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A Prospective Study Comparing Therapeutic Efficacy and Safety of Oral Methotrexate and Oral Prednisone in the Treatment of Generalized Cutaneous Lichen Planus

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Abstract: *Lichenplanus is a chronic inflammatory skin disorder.Treatment of generalized cutaneous lichen planus is often difficult and associated with relapse. Recently there have been studies reporting beneficial role of weekly oral methotrexate in lichen planus.Atotal of 30 patients were selected after proper history taking and physical examination and normal laboratory investigation.They were divided into two groups A and B containing 15 patients each. Group A received oral methotrexate 15 or 20 mg weekly up to complete response was achieved or for maximum 20-24 weeks whichever was earlier.Then the dose of methotrexate was tapered by 5mg weekly and stopped.Group B received oral prednisone in dose of 0.5-1 mg/kg daily initially then tapered gradually and given for same duration as in group A. Post treatment follow-up done for 6 months.At the end of treatment 14 out of 15 patients in group A and 11 out of 15 patients in group B showed complete response, chi-square test value was 2.088 and p value≤0. 148.This shows methotrexate has equal efficacy as systemic corticosteroids.There was no relapse in group A but in group B 5 patients had relapse.So,methotrexate has a promising role in lichen planus.*

Keywords: *cutaneous, generalized form, lichen planus, methothrexate, prednisone*

I. Introduction

Lichen planus is a common inflammatory disorder[1] that affects the skin, mucosa, nails and hair follicles[2]. It is usually a self-limiting disease[3] but in some patients its course is relapsing and remitting, which makes its treatment difficult and challenging. Moreover, pruritus is a disabling factor in generalized cutaneous lichen planus. Although the exact aetiopathogenesis is unclear, evidence show T lymphocyte mediated process[4].In an experiment done by Jeffes and colleagues , methotrexate inhibited proliferation of lymphocytes 1000 times greater than that of keratinocytes[5].Further studies have proved that methotrexate also inhibits chemotaxis of activated T cells into tissues[6].Topical and systemic corticosteroids are considered as first line treatment in lichen planus but long duration of their use can have some serious side effects. Recently some studieshave been published showing good response of methotrexate in lichen planus but to our knowledge none of them compared efficacy and safety of oral methotrexate to oral corticosteroid in the treatment of generalized cutaneous lichen planus.So, we did this study to show beneficial role of oral weekly methotrexate in generalized cutaneous lichen planus.

II. Aim and objective

To compare therapeutic efficacy and safety of oral methotrexate to oral prednisone in the treatment of generalized cutaneous lichen planus.

III. Materials And Methods

Our was a prospective study. A total of 32 patients diagnosed clinically as generalized cutaneous lichen planus involving >10% of body surface area wasselected after proper history taking and physical examination. A written informed consent was taken from each patient. Approval from Institute ethics committee was taken. The period of study was 1 year from march 2016 to February 2017. Baseline laboratory investigations done of each patients included complete blood count(CBC), liver function test(LFT), renal function test(RFT), blood sugar(BS), urine pregnancy test, hepatitis B surface antigen(HbsAG), antibodies to hepatitis C virus(HCV) and human immunodeficiency virus(HIV) and chest X-ray. The exclusion criteria included pregnant and lactating

mothers, haemoglobin <9 gm%, total leucocyte count <4000/mm^3, platelet count <1lac/mm^3,liver enzymes >2 times the reference limit, active tuberculosis infection, HbsAG positive status,anti HCV antibodies positive and HIV positive statusOne patient had raised blood sugar and another patient was lost in follow-up visit, so were exempted from the study. Rest 30 patients had normal laboratory investigations were included in the study. We divided them into 2 groups A and B containing 15 patients each. Subsequent laboratory investigations were done in each follow up visit which included CBC,LFT,RFT and blood sugar. Follow-up during treatment was done every 2 weeks in 1st month then every month, treatment duration in both group was 20-24 weeks or till complete response achieved whichever was earlier but not exceeded beyond 20-24 weeksand post treatment follow-up was of 6 months duration in both groups.

Group A received oral methotrexate 15 or 20mg weekly in divided doses. Before starting methotrexate 5mg of test dose was given to all patients and CBC and LFT done after 1 week, all 15-patient had normal CBC and LFT after 1 week of test dose. Methotrexate was given for 20-24 weeks or till complete response achieved whichever was earlier then tapered by 5mg every week and stopped. Folic acid 5mg tablets were advised all days except for the day of taking methotrexate. Group B received oral tablet of prednisone in dose of 0.5-1 mg/kg daily which was gradually tapered according to the response in each follow-up visit and given maximum up to 20-24 weeks. Oral antihistamines and emollients were allowed if required but topical corticosteroid was not allowed.On every follow-up visit, patients were asked to assess themselves and express it in percentages as there are no standard scoring system for cutaneous lichen planus and the assessment was based on relief in pruritus, reduction in appearance of new lesions and reduction in elevation of lesions. The response was graded as 'complete response' for complete disappearance of pruritus and cutaneous lesions, residual pigmentation left was not taken into account. 'Partial response'was considered if >50% reduction in pruritus and cutaneous lesions and 'no response' if <50% reduction in pruritus and cutaneous lesions. Adverse effects were inquired at each follow-up visit from patients of both the groups. Post treatment follow-up was done for 6 months to note any relapse, relapse was defined as appearance of new cutaneous lesions.

