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#### **Comparative study of weekly pulse doses of azathioprine versus weekly pulse doses of prednisolone in parthenium dermatitis**

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#### **Abstract**

**Background:** Parthenium dermatitis is one of the most common, chronic, relapsing and distressing allergic contact dermatitis from plants, particularly in India. Steroids have been the mainstay of treatment. For many years now, various immunosuppressive drugs particularly Azathioprine, with different dosage schedules are in use.

**Aims and objectives:** We evaluated the efficacy of weekly pulse doses of Azathioprine and weekly pulse doses of Prednisolone in the treatment of Parthenium dermatitis and compared the two treatment regimens.

**Methods:** Sixty Parthenium dermatitis patients were randomly divided into 2 equal groups. Patients of first group were given oral Azathioprine 300 mg weekly and those of second group oral Prednisolone 100 mg weekly. Therapy in both groups was given for a total of 12 weeks with follow up at 4, 8 and 12 weeks.

**Results:** In the Azathioprine group of patients, the mean Clinical Severity Score (CSS) at 4, 8 and 12 weeks decreased respectively to values of 51.7, 39 and 22.3, from the mean value of 66 at 0 week, with statistically significant percentage decline in the mean of 47.78, 90 and 145.55 respectively. In the Prednisolone group of patients, the mean CSS at 4, 8 and 12 weeks decreased from 68.3 at 0 week to mean CSS values of

63, 52.3 and 43.3 respectively, with percentage decline of 17.78, 53.3 and 83.33 respectively. No significant side effects of the two regimens were detected.

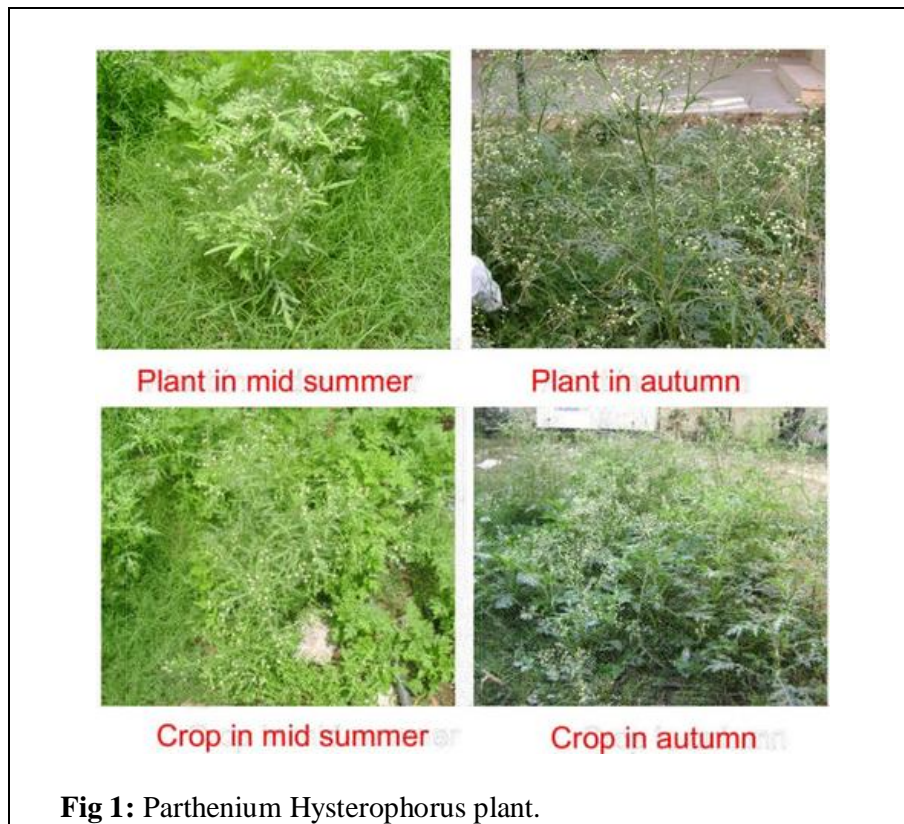
**Conclusions:** In this preliminary open study, both Azathioprine in weekly pulse doses and Prednisolone in weekly oral mini-pulse were found to be effective without any serious adverse effects in the treatment of Parthenium dermatitis.

