ORIGINAL ARTICLE

EFFICACY OF METHOTREXATE VERSUS AZATHIOPRINE IN THE TREATMENT OF CHRONIC ACTINIC DERMATITIS: A RANDOMIZED CONTROL TRIAL

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Background: Azathioprine is first line immunosuppressive agent in treatment of chronic actinic dermatitis. The role of methotrexate has been effective in different dermatosis and it seems reasonable to use it in the treatment of chronic actinic dermatitis. **Aims:** We sought to compare the efficacy of methotrexate versus azathioprine in treatment of chronic actinic dermatitis. **Methods:** Patients with chronic actinic dermatitis were randomized to receive methotrexate in group A and azathioprine in group B. The response to treatment in terms of percentage PASI reduction and side effects of medications were assessed 12 weeks follow-up. **Results**: In group A, the percentage PASI reduction was <25% in 2 (1.19%) patients, 25–49% in 47 (27.9%) patients, 50–74% was achieved by 35 (20.8%) patients while in group B, the percentage PASI reduction of 25% was achieved by 2 (1.19%) patients, 25–49% in 45 (26.7%) patients, 50–74% in 37 (22.0%) patients. More than or equal to 75 percentage PASI reduction was not achieved by any patient in the study. Both drugs were found efficacious in treatment of CAD. A total of 23 (27.38%) patients in group A and 22 (26.19%) patients in group B showed derangement in laboratory investigations during 12 weeks treatment. The limitation of study was inability to do photo-patch test, so patients were diagnosed clinically and biopsy was done in clinically challenging cases. **Conclusion:** This study shows that methotrexate is equally effective as azathioprine in the treatment of chronic actinic dermatitis with its added benefits of being cost effective and better safety profile.

Keywords: Methotrexate; Azathioprine; Dermatitis

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INTRODUCTION

Chronic actinic dermatitis (CAD) is an immunologically mediated chronic persistent or recurrent dermatitis that predominantly affects the photo exposed areas, along with objective evidence of photosensitivity.[1] The photosensitivity is primarily to broadband, mostly ultraviolet B wavelengths and less frequently to ultraviolet A (UVA) and visible light. The term CAD comprises a spectrum of conditions including persistent light reactivity, photosensitive eczema, actinic reticuloid and photosensitivity dermatitis/actinic reticuloid.[2]

Chronic actinic dermatitis is clinically characterized by persistent eczematous pruritic eruption notably on sun-exposed areas with development of lichenified papules and plaques. Chronic actinic dermatitis has a worldwide incidence although more prevalent in temperate climates and with increased number of cases in summer time as the sun exposure is maximum.[3] CAD typically occurs in elderly, albeit onset in younger age has occurred. There is a significant male preponderance, and it can affect any skin type.[4] The mean age of onset ranges between 60–62.7 years. CAD follows a chronic relapsing and remitting course, significantly impairing the quality of life.[5]

Management of CAD includes strict photoprotection and topical agents, including corticosteroids, emollients and calcineurin inhibitors. If these measures are inadequate alone, systemic steroids can be given. Topical/systemic steroids are the hallmark of the treatment although their prolong use results in adverse effects. So immunosuppressants may be considered as steroid sparing. Primarily immunosuppressant's including azathioprine, cyclosporine and mycophenolate mofetil have been used to treat CAD with variable results.[6] Therefore an effective and cheap alternative is still lacking.

Methotrexate has been used effectively to treat cases of chronic actinic dermatitis although the number of studies is very scarce. Methotrexate is folic acid analogue, inhibits purine and pyrimidine synthesis.[7] It is cheap and a good safety profile and easy to monitor for side effects and no special preliminary TPMT levels are required as with azathioprine. It has a rapid onset of action providing rapid relief of symptoms. In a pilot study out of total

thirty patients, Six patients (20%) showed complete recovery, 13 (43%) showed 50-75% recovery, 7 (23%) showed 25–49% recovery while rest showed no improvement.[8] Also the results with azathioprine were very encouraging according to one study, out of fifteen patients completing 9 months of treatment, six (40%) showed >90% reduction in PASI score, and 7 (46.6%) showed >50% reduction while 1 (1.6%) showed <50% improvement.[9]

The rationale of this study is to compare the efficacy of methotrexate versus azathioprine in the treatment of chronic actinic dermatitis as no head-to-head trials have been conducted between the aforementioned medications regarding their efficacy. This study will also provide with the latest and updated information regarding the effectiveness of methotrexate in chronic actinic dermatitis for long term therapy and recommendations will be given so that the patients are treated effectively with a cheaper and easy to administer drug with vast experience of its use in another dermatosis.

