Methotrexate Versus Methotrexate Plus Folic Acid in the Treatment of Moderate to Severe Plaque Psoriasis: A Randomized Clinical-Trial

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Abstract

Background: Psoriasis is a chronic, recurring inflammatory disease affecting the skin, joints and nails that has a significant negative impact on the quality of life. Efficacy of methotrexate versus combination of methotrexate plus folic acid in the treatment of psoriasis has been rarely assessed.

Objectives: To compare the efficacy of methotrexate versus methotrexate plus folic acid in the treatment of moderate to severe chronic plaque psoriasis

Material and Methods: Eighty patients with moderate to severe chronic plaque psoriasis were randomized to receive either methotrexate (group A) or methotrexate plus folic acid (group B). End point of treatment was 75% reduction in Psoriasis Area and Severity Index (PASI 75) score or upto 3 months, whichever was earlier. Patients were then followed up for a period of 12 weeks for assessment of relapse, DLQI and adverse effects.

Results: Of 80 patients, 71 completed the treatment and follow up period (33 in group A, and 38 in group B). PASI 75 was achieved in 34/40(85%) patients in group A and 32/40(80%) patients in group B ($P < 0.142$). There was statistically significant number of patients who had greater adverse effect in methotrexate than in methotrexate plus folic acid ($p=0.020$). There was significant difference in the number of patients who relapsed during the follow-up period ($P = 0.013$) with more relapse in group B.

Conclusion: Combination of methotrexate and folic acid developed lesser adverse effect and greater relapse in comparison to methotrexate alone.

Key words: DLQI, Folic acid, Methotrexate, PASI, Psoriasis

Introduction

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin and has remitting and relapsing course. The characteristic lesion consists of red, scaly, sharply demarcated, indurated plaque, presents particularly over the extensor surface of the extremities and scalp. The disease is variable in duration, periodicity of flares and extent. Morphological variants are common.[1] The prevalence of psoriasis varies from 1.5 to 3% and incidence indicated to 60 individuals per 100 000 per year.[2] The prevalence of psoriasis is 2% in a study conducted in eastern Nepal to identify the patients profile and belief regarding the disease psoriasis.[3] Psoriasis may have a major impact on quality of life and self-esteem. It can lead to limitations with daily activities, occupational functioning and relationship.[4] The severity of the disease determines the therapeutic approach.[5] Monotherapy with systemic agents may be insufficiently effective or produce many side-effects. In these cases, combination, rotational or sequential treatment strategies may be utilized for better results.[3] Methotrexate a folic acid antagonist though effective produces many side effects associated with liver toxicity in long-term and gastrointestinal intolerance in short-term use. Folic acid supplementation found to reduce its side effects but in a recent small study, suggestions are made that supplementary folic acid might reduce the effectiveness of methotrexate. Therefore, we had planned to undertake the study

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to compare the therapeutic efficacy of methotrexate versus methotrexate plus folic acid in the treatment of moderate to severe plaque psoriasis and identify the adverse effects, Dermatology life quality index (DLQI), and relapse associated with these regimes.

Material and methods

Patients with plaque psoriasis attending the outpatient department (OPD) of Dermatology department, BPKIHS, Dharan with more than 2% BSA involvement were included and patients with less than 2% BSA, pregnant and lactating women, patients with systemic diseases and those who received systemic treatment for psoriasis within the past 4 weeks and topical treatment within the past 2 weeks, those with history of skin cancer and immunosuppression due to disease or drugs were excluded in the study. This study is an observer blinded, randomized, clinical trial and was approved by the Institutional Ethical Committee.

The sample size of 40 patients were recruited in each arm of the study, considering 80% power, 5% alpha error, two sided and percentage of PASI 75 reduction at 12 weeks in methotrexate group 50%.

Subject enrollment

A prior informed and written consent was taken from all patients. Particulars of an individual patient and detailed history with respect to the chief complaints, duration of illness, associated symptoms and site of involvement were documented in a preset proforma for each patient. Seasonal variation, precipitating factors, joint involvement, family history and past treatment taken were also recorded. A complete clinical examination was done in all patients. The sites involved and the morphology of the lesion were documented in the proforma. Body surface area (BSA) was measured using the rule of nine as in burn. Severity of the disease was assessed using PASI (Psoriasis Area and Severity Index).