**Key message:** Weekly pulse doses of Azathioprine and Oral Mini Pulse therapy of steroids can be a safe and effective alternative to daily dosage regimens of Azathioprine and systemic steroids.

**Limitations:** The study group was small and the therapy was given for 12 weeks only, although therapy with both Azathioprine and oral mini pulse therapy with steroids is more effective if given for a prolonged period of time. Follow up was short and Thio Purine Methyl Transferase (TPMT) level was not done as the facility does not exist.

## Introduction

Parthenium hysterophorus [1,2,3,4], which belongs to family Compositae, is the most common cause of contact dermatitis from plants in India [5,6,7], though there is cross sensitivity with other Compositae plants [8,9] (fig 1).



**Fig 1:** Parthenium Hysterophorus plant.

Various preventive and control measures, eradication of weed, desensitization of patients with plant material and other treatment modalities have been tried [10,11,12], with ineffective, inconsistent and unsuccessful results. The mainstay of treatment has been the use of local and systemic steroids, which is associated with several serious and often irreversible side effects [13,14,15,16], forcing researchers to find modifications in dosage schedules and alternative therapeutic regimens. Pulse therapy of systemic steroids has been found to be equally effective to daily regimens, with lesser side effect profile [17]. Various immunosuppressive agents like Methotrexate [18], Cyclosporine [19], Azathioprine have recently emerged as good therapeutic alternatives to steroids for use in Parthenium dermatitis. Preliminary studies on the use of Azathioprine, a potent immunosuppressant in air borne contact dermatitis [20], actinic reticuloid [21], chronic actinic dermatitis [22], atopic dermatitis [23,24] as well as Parthenium Dermatitis [25,26,27,28,29,30], have given encouraging and consistently good results, having been used both as daily [27,30,31] and also weekly pulse dosage schedules [29].

Only few studies have been conducted in India or abroad to prove the efficacy of weekly pulse of Azathioprine in Parthenium dermatitis. In the present study, the efficacy of weekly pulse doses of Azathioprine was evaluated and compared with weekly oral mini pulse therapy of Prednisolone for the treatment of Parthenium dermatitis, which is quite distressing ailment for patients and equally disappointing for dermatologists to manage because of remissions and recurrences associated.

