Safety and efficacy of methotrexate (0.3 mg/kg/week) versus a combination of methotrexate (0.15 mg/kg/week) with cyclosporine (2.5 mg/kg/day) in chronic plaque psoriasis: A randomised non-blinded controlled trial

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Abstract

Background: Psoriasis is a chronic, inflammatory, relapsing and remitting disease with no cure till date. There is a paucity of trials using a combination of methotrexate (MTX) and cyclosporine (CsA) in chronic plaque psoriasis, due to fear of added toxicity, although they are time tested treatment options for monotherapy.

Aims: The study aimed to compare the efficacy and adverse effect profile of the standard recommended dose of MTX (i.e. 0.3mg/kg/week) versus a combination of reduced doses of MTX and CsA (i.e. MTX 0.15 mg/kg/week with CsA 2.5mg/kg/day) in patients with chronic plaque psoriasis.

Methods: Study design was a non-blinded randomised controlled trial. Patients of chronic plaque psoriasis with PASI more than 10 were randomised in 1: 1 allocation to receive either 0.3 mg/kg/week of intramuscular MTX injection or a combination of 0.15 mg/kg/week of intramuscular MTX injection and 2.5 mg/kg/day of CsA rounded off to the nearest 25 mg. Patients were followed up at every 2 weeks for 12 weeks. The doses were kept fixed throughout the study period.

Results: A total of 66 patients received MTX monotherapy, whereas 67 patients received the combination. At baseline, both groups were comparable in their BSA ($P = 0.105$, Student t-test) and PASI ($P = 0.277$, Student t-test), which reduced significantly at 12 weeks in both groups ($P < 0.001$, paired t-test). The achievement of PASI-75 ($P = 0.005$), PASI-90 ($P < 0.001$) and PASI-100 ($P = 0.001$) was more in the combination group (Chi square test). Intention to treat analysis using Chi square test also showed better outcomes for PASI-75 ($P = 0.027$), PASI-90 ($P < 0.001$) and PASI-100 ($P = 0.001$) in the combination group. Combination group also had earlier onset of action ($P = 0.001$, Chi square test). There was no significant difference between the groups in terms of laboratory and clinical adverse events.

Limitations: Non-blinded, no comparison with CsA monotherapy arm, no follow up beyond 12 weeks.

Conclusion: The combination of reduced doses of MTX and CsA is more efficacious with earlier onset of action and similar adverse effects as with MTX monotherapy.

Key words: Chronic plaque psoriasis, combination therapy, methotrexate and cyclosporine, randomised controlled trial

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Introduction

Psoriasis is a common, chronic, inflammatory, genetically determined and hyper-proliferative disorder which involves mainly skin, but sometimes joints. It is characterised by well-defined scaly erythematous plaques. It affects approximately 2-3% of the world population.[1] The prevalence of psoriasis in India ranges from 0.4-2.8 per cent.[2] Till date, there is no cure for psoriasis, and therefore the aim of treatment is to minimise the severity to such an extent that it no longer disrupts the quality of life.

The choice of treatment depends on clinical presentation, as well as patient-related factors such as age, severity, accompanying diseases and therapies, individual patient preferences, renal and hepatic status and the risks of treatment. Systemic treatment is indicated in patients with moderate to severe psoriasis and should also be favoured, if concomitant psoriatic arthritis (PsA) is evident.

There are various forms of systemic treatments for chronic plaque psoriasis with different mechanisms of action and toxicities. A combination of treatments may provide a better therapeutic option, with earlier onset of action, while minimising the individual cumulative dose and safety concerns that are present with higher doses in monotherapy.

Both methotrexate (MTX) and cyclosporine (CsA) are FDA approved time tested treatments for chronic plaque psoriasis. There is a paucity of randomised controlled trial evaluating the safety and efficacy of the combination of MTX and CsA in chronic plaque psoriasis even though such a combination has been tried in rheumatoid arthritis[3] and psoriatic arthritis.[4] This was mainly due to fear of both drugs increasing each other's blood level and decreasing elimination of each other.[5]

Therefore this study was undertaken to determine the efficacy and safety of a combination of reduced doses of MTX and CsA in chronic plaque psoriasis.

