Hypothesis

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Safety and Efficacy of Tofacitinib *vs* Methotrexate in the Treatment of Psoriatic Arthritis- an Open Label Randomized Study

Background: Methotrexate, an anti-folate drug, is widely accepted and commonly used DMARD for the treatment of PsA. Tofacitinib is a JAK inhibitor, and relatively a new drug for PsA.

Aims: To assess and compare safety and efficacy of Tofacitinib and Methotrexate in the treatment of PsA.

Methodology: This open label, randomized, prospective, single center study was conducted in Department of Rheumatology, BSMMU, Dhaka for 1½ years from September, 2017 to February, 2019. 61 patients, aged > 18 years with the diagnosis of PsA with predominant peripheral arthritis for > 3 months were randomized into two groups. 29 patients (Tofacitinib 5mg BD) and 32 patients (MTX from 15 mg/week to 25 mg/week over 1 month) were enrolled and followed-up at the end of 1, 3 and 6 months. Primary endpoint was assessed by ACR 20 response at the end of 3 months. Patients who achieved treatment target on the basis of DAPSA score at the end of 3 months were allowed to continue previous treatment and assessed for safety and efficacy till 6 months. Treatment target non-achievers in both groups were put on alternative treatment, and were assessed for safety at the end of 6 months. Secondary outcome measures were 66/68 joints SJC/TJC, VAS for pain, ESR, CRP, DAPSA, DAS28, PASI, PASI 75 response, MASES and HAQ-DI. Safety assessment was done on the basis of clinical history, examination and laboratory findings at each follow-up. Ethical clearance was obtained from IRB, BSMMU at the beginning. Statistical analysis was done using chi-square test, Fisher's exact test, paired sample t-test and independent sample t-test. Missing data was interpreted by ITT analysis.

Results: Of the 61 patients, mean age of onset was 39.5 years, mean BMI was 27.7 kg/m^2, M:F ratio was 1.25:1 and mean duration of disease was 3.4 years. ACR 20 response was achieved by 79.3% and 68.8% of patients in Tofacitinib and MTX group respectively at the end of 3 months (p=0.395, 95% CI). Treatment target (DAPSA) was achieved by 37.9% in Tofacitinib group and 43.75% in MTX group (p=0.795, 95% CI). PASI 75 responses also showed similar results in both the groups with 15.4% and 14.8% (p=1.000, 95% CI) at 3 months in Tofacitinib and MTX group respectively. Tofacitinib group of patients had earlier achievement of ACR 20 response from month 1, which was significantly greater than in MTX group (51.3% vs 25%, p=0.038, 95% CI). Changes in clinical parameters- (TJC/SJC and VAS for pain); composite measures (DAPSA and DAS28), and functional assessment (HAQ-DI) showed significant improvement starting from month 1 in both the groups. ESR started showing significant results in both groups from 3 months. Improvement in mean CRP was significant only in Tofacitinib group at 3 months (p=0.003, 95% CI) and 6 months of therapy. Significant change in mean MASES was seen in Tofacitinib group at the end of 3 months (p=0.001, 95% CI). Over the duration of 6 months of treatment, 69% (20) and 71.9% (23) of patients experienced some AEs, 6.1% (2) patients and no (0) patients suffered from SAEs, and 10.3% (3) patients and 3.1% (1) patient had to be withdrawn from study due to some AEs in Tofacitinib and Methotrexate groups respectively. Conclusion: In this study, Tofacitinib was found to be as efficacious as Methotrexate in the treatment of Psoriatic arthritis. Tofacitinib showed better efficacy in improvement of CRP, and also in the improvement of enthesitis as compared to Methotrexate. Both the drugs showed similar improvement in skin psoriasis. Infection related AEs were more common in Tofacitinib treated patients and GI-related AEs are common in MTX treated patients. This study was funded by Globe Pharmaceuticals Limited.

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Keywords: sPsA- Psoriatic Arthritis ● DMARD- Disease Modifying Anti-Rheumatic Drugs ● JAK inhibitor- Janus Kinase inhibitor ● DAPSA- Disease Activity in Psoriatic Arthritis ● ACR- American College of Rheumatology ● TJC/SJC- Tender Joint Count/Swollen Joint Count ● DAS-28- Disease Activity Score-28 ● VAS- Visual Activity Score ● AEs- Adverse Events ● SAEs- Serious Adverse Events ● MASES- Maastricht Ankylosing Spondylitis Enthesitis Score ● ITT- Intention To Treat

Introduction

Psoriatic arthritis (PsA), a member of the spondyloarthritis (SpA) family is a chronic inflammatory arthritis with heterogeneous presentation. It may present as progressive arthritis, skin psoriasis, nail changes, sacroiliitis, spondylitis, enthesitis, dactylitis or uveitis. Prevalence varies from 0.3%-1% [1]. Among patients with psoriasis, 7% to 42% develop arthritis, and plaque psoriasis is the most common phenotype [2].

Treatment with NSAIDs, I/A steroid and csDMARDs had been the backbone of management of PsA for many years. Improvement in our understanding of immunopathogenesis of PsA, including Th17-Th22-IL-23 axis in mouse models of both psoriasis and PsA [3] and elevated TNF levels in psoriatic skin, synovium, and joint fluid [4] has led to new immunomodulatory therapies. Synovial explant tissues obtained from psoriatic arthritis joints have shown to produce higher levels of the Th1 cytokines, IL2 and IFN-amma [5]. Other innate cytokines, such as IL18 and IL15 are also present in psoriatic arthritis synovial tissue. Increase in circulating Th17 and an increase in IL17 has been found in skin, and synovial tissue and fluid of psoriatic arthritis patients [6].

EULAR 2015 guidelines have recommended early consideration of csDMARDs in patients with peripheral arthritis with adverse prognostic factors and bDMARDs in patients with predominantly axial disease that is active, and has insufficient response to NSAIDs. Use of NSAIDs is considered the first choice in both peripheral as well as axial disease, but many patients fail to respond to NSAIDs [7].

The efficacy of csDMARDs and the role of glucocorticoids remain unclear, and combination therapy with biologics is under-researched in inflammatory arthritis [8]. Methotrexate, an antifolate drug has been recommended as first line treatment after failure of NSAIDs, and has so far shown a promising result in peripheral arthritis, as well skin psoriasis, but its efficacy in axial involvement, enthesitis or dactylitis is not promising [9].