Baseline investigations of routine blood counts (Hb, TLC, DLC, platelets), liver function test (total bilirubin/ conjugated, SGOT, SGPT, ALP) and renal function test (S.Urea, S. Creatinine), Urine R/M, and X-ray chest PA view were done to rule out any systemic involvement. A HIV test was done after sending the patient for the pre-test counseling only in high risk patients. All females of reproductive age group underwent the pregnancy test and were also advice to use contraceptives during the treatment period.

A wash off period of 2-4 weeks was given to patients on any kind of past treatment (i.e. 2 weeks for topical and 4 weeks for any systemic treatment).

No concomitant therapy was allowed except for emollients and anti-histamines during treatment and follow-up period.

Two parallel groups (1:1) generated with the help of Ralloc software and were randomized into two intervention group. Group A (Methotrexate(MTX)) and Group B (Methotrexate plus folic acid(MTX+FA).

Methotrexate (Group A)

Oral MTX was given in the dose of 0.4mg/kg/week with maximum of 25 mg/week for a period of 12 weeks. No changes were permitted in the dose of MTX used during the study.

Methotrexate plus folic acid (Group B)

Oral MTX was given in the dose of 0.4mg/kg/week with maximum of 25 mg/week for a period of 12 weeks similar to group A, in addition single dose of 5 mg folic acid was administered 24 hours after.

Assessment

Assessment was done by calculating PASI and TBSA (%) during follow-up. DLQI were assessed at 12 and 24 weeks using Nepali version. Relapse assessed at 16, 20 and 24 weeks of follow-up. TLC, DLC, Hb, platelets, LFT repeated twice weekly for first 4 weeks and every 4 weekly for remaining 8 weeks. Cumulative dose of methotrexate was calculated. The primary end point was change in PASI at 12week and secondary end point was adverse effect, DLQI, and Relapse. Level of outcome measured as:

1. Excellent/good : clearance/minimal residual disease, or PASI 90
2. Satisfactory: PASI 75
3. Improvement: PASI 50
4. Mild improvement: PASI 1-<50
5. No improvement: PASI 0
6. Relapse: PASI >25 from baseline

Treatment discontinuation was done if there were any serious adverse effect and if there were any abnormal laboratory findings.

Statistical analysis

Data from all randomized patients were included on intent-to treat basis. T-test was used where equal variance was demonstrated. Chi square test was

used in the initial exploration of the data. Otherwise, equivalent nonparametric statistics (Wilcoxon rank sum test) was used. Kaplan-Meir test used to assess the relapse after completion of the treatment period.

Results

Of 116 patients, 36 patients were excluded from the study and 80 patients were randomized.

Among 80 randomized patients (40 in each group), a total of 71 (33 in Group A and 38 in Group B) completed the treatment and follow-up (Figure 1).

A baseline demographic comparison of the 2 groups (Group A and B) of patients is shown in Table 1. The patients of both groups were not statistically different in regards to age (p=0.475), duration (p=0.867), PASI (p=0.432), TBSA (p=0.263), and DLQI (p=0,137).

Psoriasis area severity index (PASI)

There was marked reduction in percentage score of PASI between the two treatment groups, however there was no statistical significance (p=0.682) (Table 2). During the follow-up period of 12 weeks carried at 4 weekly interval, the mean PASI reduction at 24 weeks was also statistically not significant (P=0.260)(Table 3). PASI 75 was achieved at 8th week in Group A, whereas it was at 9th week in group B (p=0.058) and the total cumulative dose of methotrexate was slightly lower in Group A than Group B (p=0.050). Both were statistically insignificant (Table 4).

Total body surface area (TBSA)

Reduction in percentage of total body surface area was marked in both the groups but was statistically insignificant (P=0.732), at 12 weeks (Table 5) and during follow-up period of 12 weeks after completion of treatment (i.e. at 24 weeks) (p=0.174) (Table 6).

Dermatology life quality index (DLQI)

Marked reduction in DLQI was present both at 12 weeks and at 24 weeks, however statistically significant reduction was at 12 weeks (P=0.041) and favored Group A over Group B (Table 7).

