

Original Article

Efficacy and safety of azathioprine in the treatment of chronic actinic dermatitis

Shahzana Naqqash, Faria Asad*, Sabrina Suhail Pal*

Department of Dermatology, Services Institute of Medical Sciences, Services Hospital, Lahore.

*Department of Dermatology, King Edward Medical University/ Mayo Hospital, Lahore.

Abstract *Background* Chronic actinic dermatitis (CAD) is a rare intractable photosensitive predominantly eczematous eruption sometimes with infiltrated plaques on the exposed areas and has a tendency to progress to erythroderma. Along with sun protection, the use of corticosteroids gives only partial response and is associated with many unwanted effects. There are promising reports of usefulness of azathioprine in the treatment of CAD.

Objectives To evaluate the efficacy and safety of azathioprine in the treatment of chronic actinic dermatitis in our patients.

Patients and methods The study was conducted in the dermatology department of Mayo Hospital, Lahore over a period of 18 months. Patients of CAD fulfilling the inclusion criteria were put on azathioprine 2-3mg/kg/day. The clinical severity was assessed at 0, 1, 3, 6, 9 and 12 months of azathioprine treatment using modified PASI score. Complete hemogram, hepatic and renal function tests, chest X-ray and urinalysis were carried before putting the patients on azathioprine. Hemograms were repeated at monthly intervals while liver enzymes were monitored at 2, 4 and 8 weeks and then at intervals of 2 months. Renal function tests were repeated at 3-monthly intervals.

Results Eighteen patients, all men, were studied. The mean duration of disease was 6.5 years. Of the fifteen patients completing 9 months of treatment, six (40%) showed >90% reduction in PASI score, 7 (46.6%) showed >50% reduction while 1 (1.6%) showed <50% improvement. One (1.6%) patient discontinued the treatment on his own after no improvement of 4 months treatment.

Conclusion A definite conclusion could not be derived from this study as the number of patients was limited but the azathioprine can be used as an effective and safe treatment modality in chronic actinic dermatitis.

Key words

Chronic actinic dermatitis, azathioprine.

Introduction

Chronic actinic dermatitis (CAD) is a severe, socially disabling and intractable photosensitive disorder particularly affecting elderly men.¹ It has been shown to be a spectrum of diseases including actinic reticuloid and photosensitive eczema.² The dermatitis is characterized by a light sensitive

predominantly eczematous eruption sometimes with infiltrated plaques on the exposed areas and a tendency to progress to erythroderma, sometimes with circulating Sèzary cells in severe cases.³

The histological picture is usually eczematous, although sections from plaques may show a more marked reaction occasionally simulating a cutaneous lymphoma.^{2,3} CAD is usually very persistent, and it seems probable that very occasionally it may transform to a cutaneous lymphoma.⁴ The treatment of CAD is very challenging; exposure to UVR, visible light,

Address for correspondence

Dr. Shahzana Naqqash
Assistant Professor, Dermatology Department
Services Institute of Medical Sciences,
Services Hospital, Lahore.
E mail: dr_shahzana_naqqash@hotmail.com

even to fluorescent room light has to be minimized. Even regular use of photoprotective measures gives only partial improvement leading to non compliance by the patients. Patients have to use regularly either topical or systemic corticosteroids to achieve and maintain clinical remissions, but prolonged usage can cause serious side effects. Mild cases are treated with topical corticosteroids but these are often not adequately effective in severe cases and there is also concern about the risk of cutaneous atrophy when large quantities are used on regular basis. The advent of topical immunosuppressant agents such as tacrolimus⁵ seems likely to represent a significant advance in mild to moderate cases but it is not clear how useful these will be in more severe disease. Systemic corticosteroids are usually effective but patients require high and prolonged dosage regimen to maintain a reasonable quality of life and even with low dose there is an increased risk of osteoporosis. There are reports of treatment of eczema with immunosuppressive drugs such as cyclophosphamide⁶ and azathioprine.^{7,8} Limited open studies suggest that azathioprine may be effective in controlling chronic actinic dermatitis.^{9,10}

Azathioprine, a derivative of 6-mercaptopurine, exhibits an impressive immunosuppressive effects and has been successfully used in rheumatoid arthritis, autoimmune bullous disorders, renal transplant patients and other autoimmune diseases.^{11,12} There is evidence to suggest that both the number and antigen-presenting capacity of Langerhan cells are affected by azathioprine, which prevents lymphocyte proliferation after antigenic stimulus.¹³ Although its exact mechanism of action is not known, the major immunosuppressive effect is thought to result from blocking of DNA replication due to incorporation of the azathioprine metabolite 6-thioguanine nucleotide.¹⁴