Tofacitinib is an oral Janus Kinase (JAK) inhibitor with immunomodulatory and anti-inflammatory properties. Upon administration, tofacitinib binds to JAK and prevents the activation of the JAK-signal transducers and activators of transcription (STAT) signaling pathway. This decreases the production of pro-inflammatory cytokines and prevents inflammatory response and the inflammation-induced damage caused by immunological diseases. Studies have shown the role of tofacitinib in treatment of many immunological disease (viz. Rheumatoid arthritis, Psoriasis, Psoriatic arthritis, Alopecia aereata, Dry eye disease) and metastatic diseases. The common adverse effects of Tofacitinib are risk of infection, especially URTI, hypertension, nephrotoxicity, hepatotoxicity and hyperlipidemia.

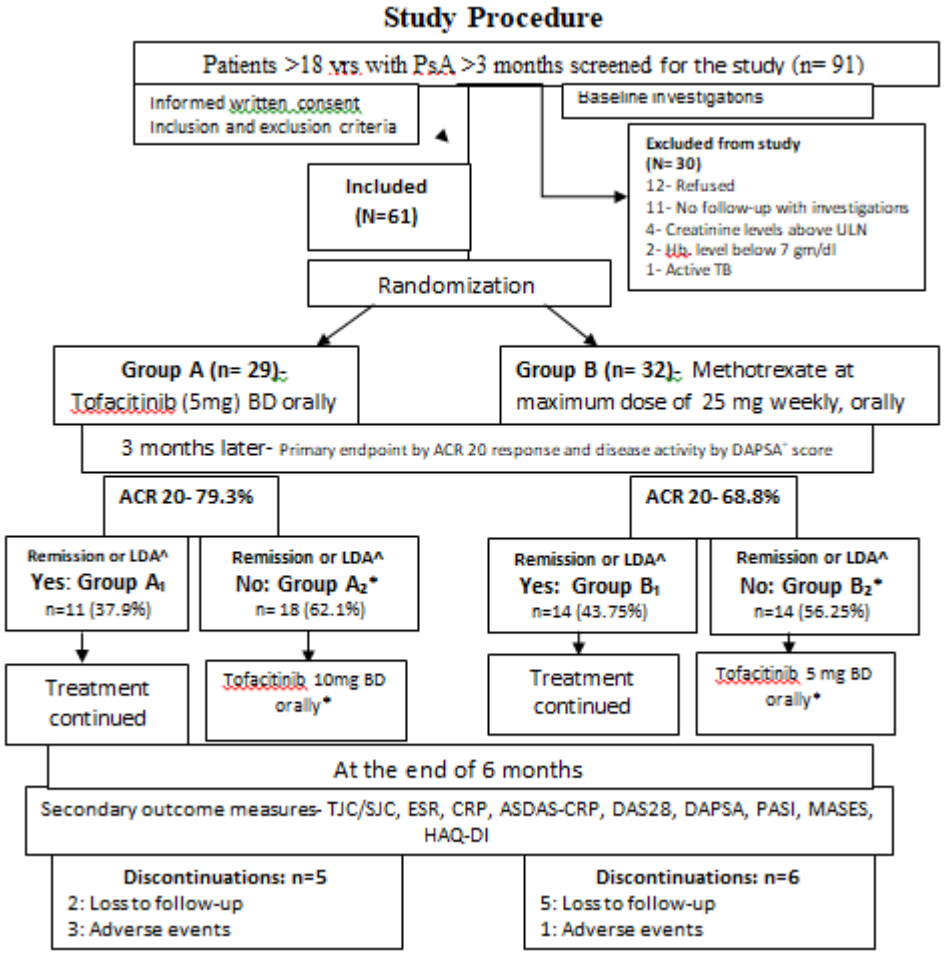
Evidences suggest the role of tofacitinib in regulation of synovitis through modulation of innate and adaptive immune responses [10], inhibition of interferon and interleukin-17 production by human CD4 T Cells [11] and inhibition of TNF-induced chemokine expression in fibroblast-like synoviocytes [12].

Materials and Methodology

This open label, randomized, prospective study was conducted in Department of Rheumatology, BSMMU, Dhaka, for 1½ years from September, 2017 to February, 2019. 61 patients with PsA for >3 months, aged >18 years, with predominant peripheral joint involvement, not responding to at least 2 NSAIDs over a duration of 4 weeks were enrolled in the study.

We came across 91 patients of PsA in our center over a duration of 1 year (September, 2017 to August, 2018), who were DMARD naïve or DMARD-free for at least last 3 months. Of the 91 patients, 30 couldn't be enrolled to the study (12 patients refused, 11 patients didn't come to follow-up, 4 patients had creatinine levels above ULN, 2 had Hb. level below 7 gm/dl and 1 had Active TB) (**Figure 1**).

The patients fulfilling inclusion criteria were randomized prospectively into two groups by random number table, which was generated by the statistician of our study. 29 patients were enrolled in Tofacitinib group (Group A) and 32 patients were enrolled in MTX group (Group B). Doses were Tofacitinib 5mg BD and MTX in increasing dose from 15 mg weekly to 25 mg weekly over a duration of 1 month. Detailed history, clinical examination, composite measures and baseline investigations were recorded in a pre-structured data collection sheet.



* Regular follow-up and safety assessment, excluded from the efficacy assessment
˚DAPSA: Disease activity for Psoriatic Arthritis
^Remission- DAPSA<4 or LDA (Low disease activity)- DAPSA 4-14

Figure 1. Flowchart showing study procedure.

Primary endpoint was assessed by ACR 20 response at the end of 3 months. DAPSA was the tool used to assess treatment target at the end of 3 months. Patients who achieved remission or low disease activity (treatment target achievers) were allowed to continue previous medications. Patients in Tofacitinib group, not achieving treatment target were put on Tofacitinib 10 mg BD i.e. at an increased dose. Similarly, MTX group patients not achieving it were put on Tofacitinib 5 mg BD.

This research was structured into two phases. Phase I was the study till primary endpoint or the initial 3 months, and phase II from month 3 to month 6 in the treatment target achievers.

After 3 months, only the treatment target achievers were followed-up for the assessment of efficacy till 6 months. Patients not achieving treatment target were followed-up for treatment monitoring and safety assessment, and were excluded from the efficacy assessment. Those patients not responding to treatment at the end of 6 months were not allowed to continue the therapy and put on alternative treatment.

The baseline investigations were CBC with ESR, Urine RME, CRP, CXR PA view, tuberculin skin test, SGPT and serum Creatinine. Active and latent TB infection was ruled out on the basis of thorough history, clinical examination, tuberculin skin test and chest X-ray. The secondary endpoints were assessed at the end of 1, 3 and 6 months.