Adverse effects (ADRS)

In methotrexate group, 11(27.5%), patients developed the side effects, in methotrexate plus folic acid 5(12.5%). There was statistically significant difference in side effects at the end of study among the two treatment group (P=0.020) (Table 8). However the side effects were not serious.

Relapse

There was significant difference in number of patients who relapsed at the end of study among the two groups (p=0.013) (Table 9). Higher number of patients relapsed during follow-up period of 12 weeks in methotrexate plus folic acid group compared to methotrexate alone (36.8% vs 21%)

Table: 1: Baseline characteristics of study populations

Characteristics	Categories	Methotrexate (N=40)	Methotrexate+FA (N=40)	P-value
Age group (years)	Mean±SD	41.33±16.127	40.32±13.667	0.475
Sex	Male Female	25(62.5%) 15(37.5)	22(55%) 18(45%)	0.771
Duration(yrs)	Mean±SD	3.38±1.628	3.55±1.739	0.867
Family history	Present Absent	3(7.5%) 37(92.5%)	8(20%) 32(80%)	0.247
PASI	Mean±SD	10.97±5.903	11.93±7.586	0.432
TBSA	Mean±SD	20.55±15.30	22.08±19.49	0.263
DLQI	Mean±SD	10.20±5.36	10.77±5.52	0.137
Methotrexate dose	Mean±SD	12.5±10.05	13.5±8.64	0.266

Table 2: Change in PASI during treatment

Characteristics		Group					
weeks	N	MTX	N	MTX+FA	Tests*	P-value	Remarks
		Mean±SD (Median)		Mean±SD (Median)			
PASI 0	40	10.97±2.838 (9.45)	40	11.94±7.587 (10)	667.000	0.730	NS
PASI 1	40	8.34±5.101 (7.19)	40	9.05±4.518 (7.58)	677.000	0.952	NS
PASI 2	38	6.56±3.949 (5.66)	39	7.84±3.383 (6.58)	578.000	0.345	NS
PASI 3	36	3.16±1.775 (2.73)	39	4.05±1.750 (3.4)	516.000	0.739	NS
PASI 4	36	1.88±1.592 (1.62)	39	2.34±1.360 (1.97)	511.000	0.646	NS
PASI 8	35	1.097±2.165 (0.95)	38	1.44±1.729 (1.22)	538.000	0.981	NS
PASI 12	33	1.097±2.838 (0.95)	38	1.09±3.008 (1.0)	366.000	0.682	NS

Table 3: Change in PASI during follow-up after treatment

Characteristics		Group					
weeks	N	MTX	N	MTX+FA	Tests*	P-value	Remarks
		Mean±SD (Median)		Mean±SD (Median)			
PASI 16	33	1.669±1.557 (1.44)	38	1.223±4.426 (1.81)	535.000	0.692	NS
PASI 20	33	1.669±1.395 (1.44)	38	1.220±4.616 (1.81)	322.000	0.089	NS
PASI 24	33	1.909±1.724 (1.65)	38	1.200±4.537 (1.8)	214.000	0.260	NS

Table 4: PASI 75 response to treatment

Characteristics	Group			P-value	Remarks
	MTX (N=40)	MTX+FA (N=40)	Tests*		
Attainment of PASI 75	34 (85%)	32 (80%)	560.000	0.142	NS
No. weeks required for attaining PASI 75 (mean±SD)	8.5±4.5	9.5±4.5	587.000	0.058	NS
Total MTX dose required for attaining PASI 75 (mean±SD) mg	140.75±60.5	170±40.5	563.000	0.050	NS
Total folic acid dose (mg) required attaining PASI 75 (mean±SD)		50±15.5			