Methods

The study design was a non-blinded randomised controlled trial in which a standard therapy was compared with the newer option. Efficacy and adverse effect of MTX in standard dose was compared with a combination of lower doses of MTX and CsA. The trial was conducted in the dermatology department of Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi. The study protocol was approved by the institutional ethics committee. This trial was registered under CTRI (CTRI/2018/07/015044). Inclusion criteria were adult patients of 18-65 years of age of chronic plaque psoriasis with PASI >10 who had given consent, had cumulative MTX dose <1.5 gram and were not taking systemic immunosuppressants for 1 month and topical immunosuppressant for 2 weeks prior to enrolment. The exclusion criteria were pregnancy or lactation, history of alcoholism or taking hepatotoxic or nephrotoxic drugs, hypertension defined as ≥140 mm systolic and ≥90 mm diastolic at baseline or rise in BP to ≥150 mm systolic and ≥100 mm diastolic during the study in two consecutive visits after the addition of amlodipine 5 mg, haemoglobin <8 gram/dl, TLC <4000 cells/mm3, platelet count <1 lakh/mm3, lymphocytes <1500 cells/mm3, raised aminotransferases ≥ twice the upper limit of normal at baseline and ≥ thrice the upper limit at follow up, raised total bilirubin >1.2 or 30% increase of baseline, serum creatinine values of >1.4 mg/dl at baseline or more than 30% increase in baseline at two consecutive visits, tuberculosis and immunosuppression or any chronic disease, peptic ulcers, any reliable sign of infection and an unreliable patient.

Randomisation

The study was a non-blinded trial. Participants were randomised equally in a 1:1 allocation (unstratified) into two treatment groups by a computer generated random number sequence using the MS Excel software.

Study groups and medications

Group 1: MTX intramuscular injection 0.3 mg/kg/week.

Group 2: combination of MTX intramuscular injection 0.15 mg/kg/week plus CsA 2.5 mg/kg/day orally rounded off to the nearest 25 mg in two divided doses.

For obese patients, CsA was dosed as per the ideal body weight[6] using Devine formula.[7] Only antihistamines were administered to the patients other than the study drugs. No other topical or systemic immunosuppressant was allowed during the study period.

Sample size

The sample size was calculated with level of confidence 95%, power of the test 80%, efficacy in combination group 75% and efficacy in methotrexate group 45%. [8] By taking one to one allocation, then sample size in each group came to be 60. Assuming the dropout rates to be 10%, the final sample size was 67 in each group which was approximated to 70 cases in each group.

Visits and follow-up

The study period for each subject was of 12 weeks and efficacy and safety assessments were done for every patient once in 2 weeks. If a patient didn't report for 2 consecutive follow-ups, he was considered lost to follow-up. The first patient was enrolled in August 2018 and the final follow up of the last enrolled patient was done in July 2019.

At the screening visit, the clinical history and baseline BSA, PASI and blood pressure (BP) recordings were done. Baseline

investigations included a complete blood count (CBC), liver function test (LFT), renal function test (RFT), ELISA for HIV I and II and fasting blood sugar and serum potassium. The BSA, PASI and BP were recorded every 2 weeks along with CBC, LFT and RFT. For patients randomised to the combination group, fasting lipid profile was also done at baseline. All the clinical assessments were done by a single examiner. Monitoring for adverse effects (AE) was done using open-ended questions to identify new problems or changes that had occurred since the last visit. Treatment as per the designed protocol was continued till 12 weeks. If however during the study, the patient developed any of the above mentioned exclusion criteria, treatment was then stopped immediately and patient was switched to other alternative treatment. The patients who had achieved target prior to exclusion were also analysed.

Study parameters

Our primary outcome measure was achievement of PASI-75 by the end of 12 weeks. Our secondary outcome measures were achievement of PASI-50, PASI-90, and PASI-100 by 12 weeks, onset of action (defined by the number of patients achieving PASI-50 at 4 weeks) and adverse effects.