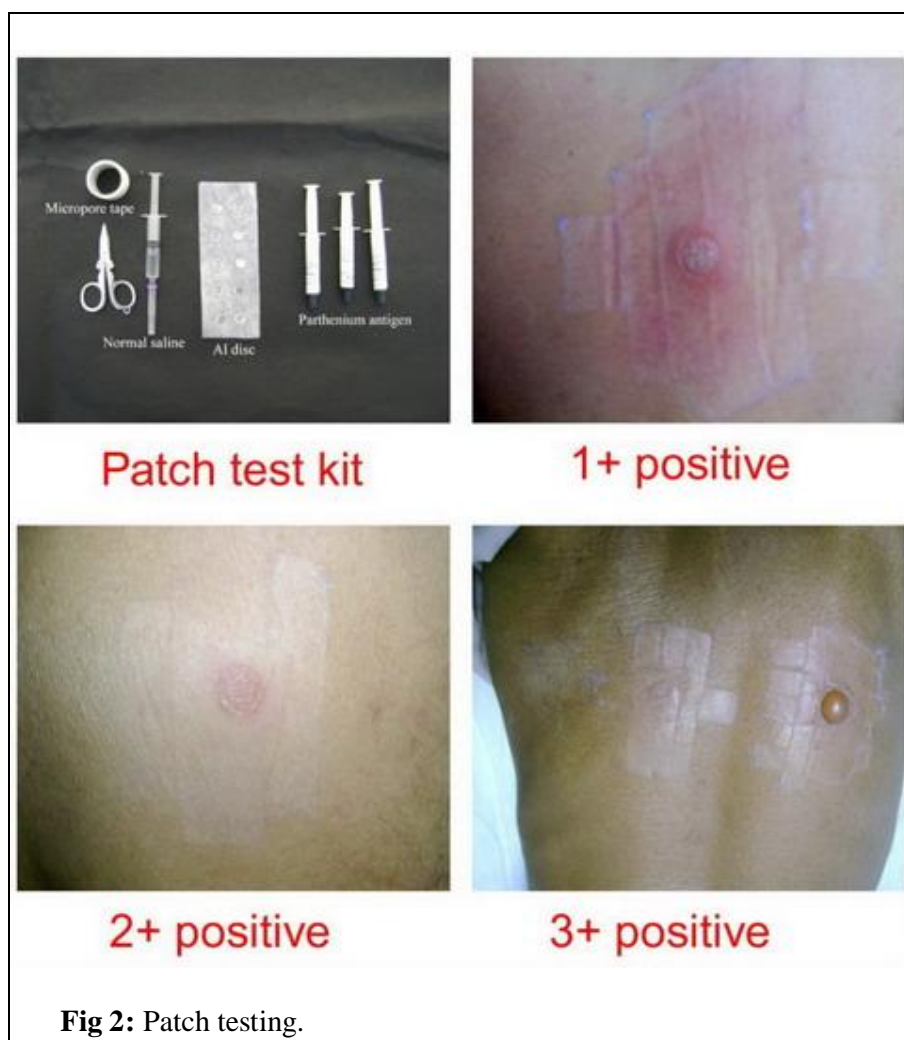
## Materials and Methods

The study was conducted in the Department of Dermatology, Venereology and Leprosy in a Government Medical College hospital over a period of one year from November 2007 to October 2008.

Sixty cases of Parthenium dermatitis, both old and new, in the age group 25-65 years, visiting the department on out-patient and in-patient basis, confirmed by standard patch testing to Parthenium, were included in the study after a proper written consent. Patch testing was done using standard Parthenium patch test kit developed in R and D section of Systopic labs New Delhi, through Contact and Occupational Dermatoses Forum of India (CODFI), from which the kit was purchased. Each antigen bottle contained 2 ml of 15% Parthenium antigen. It was ensured that patients are not on local or systemic steroids for at least 2 weeks prior to patch testing. Patch test result was read after 48 hours and grading done according to International Contact Dermatitis Research (ICDR) group as given in **table 1** [32] (**fig 2**).

-	Negative
?+	Doubtful reaction ; faint erythema only
+	Weak positive reaction ; palpable erythema, infiltration, possibly papules
++	Strong positive reaction; erythema, infiltration, papules, vesicles
+++	Extreme positive reaction ; intense erythema & infiltration, coalescing vesicles
IR	Irritant reaction of different types

**Table 1:** Grading of patch test



Patients <25 years or >65 years, pregnant and lactating females, those with hypertension, diabetes, history of tuberculosis, liver or kidney disease were not included in the study. The patients were randomly divided into 2 equal groups of 30 patients each, statistically comparable for each variable studied.

A detailed history was taken particularly regarding the grade of itching, duration of present episode, total duration of disease, seasonal variation and previous treatments taken. A general physical and systemic examination was performed to clinically rule out any systemic abnormality. Cutaneous examination with special reference to the morphology, distribution, symmetry of lesions was performed and the lesions were mapped on a chart. Pattern of Parthenium dermatitis was noted. Clinical severity was assessed using the clinical severity score (CSS), on the basis of itching, type of lesions and the area of body involved, using the scoring method used in a previous study [33], where 3 points each are given to itching and morphology and 4 points to area of body involved, as follows:

a) Itching: 0 - no itching; 1 - mild; 2 - moderate; 3 - severe itching

b) Morphology of lesions: 0 - no lesions; 1 - papules; 2 - plaques; 3 - lichenified plaques.

c) Area of body: 1 - face only; 2 - face, neck and hands; 3 - all exposed sites and flexures; 4 - erythroderma.

Total score (a + b + c) is multiplied by 10 to get CSS of 100.

Each patient was subjected to baseline investigations like complete haemogram, liver function tests, kidney function tests, urine analysis, ECG, chest X ray at the start and at each follow up visit.

Thirty patients of the first group were given oral Azathioprine 300 mg weekly as a single dose of 6 tablets of 50 mg each, half an hour after meals. Forty-eight hours before giving this large dose, an initial test dose of 50 mg orally was given to look for any idiosyncrasy and gastric intolerance.

Thirty patients of the second group were given oral Prednisolone 100 mg weekly in 2 divided doses of 50 mg each on 2 consecutive days.

