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CLINICAL TRIALS

Comparison between methotrexate and apremilast in Psoriatic Arthritis-a single blind randomized controlled trial (APREMEPsA study)

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Abstract

To compare the efficacy of methotrexate and apremilast in psoriatic arthritis (PsA). This Single blinded (physician), parallel group, randomized controlled trial was conducted at a single centre between October 2019 and December 2020. Adult PsA patients (age > 18 years), fulfilling CASPAR criteria, not on methotrexate/apremilast in last 3 months and never receiving bDMARDs or, JAK inhibitors, having active articular disease (one or more swollen joint or, having one or more tender entheseal point) were recruited. Primary outcome measure was rate of major cDAPSA response at week 24 and secondary outcome measures were ACR 20 response, change in PASI score, Maastricht enthesitis score, Leeds dactylitis index, and health assessment questionnaire-disability index (HAQ-DI) and number of adverse events at week 24 between methotrexate and apremilast groups. A total of 31 patients were recruited (15 in the apremilast arm and 16 in the methotrexate arm) amongst whom 26 patients completed 24 weeks follow up (13 patients in the apremilast arm and 13 patients in the methotrexate arm). Median cDAPSA score at baseline was 23 (9) in the apremilast group and 20 (21) in the methotrexate group. No difference in major cDAPSA response at week 24 was observed between apremilast and methotrexate arm (20% vs. 37.5%; p = 0.433). In the secondary outcome measures, there was no significant differences between both the groups. Both the drugs were safe without any serious adverse events. There was no significant difference between methotrexate and apremilast in terms of efficacy as measured by cDAPSA and ACR20 responses.

Keywords Psoriasis · Psoriatic arthritis · Spondyloarthritis · Antirheumatic agents · Methotrexate · Apremilast

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Introduction

Psoriatic arthritis (PsA) is a chronic musculoskeletal inflammatory disease associated with psoriasis with a prevalence of 7% to 42% in psoriasis patients in the US and 7.8% in India [1–3]. Treatment option for PsA ranges from conventional synthetic disease-modifying antirheumatic drugs (csDMARD) like methotrexate to biological DMARDs (bDMARDs) like TNFi, IL-17i, or IL-12/23i with targeted synthetic DMARDs or, small molecules like Janus kinase inhibitors (JAKinibs) and, apremilast being recent addition to the growing therapeutic armamentarium.

Methotrexate has traditionally been the first-line choice for both psoriasis and PsA with apremilast being a new addition. Although, various studies have shown that apremilast to be efficacious for both "treatment-modified" and "naive" PsA patients, the EULAR task force, in their 2019 recommendations, still advocated methotrexate as the preferred agent and recommended apremilast only in mild cases after failure of csDMARDs and with contraindications to other agents like bDMARDs or, JAKinibs [4]. Besides, there is a paucity of data on head-to-head comparison between methotrexate and apremilast in PsA patients. In this single-blind randomized controlled trial, we studied the efficacy of oral methotrexate with apremilast in patients with active psoriatic arthritis.

Methods

Trial designs and patients

This was a single-blind (assessor), parallel-group, randomized controlled trial with both active arms. It was a single-centre study conducted in a tertiary care hospital in north India. Ethical clearance was obtained from the institutional ethics committee (Protocol number-INT/ IEC/2019/2234; Date-15.10.2019) and trial was prospectively registered under Clinical Trial Registry-India ((Trial registration number-CTRI/2019/10/021723). Patients with active PsA presenting to rheumatology or, dermatology services between October 2019 and June 2020 were screened for enrolment in the study. Inclusion criteria were: (1) Age > 18 years, 2) Fulfilling CASPAR criteria for PsA, 3) Swollen joints ≥ 1 and /or tender entheseal point ≥ 1, 4) Consenting to participate in the study. Exclusion criteria were: 1) receiving the study drugs, methotrexate or apremilast, in the last 3 months, (2) receiving any biological DMARDs or another small molecule DMARDs like JAK inhibitors anytime in the past, (3) history of recent initiation or a change in the dose of other

csDMARDs in the last 3 months before randomization, (4) use of oral glucocorticoids at a dose of more than 10 mg/ day of prednisolone or equivalent, (5) presence of liver or, renal dysfunction and 6) presence of haematological abnormalities. Detailed inclusion and exclusion criteria are provided in the supplementary table.