Statistical analysis

Data of quantitative variables is presented as mean ± SD and categorical variables as number and percentage. Student t-test is used to compare the mean value of two treatment groups and paired t-test is used to see the changes from baseline to various follow ups. Chi square test/ Fisher's exact probability test is used to see the association between categorical variables and treatment groups as well as changes within the groups from baseline to various follow-ups. Level of significance is taken as 5% at two tailed test.

One hundred and forty patients were included and randomised equally into the 2 treatment arms. Four patients from group 1 and three patients from group 2 were lost to follow-up. Out of the remaining patients, 4 were excluded due to adverse effects from Group 1 and 7 from group 2. Among the patients excluded due to adverse effects, 2 patients in Group 1 and 3 patients in Group 2 achieved one of the target PASIs before exclusion and have been included in the efficacy analysis. The analysis for adverse effects included all patients excluding the ones who were lost to follow up. Per protocol analysis was initially done. The parameters found to be significant were also subjected to intention to treat analysis (ITT).

Results

A total of 190 patients were enrolled for the study. After evaluation, 50 patients were excluded as they did not meet the inclusion criteria or declined to participate. Finally, 140 patients were included and randomised equally into the 2 treatment arms. The flow of study participants is depicted in Figure 1.

The clinico-epidemiologic data of our study participants are depicted in Table 1. Both the groups could be matched in all parameters except for weight and height. The weight and height was more in the combination group (P = 0.005 and P = 0.025 respectively).

Both the groups were comparable in terms of baseline BSA (P = 0.105) and PASI (P = 0.277). Per protocol analysis showed both groups to be comparable in terms of achieving PASI-50 by 12 weeks (P = 0.365). However, by 12 weeks, PASI-75 was achieved by 55 (88.7%) patients in the combination group vs. 43 (68.3%) in the monotherapy (P = 0.005). PASI-90 was achieved by 46 (75.4%) patients in the combination group vs. 22 (35.5%) in monotherapy (P < 0.001) and PASI-100 was achieved in 27 (44.3%) patients in the combination group vs. 10 (16.1%) in the MTX monotherapy group. (P = 0.001). On further subjecting the parameters to ITT analysis, the combination group still had a significantly better outcome at 12 weeks in terms of achieving PASI-75 (P = 0.027), PASI-90 (P < 0.001) and PASI-100 (P = 0.001). The comparison between the two groups for achieving target PASI at or before 12 weeks of follow up is shown in Table 2.

Onset of action, defined by the achievement of PASI-50 at 4 weeks was earlier in the combination group with 29 (46.0%) patients achieving PASI-50 at 4 weeks vs. 11 (17.2%) in monotherapy (P = 0.001).

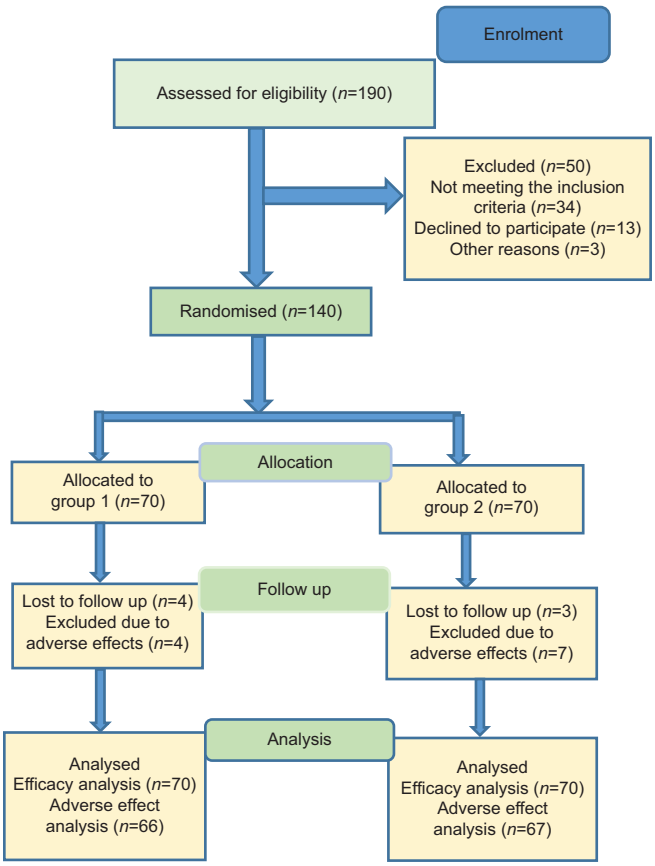

Figure 1: Flow of participants in our study

On intra-group comparison, both the groups had a decline in their BSA and PASI scores from their baseline score ($P < 0.001$). The mean decrease in BSA and PASI from baseline in both groups is shown in Table 3.