MATERIAL AND METHODS

A randomized controlled trial was conducted in Department of Dermatology in tertiary care hospital from February 2019 to October 2020 over period of 20 months after ethical approval from ethical review board(74/LRH). Data was collected from 168 patients by non-probability convenience sampling technique from 168 patients. The sample size calculation was done by WHO sample size calculation formula.[10]

Patients of either sex, any age, clinically suggestive of chronic actinic dermatitis presenting to both outpatient and inpatient departments were enrolled in the study. Patients on any treatment that is likely to affect the course of disease, on immunosuppressant, with haematological, hepatic or renal impairment were excluded from the study. Most of the patients were diagnosed clinically. Skin biopsy was done to confirm the diagnosis in patients where diagnosis was clinically not clear. Written informed consent was taken from all patients. Laboratory investigations like complete blood count, hepatic and renal function tests, urinalysis, virology, chest X ray and ultrasound abdomen were done before starting the therapy. Female patients underwent pregnancy test prior to commencement of methotrexate and informed consent was taken regarding avoidance of pregnancy for the duration of therapy and six months thereafter. Clinical severity of disease was assessed by using Psoriasis Area Severity Index (PASI) scoring method.[11]

Erythema, scaling and skin thickness was scored as done for psoriasis. The area of distribution of skin lesions was calculated in the same manner as in PASI skin scoring system. This score was used in pilot study by author while evaluating the efficacy of azathioprine in chronic actinic dermatitis.[9] Moreover we are more familiar with PASI as it is used frequently in psoriasis. Patients in group A were given methotrexate at the dose of 10 mg/week. Patients in group B were given azathioprine 2.5—4 mg/kg/day. PASI score was calculated at presentation. Laboratory investigations of Complete Blood Count, liver and renal function tests were repeated at 4-, 8- and 12-weeks follow-up visit as per protocol. PASI score and percentage reduction of PASI was also calculated at each follow up visit. The treatment was considered efficacious in patients with percentage PASI reduction of 50 or more at 12 weeks. The findings were recorded in predesigned proforma and analysed. Analysis of results was made using SPSS version 20. Frequencies and percentages were calculated for all the categorical variables like gender, age range, duration of illness, Fitzpatrick skin type, PASI score and percentage PASI reduction. Mean±standard deviation was calculated for continuous variable like age. Chi-square test was utilized for the categorical variables. Test of significance was two-tailed and p-value of <0.05 was considered significant. Moreover, for standardization, findings were compared with published data.

RESULTS

The total of 168 patients were included in the study. The mean age of patients was 53.21 (±4.368) years, with age range from 39 to 63 years in the study (Table-1).

Maximum 121 (87.68%) number of patients belonged to the age group of 50–59 years, with least number of patients, only 1 (0.5%) belonged to the age group of less than 40 years (Table-2). There were 126(75%) male and 42 (25%) female patients in the study (Table-2). Based on Fitzpatrick skin types, 4 (2.3%) patients in the study had skin type II, 52 (30.9%) patients had skin type III, 101(60.1%) patients had skin type IV and only 11 (6.5%) patients had skin type V (Table-2).

In the study, duration of disease was less than 1 year in 27 (16.1%) patients, it was 1–2 years in 80 (47.6%) patients, 2–3 years in 48 (28.6%) patients and more than 3 years in 13 (7.7%) patients (Table-3).

The treatment was considered efficacious in patients with percentage PASI reduction of 50 or more at 12 weeks follow-up. The treatment was found efficacious in 35 (20.8%) patients in group A on methotrexate (Figure-1A, 1B), while the efficacy was found in 37 (22%) patients in group B who were on azathioprine for chronic actinic dermatitis (Figure-2A, 2B) (Table-4). On stratifying efficacy of

treatment in both groups, there was no significant difference in treatment efficacy between two groups and p-value was more than 0.05 (0.757) (Table-4).

The laboratory investigations done at 4,8 and 12 weeks, Complete blood count was found abnormal (low Hb) in 7 (4.16%) patients in group A and 8 (4.7%) patients in group B. There were 10 (5.9%) patients who showed deranged liver function tests (raised ALT) at end of 8 weeks of treatment in group A and 9 (5.3%) patients showed deranged LFTs in group B. There were 6 (3.5%) patients in group A and 5 (2.9%) patients in group B with abnormal renal function tests (raised creatinine) at the end of 8 weeks treatment on follow-up (Table-5). But hematological, renal and hepatic function derangements were transient and not severe enough to stop the treatment. The percentage PASI reduction was <25% in 4 (2.4%) patients, 2 (1.19%) in each group. There was 25–49 percentage PASI reduction in 47 (27.9%) patients in group A and in 45 (26.7%) patients in group B. Percentage PASI reduction of 50–74 was achieved by 35 (20.8%) patients in group A and by 37 (22.0%) patients in group B. More than or equal to 75 percentage PASI reduction was not achieved by any patient in the study (Table-6).