Randomization and treatment

Patients were randomized by variable block randomization (block size of 4 and 6) in a 1:1 ratio to the methotrexate or apremilast arm. Considering the low prevalence of PsA, variable block randomization was planned to avoid any bias and achieve balance in allocation of the participants between the two groups. Allocation concealment was done using serially numbered opaque sealed envelopes. In the methotrexate arm, methotrexate was started at a dose of 15 mg weekly with subsequent dose increments by 5 mg every 4 weeks depending on disease activity with the maximum target dose being 25 mg per week. In the apremilast arm, apremilast was started at a dose of 10 mg once per day which was increased by 10 mg every day to a target dose of 30 mg twice daily. Up to two doses of intraarticular glucocorticoids were allowed during the study period. csDMARDs, not mentioned in the exclusion criteria, and oral glucocorticoids, up to 10 mg per day of prednisolone or equivalent, were continued during the study period if the patient was already receiving those drugs before enrolment into the study. Treatment failure was defined as an increase in the swollen joint count by two or more joints from baseline, despite the use of maximum permitted doses of study drugs and two doses of intraarticular glucocorticoids, after 16 weeks of randomization. Patients having treatment failure after 16 weeks were eligible for rescue treatment and the drugs used were at the discretion of the treating physician.

Patient assessment and follow up

Demographic, clinical, and laboratory parameters (Complete blood count, ESR, C-reactive protein, liver and renal function tests) and radiological investigations were noted at baseline in all patients. Patients were then followed up with physical visits at 4, 8, 16, and 24 weeks. At each visit, the patient was clinically assessed and the results of blood counts, liver and renal function tests, ESR and CRP were noted.

Disease activity was assessed at each visit using 68 tender joint counts (TJC) and 66 swollen joint counts (SJC), patient global assessment of disease (PGA, 0–10) and physician global assessment of disease (PhGA, 0–10), patient assessment of pain (PAP, 0–10), Leeds dactylitis index (LDI), Psoriasis area and severity index score (PASI), Maastricht ankylosing spondylitis enthesitis score (MASES), were

assessed at each visit. Functional status was assessed by the health assessment questionnaire disability index (HAQ-DI) Indian version [5]. The clinical disease activity index for PsA (cDAPSA) was calculated at baseline and 24 weeks and it included TJC, SJC, PAP and PGA. Based on the cDAPSA score at 24 weeks, patients were categorized into remission (< 4), low disease activity (4–13), moderate disease activity (14–27) and high disease activity (> 27). Major response was defined as a decrease of $\geq 85\%$ from baseline in cDAPSA score [6].

Outcomes

The primary efficacy outcome was a major cDAPSA response at week 24. Secondary outcomes included ACR 20 response at week 24 and change in HAQ-DI, PASI, MASES and LDI from baseline to week 24. Safety outcomes were the number of adverse events and serious adverse events from baseline to week 24.

Statistical analysis

A sample size of 194 was calculated by taking a response rate of 60% in methotrexate as per currently available data, a non-inferiority margin of 20%, a power of 80% and a two-sided alpha error of 0.05. However, due to the COVID-19 pandemic and the resultant closure of routine medical services at our institute, only 31 patients were enrolled in the study. Both intention-to-treat (ITT) and per-protocol analysis were performed. The last observation carried forward method was used for patients who dropped out of the study before 24 weeks. Continuous variables were expressed as medians with interquartile range and categorical variables were expressed as proportions and percentages. Fisher's exact test was used for comparing categorical variables while the Mann–Whitney U test or Wilcoxon signed-rank test were used for comparing continuous variables. Statistical analysis was done using SPSS software version 25 (IBM Corp, New York, USA). A p-value of < 0.05 was considered significant.

Results

A total of 65 patients were screened for eligibility and after excluding 34 patients for various reasons, 31 patients were enrolled in the study. Fifteen patients were randomized to the apremilast arm and 16 patients were randomized to the methotrexate arm. Two patients in the apremilast arm and three patients in the methotrexate arm were lost to follow-up during the study period. Thus, a total of 26 patients completed 24 weeks of follow-up. The patient's disposition has been depicted in Fig. 1.