Table 5: Change in Total Body Surface Area during treatment

Characteristics	Group					P-value	Remarks
		MTX		MTX+FA	Tests*		
TBSA	N	Mean±SD (Median)	N	Mean±SD (Median)			
0 (Baseline)	40	20.55±15.30 (15)	40	22.08±19.49 (16)	694.500	0.953	NS
1st week	40	18.55±15.57 (13.5)	40	19.20±17.29 (13.9)	658.500	0.795	NS
2nd week	38	9.22±10.99 (6.74)	39	11.73±16.2 (8.11)	630.500	0.717	NS
3rd week	36	7.16±8.347 (5.3)	39	6.147±16.50 (4.48)	530.000	0.889	NS
4th week	36	5.76±4.20 (4.21)	39	4.68±15.28 (3.4)	539.000	0.987	NS
5 (8th week)	35	4.23±4.15 (3.1)	38	4.84±15.28 (3.51)	527.000	0.839	NS
6 (12th week)	33	3.87±3.78 (2.83)	38	4.99±15.40 (3.31)	370.000	0.732	NS

Table 6: Change in Total Body Surface Area during follow-up after treatment

Characteristics	Group					P-value	Remarks
		MTX		MTX+FA	Tests*		
TBSA	N	Mean±SD (Median)	N	Mean±SD (Median)			
(16th week)	33	3.81±2.68 (2.79)	38	4.90±14.92 (3.12)	540.000	0.756	NS
(20th week)	33	3.70±2.88 (2.78)	38	4.88±14.87 (3.12)	322.000	0.089	NS
(24th week)	33	3.99±2.55 (2.92	38	5.03±14.60 (3.65)	204.000	0.174	NS

Table 7: Change in Dermatology Life Quality Index

Characteristics	Group		Tests*	P-value	Remarks
	MTX (N=40)	MTX+FA (N=40)			
DLQI	Mean±SD (Median)	Mean±SD (Median)			
0 (Baseline)	10.20±5.360 (11)	10.77±5.526 (9)	212.000	0.182	NS
1 (12 weeks)	1.43±2.111 (1.55)	2.78±3.445 (2.33)	200.000	0.041	S
2 (24 weeks)	0.46±1.484 (0.5)	0.88±2.534 (0.74)	260.000	0.077	NS

Table 8: Adverse effects

S.N.	Side effects	MTX	MTX+FA	p-value
1	A.N.V	11 (33%)	3 (7.8%)	0.136
2	Fatigue	7 (21%)	4 (10.5%)	0.420
3	Pruritis	7 (21%)	5 (13%)	0.810
4	Burning sensation	3 (9%)	4 (10.5%)	0.542
5	Mucositis	3 (9%)	0 (0%)	0.562
6	Transaminitis	6 (18%)	2 (5.2%)	0.678
7	Anaemia	1 (3%)	3 (7.8%)	0.320
8	Leucopenia	1 (3%)	2 (5.2%)	0.298
9	Thrombocytopenia	0 (0%)	2 (5.2%)	-
10	Total cummulative	39	25	0.020

Table 9: Relapse

Characteristics	Methotrexate	Methotrexate+FA	p-value	Remarks
Relapse	N-33	N-38		
1 (16 weeks)	3 (9%)	6 (15.7%)	0.285	NS
2 (20 weeks)	5 (15%)	9 (23.6%)	0.084	NS
3 (24 weeks)	7 (21%)	14 (36.8%)	0.013	S