Adverse effects were assessed in terms of laboratory and clinical parameters. Seven (10.4%) patients were excluded from group 2 vs. 4 (6%) in group 1, however this difference was not significant. ($P = 0.54$) All the laboratory and clinical adverse effects were comparable between the two groups. Increase in AST ≥ twice the upper limit of normal was the most common laboratory AE with MTX monotherapy, whereas a rise in systolic BP ≥ 140 mm of mercury was the most common AE in the combination group. Most of the clinical adverse effects were minor and resolved on their own even with continuation of therapy at the same doses. No patient was excluded due to clinical AE in any group. Gastrointestinal AE were the most common clinical adverse effect seen in both groups. The laboratory and clinical AE are shown in Table 4.

Discussion

Exact etiopathogenesis of psoriasis is still not known. There are different systemic drugs in the armamentarium of psoriasis treatment. MTX and CsA are FDA approved and time tested treatments for chronic plaque psoriasis with different mechanisms of action and toxicity profiles. Total cumulative dose of MTX is said to be 3.5- 4 g in non-alcoholic patients.[9-11] The adverse effects of CsA are also dose dependent. Continuous therapy of

Table 1: Baseline characteristics of study participants

Parameters	Total number of patients enrolled (*n*=140)		
	Group 1 (*n*=70)	Group 2 (*n*=70)	*P*
Male, *n* (%)	51 (72.9)	51 (72.9)	1
Female, *n* (%)	19 (27.1)	19 (27.1)	
Age (years), mean±SD	38.04±14.97	38.77±15.03	0.774
Weight (kg), mean±SD	55.84±11.51	61.67±12.58	0.005
Height (cm), mean±SD	159.46±8.79	162.70±8.11	0.025
Duration of disease (years), mean±SD	7.06±7.32	5.06±5.49	0.069
Family history, *n* (%)	4 (5.71)	6 (8.57)	0.512
Smoking, *n* (%)	5 (7.14)	12 (17.14)	0.070
Tobacco chewing, *n* (%)	10 (14.3)	11 (15.7)	0.813
Past immunosuppressive treatment history, *n* (%)	55 (78.6)	53 (75.71)	0.909
BSA_0 week, mean±SD	22.20±12.79	25.86±13.74	0.105
PASI_0 week, mean±SD	18.26±9.65	20.10±10.33	0.277

P value is from Chi-square test for male-female sex distribution, family history, smoker, tobacco chewer and past immunosuppressive treatment history. Student's *t*-test for age, weight, height, duration of illness, BSA_0 week and PASI_0 week. BSA: Body surface area, PASI: Psoriasis area and severity index, SD: Standard deviation

Table 2: Total patients who achieved target psoriasis area and severity index at or before 12 weeks

Outcome measures	Group				*P*
	1		2		
	n	Number of patients who achieved target (%)	*n*	Number of patients who achieved target (%)	
Per protocol analysis					
PASI-50	64	60 (93.75)	63	62 (98.41)	0.365
PASI-75	63	43 (68.25)	62	55 (88.71)	0.005*
PASI-90	62	22 (35.48)	61	46 (75.41)	<0.001†
PASI-100	62	10 (16.12)	61	27 (44.26)	0.001*
Intention to treat analysis					
PASI-50	70	60 (85.71)	70	62 (88.57)	0.61
PASI-75	70	43 (61.43)	70	55 (78.57)	0.027*
PASI-90	70	22 (31.43)	70	46 (65.71)	<0.001†
PASI-100	70	10 (14.29)	70	27 (38.57)	0.001*