Patients and methods

The study was conducted at the department of dermatology King Edward Medical University/Mayo hospital Lahore over a period of 18 months. Patients of either sex, presenting to our department, clinically suggestive of having chronic actinic dermatitis were enrolled. The disease was severe enough to impair quality of life and resistant to daily use of topical steroids and sun protection. Any patient having history of chronic active infection or sensitivity to azathioprine was excluded. Patients who were on any drug likely to influence the eczema were not enrolled. Skin biopsy was done to confirm the diagnosis after taking an informed consent. Complete hemogram, hepatic and renal function tests, chest X-ray and urinalysis were carried out before the start of azathioprine therapy. Those with immunosuppression, hepatic or renal impairment were also not included in the study. The clinical severity was evaluated using the psoriasis area severity index (PASI) scoring method^{15,16} with slight modification at 0, 1, 3, 6, 9 and 12 months after azathioprine therapy. Erythema and scaling were scored as for psoriasis; infiltration was taken as thickening or lichenification of the skin. The area of distribution was the same as in the PASI scoring system. Patients were given 2 mg/kg azathioprine in two divided doses, which was increased to 3mg/kg if no significant improvement was observed after 8-12 weeks. The dose was gradually tapered after near complete clearance was obtained i.e. more than 90% reduction in score. Hemograms were repeated at monthly intervals. Liver enzymes were tested at 2, 4 and 8 weeks then at the interval of 2 months. Renal function tests were performed at 3-monthly intervals.

Results

Eighteen patients, all men, with a mean age of

Table 1 Total number of patients (n=18)

Age	Mean 54 years, range 40-72 years
Sex	All men
Duration	7.6 years (2 to 30 years)
Skin biopsy	Chronic dermatitis 12
	Actinic reticuloid 6

Table 2 Response to azathioprine therapy n=15

Percentage reduction in modified PASI Score	N (%)
>90%	6 (40%)
>50%	7 (46.6%)
<50%	1 (1.6%)
No improvement	1(1.6%)

54 years (range 40-72 years), were studied. The mean duration of dermatitis was 6.5 years (range 2-30 years). All patients had been treated with prednisolone at doses in the range of 10-30 mg at interrupted periods varying from 4 months to 10 years. The demographic data and skin histology are summarized in **Table 1**. Fifteen patients completed 9 months of azathioprine therapy which were followed up for a period of 9 months. One patient stopped treatment because of mild gastrointestinal side effects and non compliance. Two of the patients were lost to follow up and were excluded from further analysis.

Of the 15 patients evaluated at 6 months, all but one showed improvement. The mean initial modified PASI score of 14.6 (range 4.7-17) showed a progressive decrease to 8.9 (range 1.5-16.2) at 3 months, 4.6 (range 0.6-14.2) at 6 months and 0.7 (range 0.2-1.3) at the end of 9 months. The clinical response was evident at 2 months and was the maximum at 9 months. Six (40%) patients showed near complete clearance (>90%) reduction in score [**Figures 1** and **2**], seven patients (46.6%) more than 50% reduction and one (1.6%) patient showed less than 50% improvement. One patient who had no improvement at 4 months discontinued the drug independently at 5 months (**Table 2**).

All the patients tolerated the drug well except



Figure 1 Before treatment.

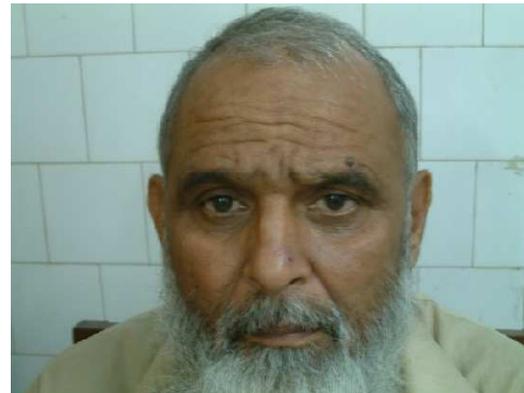


Figure 2 Marked improvement after treatment.

for one patient who experienced nausea and vomiting and was not willing to continue the treatment. Biochemical monitoring demonstrated transient mild elevation of liver enzymes (alanine aminotransferase, gamma glutamyl transferase or alkaline phosphatase) in two patients during azathioprine treatment, but this was not severe enough to stop the treatment. No hematological abnormality was noted in any patient.

Discussion

Azathioprine produced an objective response in all but one of our patients with chronic actinic dermatitis. Six (40%) of the 15 patients showed near complete clearance i.e. more than 90% reduction in score, The response was directly related to the duration of azathioprine therapy, as the mean score was reduced progressively from 18.9 to 0.7 over 9 months. The clinical response was not related to the

duration of the disease. Most of our patients had been on oral corticosteroid therapy off and on. In all the patients corticosteroids were withdrawn over a period of 2 months before putting them on azathioprine. Our results closely correspond to the results shown by other dermatologists in their studies of efficacy of azathioprine in chronic actinic dermatitis, contact dermatitis and atopic dermatitis.^{7,12,17}

The data from the current study do not provide any conclusive evidence of continued benefit after treatment was stopped; however, the data are compatible with some persistence of the clinical improvement. This study was not designed to investigate this issue.