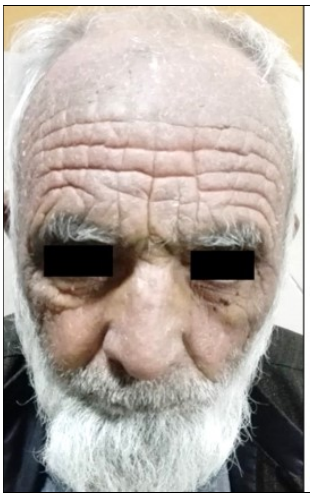

Figure-1 (A)
Before starting treatment

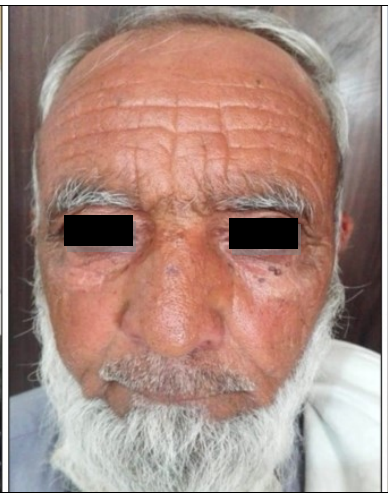

Figure-1 (B)
At 4 weeks follow-up

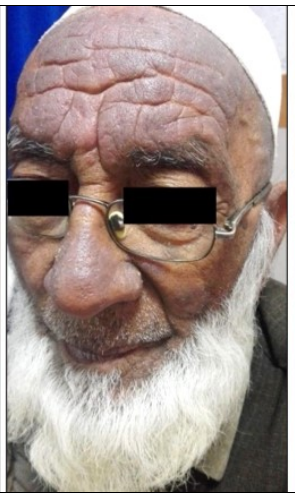

Figure-2 (A)
Before treatment

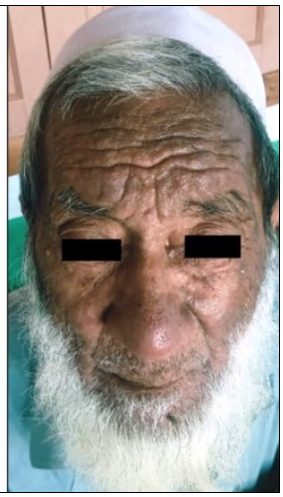

Figure-2 (B)
After 4 weeks

Table-1: Mean age with standard deviation of patients with chronic actinic dermatitis (n=168)

Age (years)	Minimum	Maximum	Mean	Standard deviation
	39	63	53.21	4.368

Table-2: Frequency and percentages of demographic characteristics of patients with chronic actinic dermatitis (n=168)

Demographic characteristics		Frequency	Percentage
Age range (years)	<40 years	1	0.5
	40–49 years	38	22.6
	50–59 years	121	87.68
	>59 years	8	4.7
Gender	Male	126	75
	Female	42	25
Fitzpatrick skin type	I	0	0.0
	II	4	2.3
	III	52	30.9
	IV	101	60.1
	V	11	6.5
	VI	0	0.0

Table-3: Frequency and percentage of duration of disease in patients with chronic actinic dermatitis (n=168)

Duration of disease	Frequency	Percentage
< 1 year	27	16.1
1–2 years	80	47.6
2–3 years	48	28.6
>3 years	13	7.7

Table-4: Efficacy of treatment in both groups with correlation of treatment efficacy among two groups in patients with chronic actinic dermatitis (n=168)

Efficacy (PASI reduction of ≥ 50)	Group A Methotrexate (%age)	Group B Azathioprine (%age)	*p*-value
Yes	35 (20.8)	37 (22.0)	0.757
No	49 (29.1)	47 (27.9)	

Table-5: Derangement of laboratory investigations in patients with chronic actinic dermatitis (n=168)

Derangement of laboratory investigation	Group A	Group B
CBC	7 (4.16%)	8 (4.7%)
LFTs	10 (5.9%)	9 (5.3%)
RFTs	6 (3.5%)	5 (2.9%)
Total	23 (27.38%)	22 (26.19%)