*Significantly more numbers of patients have achieved target PASI by 12 weeks in group 2, †Highly significant difference between the two groups. *P* value between two groups is determined by Fischer's exact test and Chi-square test. Note: Two patients in group 1 and three patients in group 2 had achieved one of the target PASIs before being excluded from the study due to adverse effects. The details of those patients are given below: Group 1: 1 patient achieved PASI-50 at 4 weeks, PASI-75 at 8 weeks and then excluded after 8th week due to a rise in AST ≥3 ULN. 1 patient achieved PASI-50 at 8 weeks and then excluded at 10th week due to a drop in platelet <1 lakh/mm^3 and a rise in AST ≥3 ULN. Group 2: 1 patient achieved PASI 50 at 4 weeks and then excluded at 6th week due to TB >30% of baseline. 1 patient achieved PASI 50 at 6 weeks, PASI-75 at 8 weeks and then excluded after 8 weeks due to drop in haemoglobin <8 g/dl and increase in blood pressure - SBP ≥150 and DBP ≥100 mm of Hg during the 8th week readings. 1 patient achieved PASI-50 at 2 weeks, PASI-75 at 4 weeks, and PASI-90 at 6 weeks and PASI-100 at 8 weeks and then excluded at 8th week because of rise in AST ≥3 ULN as well as TB >30% of baseline. BSA: Body surface area, PASI: Psoriasis area and severity index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, AST: Aspartate transaminase, ULN: Upper limit of normal, TB: Total bilirubin

Table 3: Mean decrease in body surface area and psoriasis area and severity index at 12 weeks in the two groups

Mean decrease in BSA and PASI	Group 1 (*n*=62), mean±SD	*P*	Group 2 (*n*=60), mean±SD	*P*
BSA				
BSA_baseline	21.84±11.81	<0.001†	25.20±13.15	<0.001†
BSA_12 weeks	4.37±5.10		3.05±5.33	
PASI				
PASI_baseline	17.92±8.74	<0.001†	19.49±9.34	<0.001†
PASI_12 weeks	3.66±3.93		2.20±3.75	

†Highly significant decrease in the BSA and PASI from the baseline values in both groups. *P* value has been determined using paired *t*-test. BSA: Body surface area, PASI: Psoriasis area and severity index, SD: Standard deviation

CsA is recommended for 1 year (U.S)[12] or 2 years (U.K).[6,13] The combination of the two drugs in chronic plaque psoriasis was feared due to risk of added toxicity.[5] However, randomised controlled trials using this combination in RA[3] and PsA[4] were tried and found to be safe and effective. A few retrospective[14,15] and prospective[16] cohort studies have evaluated this combination in lowered doses in psoriasis and have increased or decreased the dosage as per response and adverse effects. Our study has been the one with the largest sample size thus far to assess a fixed-dose combination of MTX and CsA at half their standard doses for chronic plaque psoriasis.

We chose the weekly intramuscular route of administration of MTX instead of the more commonly used oral route in order to ensure bioavailability, patient compliance,[6] minimise gastrointestinal adverse effects[6] and to prevent accidental overdose of MTX which is one of the most common causes of acute MTX toxicity in our set up.

The male: female ratio in our study was 2.6:1. This ratio is comparable to that seen in other study of North India.[17] Family history was present in 10 (7.1%) patients- of whom 4 were in Group 1 and 6 in Group 2. (*P* 0.512). Indian studies report a lower familial incidence as compared to the Western studies.[2] Bedi[18] reported a positive family history of psoriasis in 14% of the patients whereas, Kaur *et al.*[19] reported family history in only 2% of the patients.

Patients in the combination group weighed more than the monotherapy group ($P = 0.005$). The height of the patients was also more in the combination group ($P = 0.025$). Since we have used the dosing of CsA as per the ideal body weight for obese patients, this difference in weight and height may not affect our result.

A meta-analysis of MTX in 2016 found that 45.2% [95% confidence interval 34.1-60.0] of patients achieve PASI 75 at primary end point (12 or 16 weeks, respectively, n = 705 patients across all studies).[8] In our study, the MTX monotherapy arm yielded a PASI-75 response in 43 (68.3%) patients at the end of 12 weeks.

