed fair response and 3 (7.5%) showed poor response even after three months of therapy.

The response was slow for initial 06 weeks of starting therapy and maximum response was observed between 8 to 12 weeks. The initial slow response can be explained by the time taken for azathioprine to act. The response was maintained at a steady rate over next 3 months, though there was no further improvement in the PASI score.

Ejaz et al had conducted a study on 50 patients of chronic plaque psoriasis.[10] 25 patients were treated with azathioprine and 25 with methotrexate. 76% patients in azathioprine group showed improvement as compared to 76.66% patients in our study. 76% patients in methotrexate group had shown improvement in their study as compared to 100% patients in our study. In their study, 13 (73%) patients in methotrexate group and 5

(27%) patients in azathioprine group showed excellent response i.e. more than 80% clearance at 8th week. 5 (45%) patients in methotrexate group and 8 (55%) patients in azathioprine group showed good response i.e. more than 60% clearance at 8th week. One patient in each group showed poor response.

Du Vivier et al conducted a similar study on azathioprine in 29 patients of psoriasis.[15] Azathioprine was started at a dose of 100 mg/day and over a period of two weeks it was increased to 200 mg/day. This was maintained until the disease was in remission and dose was reduced thereafter. In few patients a maximum dose of up to 300mg daily was given for six months. 19 (66%) of their patients showed improvement as compared to 76.66% in our study. They concluded that azathioprine was a useful drug in the management of chronic psoriasis. Mezzadara et al in their study treated 20 patients of psoriasis with azathioprine.[16] They found that the results were comparable to efficacy of methotrexate observed in other studies. Various studies have reported methotrexate to be safe and effective drug in the treatment of extensive psoriasis vulgaris.[7,17]

In our study, there was no significant difference in percentage reduction in the PASI score at the end of 2 weeks. In patients treated with azathioprine, the mean baseline PASI was 14 and at 12 weeks it reduced to 6.5 and subsequently at 24 weeks PASI further reduced to 5. The overall improvement in PASI was 65.94% in azathioprine.

A study done by Greeves and Dawber, showed improvement of only 25% in PASI clearance in half of the patients on azathioprine.[18] Their study lasted only for 6 weeks and as azathioprine needs about six to eight weeks for its maximum anti-proliferative effects, the results could have been biased.

Mezzadara et al, 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.[16] They found efficacy of azathioprine to be comparable to methotrexate in psoriasis.

A study done by Du Vivier et al showed >75% PASI improvement in 16 patients (55.17%) and 50-75% PASI improvement in 3 patients (10.34%) treated with azathioprine.[15]

In a study done by Kumar et al 197 patients of psoriasis were treated with 243 cycles of methotrexate.[19] The study revealed that more than 75% improvement occurred in 88% of patients in 8.5±5.1 weeks. Similar results were also seen in various other studies with methotrexate.[20]

Adverse effects profile

In our study, out of 50 patients of psoriasis treated with azathioprine, there were 13 drop outs. 10 were due to exacerbation of lesions and three was due to poor response. Exacerbation was observed after 1-2 weeks of starting azathioprine in 10 patients in the form of increase in erythema and edema of pre existing lesions along with appearance of new lesions. There were also few pustular lesions observed in 02 patients. Since azathioprine takes 4 to 6 weeks for its action, exacerbation could have been part of disease progression.No other study previously has mentioned exacerbation of lesions with azathioprine. 02 patients experienced nausea and vomiting initially which subsided after 2 days while continuing the drug. 01 patient had mild derangement of liver function tests with serum bilirubin of 1.4 mg/dl and raised enzyme levels which was less than 3 times the normal values. The levels returned to normal within 2 weeks. Hence the drug was not stopped (Table 2).

Mezzadara et al in their study had 7 dropouts due to various side effects of azathioprine.[16] Diarrhea and GI bleeding were the most common among those mentioned.

Du Vivier et al did the trial on azathioprine in 29 patients of psoriasis. In their study, incidence of hepatic fibrosis was very high, to the tune of fifty percent.[15] This was perhaps because of higher doses and longer duration of therapy employed in their study. In our study only one patient showed deranged LFTs for which discontinuation of therapy was not required. Leukopenia also occurred in about half of the patients in their study as compared to none in ours. This could again be attributed to higher doses and longer duration employed in their study.

Ejaz et al, in their study had 5 drop outs in azathioprine group. Two patients had severely deranged liver function tests, two had severe gastrointestinal symptoms and one patient had thrombocytopenia. The principal toxicity of azathioprine is myelosupression, which was however not observed in our study.[21] Lower incidence of myelosupression in our study could probably be attributed to normal TPMT enzyme levels in our population.