IV. Results

Demographic,clinical and treatment data of group A and B given in TABLE 1 and 2 respectively. Group A containing 15 patients (8 males and 7 females),the age varying from 29-55 years, mean 42.46±7.56 years and group B containing 15 patients (9 females and 6 males) presenting with age varying from 18-60 years with mean of 41.20±15.78 years, paired t test at 0.304 and p value ≤0.765 (which was statistically not significant). Similarly,the duration of disease in group A ranges from 2 months to 24 months with mean of 11.66±8.58 months and group B ranges from 3 months to 24 months with mean of 10.46±6.71 months, paired t at 0.526 and p value ≤0.606 (which was statistically not significant).

The previous treatment taken by patients in group A included homeopathy 7 patients (46.66%), topical corticosteroids 4 patients (26.66%), Ayurveda 1 patient (6.66%) and 3 patients (20%) took no treatment. In group B homeopathy 7 patients (46.66%), topical corticosteroids 3 patients (20%), Ayurveda2 patients (13.33%) and 3 patients (20%) took no treatment. This shows strong incline towards homeopathy treatment among Indian patients.

In group A the total cumulative dose of methotrexate required for complete response ranged from 360 - 480 mg and in group B oral prednisolone was given in dose of 0.5-1 mg/kg daily and tapered gradually, calculation of cumulative dose of systemic corticosteroid is not considered significant so not calculated. The duration of treatment with methotrexate ranged from 20-24 weeks, mean of 23.06±1.66 weeks and for group B with oral prednisone ranged from 20-24 weeks mean of 22.93±1.66 weeks, paired t test at 0.222 and p value ≤0.827, which was statistically not significant. There was no adverse drug reaction noticed in both the groups. In group A, none of the patients had relapse during post treatment follow-up of 6 months but in group B ,5 patients (33.33%) had relapse, one patient in 2nd month, two patients in 3rd month and one patient each in 4th and 5thmonthsduring post treatment follow-up of 6 months, for which chi square test at 5.799 and p value ≤0.016, which was statistically significant.

In group A (fig 1) 'complete response' was seen in 14 out of 15 patients (93.33%) and in group B, 11 out of 15(73.33%) patients showed 'complete response',chi square test at 2.088 and p value ≤0.148 which was not statistically significant. 'Partial response' seen in one patient (6.66%) in group A and 3 patients (20%)in group B(fig 2) at the end of 20-24 weeks , chi square test at 1.117 and p value ≤0.290 , which was statistically not significant. This shows that oral methotrexate in dose of 15 or 20 mg/week in generalized cutaneous lichen planus is equally efficacious and safe as oral prednisone in daily dose of 0.5-1 mg/kg given for maximum 24 weeks. Methotrexate was better as none of the patients had relapse while prednisone group had relapse in 5 patients during 6 months of follow-up after treatment.

TABLE-1 DEMOGRAPHIC CLINICAL AND TREATMENT DATA IN GROUP-A

Sno.	Age (Years)	Gender	Duration of disease (Month)	Extracutaneous involvement	Previous treatment	Methotrexate (Mg/Week)	Cumulative dose of Methotrexate (Mg)	Status of Treatment	Duration of Treatment (Weeks)	Relapse
1	40	Female	24		Homeopathy	20	480	Complete	24	
2	42	Male	6		Tropical Corticosteroid	15	360	Complete	24	
3	35	Male	12	Oral	Ayurveda	20	400	Complete	20	
4	29	Female	18		Tropical Corticosteroid	15	360	Complete	24	
5	45	Male	24		Homeopathy	20	480	Complete	24	
6	43	Female	3		-	20	440	Complete	22	
7	42	Male	2		-	15	360	Complete	24	
8	40	Female	6	Oral	Homeopathy	20	400	Complete	20	
9	55	Male	24		Tropical Corticosteroid	20	480	Complete	24	
10	53	Female	6		Homeopathy	15	360	Complete	24	
11	35	Female	8		Homeopathy	15	360	Complete	24	
12	50	Male	6		Tropical Corticosteroid	15	360	Complete	24	
13	39	Female	8		Homeopathy	20	480	Complete	24	
14	53	Male	24	Oral	Homeopathy	20	400	Complete	20	
15	36	Male	4		-	15	360	Complete	24	