Baseline characteristics and treatment details

The median (IQR) age of the study population was 38 (16) years and 17 (54.8%) were males. The median (IQR) duration of arthritis was 2 (2) years. Other baseline characteristics of the patients recruited in the study are depicted in Table 1. The median (IQR) tender joint count was 3 (4) in the apremilast group and 4.5 (14.5) in the methotrexate group. The median (IQR) swollen joint count was 2 (1) in the apremilast group and 2.5 (4) in the methotrexate group. Dactylitis was present in two (13.3%) patients in the apremilast group and seven (43.7%) patients in the methotrexate group. Enthesitis was present in four (26.7%) patients in the apremilast group and eight (50%) patients in the methotrexate group. The median (IQR) PASI score at baseline was 3.6 (5.7) in the apremilast group and 1.2 (5.6) in the methotrexate group. The median (IQR) cDAPSA score at baseline was 23 (9) in the apremilast group and 20 (21) in the methotrexate group. As per the cDAPSA score, two patients each in the apremilast and methotrexate groups had low disease activity, while the rest had moderate to high disease activity at baseline. None of the patients were receiving other csDMARDs and only one patient in the apremilast group was receiving low-dose oral glucocorticoid at the time of enrolment. The baseline clinical and laboratory parameters of the study population are presented in Table 2.
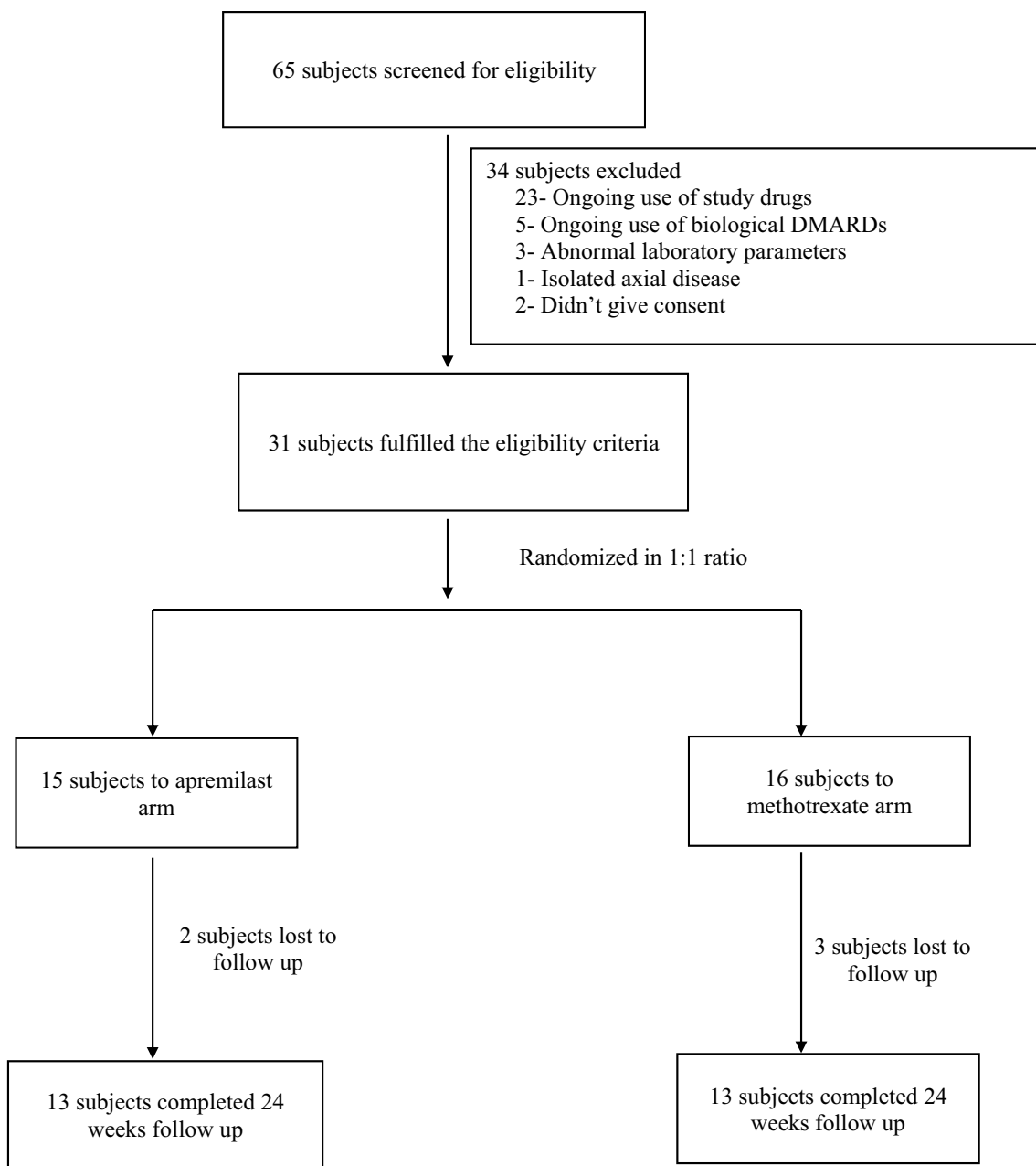
Primary outcome