Drugs were supplied free of cost to the patients. Therapy in both groups was given for a total of 12 weeks. No topical corticosteroid or other immunosuppressive agents were given during the study period other than emollients and anti-histamines. Each patient was followed up at 4, 8 and 12 weeks. At each follow up, compliance to treatment was checked, improvement in subjective symptoms noted and condition of cutaneous lesions recorded. Improvement in cutaneous lesions of >80 % was taken as marked, 60-80% as moderate and <60% as mild. Clinical severity score was re-assessed, side effects and any abnormality in investigations after the start of treatment noted.

At the end of study, the data was subjected to statistical analysis performed by using computer software Microsoft Excel and SPSS 12.0 for windows. Data was reported as percentage for qualitative variables and

CSS was reported as mean  $\pm$  SD. Statistical significance and difference between the two groups was evaluated using unpaired student 't' test and chi square tests. A 'P' value of  $<0.05$  was considered statistically significant. All 'P' values used were two tailed. The efficacy was assessed on the basis of a decrease in the mean CSS at 4, 8 and 12 weeks follow up relative to the pre treatment clinical severity score (CSS 0).

## Results

The demographic profile and other variables between the two study groups are given in table 2 and 3.

Age (mean $\pm$ SD)	46.8 $\pm$ 9.44	46.6 $\pm$ 8.35	T 0.10, p 0 .92 NS
Sex (M/F)	41084	41173	$\chi^2$ 0.80 p 0 .37 NS
Residence (R/U/SU)	39615	39191	$\chi^2$ 0.72 p 0.69 NS
Occupation (Fa/S/O)	39034	40402	X <sup>2</sup> 1.51 p 0.46 NS
Grade of itching (Mild/Mod/Severe)	1/29/0	1/24/5	X <sup>2</sup> 5.47 p 0.06 NS
Duration of present illness in weeks (mean $\pm$ SD)	4.69 $\pm$ 3.75	3.68 $\pm$ 2	T 1.28 p 0.21 NS
Duration of disease in years (mean $\pm$ SD)	6.33 $\pm$ 6.45	6.63 $\pm$ 5.43	T 0.20 p 0.84 NS
CSS 0 (mean $\pm$ SD)	66 $\pm$ 12.48	68.3 $\pm$ 10.85	T 0.77 p 0.44 NS
Patch test positivity (1+/2+/3+)	6/15/9	8/16/6	X <sup>2</sup> 0.92 p 0.63 NS

**Table 2:** Comparison of various variables between the two study groups

Note: M, Male; F, Female; Fa, Farmer; S, Service (Govt or Private); O, Other (household or business); R, Rural; U, Urban; SU, Suburban; CSS 0, Clinical severity score at 0 week; NS, not significant

Age groups	Azathioprine group (n=30)	Prednisolone group (n=30)
25 – 35	4 (13.33%)	2 (6.67%)
36 – 45	7 (23.33%)	11 (36.67%)
46 – 55	15 (50%)	10 (33.33%)
56 – 65	4 (13.33%)	7 (23.33%)
Total no of patients	30	30
Mean age	46.8 ± 9.44	46.6 ± 8.35
t 0.10 p 0.92 NS		

Table 3: Distribution of patients as per age groups in Azathioprine and Prednisolone groups

The pattern of Parthenium dermatitis in the two groups is given in **table 4**.

Pattern of disease	Azathioprine group (n = 30)			Prednisolone group (n = 30)		
	Males	Females	Total	Males	Females	Total
Airborne pattern	12.000	5.000	17.000	15.000	6.000	21.000
	-0.400	-0.167	-0.567	-0.500	-0.200	-0.700
Photo-exposed	09 (30%)	0.000	09 (30%)	05(16.67%)	03(10%)	08 (26.67%)
Erythroderma	03(10%)	0.000	03 (10%)	0.000	0.000	0.000
Flexural	0.000	01 (3.33%)	01(3.33%)	01(3.33%)	0.000	01(3.33%)
Total	24(80%)	06 (20%)	30(100%)	21(70%)	09(30%)	30(100%)

**Table 4:** Distribution of patients as per pattern of Parthenium dermatitis

The mean CSS at 0 week in the present study was  $66 \pm 12.48$  in the Azathioprine group and  $68.3 \pm 10.85$  in the Prednisolone group, with no statistically significant difference in pre treatment score between the two groups (t 0.77 p 0.44 NS).