Secondary outcome measures were ACR 20/50/70 responses, 68/66 TJC/SJC, VAS for pain, ESR, CRP, DAPSA, DAS28-ESR, PASI, PASI 75 response, MASES, and HAQ-DI.

Safety was monitored clinically and by laboratory investigations at each follow up. Patients were explained about each and every possible side effects and the

importance of regular follow up. They were also informed about any conditions requiring urgent medical check-up and hospital admission. The investigations at each follow-up were CBC with ESR, CRP, Urine RME, SGPT, and Serum Creatinine.

Clinical evaluation of joint disease was done by a rheumatologist, while clinical evaluation of cutaneous manifestations was performed by a dermatologist at baseline and at each follow up.

Follow-up schedule was maintained regularly and every call of the patient was attended by the investigator group. Patients who developed serious adverse effect like life threatening infection with organ involvement or requiring hospital admission were withdrawn from the therapy.

Statistical analysis was done using chi-square test, Fisher's exact test, paired sample t-test and independent sample t-test. Missing data was interpreted by ITT analysis.

Results

Result has been divided into two sections, Phase I (Initial 3 months) and Phase II (3 to 6 months). Out of the 61 enrolled patients, 11 patients didn't continue their treatment; 11.4% (7) of patients (2 in Group A and 5 in Group B) missed their follow-up, and 6.5% (4) of patients (3 in Group A and 1 in Group B) had to be withdrawn from the study due to some serious adverse events.

Baseline Variables

Among the 61 patients, M:F ratio was 1.25: 1, [55.7% (34) males and 44.3% (27) females], mean age of onset was 39.5 years, mean BMI was 27.7 kg/m², mean duration of disease was 3.4 years, and mean monthly family income was 22,443 BDT. 14.8% (9) of patients had a history of tobacco use (smoking or chewing tobacco) and 21.3% (13) patients were suffering from DM or HTN (**Table 1**).

Intergroup comparison of the demographic variables, clinical and inflammatory parameters, composite scores, PASI score, MASES and HAQ-DI are shown in (**Table 1**).

Table 1. Numbers, mean values and percentages of baseline variables in both groups.

Group Variables	Group A (n=29, 26[w], 23[P]) Mean ± SD/ n (%)	Group B (n=32, 27[w], 19[P]) Mean ± SD/ n (%)
Age in years	40.1 ± 12.45	39.06 ± 12.57
Sex	Male: n= 15 (51.7%) Female: n= 14 (48.3%)	Male: n= 19 (59.4%) Female: n= 13 (30.6%)
BMI[a] (kg/m²)	22.17 ± 3.52	23.32 ± 3.02
Disease duration (years)	3.79 ± 1.33	3.21 ± 1.75
Tobacco use*	4 (13.8%)	5 (15.6%)
Comorbidities^	7 (24.1%)	6 (18.8%)
Entheseal involvement	23 (79.3%)	19 (59.4%)
Skin psoriasis[β]	26 (89.7%)	27 (84.4%)
Monthly family income (Taka)	26069 ± 16390	19156 ± 10396
Occupation Housewife Student Shopkeeper Others[∃]	 11 (37.9%) 3 (10.3%) 3 (10.3%) 12 (41.3%)	 11 (34.4%) 4 (12.5%) 2 (6.3%) 15 (46.9%)
TJC*	25.14 ± 16.73	19.06 ± 12.7
SJC^	17.93 ± 13.63	13.22 ± 10.03
VAS[a] for pain	7.41 ±2.07	7.72 ± 1.98
ESR[®]	64.83 ± 36.52	50.84 ± 37.25
CRP[°]	22.02 ± 20.06	16.72 ± 23.17
DAPSA[¯]	59.66 ± 31.35	48.35 ±22.34
DAS28[x]	6.44 ±1.44	5.8 ± 1.48
PASI[w]	3.49 ± 3.33	5.55 ± 5.1
MASES[P]	3.04 ±2.05	2.89 ± 2.15
HAQ-DI[h]	1.61 ± 0.61	1.46 ± 0.6

n= number of patients, %= Percentage, SD: Standard deviation, Group A: Tofacitinib group; Group B: Methotrexate group, [a]Body mass index; *Tobacco use: Chewable tobacco or smoking; ^Comorbidities: Diabetes mellitus or Hypertension, [∃]Others: Pvt. Institute job, ex-migrant worker, teacher, garment industry job, businessman, farmer, goldsmith, salesman; *TJC: tender joint count; ^SJC: Swollen joint count; [β]Current, past or family history of skin psoriasis; [a]VAS: Visual analog score, [®]ESR: Erythrocye sedimentation rate; [°]CRP: C-reactive protein; [¯]DAPSA: Disease Activity index for Psoriatic Arthritis; [x]DAS-28: Disease activity score- 28 joint, [w]PASI: Psoriasis Area and Severity Index; [P]MASES: Maastricht Enthesitis Score; [h]HAQ-DI: Health Assessment Questionnaire- Disability Index

At the end of 1 month, significant ACR 20 response was seen in Tofacitinib group (p=0.038, 95% CI) (**Table 2**). Thus, Tofacitinib was equally efficacious to Methotrexate after 3 months of therapy, while its efficacy was significantly greater than that of Methotrexate at the end of month 1.

Composite measures (DAPSA and DAS28), and treatment target achievers by DAPSA

Decrease in mean DAPSA and DAS28 were statistically significant from baseline through month 1 to month 3 (p-value<0.001, 95% CI) in both the groups (**Table 3 and 4**). Trend of decrease in mean DAPSA and DAS28 from baseline to month 3 were from high disease activity to moderate or low disease activity in both the groups. Intergroup analysis of DAPSA and DAS28 from month 1 to month 3 showed similar decline of scores in both the groups (**Table 5**).

Patients achieving remission or low disease activity on the basis of DAPSA score at month 3 were the treatment target achievers, and were allowed to continue previous treatment. Frequencies of treatment target achievers at 3 months were 37.9% (11) in Tofacitinib group and 43.75% (14) in MTX group (p-value=0.795 by chi-square test) (**Figure 2**).

Clinical parameters (TJC/SJC, VAS for pain) and inflammatory markers (ESR and CRP)

Clinical parameters showed statistically significant improvement in both the groups starting right from month 1, which was sustained till the end of 3 months (**Tables 3 and 4**).

Among inflammatory markers, improvement in ESR showed significant results at the end of 3 months in both the groups. CRP showed significant result only in Tofacitinib group at the end of 3 months (p-value=0.003 and 0.607 in Tofacitinib and MTX groups respectively, 95% CI) (**Table 3**).