Azathioprine appears to be effective in the treatment of moderate to severe recalcitrant plaque-type psoriasis but its efficacy is less when compared with methotrexate.[22] Although myelosuppression is most important risk in patients given azathioprine, it can be monitored with the help of routine blood counts.[23] Enzyme TPMT levels estimation may be helpful in calculating dose and predicting the risk of developing myelosupression. TPMT levels estimation is not easily available in most of the centers and is not routinely done prior to the therapy. Most of the other adverse effects associated with azathioprine are, mild to moderate in severity, and usually resolve without a reduction in dosage. Incidence of hepatotoxicity is less when compared to methotrexate. 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.

CONCLUSION

It can be concluded that azathioprine is safe and effective drug and could be considered as an alternative treatment in selected patients of chronic plaque type psoriasis in whom standard drugs like methotrexate cannot be administered either due to development of side effects or in cases where it is contraindicated.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Griffiths CEM, Barker JNWN, Burns T, Breathnach S, Cox N, Griffiths C. Psoriasis. Rook's Textbook of Dermatology. 8th edition. Wiley-Blackwell; 2010;20:1.
2. Burns T, Breathnach S, Cox N, Griffiths C, eds. Rook's Textbook of Dermatology, 8th edition. Wiley-Blackwell; 2010;20:2.
3. Van de Kerkhof PCM, Pathogenesis, Textbook of psoriasis. Blackwell Sci; 1999: 79-105.
4. Gudjonsson JE, Elder JT, Wolff K, Lowell A, Goldsmith, Barabara K, et al. Fitzpatrick's dermatology in general medicine 7th edition. 2008: 169-193.
5. Badalamenti SA, Kerdel FA. Comprehensive Dermatologic Drug; Second Edition. Chapter 9. 2007: 186.
6. Hacker SM, Ramoscaro FA, Ford MJ. Azathioprine; A forgotten alternative for treatment of psoriasis. Int J Dermatol. 1992;31(12):873-914.
7. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009;61(3):451-85.
8. Patel AA, Swerlick RA, McCall CO. Azathioprine in Dermatology: Past the present and the future. JAAD. 2006;55(3):369-89.
9. Younger IR, Harris DWS, Colver GB. Azathioprine in Dermatology; JAAD. 1991;25(2):281-6.
10. Malik T, Ejaz A. Comparison of methotrexate and azathioprine in the treatment of psoriasis: a randomized controlled trial. J Pakistan Assoc Dermatol. 2010;20:152-7.
11. Farber EM, Nall ML. Psoriasis Epidemiology, natural history and genetics. In Henry H. Roenigk, Howard I. Maibach, editor's. Psoriasis. 3rd ed. New York. Marcel Dekker; 1998: 107–158.
12. Gunawardane DA, Gunawardane KA, Vasanthanthan NS, Gunawardane JA. Psoriasis in Sri Lanka-A computer analysis of 1366 cases. Br J Dermatol. 1978;98:85-96.
13. Chritophers E, Mrowietz U, Irwin M, Arthur R, Wolf K, Frank K, et al. editor's. Fitzpatrick's Dermatology in general medicine. 6th ed. McGraw-Hill. 2008;42:407–34.
14. Long-term maintenance treatment of moderate-to-severe plaque psoriasis with infliximab in combination with methotrexate or azathioprine in a retrospective cohort. Epub. 2008.
15. Du Vivier A, Munro DD, Verbov J. Treatment of psoriasis with azathioprine. Br Med J. 1974;1:49-51.
16. Mezzadra G. Therapeutic experience with azathioprine in psoriasis. G Ital Dermatol Minerva Dermatol. 1972;47:72-6.
17. Boffa MJ, Chalmers RJG. Methotrexate for psoriasis. Clin Experimental Dermatol. 1996;21:399–408.
18. Greaves MW, Dawber W. Azathioprine in psoriasis. Br Med J. 1970;4:237-8.
19. Kumar B, Saraswat A, Kaur I. Short-term methotrexate therapy in psoriasis: a study of 197 patients. Int J Dermatol. 2002;41(7):444-8.
20. Collins P, Rogers S. The efficacy of methotrexate in psoriasis--a review of 40 cases. Clin Exp Dermatol. 1992;17(4):257-60.
21. Saway PA, Heck LW, Bonner JR et al. Azathioprine efficacy and/or side effects of azathioprine therapy in dermatologic patients. Arch Dermatol. 1995;131:193-5.
22. Wolverton SE. Optimizing clinical use of azathioprine with newer pharmacogenetic data. Arch Dermatol. 2009;145:707-710.
23. Patel AA, Swerlick RA, McCall CO. Azathioprine in dermatology: The past, the present, and the future. J Am Acad Dermatol. 2006;55:390-1.

Cite this article as: Badad AS, Badad SA. Efficacy and safety of azathioprine in psoriasis. Int J Res Dermatol 2019;5:471-5.