Major cDAPSA response at week 24 was achieved in three (20%) patients in the apremilast group and six (37.5%) patients in the methotrexate group (p = 0.433). Even on per-protocol analysis, there was no difference in the major cDAPSA response between the two groups (23.07% vs 46.15%, p = 0.411). Major cDAPSA response in both groups is shown in Table 3. The change in individual components of cDAPSA from baseline to week 24 is shown in Fig. 2. On post-hoc analysis of patients with moderate to high disease activity at baseline, four out of 13 patients (30.8%) achieved remission and two out of 13 patients (15.4%) achieved low disease activity in the apremilast group. Similarly, five out of 14 patients (50%) achieved remission while none achieved low disease activity in the methotrexate group.

Secondary outcomes

ACR-20 response at week 24 was achieved in seven (46.67%) patients in the apremilast group and nine (56.25%) patients in the methotrexate group (p = 0.724).

The median PASI score at week 24 was 0.1 (0.88) in the apremilast group and 0.1 (0.33) in the methotrexate group. The within-group change in PASI score from baseline to week 24 was significant in both apremilast (2.0 (6.0);

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                    │  65 subjects screened for        │
                    │  eligibility                     │
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                                    │    │  34 subjects excluded                │
                                    │    │     23- Ongoing use of study drugs    │
                                    │    │     5- Ongoing use of biological     │
                                    │    │        DMARDs                        │
                                    │    │     3- Abnormal laboratory parameters │
                                    │    │     1- Isolated axial disease         │
                                    │    │     2- Didn't give consent            │
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                    │  31 subjects fulfilled the       │
                    │  eligibility criteria            │
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                          Randomized in 1:1 ratio
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Fig. 1 Details of patient disposition

15 subjects to apremilast arm	16 subjects to methotrexate arm
2 subjects lost to follow up	3 subjects lost to follow up
13 subjects completed 24 weeks follow up	13 subjects completed 24 weeks follow up

$p = 0.003$) and methotrexate (0.35 (2.33); $p = 0.003$) groups. However, there was no significant difference in the mean change in PASI score from baseline to week 24 between the two groups ($p = 0.378$).

The median (IQR) MASES at week 24 was 0.0 (1.0) in the apremilast group and 0.0 (1.5) in the methotrexate group. There was no significant difference in the change in MASES from baseline to week 24 both within the two groups ($p = 1.0$ for the methotrexate group and $p = 0.285$ for the apremilast group) and between the two groups ($p = 0.621$). The median change in dactylitis score from baseline to week 24 was significant in the methotrexate group (0.0 (9.1); $p = 0.028$) while the change in the apremilast group was not significant ($p = 0.18$). However, there was no significant difference in the change in dactylitis score between the two groups ($p = 0.224$). The change in HAQ-DI from baseline to week 24 was significant in the methotrexate arm (0.33; $p = 0.01$) but not in the apremilast arm (0.41; $p = 0.059$). However, when compared between the two groups, the change in HAQ-DI was not significant ($p = 0.672$).

Details of the secondary outcomes are depicted in Table 3.