Intergroup comparision of mean differences of clinical parameters shows significant improvement of TJC/SJC in Tofacitinib group at month 1. Inflammatory markers between group A and group B at month 1 and month 3 shows insignificant results (p-value>0.05, 95% CI) (**Table 5**).

Table 2. Intergroup comparison of frequencies of ACR 20/50/70 responses between group A and group B patients at month 1 and month 3.

Duration	Month 1			Month 3		
ACR responses	**Group A (n= 29), n (%)**	**Group B (n= 32), n (%)**	**p-value**	**Group A (n= 29), n (%)**	**Group B (n= 32), n (%)**	**p-value**
ACR* 20 response	15 (51.7%)	8 (25%)	0.038$^{\exists}$	23 (79.3%)	22 (68.8%)	0.395$^{\exists}$
ACR 50 response	2 (6.9%)	1 (3.1%)	0.6^	8 (27.6%)	7 (21.9%)	0.879^
ACR 70 response	2 (6.9%)	0 (0%)	0.222^	3 (10.3%)	1 (3.1%)	0.338^

Group A: Tofacitinib group; Group B: Methotrexate group; Primary endpoint; *ACR 20/**ACR 50/***ACR 70: American college of Rheumatology (ACR) 20/50/70 responses i-square test; ^Fisher's exact test
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Table 3. Intragroup comparison of mean value of clinical parameters, inflammatory markers, composite measures, and functional assessment of group A and group B at baseline and 3.

Group	Group A (n= 29, 26^{2}, 23°) Mean ± SD			Group B (n= 32, 27^{2}, 19°) Mean ± SD		
Variables	**Baseline**	**Month 3**	**p-value**	**Baseline**	**Month 3**	**p-value**
TJC/SJC$^{\beta}$	25.14 ± 16.73/ 17.93± 13.63	11.03 ± 11.17/ 5.62 ± 5.87	0.000^	19.06 ± 12.7/ 13.22 ± 10.03	7.5 ± 9.92/ 3.97 ± 5.6	0.000^
VAS^{W} for Pain	7.41 ± 2.07	4.17 ± 2.34	0.000^	7.72 ± 1.98	4.69 ± 1.73	0.000^
ESR$^{\theta}$	64.83 ± 36.52	46.55 ± 27.96	0.006^	50.84 ± 37.25	30.03 ± 26.51	0.001^
CRP^{H}	22.02 ± 20.06	8.96 ± 7.71	0.003^	16.72 ± 23.17	13.49 ± 29.55	0.607^
DAPSA*	59.66 ± 31.35	26.04 ± 19.6	0.000^	48.35 ± 22.34	21.55 ± 17.5	0.000^
DAS28^{a}	6.44 ± 1.44	4.85 ± 1.62	0.000^	5.8 ± 1.48	3.88 ± 1.46	0.000^
PASI^{2}	3.49 ± 3.33	1.73 ± 2.35	0.001^	5.55 ± 5.1	2.1 ± 1.64	0.001^
MASES$^{\circ}$	3.04 ± 2.05	1.83 ± 1.46	0.001^	2.89 ± 2.15	2.63 ± 2.03	0.56^
HAQ-DI$^{\delta}$	1.61 ± 0.61	0.96 ± 0.61	0.000^	1.46 ± 0.6	0.61 ± 0.5	0.000^

n= number of patients; SD: Standard deviation; Group A: Tofacitinib group; Group B: Methotrexate group
$^{\beta}$Tender joint count/swollen joint count in 68/66 joint count; ^{W}Visual analog scale; $^{\theta}$Erythrocyte sedimentation rate; ^{H}C-reactive protein; *DAPSA: Disease activity score for psoriatic arthritis, ^{a} DAS28: Disease activity score- 28 joint; $^{\delta}$HAQ-DI: Health assessment questionnaire- disability index; ^{2}PASI: Psoriasis area and severity index $^{\circ}$MASES: Maastritch enthesitis score; $^{\exists}$Comparision with baseline; ^Paired sample t-test

Table 4. Intragroup comparison showing early responses of variables at 1 month.

Group	Group A (n= 29, 26[5], 23˚) Mean ± SD			Group B (n= 32, 27[5], 19˚) Mean ± SD		
Variables	**Baseline**	**Month 1**	**p-value**	**Baseline**	**Month 1**	**p-value**
TJC/SJC[β]	25.14 ± 16.73/ 17.93± 13.63	14.55 ± 12.93/ 8.21 ± 8.19	0.000^	19.06 ± 12.7/ 13.22 ± 10.03	13.28± 12.49 /8.38 ± 8.33	0.000^
VAS[W] for Pain	7.41 ± 2.07	5.21 ± 2.19	0.000^	7.72 ± 1.98	5.75 ± 2.03	0.000^
ESR[ə]	64.83 ± 36.52	55 ± 35.87	0.119^	50.84 ± 37.25	39.5 ± 30.24	0.2^
CRP[H]	22.02 ± 20.06	14.65 ± 15.81	0.075^	16.72 ± 23.17	20.59 ± 36.79	0.539^
DAPSA*	59.66 ± 31.35	34.37 ± 23.39	0.000^	48.35 ± 22.34	35.45 ± 23.71	0.000^
DAS28[4]	6.44 ± 1.44	5.32 ± 1.81	0.000^	5.8 ± 1.48	4.94 ± 1.68	0.000^
PASI[5]	3.49 ± 3.33	2.5 ± 3.96	0.339^	5.55 ± 5.1	3.33 ± 2.26	0.003^
MASES˚	3.04 ± 2.05	2.45 ± 1.78	0.303^	2.89 ± 2.15	2.74 ± 1.93	0.820^
HAQ-DI[δ]	1.61 ± 0.61	1.16 ± 0.64	0.000^	1.46 ± 0.6	0.76 ± 0.55	0.000^

n= number of patients; SD: Standard deviation; Group A: Tofacitinib group; Group B: Methotrexate group
[β]Tender joint count/swollen joint count in 68/66 joint count; [W]Visual analog scale; [ə]Erythrocyte sedimentation rate; [H]C-reactive protein; *DAPSA: Disease activity score for psoriatic arthritis, [4]DAS28: Disease activity score- 28 joint; [δ]HAQ-DI: Health assessment questionnaire- disability index; [5]PASI: Psoriasis area and severity index
˚MASES: Maastritch enthesitis score; ∃Comparision with baseline; ^Paired sample t-test

Table 5. Intergroup comparision of mean differences of secondary outcome measures from baseline to month 1 and month 3 between group A and group B.

