Research Article

Efficacy of Methotrexate versus Azathioprine and Their Steroid Sparing Role in the Treatment of Chronic Actinic Dermatitis: A Randomized Control Trial

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Abstract

Background

Azathioprine is first line immunosuppressive agent in treatment of chronic actinic dermatitis. Steroid sparing role of methotrexate has been effective in different dermatosis and it seems reasonable to use it in the treatment of chronic actinic dermatitis.

Methods

Patients with chronic actinic dermatitis were randomized to receive methotrexate and systemic steroids in group A and azathioprine and systemic steroids in group B. Tapering of systemic steroids was started at 4 weeks. The response to treatment, exacerbation of disease and side effects of medications were assessed at 4, 8 and 16 weeks follow-up by calculating percentage PASI reduction.

Result

Among 168 patients, 35(38.09%) patients in group A and 37(44%) patients in group B showed efficacy to the treatment at 4 weeks. On follow-up at 16 weeks, exacerbation of skin lesions was observed in total of 14 (19.44%) patients on tapering of systemic steroids among 72 (42.9%) patients previously showing efficacy to the combination therapy, with 9(24.71%) patients in group A and 5(13.51%) patients in group B.

Conclusion

This study shows that methotrexate and azathioprine are effective in the treatment of chronic actinic dermatitis in the presence of systemic steroids but there was exacerbation of skin lesions in few patients on tapering of steroids. Disease exacerbation was significantly more in patients on methotrexate as compared to patients on azathioprine used as steroid sparing agent.

Keywords: azathioprine, methotrexate, photosensitivity, photosensitive disorders, sunlight

1. 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].

CAD 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 Youngers has occurred. There is a significant male preponderance, and it can affect any skin type [4]. The mean age of onset ranges between 60 to 62.7 years. CAD follows a chronic relapsing and remitting course, significantly impairing the quality of life [5].

Management of CAD includes strict photo protection 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 immune suppressants 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, *and* inhibits purine and pyrimidine synthesis [7]. It is cheap, has 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, as 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 as steroid sparing agent in the treatment chronic actinic dermatitis as no head-to-head trials have been conducted between the aforementioned medications regarding their efficacy

and methotrexate is never used for treatment of chronic actinic dermatitis as a steroid sparing agent. 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 other dermatosis.

2. Materials and Methods

This randomized controlled trial was conducted in Department of Dermatology, Lady Reading Hospital, Peshawar from February 2019 to October 2020 over period of 20 months. Data was collected 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.

A criterion for diagnosis of chronic actinic dermatitis was pruritic, recurrent or persistent eczematous eruption predominantly affecting photo-exposed sites and worse in summers. Skin biopsy was done to confirm the diagnosis in patients where diagnosis was clinically not clear. Histological features used to establish a diagnosis of chronic actinic dermatitis were epidermal hyperplasia, a deep, dermal, inflammatory infiltrate and increased numbers of perivascular histiocytes and granulomatous changes. Patients on any treatment that is likely to affect the course of disease, on immunosuppressant, hematological, hepatic or renal impairment were excluded from the study. 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 [14].

Erythema, scaling and skin thickness was scored as done for psoriasis. The area of distribution of skin lesions was calculated the same as in PASI skin scoring system [14]. Patients in group A were given systemic prednisolone at a dose of 0.5-1mg/kg/day and methotrexate at a dose of 10mg/week. Patients in group B were given systemic prednisolone at a dose of 0.5-1mg/kg/day and azathioprine at a dose of 2.5-4mg/kg/day. Maximum dose of systemic prednisolone was 60mg per day. PASI score was calculated at presentation. Systemic prednisolone tapering was started at 4 weeks according to protocol over 6 weeks. Follow-up visits were planned for each patient in both groups at 4, 8 and 16 weeks of starting the treatment and laboratory investigations of CBC, liver and renal function tests were repeated at each visit. PASI score and percentage reduction of PASI was also calculated at each visit. The treatment was considered efficacious in patients with percentage PASI reduction of 50 or more at 4 weeks. The findings were recorded in predesigned proforma and analyzed. 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.