Table 1 Baseline characteristics of study subjects

Characteristics	Apremilast group (n = 15)	Methotrexate group (n = 16)
Age, (Years) [Median (IQR)]	38 (15.5)	39 (14.7)
Male: Female	8:7	9:7
Comorbidities		
Diabetes mellitus, n (%)	4 (26.7)	3 (18.7)
Hypertension, n (%)	3 (20)	3 (18.7)
Coronary artery disease, n (%)	1 (6.7)	0
Hypothyroidism, n (%)	1 (6.7)	0
Previous use of DMARDs, n (%)	2 (13.3)	1 (6.2)
Duration of PsA, (years) [Median (IQR)]	1 (1.5)	3 (4.2)

Adverse effects

A total of nine adverse events in seven patients were noted during the study period. All the adverse events noted were mild and there was no difference in the rate of adverse events

between the two groups (p = 0.394). Transaminitis was the commonest adverse event noted, 25% in methotrexate group and 6.7% in apremilast group (p = 0.333). Liver enzymes normalised with discontinuation of the study drugs for two weeks in all patients and none of them had recurrence of transaminitis after restarting the study drugs after that period. The target dose of 30 mg twice a day of apremilast was achieved in all the patients in apremilast group. The median dose of methotrexate given was 15 mg (5) per week in the methotrexate group. Maximum dose of methotrexate used was 25 mg per week, in three patients.

Table 4 shows the details of adverse events noted during the study period.

Discussion

In this single-blind, randomized controlled study, we randomized 31 patients of PsA with active peripheral arthritis or enthesitis to receive either methotrexate or apremilast for 24 weeks. There was no difference in the efficacy of

Table 2 Baseline characteristics of the study subjects

Parameters*	Apremilast group (n = 15)	Methotrexate group (n = 16)
Tender joint count	3 (4)	4.5 (14.5)
Swollen joint count	2 (1)	2.5 (4)
Patients having dactylitis, n (%)	2 (13.3)	7 (43.7)
Leeds dactylitis index	0.0 (0.0)	0.0 (24.36)
Patients having enthesitis, n (%)	4 (26.7)	8 (50)
MASES	0.0 (3)	0.0 (1)
PASI score	3.6 (5.7)	1.2 (5.6)
cDAPSA score	23 (9)	20 (21)
cDAPSA score		
Remission (≤4) n (%)	0	0
Low disease activity (> 4 to ≤ 13), n (%)	2 (13.3)	2 (12.5)
Moderate disease activity, (> 13 to ≤ 27), n (%)	11 (73.3)	10 (62.5)
High disease activity (> 27), n (%)	2 (13.3)	4 (25)
HAQ-DI	0.67 (0.58)	0.67 (0.64)
Presence of radiographic erosions n (%)	0	2 (12.5)