Table-6: Percentage PASI reduction at 12 weeks in patients with chronic actinic dermatitis (n=168)

Percentage PASI reduction (At 12 weeks follow-up)	Group A (%age)	Group B (%age)	Total (%age)
<25%	2 (1.19)	2 (1.19)	4 (2.4)
25–49%	47 (27.9)	45 (26.7)	92 (54.7)
50–74%	35 (20.8)	37 (22.0)	72 (42.8)
≥ 75%	0	0	0 (0.0)
100%	0	0	0 (0.0)

DISCUSSION

Chronic actinic dermatitis usually needs immunosuppressants for long term treatment.[13] Azathioprine is considered both safe and efficacious in the treatment of chronic actinic dermatitis.[14] Methotrexate can be used as cost effective alternative for the treatment of chronic actinic dermatitis.[8]

The patients enrolled in this study had age range of 39–63 years with mean age of 53.21 years. Lim *et al* study on chronic actinic dermatitis showed age range of patients included in the study from 27–81 with mean age of 62 years.[15] Yap *et al* also showed that the patients with chronic actinic dermatitis enrolled in his study had age range from 26–85 years with mean age of 62 years.[16] Gender wise distribution of patients in the present study showed that there were 75% male and 25% female patients with male to female ratio on 3:1. These finding were consistent with the finding in Dave *et al* in which 78% patients diagnosed with CAD were men.[17] Artz *et al* stated that the male to female ratio of patients with CAD was in the range from 1.5–2.6:1 which was almost consistent with our study.[18]

Maximum patients in this study had Fitzpatrick skin type III and IV. In Yap *et al*, patients showed skin type of VI and V, showing that the condition of chronic actinic dermatitis is not uncommon in dark skinned population as well.[16] Also in North American patients, trend of two classes of patients were reported with chronic actinic dermatitis, patients with skin type IV and VI were mostly young women and patients with skin types I and II were mostly old men.[19]

Systemic steroids side effects necessitate the use of immunosuppressive agents for long term remission of disease. Dawe *et al* stated that azathioprine is the first choice for long term immunosuppressing effects in patients with chronic actinic dermatitis.[17] This study showed that among 84 patients on azathioprine, 5.3% patients showed deranged liver function tests and 4.7% showed abnormal haematological profile. Contrary to that, in Naqqash *et al* among 18 patients on azathioprine for chronic actinic dermatitis, 11.1% patients showed deranged LFTs which was higher than this study, while no patient had any haematological abnormality on follow up visit. Among 84 patients on methotrexate, 5.9% patients showed abnormal liver function tests and 4.16% patients showed abnormal haematological profile on follow-up visit. In a pilot study to see response of methotrexate in patients with chronic actinic dermatitis, only 3.3% patients showed abnormal LFTs and no haematological abnormality was found on follow-up visit.[8,9] This difference in laboratory findings may be due to smaller sample size in Naqqash *et al* and Paracha *et al* and short follow-up duration.

Scerri *et al* also employed azathioprine in treatment of patients with non-bullous inflammatory dermatosis including chronic actinic dermatitis, showing good or excellent response to treatment in 75% of the cases.[20] In the study by Naqqash et al, the patients with chronic actinic dermatitis on azathioprine alone showed PASI reduction of <50% in 1.6% cases and PASI reduction of >50% in 86.6% cases.[9] In this study, among 84 patients, 52 patients showed PASI reduction of less than or equal to 50%, while only 32 patients showed PASI reduction of more than 50%.

A study by Agarwal *et al* on patients with difficult to treat dermatosis including chronic actinic dermatitis showed that the combination of azathioprine and methotrexate was effective.[6]

Another pilot study conducted on effects of methotrexate in patients with chronic actinic dermatitis showed more that 50% improvement of skin lesions in 63% patients.[8]

Limitations: The limitations of the study include the inability to do the photo-patch test without which the diagnosis of patients with chronic actinic dermatitis was difficult with conviction. The clinical features were preferably used to offer the significant clue to the diagnosis, and skin biopsy was performed in those cases where clinical diagnosis was not clear. All patients were given 10mg of methotrexate as this dosage has been used to treat other inflammatory and difficult to treat dermatosis.

CONCLUSION

To conclude, both azathioprine and methotrexate are effective for their immunosuppressive role for the treatment of chronic actinic dermatitis.

AUTHORS' CONTRIBUTION

MMP, AQK, HZ: Idea, concept, study design and methodology, data collection. FS: Data analysis. SMN: Final approval.

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