TABLE 2-DEMOGRAPHIC CLINICAL AND TREATMENT DATA IN GROUP-B

Sno.	Age (Years)	Gender	Duration of disease (Month)	Extracutaneous involvement	Previous treatment	Initial Oral Prednisone	Status of Treatment	Duration of Treatment (Weeks)	Relapse (Month)
1	60	Male	12		Tropical Corticosteroid	50	Complete	24	
2	18	Female	8		-	40	Complete	24	2nd
3	29	Female	24		Tropical Corticosteroid	50	Complete	24	
4	25	Female	8		Homeopathy	40	Complete	24	
5	60	Male	12		Homeopathy	60	Complete	24	
6	50	Female	4		Ayurveda	50	Complete	20	3rd
7	60	Female	12		Homeopathy	50	Complete	20	
8	22	Male	6		-	50	Complete	22	3rd
9	58	Male	24	Oral	Homeopathy	60	Complete	20	
10	26	Male	6		Tropical Corticosteroid	50	Complete	24	
11	40	Female	3		-	60	Complete	24	4rth
12	28	Female	5		Homeopathy	50	Complete	24	
13	59	Male	18	Oral	Homeopathy	50	Complete	22	
14	45	Female	6		Ayurveda	40	Complete	24	5th
15	38	Female	9		Homeopathy	60	Complete	24	

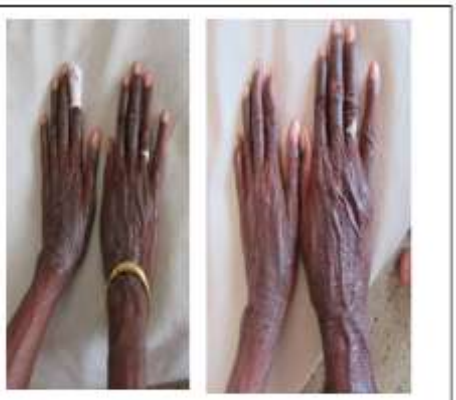

Fig 1: Picture of patient in group A before and after treatment showing complete response

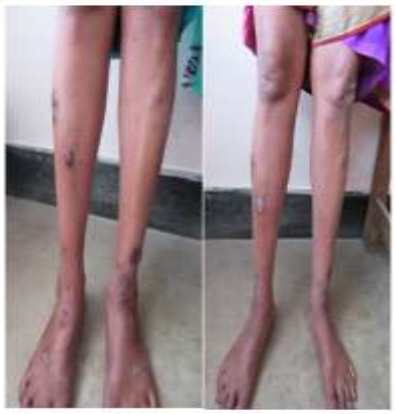

Fig 2: Picture of patient in group B before and after treatment showing partial response

V. Discussion

Lichen planus is an immune mediated disorder[7], T lymphocytes both $CD4^+$and $CD8^+$collects in the dermis while $CD8^+$ T cells are found in epidermis of lesional skin of lichen planus; it has been hypothesized that $CD8^+$ T cells recognize an antigen (unknown till now) associated with major histocompatibility complex (MHC) class I on lesional keratinocytes and destroy them[8,9,10,11,12]. Keratinocyte cytokines may upregulate expression of cell surface adhesion molecules and migration by Tcells [13,14,15]. Itching is a consistent feature of lichen planus and ranges from mild to severe itching but sometimes itching may be completely absent[16]. The residual pigmentation may be intense, especially in dark skinned races[16]. Some papules and plaque persists much longer and develop roughenedsurface with violaceous hue called hypertrophic lichen planus[16]. So, early and aggressive treatment might be helpful to patients. Methotrexate is an anti-metabolite that inhibits synthesis of DNA by competitively inhibiting dihydrofolatereductase enzyme which is involved in conversion of folic acid to reduced folate cofactors, required for 1 carbon unit transfer in DNA synthesis. Thereby it inhibits lymphocytes replication and function[17]. It has anti-inflammatory property due to release of adenosine at sites of inflammation by fibroblasts and endothelial cells[17].

The beneficial role of methotrexate in cutaneous, oral and vulvovaginal lichen planus has been reported in some studies. Jang and Fischer reported in case series of 4 cases treated with low dose methotrexate 2.5-7.5 mg oral weekly in combination with topical corticosteroid or topical tacrolimus for erosive vulvovaginal lichen planus which showed good response[18]. Lundquist *et al* reported low dose methotrexate, efficacious and safe, to use in mucosal lichen planus[19]. Tori *et al* also evaluated low dose weekly methotrexate effect in oral lichen planus and proposed that it should be included in the treatment protocol of oral lichen planus[20]. Turan *et al* in a retrospective study in 11 patients reported good response of 15 or 20 mg weekly dose of methotrexate in mucocutaneous lichen planus within 1^{st} month of treatment[21].

Our study also has findings similar to these studies. In our study we compared methotrexate with first line treatment of lichen planus that is systemic corticosteroids (oral prednisone) ,and methotrexate was found to be equally efficacious and safe as prednisone, in addition to this, none of the patients on methotrexate had relapse as compared to 5 patients on oral prednisone during 6 months of post treatment follow-up.So, methotrexate can be used as an alternative to systemic corticosteroids in the treatment of generalized cutaneous lichen planus for short duration, in low dose and with lesser side-effects.

VI. Conclusion

Lichenplanus is not as chronic and severe as psoriasis which requires high dose and long duration of treatment with methotrexate that leads to harmful hepatic andhaematological side effects. Treatment of lichen planus with methotrexate in weekly low dose for short duration has lesser adverse effects, reduces dependency on systemic corticosteroids thereby reducing long term side effects of corticosteroids and also decreases chance of relapse.

Conflict Of Interest- No conflict of interests
Financial Support-None

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