*All parameters were expressed as median with IQR unless mentioned

Table 3 Primary and secondary outcomes at week 24-ITT analysis

Outcome	Apremilast group (n = 15)	Methotrexate group (n = 16)	p value
Major cDAPSA response	3 (20)	6 (37.5)	0.433
ACR 20 response at week 24, n (%)	7 (46.67)	9 (56.25)	0.724
Change of PASI score at week 24, median (IQR)	2.0 (6.0)	0.35 (2.33)	0.378
Change in MASES at week 24, median (IQR)	0.0 (0.0)	0.0 (0.0)	0.621
Change in dactylitis score at week 24, median (IQR)	0.0 (0.0)	0.0 (9.13)	0.224
Change in HAQ-DI score at week 24, median (IQR)	0.41 (0.67)	0.33 (0.58)	0.672
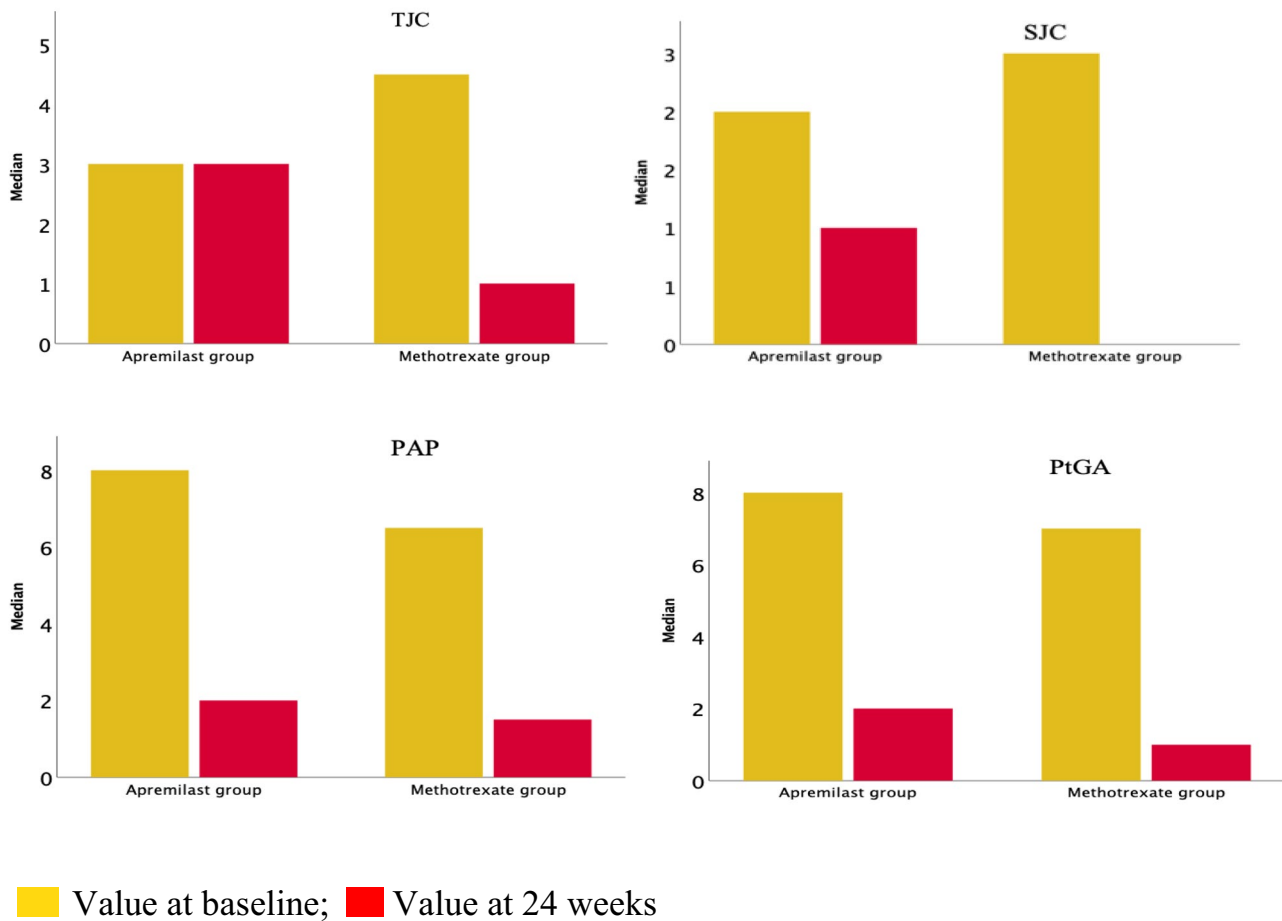
Fig. 2 Components of cDAPSA. TJC-Tender joint count; SJC-Swollen joint count; PAP-Patient assessment of pain; PtGA-Patient global assessment

Table 4 Comparison and details of adverse effect profile in apremilast and methotrexate group

Parameters	Apremilast group (n = 15)	Methotrexate group (n = 16)	p value
Adverse events	3	6	0.394
Number of subjects with at least one adverse event	2	5	
Transaminitis n (%)	1 (6.67)	4 (25)	0.333
Gastro-intestinal intolerance (nausea/vomiting) n (%)	1 (6.67)	1 (6.25)	1.0
Renal dysfunction n (%)	0	1 (6.25)	1.0
Palpitation n (%)	1 (6.67)	0	0.484

both the drugs as measured by major cDAPSA response, ACR20 response, and PASI. Both the drugs were well tolerated and had similar adverse event profiles.

Major cDAPSA response at 24 weeks was noted in 20% patients in the apremilast group and 37.5% in the methotrexate group in our study. Previously, Appani et al. reported major cDAPSA response in 43.8% of patients receiving methotrexate for 24 weeks, which is similar to that noted in our study [7]. Although there is no data about the major cDAPSA response with apremilast, recently Mease et al. in their post-hoc analysis showed that around 25–47% patients achieved cDAPSA remission/low disease activity with apremilast depending on baseline disease activity [8].