When CsA was used at 2.5 mg/kg/day, a PASI-75 response at 12 weeks was seen in 52% by Timonen *et al.*[20] and Laburte *et al.*[21] On using at 3mg/kg/day, it was seen in 58% of patients at 12 weeks by Flytström *et al.*[22] and 60% of patients at 16 weeks by Heydendael *et al.*[23]

A comparison of our study with previous studies which had used CsA[20,21,23] or MTX[22-26] and done an assessment at similar end points is shown in Table 5. It can be seen that the combination of the two drugs at half their dose had a higher achievement of PASI-75 at 12 weeks compared to monotherapy with either drug.

Table 6 compares our study with previous studies which had used the same combination in chronic plaque psoriasis. All the previous studies reported a good or better outcome when a combination was used. In our study too, better response is seen with the combination group as compared to monotherapy. Though there was no difference between the groups in achieving PASI-50, higher number of patients in the combination group achieved PASI-90 and PASI-100 ($P < 0.001$). PASI-90 was achieved in 2 out of 18 patients in a previous study by Mohanan *et al.*[15] It was seen in 46 (75.4%) of our patients using the combination vs. 22 (35.5%) in the monotherapy group ($P < 0.001$).

We were unable to find any previous study using the combination which commented on the achievement of PASI-100. This was seen in 27 (43.3%) patients in the combination group vs. 10 (16.1%) in the monotherapy group.

Earlier achievement of target PASI was seen in the combination group which may be attributed to the rapid onset of action of CsA.[6]

Exclusion due to adverse effects was more in the combination group as compared to the monotherapy group. However this difference was not significant ($P = 0.54$). More patients were excluded in the combination group due to adverse events in a prior RCT in PsA.[4] However, this may be due to the longer duration of the study (12 months) in contrast to the 12 weeks in our study. We had decided the 12 weeks study period keeping in mind that CsA is preferably used intermittently in duration of 12-16 weeks.[27] After 12 weeks our plan was to stop CsA[28] and continue MTX at same dose in the combination group. In the monotherapy group, we gave MTX injection at every 2 weeks[29] instead of weekly for further 12 weeks.

Table 4: Adverse effects

Parameters	Group 1 (*n*=66), *n* (%)	Group 2 (*n*=67), *n* (%)	*P*
Laboratory adverse effects not leading to exclusion			
Deranged MCV	0 (0.0)	1 (1.5)	1.000
Platelet <150,000	4 (6.1)	5 (7.5)	0.748
AST >2x ULN, <3 ULN	9 (13.6)	7 (10.4)	0.605
ALT >2 ULN, <3 ULN	5 (7.6)	2 (3.0)	0.236
Raised TB <30% of baseline	6 (9.1)	5 (7.7)	0.773
Raised creatinine <30% of baseline	3 (4.5)	5 (7.5)	0.479
SBP ≥140 mm of Hg	5 (7.6)	11 (16.4)	0.117
DBP ≥90 mm of Hg	7 (10.6)	8 (11.9)	0.808
Laboratory adverse effects leading to exclusion			
Haemoglobin <8 g/dl	0 (0.0)	1 (1.5)	0.319
Platelet <100,000	1 (1.5)	0 (0.0)	0.496
AST ≥3 ULN	2 (3.0)	2 (3.0)	0.988
ALT ≥3 ULN	0 (0.0)	1 (1.5)	1.000
TB ≥30% of baseline	1 (1.5)	4 (6.0)	0.177
Creatinine ≥30% of baseline	1 (1.5)	1 (1.5)	0.991
SBP ≥150 mm of Hg	1 (1.5)	1 (1.5)	0.991
DBP ≥100 mm of Hg	0 (0.0)	1 (1.5)	1.000
Clinical adverse effects			
Nausea	16 (24.2)	13 (19.4)	0.499
Vomiting	11 (16.7)	5 (7.5)	0.117
Dyspepsia	10 (15.2)	5 (7.5)	0.161
Abdominal pain	6 (9.1)	3 (4.5)	0.290
Anorexia	9 (13.6)	5 (7.5)	0.246
Fever	2 (3.0)	1 (1.5)	0.550
Fatigue	6 (9.1)	2 (3.0)	0.139
Myalgia	1 (1.5)	4 (6.0)	0.177
Hair loss	4 (6.1)	1 (1.5)	0.166
Dizziness	3 (4.5)	0 (0.0)	0.078
Anxiety	2 (3.0)	0 (0.0)	0.244
URI	2 (3.0)	1 (1.5)	0.550
Headache	1 (1.5)	2 (3.0)	0.568
Diarrhoea	1 (1.5)	3 (4.5)	0.317
Glossitis	1 (1.5)	0 (0.0)	0.496
Acneform eruption	0 (0.0)	4 (6.0)	0.119
Hypertrichosis	0 (0.0)	2 (3.0)	0.157
Tremor	0 (0.0)	4 (6.0)	0.119
Weight gain	0 (0.0)	1 (1.5)	0.319
Insomnia	1 (1.5)	2 (3.0)	0.568
Nausea	16 (24.2)	13 (19.4)	0.499
Vomiting	11 (16.7)	5 (7.5)	0.117
Dyspepsia	10 (15.2)	5 (7.5)	0.161
Abdominal pain	6 (9.1)	3 (4.5)	0.290
Anorexia	9 (13.6)	5 (7.5)	0.246
Fever	2 (3.0)	1 (1.5)	0.550