Duration	Mean difference (Baseline –Month 1)			Mean difference (Baseline –Month 3)		
Group	**Group A (n= 29, 26[5], 23˚) Mean ± SD**	**Group B (n= 32, 27[5], 19˚) Mean ± SD**	**p-value**	**Group A (n= 29, 26[5], 23˚) Mean ± SD**	**Group B (n= 32, 27[5], 19˚) Mean ± SD**	**p-value**
TJC/SJC[β]	10.58 ± 8.31/ 9.72 ± 8.94	5.78 ± 7.17 / 4.84 ± 6.25	0.018^/ 0.015^	14.1 ± 9.52 /12.3 ± 9.95	11.36 ± 9.6 / 9.2 ± 8.8	0.304^/ 0.201^
VAS[W] for Pain	2.2 ± 2.02	1.96 ± 1.7	0.616^	3.24 ± 2.6	3.03 ± 2.29	0.738^
ESR[ə]	9.8 ± 32.88	11.34 ± 26.25	0.839^	18.27 ± 32.83	20.81 ± 31.77	0.760^
CRP[H]	7.37 ± 21.5	3.87 ± 35.32	0.646^	13.06 ± 21.24	3.22 ± 35.11	0.196^
DAPSA*	25.3 ± 18.5	12.9 ± 14.4	0.004^	33.61 ± 20.66	26.79 ± 20.14	0.197^
DAS28[4]	1.12 ± 0.9	0.85 ± 0.92	0.252^	1.59 ± 1.05	1.91 ± 1.47	0.336^
PASI[5]	0.98 ± 3.13	2.21 ± 3.57	0.188^	1.76 ± 2.35	3.44 ± 4.66	0.105^
MASES˚	0.59 ± 1.3	0.47 ± 1.26	0.764^	1.22 ± 1.47	0.26 ± 0.56	0.011^
HAQ-DI[δ]	0.45 ± 0.35	0.35 ± 0.48	0.361^	0.8 ± 0.5	0.85 ± 0.65	0.689^

n= number of patients; SD: Standard deviation; Group A: Tofacitinib group; Group B: Methotrexate group
[β]Tender joint count/swollen joint count in 68/66 joint count; [W]Visual analog scale; [ə]Erythrocyte sedimentation rate; [H]C-reactive protein; *DAPSA: Disease activity score for psoriatic arthritis, [4]DAS28: Disease activity score- 28 joint; [δ]HAQ-DI: Health assessment questionnaire- disability index; [5]PASI: Psoriasis area and severity index; ˚MASES: Maastritch enthesitis score; ^Independent sample t-test

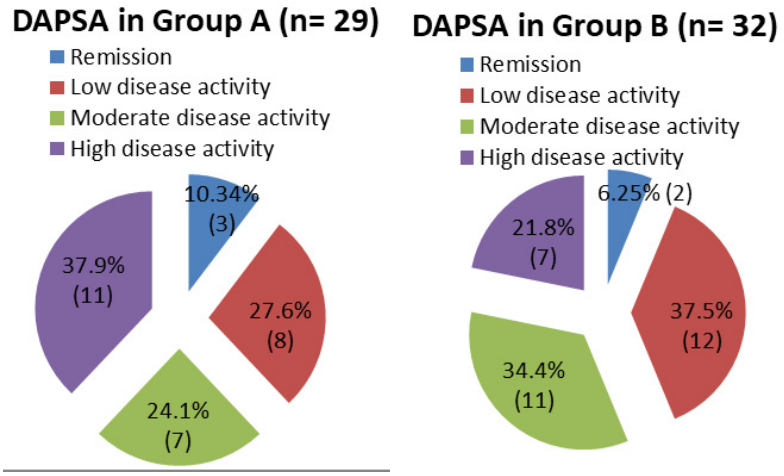

Figure 2. Comparison of frequencies of patients achieving remission, low, moderate and high disease activity in both groups at the end of 3 months.

Assessment of skin psoriasis (PASI)

Current, past or family history of psoriasis was present in 89.7% (26) and 84.4% (27) patients in Tofacitinib and MTX group respectively. Intragroup analysis shows that decrease in mean values of PASI was statistically significant (p<0.001, 95% CI) in both the groups from baseline to month 3. PASI started showing significant improvement starting from month 1 in Tofacitinib group, whereas MTX group showed significant results only at month 3 (**Tables 3 and 4**). Intergroup analysis shows no significant changes between Tofacitinib and MTX group (**Table 5**).

At month 3, 15.4% (4) and 14.8% (4) patients achieved PASI 75 response at the end of 3 months in Tofacitinib and MTX group respectively (p-value=1.000, 95% CI).

Assessment of entheseal involvement (MASES)

Entheseal involvement was present in 79.3% (23) and 59.4% (19) in group A and group B respectively; outcomes were analyzed in these patients only. Decrements in mean MASES were statistically significant in Tofacitinib group (p-value= 0.001) but was not significant in MTX group (p-value= 0.56) from baseline to month 3 (**Table 3**).

Intergroup analysis also shows significant difference in MASES response at 3 months (p-value=0.011, 95% CI) with greater improvement in Tofacitinib group (**Figure 3 and Table 5**).

Functional Assessment (HAQ-DI)

Health assessment questionnaire-disability index (HAQ-DI) was the tool used. Intragroup analysis showed statistically significant decrements in both the groups from month 1 to month 3 (p-value<0.05, 95% CI) (**Tables 3 and 4**).

Intergroup analysis of HAQ-DI **Table 5** shows similar mean differences between the two groups at baseline and month 3 (p-value>0.05).

Phase II

After 3 months of treatment, the patients from Group A (Tofacitinib) and Group B (MTX) who achieved treatment target were placed into group A1 (n=11) and group B1 (n=14) respectively. All the parameters were traced from the baseline till 6 months of treatment in these patients. The patients who didn't achieve primary endpoint at month 3 were put into group A2 and group B2, and were excluded from efficacy assessment from 3rd month onwards.

Assessment of composite measures

The improvement in composite measures also showed sustained and steady results in DAPSA and DAS-28 from month 3 to month 6 in both the groups (**Figure 4**).

The intergroup analysis shows that the decrease in composite measures were similar among group A_1 and group B_1 (p-value>0.5, 95% CI) from baseline to 6 months.

Clinical parameters (TJC/SJC) and inflammatory markers (ESR and CRP)

Intragroup analysis of clinical parameters from month 3 to month 6 shows steady pattern of improvement in both the groups (**Figure 5**).

ESR showed declining pattern and CRP showed steady pattern from month 3 to month 6 in both the groups (**Figure 6**).

Intergroup analysis of mean differences of variables between group A1 and group B1, from baseline to month 6 shows similar results in both the groups.