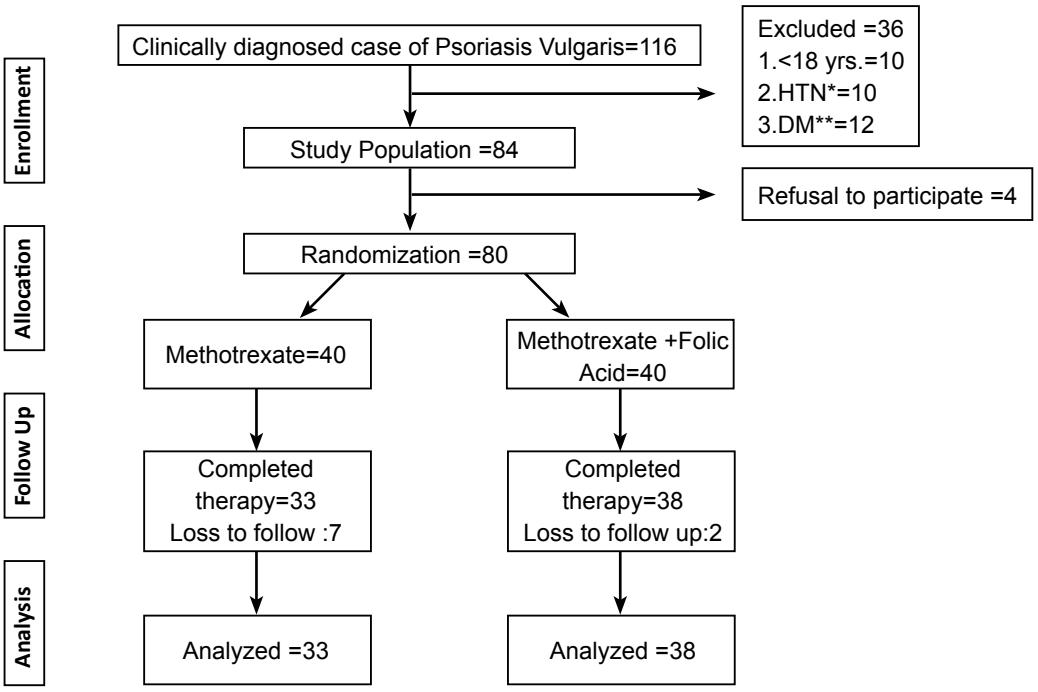

Figure 1: Flow diagram of the patients through different stages

***HTN: Hypertension,** **DM: Diabetes Mellitus

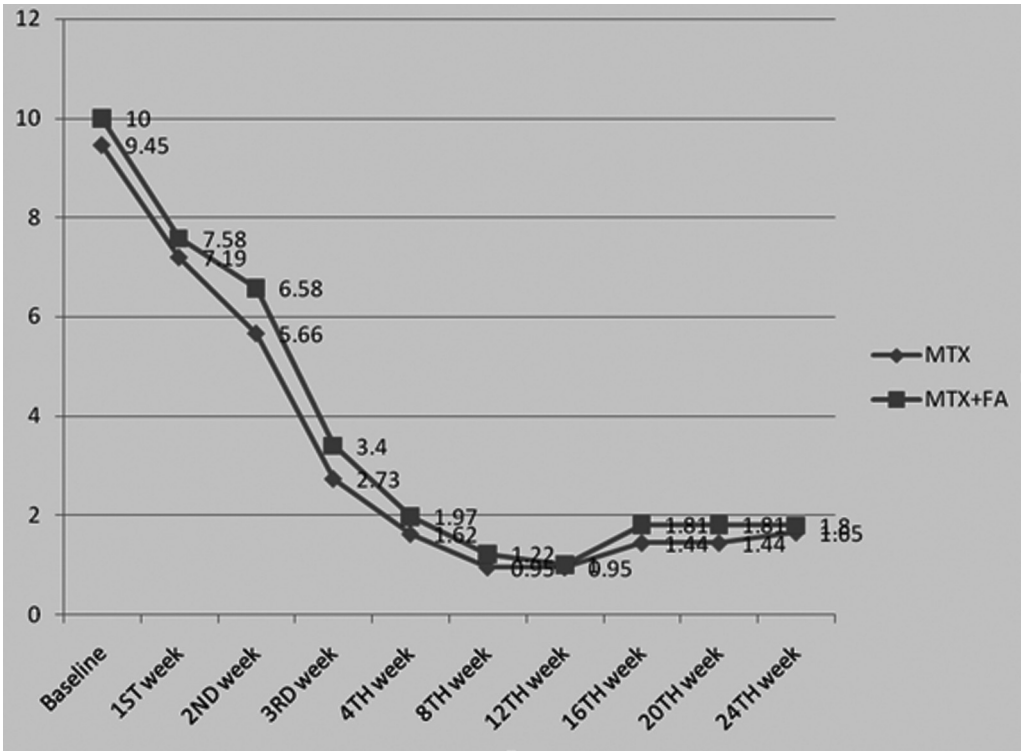

Figure 2: Change in PASI during treatment and follow-up

