

Azathioprine pulse therapy in the treatment of psoriasis

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Abstract *Objective* To document the efficacy and safety of azathioprine pulse therapy in the treatment of psoria

Patients and methods Thirty five patients (group A) were given azathioprine pulse therapy (APT) which consisted of azathioprine 500 mg orally on 3 consecutive days and repeated every month. In between low dose azathioprine (100mg) daily was given. The entire treatment was divided into four phases. In phase I, APT was continued till clearance of all the lesions. In phase II (phase of remission), APT was given for another 9 months. In phase III, if there was no recurrence, high dose azathioprine was stopped and patient continued only daily low dose (100mg) azathioprine for another 9 months. In phase IV low dose azathioprine was also stopped and patients were followed up for any relapse. Another 35 patients (group B) were given methotrexate 15mg weekly orally along with coal tar ointment till complete clearances of the lesions.

Results 30 out of 35 (85.7%) patients in group A are in clinical remission without any treatment with 5 patients lost to follow-up. 30 patients who are in phase IV, 21 are in continuous remission for more than 3 years, 6 for 1-3years while 3 for less than 1 year after all the treatment was stopped. In group B, all patients relapsed after remission period of 91.78 ± 14.19 days.

Conclusion Thus azathioprine` pulse therapy has shown promising result with no recurrence of lesions for 40.14 ± 22.56 months.

Key words

Azathioprine, azathioprine pulse therapy, APT, psoriasis, methotrexate.

Introduction

Various therapies to treat psoriasis¹⁻⁵ clear the lesions partially or completely but are not able to prevent relapse or produce long-term remission.⁶ Methotrexate (MTX) is very commonly used in under developed countries to treat psoriasis with or without coal tar²; a weekly oral dose is frequently used. Maximum remission period reported with any therapy is up to 1 year.⁶

Azathioprine has been used extensively⁷⁻¹¹ in the treatment of psoriasis with variable results, the dose being 2-5 mg/kg body weight (120-300mg)/day for 2-24 weeks. Majority of the patients relapse in 1-6 months after stoppage of azathioprine. Azathioprine has been found safe in prolonged use in pulse therapy form (800mg daily on 3 consecutive days every month and 200 mg daily in between the high dose for 12-24 month) in the treatment of ulcerative colitis, Wegener's granulomatosis, lupus nephritis, and Crohn's disease.¹²⁻¹⁵

Previously we have shown that immune mediated disease can be treated successfully by using intermittent high dose immunosuppressive

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agents (pulse therapy).¹⁶⁻¹⁸ In 2003, the author started using an arbitrarily designed regimen of azathioprine which uses an intermittent high dose (IHD) azathioprine (500 mg on 3 consecutive days, repeated every month) in combination with continuous low dose (CLD) azathioprine (100mg orally) orally given in between IHD. In difficult to treat cases like pustular psoriasis, erythrodermic psoriasis and extensive plaque psoriasis, methotrexate and topical coal tar was also used initially.

In 2008,¹⁹ we observed that a significant proportion of our patients initially treated with this regimen were in remission even after they stopped receiving treatment. The disease free duration in some cases was more than 3 years. We have subsequently treated more patients with this regimen, the results of which are reported here.

Patients and methods

A total of 70 (M=32, F=38) consecutive psoriasis patients aged between 25-72 years were included in this open-label, nonblinded study. Duration of study was 7 years. A detailed history and clinical examination was undertaken before taking the patients for study. Diagnosis of psoriasis was made clinically and in few patients confirmed by histopathology. Before starting the treatment informed written consent was taken from all the patients and details of the treatment and its purpose was explained to them. Institution Ethics Committee approval was obtained from Prayatna before starting treatment. Psoriasis Area Severity Index (PASI) and Body Surface Area (BSA) were charted in each patient on a specially designed pro forma. Pregnant women, patients on active systemic treatment for the past 8 weeks, a known history of MTX intolerance, alcohol abuse and children were excluded from

the study. All the topical treatment was stopped 4 weeks before entering into study.

Patients were allocated consecutively to group A (azathioprine pulse therapy [APT]) and group B (MTX + coal tar), all the odd number patients who came to outpatient department were put on APT therapy whereas all the even number patients were given MTX with coal tar.

Blood tests were done for hemoglobin, total and differential leukocyte count, platelet count, erythrocyte sedimentation rate (ESR), blood urea, creatinine, SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), and alkaline phosphatase. These investigations were done before starting treatment in all the patients, and every month before giving pulse.

35 out of 70 (50%) patients were given azathioprine pulse therapy (APT) which consisted of giving azathioprine 500 mg orally on three consecutive days after dinner repeated every month on the same date. In between pulse, the patient received 100 mg azathioprine orally daily after dinner. The regimen was divided into four phases. In phase 1, APT was continued till the lesions cleared completely and stopped recurring. In phase II (phase of remission), APT was continued for another 9 months. In phase III if there was no recurrence of lesions, high dose azathioprine (azathioprine 500 mg orally on three consecutive days) was stopped and patients were given only daily azathioprine 100mg for another 9 months. In phase IV if there was no recurrence of psoriasis, daily azathioprine was stopped and patients were followed-up for any relapse till the end of the study. In difficult to treat cases like pustular psoriasis, erythrodermic psoriasis and extensive plaque psoriasis, MTX and topical coal tar was also used initially.

In another 35 patients, MTX 15 mg/week and topical coal tar ointment was given till complete clearance of all lesions.