P value determined by Fisher's exact probability test and Chi-square test. MCV: Mean corpuscular volume, AST: Aspartate transaminase, ALT: Alanine transaminase, ULN: Upper limit of normal, TB: Total bilirubin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, URI: Upper respiratory tract infection

Limitations

Our study had a few limitations in that it was non-blinded and had no follow-up beyond 12 weeks. The course of the disease following withdrawal of drug after 12 weeks cannot be commented upon. We also could not compare our results with a CsA monotherapy arm as it would have required a large sample size, which would have been difficult to meet during the limited time period.

Table 5: Comparison between the present study and similar randomised controlled trials controlled trials using methotrexate or cyclosporine for psoriasis

Study	Number of patients	Treatment groups	Baseline PASI	Endpoint for assessment	Percentage of patients achieving PASI-75 at endpoint
Timonen *et al*., 1990[20]	133 285 139	CsA 1.25 mg/kg/day CsA 2.5 mg/kg/day CsA 5 mg/kg/day	-	12 weeks	24 52 88
Laburte *et al*., 1994[21]	118 132	CsA 2.5 mg/kg/day CsA 5 mg/kg/day	24.9±7.0 25.1±8.	12 weeks	52 92
Heydendael *et al*., 2003[23]	44 44	MTX 15 mg/week CsA 3 mg/kg/day	13.4±3.6 14.0±6.6	16 weeks	1.60 2.71
Flytström *et al*., 2008[22]	37 31	MTX 7.5-15 mg weekly CsA 3-5 mg/kg/day	14.1±7.0 15.5±6.3	12 weeks	24 58
Ranjan *et al*., 2007[24]	15 15	Methotrexate (15-20 mg/week) Hydroxycarbamide (3-4.5 g/week)	25.11±11.75 22.99±5.66	12 weeks	66.6 13.33
Akhyani *et al*., 2010[25]	18 20	MTX 7.5 mg/week MMF 2 g/day	1.16.46±5.29 2.17.43±7.42	12 weeks	73.3 58.8
Dogra *et al*., 2012[26]	30 30	MTX 10 mg once weekly MTX 25 mg once weekly	12.7±3.99 13.02±5.63	12 weeks	92.3 72
Present study 2018-2019	63 62	MTX 0.3 mg/kg/week intramuscular injection MTX 0.15 mg/kg/week intramuscular injection + CsA 2.5 mg/kg/day in 2 divided doses	17.92±8.74 19.49±9.34	12 weeks	68.3 88.7

MMF: Mycophenolate mofetil, MTX: Methotrexate, CsA: Cyclosporine

Table 6: Comparison between the present study and previous studies which have used a combination of methotrexate and cyclosporine for chronic plaque psoriasis