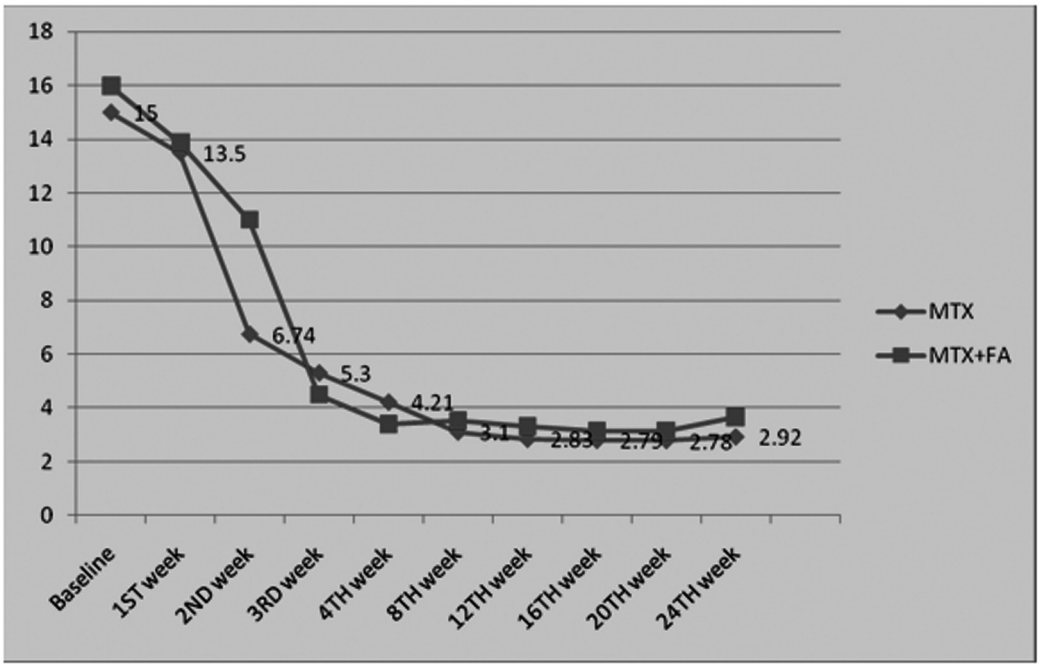

Figure 3: Change in Total Body Surface Area during treatment and follow-up

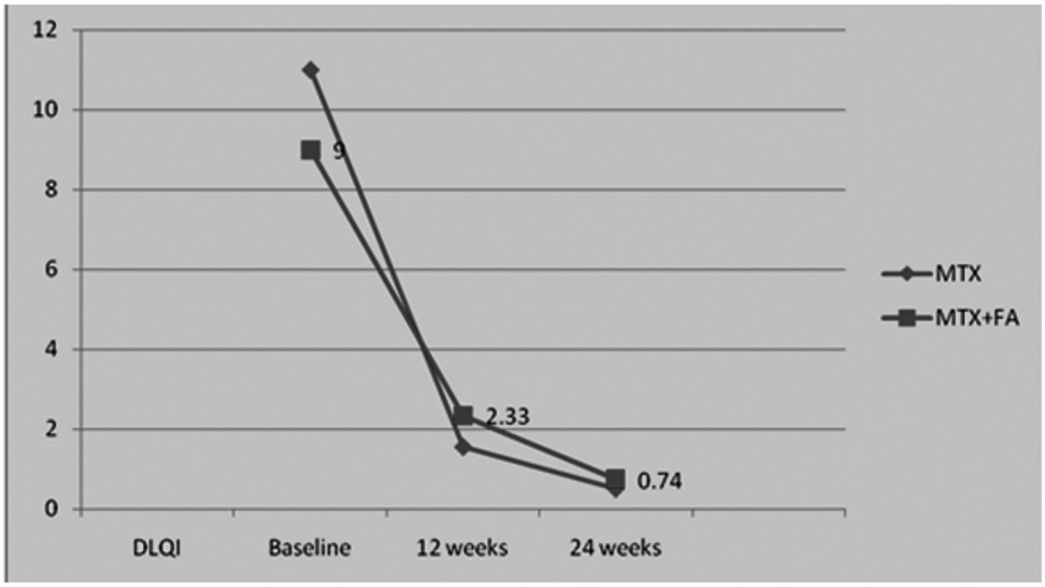

Figure 4: Change in Dermatology Life Quality Index during treatment and follow-up