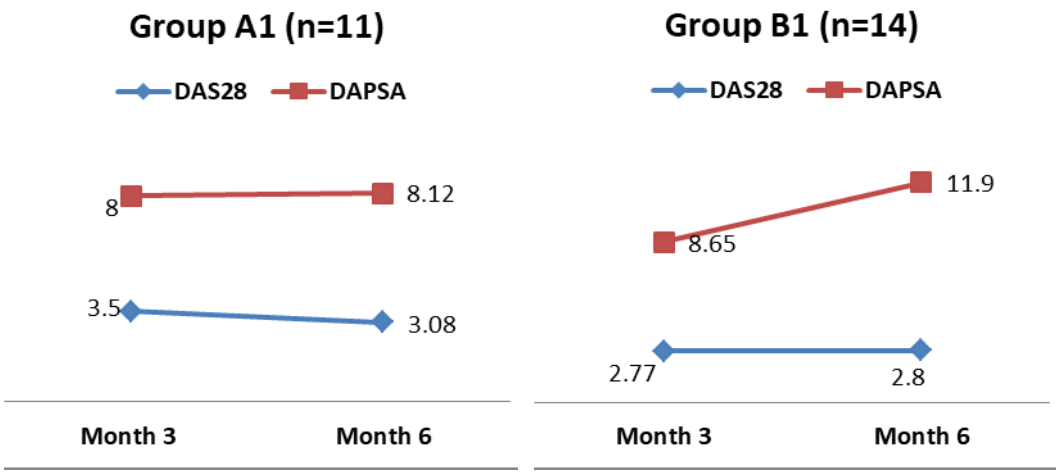

Figure 3. Mean scores of DAS-28 and DAPSA in group A1 and group B1 from month 3 to month 6.

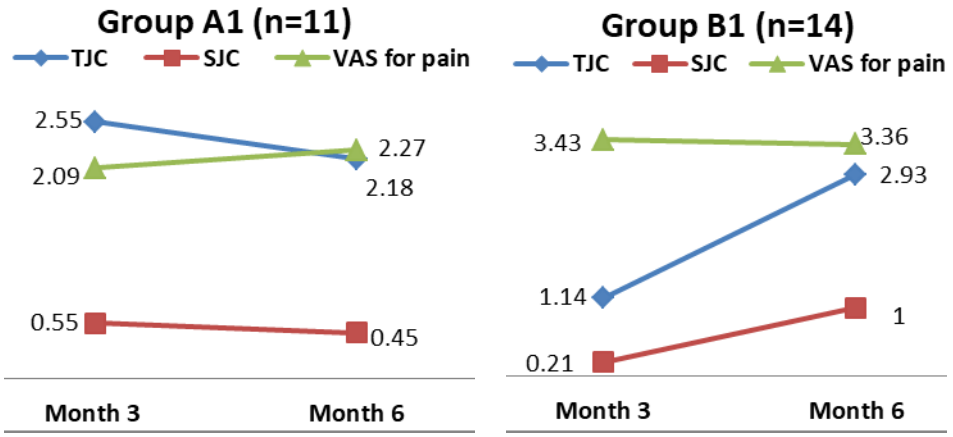

Figure 4. Mean scores of clinical parameters (TJC/SJC and VAS for pain) in group A1 and group B1 from baseline through month 3 to month 6.

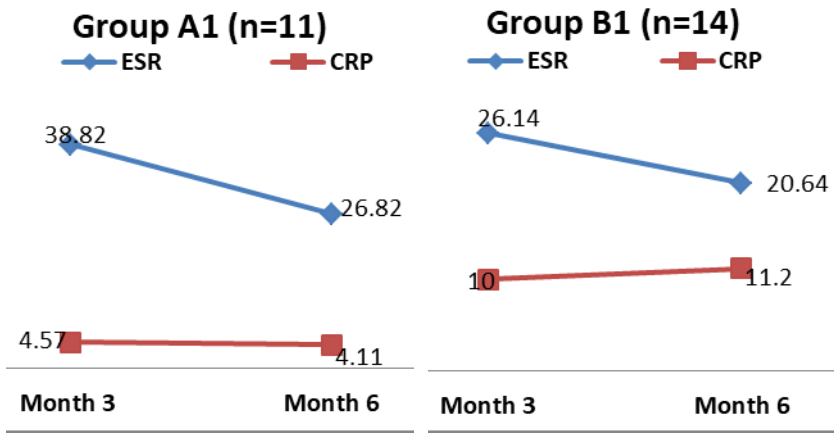

Figure 5. Mean scores of clinical parameters (TJC/SJC and VAS for pain and inflammatory markers (ESR and CRP) in group A1 and group B1 from baseline through month 3 to month 6.

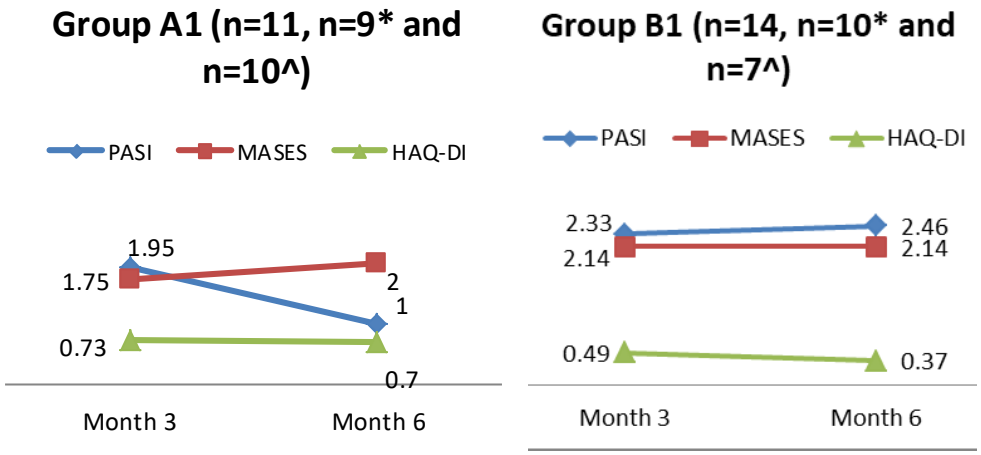

Figure 6. Comparison of mean skin score (PASI), enthsitis (MASES) and functional assessment scores (HAQ-DI) between group A1 and group B1 from baseline to month 6.

Assessment of skin psoriasis (PASI)

Among treatment target achievers, 81.81% (9/11) patients in group A1 and 71.4% (10/14) patients in group B1 had current, past of family history of psoriasis.