3. Result

The totals 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.

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 1). There were 126(75%) male and 42(25%) female patients in the study. 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 1).

Table 1: 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%

The percentage PASI reduction was calculated at 4 weeks after starting the treatment and 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 2).

Table 2: Percentage PASI reduction in both groups in patients with chronic actinic dermatitis (n=168)

Percentage PASI reduction	**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%)

The treatment was considered efficacious in patients with percentage PASI reduction of 50 or more at 4 weeks follow-up. The treatment was found efficacious in 35 (38.09%) patients in group A on methotrexate and systemic steroids therapy (Figure 1A, 1B), while the efficacy was found in 37 (44.0%) patients in group B who were on azathioprine and systemic steroids treatment for chronic actinic dermatitis (Figure 2A, 2B) (Table 3). 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 3).

Table 3: 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 with steroids (n=84) (%age)**	**Group B Azathioprine with steroids (n=84) (%age)**	**Total (n=168) (%age)**	**P value**
Yes	35 (38.09%)	37 (44.0%)	72 (42.9%)	0.757
No	49 (58.33%)	47 (55.95%)	96 (57.1%)	

On follow up at 4, 8 and 16 weeks, complete blood count was found abnormal (decreased cell counts as compared to baseline) 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 but less than 2 times upper limit of normal) in group A and 9(5.3%) patients showed deranged liver function tests 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 (mildly raised serum creatinine) during treatment on follow-up visits (Table 4). But hematological, renal and hepatic function derangements were transient and not severe enough to stop the treatment.

Table 4: Derangement of laboratory investigations at 4, 8 and 16 weeks follow up in patients with chronic actinic dermatitis

Derangement of laboratory investigation	**Group A**	**Group B**
Complete blood count	7 (4.16%)	8(4.7%)
Liver function tests	10(5.9%)	9(5.3%)
Renal function tests	6(3.5%)	5(2.9%)

Among 72 patients in the study who showed efficacy to the combination treatment of immune suppressants and systemic steroids, the relapse of disease was observed in patients on steroids tapering despite of presence of immune suppressants on follow up at 16 weeks. Relapse was found in total of 14 (19.44%) patients in the study, while there was no exacerbation of disease in 58 (80.55%) patients. In group A, among 35 patients showing efficacy to treatment, 9 (25.71%) patients showed exacerbation of disease (Figure 3A, 3B). There was no disease exacerbation in 26 (74.28%) patients belonging to group A (Table 5). In group B, among 37 patients, 5 (13.51%) patients showed exacerbation of disease on tapering of systemic steroids (Figure 4A, 4B). Disease exacerbation was absent in 32 (86.48%) patients in group B after complete tapering of steroids over 6 weeks (Table 5).

Table 5: Disease exacerbation at 16 weeks on tapering of systemic steroids among patients with chronic actinic dermatitis showing efficacy to therapy at 4 weeks in two groups (n=72)

Groups	**Efficacy in patients (n=72)**	**Disease exacerbation at 16 weeks**		**P value**
		Yes (%age)	**No (%age)**	0.000
Group A	35	9 (25.71%)	26 (74.28%)	
Group B	37	5 (13.51%)	32 (86.48%)	
Total	72	14 (19.44%)	58 (80.55%)	

On stratifying the presence and absence of disease exacerbation among the patients showing efficacy to therapy in both groups, statistically significant difference was found among two groups with p value of 0.000 (<0.05) which means that the disease exacerbation was significantly more in patients on methotrexate as compared to patients on azathioprine used as steroid sparing agent (Table 5).

Among 9 (25.71%) patients showing disease exacerbation in group A, only 1 (2.85%) patient showed exacerbation at steroids tapering dose of 10mg/day, 3 (8.57%) patients showed exacerbation at steroids tapering dose of 20mg/day and 5 (14.28%) patients showed exacerbation at steroids tapering dose of 30 mg/day (Table 6). In group B, total of 5 (13.51%) patients showing disease exacerbation, 3 (8.10%) patients showed exacerbation at steroids tapering dose of 20mg/day while 2 (5.40%) patients showed exacerbation at steroids tapering dose of 30mg/day (Table 7). Maximum number of patients (7 (9.72%)) in the study showed exacerbation at steroids tapering dose of 30mg/day in two groups (Table 6).