Subsequently all the patients were followed up for any relapse till the end of the study

Results

In 35 patients of APT group, 23 patients had plaque type, 1 pustular, 3 erythrodermic, 2 plantar and 6 palmoplantar psoriasis. Duration of the disease before starting treatment varied from 2 to 50 years, the age range of the patients was 25-72 years. An average PASI score was 19.60 ± 17.64 (1.96-37.24) and BSA was 21.62 ± 15.22 (6.40-36.84). An average 4.08 (1-25) pulses of azathioprine were needed in phase I to clear the lesion.

Thirty out of 35 (85.71%) patients in group A completed APT and entered into phase IV of the treatment i.e. there were no lesions and patients were not taking any treatment. Majority are in remission for an average of 40.14 ± 22.56 (17.58-62.70) months (**Table 1**). 5 patients could not

Table 1 Duration of remission in group A, treated with azathioprine pulse therapy (n=30).

Duration (years)	N
3-6	21
1-3	6
<1	3

Table 2 Side effects of azathioprine pulse therapy.

Side effects	Phase I	Phase II	Phase III	Phase IV
Liver function tests (SGOT, SGPT, alkaline phosphatase)	8	5	1	1
Leucopenia	3			
Nausea and vomiting	5	2		
Weakness	4			
Giddiness	2			
Restlessness	2			
Nausea	1			
Uneasiness	1			
Loss of appetite	1			
Hair loss	1			

complete the treatment and were lost to follow-up.

In group B, 32 patients had plaque type and 3 erythrodermic psoriasis. Duration of the disease was 2 to 6 years. The age of the patients varied from 25 to 60 years. Average PASI was 9.93 ± 2.86 (7.07-12.79) and BSA 10.59 ± 3.04 (7.55-13.63). All the patients needed topical coal tar ointment along with MTX 15mg every week. All the patients developed new lesions after being in remission period of 91.78 ± 14.19 (77.59-105.97) days.

On the basis of available data, in the study period, mean duration of remission in APT group is 40.14 ± 22.56 (17.58--62.70) months, whereas in MTX and coal tar group is 91.78 ± 14.19 (77.59-105.97) days, which is statistically significant ($P < 0.05$).

Side effects

Major side effects encountered in APT group are given in **Table 2**. Most of these side effects were seen in phase I and in patients in whom methotrexate was also used. These reverted back to normal 3 weeks after stopping azathioprine which was resumed again without any abnormalities.

Transient leucopenia was seen in 3 patients who returned to normal in 3-4 weeks after stopping azathioprine treatment.

In MTX group, 5 patients showed raised liver function test after 4-5 pulses which returned to normal in 3-4 weeks after stopping MTX.

Relapse

Recurrence of psoriasis lesions after complete remission in phase IV was seen in 6 out of 30 patients in APT group after being in remission for 7 to 23 months. 2 patients were again put on APT. Both completed the APT and are in phase IV (14 months). Another 2 patients after 20 and 10.5 months in remission develop few lesions on their elbows and knees and are keeping static since then with topical coal tar on their own. Another 2 patients developed relapse 9.5 and 7 months in remission and lost to follow-up subsequently. All the patients who relapsed got only 0.1-0.2 % of their original skin lesions.

All patients in MTX group developed relapse after 91.78 ± 14.19 (77.59-105.97) days of remission.

Discussion

Goal of psoriasis treatment should be initially to rapidly control the disease process, decrease percentage of involved body surface area, achieve and maintain remission for long-term, minimum adverse side effects and improvement of patient's quality of life. Thus the therapy is expected to shift from control of lesions to long-term maintenance of remission. Thus the need for more specific systemic therapy, which targets the T lymphocyte with the promise of long-term remissions and less organ toxicities, is needed.

Azathioprine is known to act on cell-mediated, as well as, humoral immune functions, especially more on T lymphocytes. Thus it suppresses activated T lymphocytes which in turn stops the proliferation of keratinocytes responsible for development of psoriasis.²⁰⁻²²

Azathioprine has been extensively studied systemically for the treatment of psoriasis. Higher doses in the form of pulse (800mg daily for 3 consecutive days repeated after a month and 200 mg daily in between for 12 to 24 months)¹²⁻¹⁵ have shown no significant side effects. Side effects seen were only very transient and returned to normal in 3-4 weeks without any recurrence when azathioprine was resumed.

Remission period produced by MTX and various therapies varies from 6 weeks to 1 year.⁶ In the present study, MTX with coal tar was able to produce maximum remission period of 105.97 days only. Thus the role of MTX and coal tar in this study seems only to clear the lesions fast and shorten the phase I of the study.

In a recent review in 2008 Halverstam and Lebwohl²³ also reported usefulness of azathioprine in psoriasis.

Thus all the workers have reported beneficial results with azathioprine but most of them invariably reported relapse of psoriasis after stoppage of azathioprine within 1-6 months.⁸⁻¹¹

With preliminary data on 30 patients of phase IV of the present study, it seems with passage of time more and more patients will enter into phase IV.

Apart from prolonged remission; the side effects following APT appear to be significantly mild and reversible. The total dose of azathioprine in

the present study is 4.2gm per month which is lesser than 6-9gm /monthly (200-300 daily) used by earlier worker.²⁴

The use of high dose of azathioprine every month with low dose azathioprine in between (APT) was aimed to produce the results we achieved previously with dexamethasone-cyclophosphamide pulse therapy (DCP) regimen in pemphigus¹⁶⁻¹⁸ and collagen vascular diseases with which we were able to obtain almost complete clinical remission without any maintenance treatment.

Our choice of drugs, their dosage and duration of different phases of treatment, especially phase II and III, were arbitrary. There is ample scope for further modification to establish the most appropriate regimen

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