Intragroup analysis of skin psoriasis showed that decrease in mean values of PASI was steady in both the groups from 3 months to 6 months of treatment.

Intergroup analysis showed that the decrease in mean

scores of PASI between two continuation groups were similar at month 3 and month 6.

Frequency of patients achieving PASI 75 response at month 3 was 22.22% (2) and 10% (1); at month 6 is 55.55% (5) and 20% (2) in group A1 and group B1 respectively. PASI 75 achievement at the end of month 3 and month 6 was seen in greater number of patients of group A, but the result was not statistically significant.

Assessment of entheseal involvement (MASES)

Entheseal involvement was present in 72.7% (8/11) patients in group A1 and 50% (7/14) patients in group B1; assessment of MASES score was done only in these patients. Comparison in mean MASES was steady in both treatment continuation groups from month 3 to month 6.

Intergroup analysis shows similar trends of mean differences at month 3 and month 6 in both the groups, which were not statistically significant.

Funtional assessment (HAQ-DI)

Intragroup analysis from month 3 to month 6 showed steady pattern of HAQ-DI in both the groups. Intergroup analysis shows similar decrease in both the groups at month 3 and month 6.

Safety Assessment

Of the total 61 patients, 70.5% (43) experienced some sort of adverse effects, 3.3% (2) patients suffered from serious adverse event and 6.6% (4) patients had to be withdrawn from the study due to some adverse events during the course of the treatment. Adverse events in both groups are shown in (**Table 6**).

Frequencies of AEs in both drug groups were similar. Infection-related AEs were more common in Tofacitinib group and GI-related AEs were more common in MTX group. Common AEs with Tofacitinib were URTI and dizziness followed by UTI, cough and nausea; while in MTX treated patients; common AEs were nausea and anorexia. Recurrent UTI was the major problem in Tofacitinib group, especially in female patients. Serious adverse event seen in group A were recurrent UTI and LRTI (**Table 6**). One patient developed HZ infection and one had leg cellulitis with Tofacitinib. One patient in Tofacitinib group developed severe weight loss more than 5 kg over 2 months, and had to be withdrawn from the study. In Methotrexate group, one patient had to be withdrawn due to rise in serum Creatinine.

Other adverse events seen in both groups were herpes zoster infection, severe weight loss, leg cellulitis, rise

Table 6. List and frequency of adverse events and serious adverse events in group A and group B patients.

Group AEs & SAEs	Group A (n=29) n (%)	Group B (n=32) n (%)
AEs	20 (69%)	23 (71.9%)
Fall in Hb.	3 (10.3%)	1 (3.1%)
GI-related AEs (Nausea, Vomiting, Anorexia, Diarrhoea)	4 (13.8%)	12 (37.5%)
Rise in SGPT >ULN	0 (0%)	4 (12.5%)
Cough	5 (17.2%)	5 (15.4%)
Oral ulcers/Sore mouth	3 (10.3%)	3 (9.4%)
Heartburn	1 (3.4%)	3 (9.4%)
Fever	5 (17.2%)	1 (3.1%)
Headache	2 (6.9%)	2 (6.3%)
Dizziness	6 (20.7%)	3 (9.4%)
Burning micturition	5 (17.2%)	2 (6.3%)
Rise in BP	2 (6.9%)	0
URTI	6 (20.7%)	3 (9.4%)
Hypersensitivity	0	0
Herpes zoster infection	1 (3.4%)	0
Severe weight loss	1 (3.4%)	0
Leg cellulitis	1 (3.4%)	0
Rise in creatinine above ULN	1 (3.4%)	1 (3.1%)
Rise in SGPT > 2 X ULN	0	1 (3.1%)
SAEs	2 (6.7%)	0 (0%)
Recurrent UTI	1 (3.4%)	0
LRTI	1 (3.4%)	0
Withdrawl due to AEs	3 (10.3%)	1 (3.1%)

n= number of patients; Group A: Tofacitinib group; Group B: Methotrexate group AE: Adverse events; SAE: serious adverse events

in Creatinine above ULN, fall in hemoglobin, nausea, vomiting, rise in SGPT >ULN, cough, oral ulcers/Sore mouth, heartburn, anorexia, diarrhea, fever, headache, dizziness, burning micturition, UTI and rise in BP.

Out of the 61 patients, 11 patients discontinued their treatment; 7 patients [2 (6.9%) in Group A and 5 (20.7%) in Group B] missed their follow-up and 4 patients [3 (10.3%) in Group A and 1 (3.1%) in Group B] had o be withdrawn from the study due to some adverse events. Intention to treat (ITT) analysis was done for these patients.

Discussion

Pharmacological interventions for treatment of PsA include NSAIDs, csDMARDs, bDMARDs and tsDMARDs. The choice of DMARD needs to be weighed against the initial presentation, because each DMARD has a specific role in the heterogeneous nature of this disease.

MTX, a csDMARD, is an established drug for the treatment of PsA recommended in second-line after NSAIDs failure in peripheral arthritis, and Tofacitinib is relatively new tsDMARD considered when there is inadequate response to at least one csDMARD and if TNF inhibitors are not appropriate [7]. Efficacy of Tofacitinib has shown good results in the recent studies (OPAL beyond and OPAL broaden studies) [13, 14]. Tofacitinib can be a drug with earlier placement in the future recommendations, and might also be promising with comparable cost benefits compared to bDMARDs in the treatment of PsA.

Mean age of the participants in this study was 39.56 years with male: female ratio of 1.25:1, which is similar to the data in previous epidemiological studies of PsA [2]. Current, past or family history of psoriasis was present in 86.9% of patients and enthesitis was present in 68.9% of patients, which was higher than that of the previous studies [15]. This might be due to the selection criteria of this study, i.e. predominant peripheral disease without axial involvement and DMARD naïve or 3 months DMARD-free patients. Clinical and inflammatory parameters were high at baseline.