At 4 weeks, in the Azathioprine group, the mean CSS decreased to a value of 51.7 from the mean value of 66 at 0 week, with statistically significant percentage decline in mean of 47.78 (t 3.97 p 0.0002 S) and in the Prednisolone group, the mean CSS at week 4 decreased from 68.3 at 0 week to a mean CSS value of 63 at week 4 with statistically insignificant percentage decline of 17.78 (t 1.82 p 0.0735 NS).

At 8 weeks, in the Azathioprine group, the mean CSS decreased to a value of 39 from the mean value of 66 at 0 week, with a percentage decline of 90, with high statistical significance (t 7.15 p 0.0001 S) and in the Prednisolone group, the mean CSS decreased to a level of 52.3 from the

mean value of 68.3 at 0 week, with statistically significant percentage decline of 53.3 (t 5.23 p 0.0001 S).

At 12 weeks, in the Azathioprine group, the mean CSS decreased to a value of 22.3 from the mean value of 66 at 0 week, with statistically significant percentage mean decrease of 145.55 (t 12.03 p 0.0001 S) and in the Prednisolone group, the mean CSS at 12 weeks decreased from 68.3 at 0 weeks to a mean value of 43.3 at 12 weeks with statistically significant percentage decrease of 83.33 (t 6.21 p 0.0001 S) (**table 5, 6 and figs 3, 4, 5, 6, 7**).

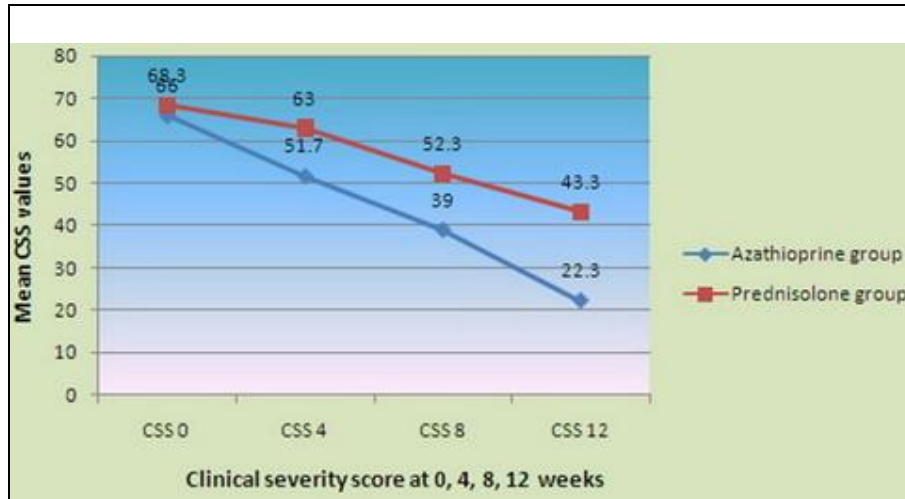
CSS (mean ± SD)	Azathioprine group (n=30)	Prednisolone group (n=30)	Significance
0 weeks	66 ±12.48	68.3 ±10.85	T 0.77 p 0.44 NS
4 weeks	51.7 ±15.33	63 ±11.79	T 3.21 p 0.0022 S
8 weeks	39 ±16.47	52.3 ±12.78	T 3.50 p 0.0009 S
12 weeks	22.3 ±15.46	43.3 ±19.18	T 4.67 p 0.0001 S

**Table 5:** Inter group comparison of efficacy of Azathioprine versus Prednisolone at 4, 8, 12 weeks

	Azathioprine group				Prednisolone group			
	0 weeks	4 weeks	8 weeks	12 weeks	0 weeks	4 weeks	8 weeks	12 weeks
Sample size	30	30	30	30	30	30	30	30
CSS	66±	51.7±	39±	22.3±	68.3±	63±	52.3±	43.3±
(mean± SD)	12.48	15.33	16.47	15.46	10.85	11.79	12.78	19.18
Significance		t3.97p .0002	t7.15p .0001	t12.0p 0.0001		t1.82p .0735	T5.23p .0001	t 6.21p 0.0001
Mean % difference		47.78	90	145.55		17.78	53.33	83.33

**Table 6:** Intra group comparison of efficacy of Azathioprine versus Prednisolone at 4, 8, 12 weeks to that at 0 week





**Fig 3:** Comparison of efficacy at 0, 4, 8, 12 weeks.



**Fig 4:** Azathioprine Group (patient 1).







The side effect profile detected in the two patient groups is shown in **table 7**.