Study	Number of patients	Dosing regimen	Baseline parameters	Duration	End of study parameters	Adverse effects
Clark *et al*. 1999[14]	19	MTX 13.9±4.4 mg weekly with CsA 2.6±0.9 mg/kg/day	Not mentioned	7 patients: 18.9±15.7 weeks 12 patients 193.2±160.6 weeks	Not mentioned	Short term treatment No toxicity Long term treatment Impairment of RFT: 6 patient (3: normalised on reduction of CsA, 3: improved but did not normalise following CsA dose reduction)
Fraser *et al*., 2005[4]	72 (PsA)	MTX 15.8 mg/ week + placebo 2.49 mg/kg/day MTX 16.2 mg/ week + CsA 2.48 mg/kg/day	PASI 2.2±2.7 2±2.3	12 months	PASI 1.9±2.8 0.8±1.3 *P*<0.001	Withdrawn due to adverse effects 2 (6%) 13 (34%) Serious adverse effects 1 (3%) 4 (11%) Adverse effects - Group 2 versus Group 1 Nausea (39% vs. 18%) Headache (24% vs. 6%) Burning sensation (13% vs. 0) Paraesthesia (11% vs. 0) Muscle cramps (11% vs. 0) Hypertrichosis (8% vs. 0)
Aydin *et al*., 2006[16]	20	MTX 10 mg/week intramuscular injection + CsA 3.5 mg/kg/day	PASI1 (Baseline)=7.2 (range 1.8-15.2)	9.5 weeks (range 4-50)	$PASI_2$ (after cessation of one agent)=7.2 (range 1.8-15.2) $PASI_3$ (end of therapy)=7.7 (range 0-30.4)	GI side effect: 4 Malaise: 2 Headache: 2 Skin infection: 3 Influenza like symptoms: 1 Depression: 2 Thrombophlebitis: 1 HTN (controlled): 2 Creatinine ≥30% of baseline: 4 Raised transaminases: 4 Macrocytic anaemia: 2 Hyperlipidemia: 2

Contd...

Table 6: Contd...

Study	Number of patients	Dosing regimen	Baseline parameters	Duration	End of study parameters	Adverse effects
Mohanan *et al*., 2014[15]	18	MTX (7.5-15 mg/week) + CsA 3 mg/kg/ day		14 patients: Short term (43.9±17.1 days) 4 patient: Long term (284.5±93.2 days)	Number of patients achieving PASI 90=2 PASI-75=3 PASI 5O=7 <PASI-50=2 Long term PASI-90=1 PASI-50=3	Raised creatinine=9 Hypertension=6 Raised liver enzymes=3 Hyperlipidemia=7 Hyperkalemia=2 Depression=2 Furuncle=1 Hyperiuricemia=1
Current study: 2018-2019	140	MTX 0.3 mg/ week injection MTX 0.15 mg/ week injection + CsA 2.5 mg/ kg/day	PASI 17.92±8.74 19.49±9.34	12 weeks	PASI 3.66±3.93 2.2±3.75 Percentage of patients achieving target PASI - (Group 1 vs. Group 2) PASI-50=93.8 versus 98.4% PASI-75=68.3% versus 88.7% PASI-90=35.5% versus 75.4% PASI-100=16.1% versus 44.3%	Patients excluded due to adverse effects 4 (6%) 7 (10.4%) *P*=0.54 No significant difference between the clinical and laboratory adverse effects between Groups 1 versus 2

PsA: Psoriatic arthritis, MTX: Methotrexate, CsA: Cyclosporine, PASI: Psoriasis area and severity index, RFT: Renal function test, HTN: Hypertension, GI: Gastrointestinal

Conclusion

The outcome of our study indicates that combination of reduced doses of MTX and CsA (i.e. MTX 0.15 mg/kg/ week with CsA 2.5mg/kg/day) is a safe and effective therapy for patients of chronic plaque psoriasis provided regular follow-up and monitoring is carried out. Higher efficacy and earlier onset of action was seen in the combination group with similar adverse effect profile as compared to methotrexate monotherapy. This finding may be more helpful in a country like India as the combination can be tried as second line treatment for refractory moderate to severe chronic plaque psoriasis, preferably before biologics where affordability is an issue. More studies which overcome the limitations of this study are needed to assess the long term risks and benefits of such a combination therapy. A comparison with a CsA monotherapy arm would also be informative.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent

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Nil.

Conflicts of interest

There are no conflicts of interest.

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