In our study, among the patients with moderate or high disease activity at baseline, the rates of remission and low disease activity as per cDAPSA at 6 months were achieved in 30.8% and 15.4% respectively with apremilast compared to 50% and 0% respectively with methotrexate. Mease et al. in their post-hoc analysis of PALACE-4 data showed likelihood of remission/low disease activity with apremilast is higher in patients with low disease activity in baseline which also corroborates with the findings in our study [8]. Also, in the Corrona Psoriatic Arthritis/Spondyloarthritis Registry

data, among the PsA patients with moderate or high disease activity, remission, and low disease activity as per cDAPSA was achieved in a much lower proportion of patients compared to our study, 5.9% and 23.5% patients on apremilast compared to none of the patients on methotrexate [9]. However, the major difference between the two studies was that most of the patients in the Corrona registry had received ≥ 1 bDMARDs prior to receiving apremilast or methotrexate while none of the patients in our study received bDMARDs. This also indicates that the response rates with apremilast and methotrexate are better in treatment naïve patients than in bDMARD unresponsive patients.

The ACR20 response rates were 46.67% and 56.25% with apremilast and methotrexate respectively at end of 24 weeks in our study. These rates were similar to that reported previously in trials using methotrexate or apremilast. In the TICOPA trial, ACR20 response rates at 48 weeks of methotrexate therapy were 44% with standard care and 61.8% with tight control strategy [10]. In the methotrexate alone arm of the RESPOND trial, the ACR20 response at week 16 was seen in 66.7% while in the SEAMPsA trial, the ACR20 response at week 24 was seen in 50.7% in the methotrexate alone arm [11, 12]. PALACE-4 trial, which studied the efficacy of apremilast in treatment naïve patients, reported an ACR20 response of 46.4% at week 24, similar to that noted in our study [13]. In the trials that studied the efficacy of apremilast in csDMARDs or bDMARDs unresponsive PsA patients, the ACR20 response rates at 24 weeks ranged between 36.6% and 56.8% [14–17].

Both methotrexate and apremilast resulted in significant improvement in skin involvement in our study and there was no difference in change in PASI score between the two groups at 24 weeks. Similar results were noted in previous studies on the use of methotrexate and apremilast in patients with PsA [7, 10, 11, 13–16, 18].

In our study, methotrexate resulted in an improvement in dactylitis similar to that noted in the TICOPA trial and the study by Appani et al. [7, 10]. However, other studies failed to demonstrate a similar efficacy of methotrexate on dactylitis [11, 12]. Previous studies demonstrated that methotrexate resulted in an improvement in enthesitis scores, a finding which could not be replicated in our study [10–12]. Contrary to the findings of PALACE 1, 2, 3 and 4 trials, apremilast did not result in an improvement of dactylitis or enthesitis in our study [13–16]. The low number of patients with enthesitis and dactylitis at baseline and the small sample size in our study might have resulted in these differences.

The change in HAQ-DI score was significant in the methotrexate arm but not in the apremilast arm in our study. Previous studies reported improvement in HAQ-DI scores with both methotrexate and apremilast [7, 12–16, 18]. Both the drugs were well tolerated by the study subjects with no serious adverse events noted with the drugs.

Transient transaminitis and gastrointestinal intolerance were the commonest adverse effects reported previously with methotrexate similar to that noted in our study [11, 18]. Similarly, gastrointestinal intolerance was the commonest adverse event with apremilast, noted in previous studies and also in this study [20].

This is the first study with a head-to-head comparison between methotrexate and apremilast in PsA, however, there were a few limitations to our study. The first and the major limitation was the small sample size. Second, the majority of the patients in our study had oligoarticular involvement with less dactylitis and enthesitis and hence these results cannot be generalized to all patients of PsA. Third, the effect of these drugs on axial involvement has not been studied in this study. However, these drugs are not expected to have much effect on axial disease anyway. Fourth, although DAPSA can be easily used in clinical practice and one of the best composite disease activity measures in PsA, it has some inherent problems. It doesn't capture some aspects of psoriatic diseases like skin, enthesitis or, dactylitis [21].

To conclude, in this small head-to-head trial between methotrexate and apremilast in treatment naïve PsA patients, both drugs were equally efficacious in controlling disease activity and were well tolerated. However, considering the small sample size in our study, a larger study is needed to confirm these findings.

Declarations

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