The drug was well-tolerated, and no serious side effects were noted. The frequency of gastrointestinal side effects, particularly nausea and vomiting, which resulted in withdrawal of one of our subjects, represents a drawback of this treatment. One patient of Morrison and Schulz⁶ patients and three of the 35 cases reported by Lear *et al.*¹⁷ had to stop treatment owing to severe nausea and vomiting and epigastric pain. However, many of our patients did not report this side effect. Although, the changes in liver enzymes observed in this study did not give rise to serious concern in any individual, the frequency of changes was sufficient to indicate that these require monitoring when azathioprine is used. There were no haematological side effects in any of our cases but the occurrence of transient leucopenia in two subjects of Jones *et al.*¹⁸ confirms the requirement for careful hematological monitoring. The manufacturer's data sheet for Imuran^(R) (Glaxo-Wellcome) recommends weekly monitoring of the full blood count for the first 8 weeks of treatment. This is probably a sensible approach, but less frequent monitoring is likely to be safe if patients are screened for deficiency of thiopurine methyl transferase (TPMT). It has been suggested that

liver enzymes should be monitored at 2, 4 and 8 weeks and then at intervals of 2 months,¹⁷ we adopted the same protocol.

The data reported here support the already reported literature that azathioprine can be an effective and useful drug in the management of chronic actinic dermatitis. It can provide an answer to this chronic and socially disabling condition provided that it is used judiciously and the treatment is carefully monitored.

As the number of patients was limited and it was not a case-control study, therefore, more studies are required to be done in the evaluation of this potentially beneficial drug in the treatment of chronic actinic dermatitis.

Conclusion

Although no definite conclusion can be derived from the present study due to its limitations but we found azathioprine to be a potentially efficacious and safe drug in the treatment chronic actinic dermatitis.

References

1. Hawk JLM, Smith NP, Black MM. The photosensitivity disorders. In: Elder DE, Elenitsas R, Jaworsky C, Johnson B Jr, eds. *Lever's Histopathology of Skin*. Philadelphia: Lippincott-Raven, 1997: 305-10.
2. Norris PG, Morris J, Smith NP *et al.* Chronic actinic dermatitis: an immunologic and photobiologic study. *J Am Acad Dermatol* 1989; **21**: 966-71.
3. Lim HW, Morrison WL, Kamide R *et al.* Chronic actinic dermatitis: an analysis of 51 patients in the United States and Japan. *Arch Dermatol* 1994; **130**: 1284-9.
4. Dawe RS, Crombie IK, Ferguson J. The natural history of chronic actinic dermatitis. *Arch Dermatol* 2000; **136**: 1215-20.
5. Uetsu N, Okamoto H, Fuji K *et al.* Treatment of chronic actinic dermatitis with tacrolimus ointment. *J Am Acad Dermatol* 2002; **47**: 881-4.
6. Morrison JG, Schulz EJ. Treatment of eczema with cyclophosphamide and

- azathioprine. *Br J Dermatol* 1978; **98**: 203-7.
7. Vinod KS, Aditi C, Vikram M. Azathioprine in the treatment of Parthenium dermatitis. *Int J Dermatol* 1998; **37**: 299-302.
 8. August PJ. Azathioprine in the treatment of eczema and actinic reticuloid. *Br J Dermatol* 1982; **107** (Suppl 22): 23.
 9. Leigh IM, Hawk JLM. Treatment of chronic actinic dermatitis with azathioprine. *Br J Dermatol* 1984; **110**: 691-5.
 10. Murphy GM, Maurice PD, Norris PG *et al.* Azathioprine in chronic actinic dermatitis: a double-blind controlled trial with monitoring of exposure to ultraviolet radiation. *Br J Dermatol* 1989; **121**: 639-46.
 11. Callen JP, Spencer LV, Burruss JB *et al.* Azathioprine: an effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. *Arch Dermatol* 1991; **127**: 515-22.
 12. Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149**: 926-37.
 13. Perkins DL, Carpenter CB, eds. *Immunobiology of Transplantation*. Philadelphia: WB Saunders; 1996.
 14. Snow JL, Gibson LE. The role of genetic variation in thiopurine methyltransferase activity and the efficacy and/or side-effects of azathioprine therapy in dermatologic patients. *Arch Dermatol* 1995; **131**: 193-7.
 15. Kirby B, Fortune DG, Bhushan M *et al.* The Salford Psoriasis Index: a holistic measure of psoriasis severity. *Br J Dermatol* 2000; **142**: 728-32.
 16. Kirby B, Richards HL, Woo P *et al.* Physical and psychological measures are necessary to assess overall psoriasis severity. *J Am Acad Dermatol* 2001; **45**: 72-6.
 17. Lear JT, English JSC, Jones P, Smith AG. Retrospective review of the use of azathioprine in severe atopic dermatitis. *J Acad Dermatol* 1996; **35**: 642-3.
 18. Berth-Jones T, Takwale A, Tan E *et al.* Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol* 2002; **147**: 324-30.