Discussion

Many therapeutic agents are used for the treatment of psoriasis vulgaris with variable efficacy but none is a definite treatment. Methorexate has been in use for more than five decades as monotherapy and in combination with other agents in the treatment of psoriasis, despite its potential short-term and long-term side-effects.[6]

In our study, there was no statistical significant difference in the number of patients who achieved marked improvement in PASI between the two groups (methotrexate and methotrexate plus folic acid) at 12 weeks (P =0.682). The mean total cumulative dose of methotrexate (140.75±60.5 mg in methotrexate, and 170.75±40.5 mg in methotrexate plus folic acid) received by the patients in the two groups to achieve marked improvement was statistically not significant (P=0.050). The difference in the time (8.5±4.5 weeks in Group A and 9.5±4.5 weeks in Group B) required to achieve marked improvement in PASI to be statistically insignificant (P=0.058). In our study 33/40 in methotrexate (82.5%), and 31/40(77.5%) in methotrexate plus folic acid achieved PASI 90 (P=0.053). PASI 75 was achieved in 34/40(85%) in methotrexate, and 32/40(80%) in methotrexate plus folic acid (P=0.072). During the follow-up period of 12 weeks carried at 4 weekly interval after stopping treatment, the mean PASI reduction at 24 was statistically insignificant (P=0.260). Kumar *et al* reviewed data on 244 psoriatics who were put on weekly oral methotrexate at full therapeutic dose (0.3–0.5 mg/kg/week) from 1981 to 2000 and found marked improvement to occur in 88% of patients in 8.5 ± 5.1 weeks.[7] These findings are similar to our findings in efficacy, dose and duration required for achieving PASI 75.

In the present study, reduction in percentage of total body surface area was statistically insignificant (P=0.732), at 12 weeks of treatment and follow-up period (P=0.174).

In the present study, the median reduction in DLQI between methotrexate and methotrexate plus folic acid was marked and statistically significant at completion of treatment at 12 weeks (P=0.041) favouring methotrexate alone. This similar reduction in PASI, TBSA and DLQI between the two groups shows folic acid do not affect the mechanism of action of methotrexate and its efficacy.

Total of 16 (20%) patients developed various side effects during treatment and follow up period among all patients in both group. In methotrexate 11 (27.5%) patients developed the side effects; in methotrexate plus folic acid 5(12.5%) patients developed the different side effects. There was statistically significant difference in side effects at the end of study among the two treatment group (P=0.020). These side effects were graded in a 4 point scale (from 0-no side effect to 3-severe) to know the severity of side effect. Majority of patients experienced grade 1 (mild) and few developed moderate degree of symptoms only and which disappeared on continuation of treatment. Majority

of side effects were gastrointestinal intolerance, like anorexia, nausea, and vomiting, followed by fatigue and malaise and pruritus. Folic acid supplementation decreases the side effects of methotrexate without affecting its efficacy. Gastrointestinal side effects are predominantly due to depletion of folic acid by the action of methotrexate (Folate antagonist).

Relapse in any patients were said to be present when there was more than 25% increase in PASI score from that of PASI score at the end of treatment. There were significant number of patients who relapsed at the end of follow-up (24 weeks) in methotrexate plus folic acid group (14) compared to methotrexate alone (7) (p=0.013). This higher relapse rate in folic acid supplementation group could be due to faster loss of effect of methotrexate by folic acid.

The study concludes that the supplementation of folic acid with methotrexate do not affect its efficacy and decreases the adverse effect of methotrexate both gastrointestinal and hepatotoxicity. The gastrointestinal adverse effect particularly the nausea and vomiting decreases the compliance of oral methotrexate and hampers its efficacy thereby increasing the morbidity of psoriasis. In addition decrease in hepatotoxicity will prevent the mortality associated with the psoriasis. However folic acid supplementation group have higher relapse, it could be because of faster loss of effect of methotrexate due to folic acid. Further randomized studies with longer follow-up are required to support these findings.

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