Side effects (clinical, investigational)	Azathioprine group (n=30)	Prednisolone group (n=30)
Abnormality in Hb, TLC, Platelet count	0	0
Abnormal LFT		02 (6.67%)
Abnormal B sugar		02 (6.67%)
Abnormal KFT	0	0
Abnormality in ECG, chest X ray	0	0
Diarrhea	04 (13.33%)	01 (3.33%)
Nausea, Vomiting	02 (6.67%)	04 (13.33%)
Epigastric pain	03 (10%)	06 (20%)
Folliculitis	01 (3.33%)	
Headache/drowsiness	01 (3.33%)	03 (10%)
Others (dry mouth, aches/pains)	01 (3.33%)	01 (3.33%)
*Few patients developed more than one side effect in the same patient		

**Table 7:** Side effect profile in both Azathioprine and Prednisolone groups

## Discussion

The present study included 60 patients in the age group 25-65 years, with mean age of 46.7 years, consistent with previous studies [27,29,30,31,34]. Forty- three patients out of 60 were in the age group 36-55 years, probably due to higher chances of exposure to Parthenium weed because of occupational or recreational activities.

There were 45 males and 15 females, with a sex ratio of 3: 1, consistent with that in other studies [22,27,30,31,34,35,36]. The increased prevalence of Parthenium dermatitis in males may be because of more exposure to parthenium [5].

Out of the 60 patients, 35 (58.33%) came from rural areas, 15 (25%) from suburban and 10 (16.66%) from urban background. No previous

study laid emphasis on the residential background of patients. We included it to ensure comparability in the two study groups and that people from rural and suburban areas may be more exposed to Parthenium weed than urban lot.

Twenty- five (41.66%) patients were farmers and involved with working in the field. Nineteen (31.66%) patients belonged to service class but frequently exposed directly to plant. Sixteen (26.66%) patients, were either housewives, elderly persons or business men. This shows more prevalence of disease with direct exposure to the plant than with indirect contact [5,37].

Various variables like level of itching, duration of present illness, grading of patch test positivity was recorded to make the two groups comparable and to remove confounding factors as well as to look for their effect on the clinical presentation of the disease.

Parthenium dermatitis is a chronic relapsing and remitting disease. The mean duration of the disease in years in the Azathioprine and the Prednisolone groups was  $6.33 \pm 6.45$  and  $6.63 \pm 5.43$  respectively, consistent with other studies [27,29,30,31,36]. Parthenium dermatitis presents in various patterns like airborne contact dermatitis, dermatitis of hands and face, chronic actinic dermatitis, photo-dermatitis, disseminated forms, hand dermatitis, prurigo nodularis, photosensitive lichenoid eruption, erythroderma, seborrheic and many other patterns [5,35,38,39,40,41,42]. Air borne contact dermatitis is the most common pattern [5,18,29,36], as found in the present study, 38 (63.33%) out of 60 patients.

The mainstay of treatment for parthenium dermatitis has been with the use of topical and systemic steroids. The use of steroids is associated with several serious and often irreversible side effects [13,14], observed more with daily regimens than pulse therapy regimens [17]. Various immunosuppressive agents are a good alternative to steroids for use in Parthenium dermatitis. Azathioprine is a potent immunosuppressant and its immunosuppressive action results from inhibition of purine synthesis, thus blocking DNA replication in T-cells and Langerhan cells [43] and suppressing cell mediated immune reactions [44]. Azathioprine is converted into its inactive metabolites mainly by Thio Purine Methyl Transferase (TPMT). The absence or deficiency of this enzyme, seen in 0.5% of normal population who are homozygotes for low activity allele may lead to Azathioprine toxicity [45]. So, prior estimation of TPMT enzyme levels is necessary before starting therapy with Azathioprine. The preliminary studies on the use of Azathioprine in air borne contact dermatitis, actinic reticuloid, chronic actinic dermatitis and also in atopic dermatitis have given encouraging results [20,21,22,23,24] and it is inferred that Azathioprine is an effective corticosteroid sparing agent with lesser side effect profile for use in Parthenium dermatitis [24,25,26,27,29,30,46]. The therapeutic response to Azathioprine usually becomes appreciable after few weeks [29,47], in contrast to earlier and

rapid response in the present study.