Table 6: Steroids doses during tapering of systemic steroids over 6 weeks as per protocol at which patients showed disease exacerbation, showing efficacy to therapy at 4 weeks in two groups (n=72)

Disease exacerbation at 16 weeks in patients showing efficacy to therapy on tapering of systemic steroids at steroids dose (n=72)	**Group A (n=35) (%age)**	**Group B (n=37) (%age)**	**Total (%age)**
At steroid dose of 10mg/day	1 (2.85%)	0	1 (1.38%)

At steroid dose of 20mg/day	3 (8.57%)	3 (8.10%)	6 (8.33%)
At steroid dose of 30mg/day	5 (14.28%)	2 (5.40%)	7 (9.72%)
Total	9 (25.71%)	5 (13.51%)	14 (19.44%)

4. Discussion

The patients enrolled in this study had age range of 39 to 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 to 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 to 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 to 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, 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 and systemic steroids, 5.3% patients showed deranged liver function tests and 4.7% showed abnormal hematological 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 hematological abnormality on follow up visit. Among 84 patients on methotrexate and systemic steroids, 5.9% patients showed abnormal liver function tests and 4.16% patients showed abnormal hematological 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 hematological 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.

Walia et al sowed that azathioprine introduced with other measures including oral prednisolone for treating chronic actinic dermatitis cleared 50% of lesions in 4 weeks with complete remission in 3 months [20]. In this study, PASI reduction of ≥ 50% was achieved in 44% patients on combination of azathioprine and systemic steroids at 4 weeks. Scerri et al also employed azathioprine as steroid sparing agent 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 [21]. 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, despite of being on combination of systemic steroids with azathiorprine, 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 in the presence of systemic steroids was effective [6]. Another pilot study conducted on effects of methotrexate as steroid sparing agents in patients with chronic actinic dermatitis showed more that 50% improvement of skin lesions in 63% patients [8].

This study surprisingly showed that among the patients who showed efficacy to the treatment with systemic steroids and immune suppressants in both groups at 4 weeks, there were patients who showed relapse of the disease with exacerbation of skin lesions when systemic steroids were tapered off. The exacerbation of the disease was found more in a group of patients on methotrexate as immunosuppressive agent and the difference between the two groups was found statistically significant. Among patients who showed efficacy to combination therapy, 25.71% patients in group on methotrexate and 13.51% patients on azathioprine showed exacerbation of disease on tapering of steroids over 6 weeks at 16 weeks follow up visit. Majority of the patients showed exacerbation at tapering steroid dose of 30mg/day. Very few studies have been found where patients have been followed for long term to show steroid sparing role of immune suppressants and exacerbation of disease, if any, after steroids tapering in patients with chronic actinic dermatitis. Walia et al showed that there was exacerbation of disease with reappearance of lesions on face and neck on stopping steroids and tapering of azathioprine to 50mg/day after 3 months [20].

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. However, because of unavailability of photo-patch testing, the clinical features were used to offer the significant clue to the diagnosis, and skin biopsy was performed in those cases where clinical diagnosis was not clear.

To conclude, both azathioprine and methotrexate were effective for their immunosuppressive role when used in combination with systemic steroids for treatment of chronic actinic dermatitis but their steroid sparing role needs to be further evaluated on long term follow up of these patients because significant number of patients in this study showed exacerbation of disease on tapering of steroids.

5. Recommendations

The relapse of chronic actinic dermatitis on tapering of systemic steroids in the presence of azathioprine and methotrexate as steroid sparing agents shows that this phenomenon needs special attention to find whether it is because of steroid tapering or due to continuous exposure to environmental allergen especially parthenium which is abundant in our part of world. We recommend more studies on larger sample size involving multi-center settings to draw

conclusion about their steroid sparing role to draw future recommendations.

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