In the Azathioprine group of patients, the mean CSS at 4, 8 and 12 weeks decreased respectively to values of 51.7, 39 and 22.3 from the mean value of 66 at 0 week, with statistically significant percentage decline in the mean of 47.78 (t 3.97 p 0.0002 S), 90 (t 7.15 p 0.0001 S) and 145.55 (t 12.03 p 0.0001 S) respectively. Such high efficacy of Azathioprine is consistent with other studies [31,27,29,46]. Pulse therapy of steroids, where supra pharmacological doses of steroids are given over a short period of time, has also promised faster response and stronger efficacy with decreased major side effect profile than the use of long term daily regimens of steroid therapy [17]. Pulse therapy may be administered either by intravenous route or orally, called oral mini pulse therapy. Oral mini pulse of steroids has been used effectively in many dermatological conditions like alopecia areata [48,49,50], connective tissue diseases [17], lichen planus [18,22,27], pemphigus vulgaris [53], vitiligo [54] and is also promising for Parthenium dermatitis.

In the present study, in the Prednisolone group of patients, the mean CSS at 4, 8 and 12 weeks decreased from 68.3 at 0 week to mean CSS values of 63, 52.3 and 43.3 respectively, with percentage decline of 17.78 (t 1.82 p 0.0735 NS), 53.3 (t 5.23 p 0.0001 S) and 83.33 (t 6.21 p 0.0001 S) respectively. Thus patients on oral mini pulse of Prednisolone also showed significant response, though the response was statistically much more significant in the Azathioprine group than that in the Prednisolone group at each follow up (t 3.21 p 0.0022 S, t 3.50 p 0.0009 S, t 4.67 p 0.0001 HS) respectively at 4, 8 and 12 weeks, as found in previous studies [30].

Total therapy in the present study was given for a period of 12 weeks, in contrast to previous studies where treatment was given for a longer duration.

In the present study, it was found that there was a progressive decrease in the mean CSS with Azathioprine at each successive follow up (table 6), consistent with previous studies [27,29,31]. Thus, the longer the therapy is given, the better the efficacy, with progressive decrease in severity score. Oral mini pulse with Prednisolone also showed increasingly good response at each follow up. Though there was excellent response to pulse therapy with both the drugs, but relapse rates were higher after stopping the treatment at 12 weeks and this was detected in those patients who were followed up for a longer period after stopping the treatment at 12 weeks.

Long-term use of Azathioprine is associated with various side effects like nausea, vomiting, abdominal pain, fever, hepatitis, transient rise in liver enzymes, bone marrow suppression, renal toxicity, diffuse alopecia, various infections, acneiform eruptions, oral ulcers, pigmentation of nails, various premalignant and malignant neoplasms and rarely shock [34,43,55,56,57,58,59,60,61]. Side effects are likely to increase in patients with deficient or absent Thiopurine Methyl Transferase (TPMT) enzyme

levels. In the present study, prior estimation of TPMT levels was not done due to lack of facilities. We detected few minor side effects with Azathioprine weekly pulse (table 7), consistent with previous studies [29,34]. Studies have shown decreased side effects of oral mini pulse therapy of steroids than the daily regimens [17], consistent with few side effects in the present study (table 7).

Thus, Azathioprine is an effective and relatively safe alternative to systemic steroids in the treatment of Parthenium dermatitis and use of weekly pulse therapy can further increase the compliance and safety and reduce the cost of therapy. Patients on Azathioprine should be regularly monitored to detect serious adverse effects at an earliest, particularly after prolonged use of the drug. Estimation of Thiopurine Methyl Transferase (TPMT) enzyme levels should be done before the start of treatment, wherever such facilities exist. Oral mini pulse therapy with steroids can also be used as an effective alternative to daily systemic steroids, with decreased side effects than the later. There were few lacunae in the present study which need to be addressed in subsequent studies, like less number of patients in the two study groups, less duration of treatment and short follow up of 12 weeks only.

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