At the end of 3 months, 79.3% patients in Tofacitinib group and 68.8% in Methotrexate group achieved primary endpoint. Tofacitinib group patients started achieving ACR 20 response from month 1, and responses were sustained till 6 months. Similar response at 3 months might be due to higher dose of MTX used in this study, i.e 15 mg weekly, titrated to 25 mg weekly at 1month. ACR 20 responses in the recent studies of Tofacitinib 5 mg BD were 50% in both OPAL broaden and OPAL beyond trials [13, 14]. The ACR 20 responses for MTX in the previous studies were 40.8% at week 12 in TICOPA trial [9], 66.7% at week 16 in RESPOND study [16] and 34% at month 6 in MIPA trial [17]. Frequency of ACR 20 responders for MTX in our study was similar to that of RESPOND study and greater than that of TICOPA and MIPA trials. Lower dose of MTX, i.e 15 mg/week were used in the MIPA trial and RESPOND study of MTX in PsA [9,16 and 17]. In TICOPA trial, the dose was up to 20 mg/week. Studies have shown that blood level of MTX has wide inter-patient variability, and >6 months duration is usually needed for MTX to reach steady state in blood. Such delays in achieving steady state suggest that more rapid dose escalation or subcutaneous administration to be considered [18]. On the other hand, Tofacitinib provided earlier ACR 20 response starting from month 1, which is consistent with one previous study of Tofacitinib in RA, where ACR20/50/70 response rates with tofacitinib 5 mg twice daily monotherapy at month 1 were 76.8%, 53.1% and 32.1%, respectively [19].

Similarly, 37.9% patients in Tofacitinib group patients and 43.75% of MTX group patients achieved treatment target (remission or low disease activity according to DAPSA scores) at the end of 3 months. Decrease in scores of mean DAPSA from baseline to month 3 was from 59.66 to 26.04 in Tofacitinib group and 48.35 to 21.55 in MTX group, and the results were significant within groups. In the recent OPAL broaden and OPAL beyond studies, the decrease in mean DAPSA scores ranged from (38.52 - 51.54) at baseline to (13.21 – 28.3) at month 12, and the result were significant [13 , 14].

Clinical parameters, 68/66 joints TJC/SJC and VAS for pain started showing significant improvement in both the groups starting right from month 1, which was sustained till month 6 of treatment. Target achievement was seen more in patients with significantly lower TJC/SJC in both the groups. Our result is consistent with previous studies of MTX and Tofacitinib on PsA and RA. In one study of Tofacitinib in RA, significant decrease in joint count was seen at the end of 3 months [20]. Similar results were seen in TICOPA and RESPOND study of MTX but MIPA trial showed insignificant results of TJC/SJC to MTX 15 mg weekly at the end of 6 months [17].

ESR started showing significant improvement in both the groups from month 3, which was sustained till 6 months. On the other hand, significant decrease in CRP starting from month 3 and sustainment till month 6 was seen only in Tofacitinib group. Among treatment target

achievers, baseline CRP score was greater in Tofacitinib group, which explains its role in decreasing CRP. Previous studies in of tofacitinib in RA have shown its role in the improvement of CRP scores, where DAS-28 (CRP) scores showed 2-fold to 5-fold higher remission rates compared with the DAS-28 (ESR) [21]. MTX didn't show significant results in the improvement of ESR and CRP levels in MIPA trial [17], while other studies have shown good role of MTX in the improvement of CRP levels. Before Tofacitinib, bDMARDs were also the known drugs which had significant effect on CRP levels, as shown in one study of Etanercept in PsA [22]. Studies have shown that high ESR and CRP levels are related to high disease activity in PsA [23]. Moreover, the baseline CRP of ACR 20 responders are significantly greater in Tofacitinib group than in MTX group. All these findings in this study go in favor of Tofacitinib in significant improvement in CRP in comparison to MTX.

DAPSA and DAS-28 started showing significant improvement starting from month 1, which was sustained till month 6 in both the treatment groups. This study has shown the similar effect of Tofacitinib as well as MTX in the improvement of composite measures of PsA. DAPSA and DAS28 scores are widely accepted composite measure for PsA. The disease specific composite measure, DAPSA score for PsA, includes 66/68 joints SJC/TJC of all four limbs including DIPs, while DAS28 score involves 28 joints, and excludes DIP joins. DAPSA is useful for measurement of peripheral disease activity with validated cut-off points. This was also shown in one of the recent studies of disease specific composite measures after treatment with Tofacitinib in PsA [24].

Assessment of skin Psoriasis also revealed significant improvement of PASI scores from baseline to month 6 in both the groups. PASI 75 responses at the end of 3 months were 15.4% and 14.8%, and this frequency increased to 55.5% and 20% at the end of 6 months in tofacitinib and MTX group respectively. Previous studies of skin Psoriasis shows similar effect on PASI scores on both the drugs with PASI 75 response of 17% in Tofacitinib 5 mg treated patients at the end of 3 months in OPAL beyond trial [14]. However, MTX treatment shows higher rates of PASI 75 response with 41% response in one study [25] and 27.2% response in TICOPA trial [16] in MTX treated patients. Meanwhile, in ESTEEM 2 study of PDE4 inhibitor Apremilast (10-30 mg/day), frequency of PASI 75 responders was 28.8% [26].

79.3% in Tofacitinib and 59.4% of patients in MTX treated groups had enthesitis. This frequency was higher than that of previous studies of PsA [15]. However, the nature of this study was different in regard to inclusion criteria of patients- DMARD naïve patients and no axial involvement. Improvement in MASES score was significant in Tofacitinib treated group from baseline to month 3, whereas in MTX treated group, it was not significant. No patients developed new enthesitis during the course of treatment. According to GRAPPA, 2015 guidelines, NSAIDs and bDMARDs are the treatment of choice, if enthesitis is present [9]. Previous studies have showed statistically significant improvement of MASES at week 12 in Tofacitinib treated patients [27], whereas TICOPA trial showed no improvement in MASES score at week 12 of treatment with MTX [9]. A study on TNF inhibitors showed that adalimumab and etanercept are effective treatments of MRI-documented refractory heel enthesitis, with progressive improvement of bone edema in a 6-month period [28]. bDMARDs other than TNF inhibitors, used for PsA and Apremilast have also shown good results in the improvement of enthesitis [29, 30].

Functional assessment (HAQ-DI) showed steady and significant improvement in both groups starting from 1st month to 6 months of treatment. HAQ-DI is a patient reported outcome measure of functional assessment, and it measures the overall health status. The result of this study is consistent with the previous studies on MTX and Tofacitinib.

Frequencies of AEs in both drug groups were similar. Infection-related AEs were more common in Tofacitinib group and GI-related AEs were more common in MTX group. 3 patients in Tofacitinib group and 1 patient in MTX group had to be withdrawn from this study due to some AEs. Common AEs with Tofacitinib were URTI and dizziness followed by UTI, cough and nausea; while in MTX treated patients, AEs were nausea and anorexia. Recurrent UTI was the major problem in Tofacitinib group, especially in female patients. One patient developed HZ infection and one had leg cellulitis with Tofacitinib. One patient in Tofacitinib group developed severe weight loss more than 5 kg over 2 months, and had to be withdrawn from the study. In Methotrexate group, one patient had to be withdrawn due to rise in serum Creatinine at the end of 3 months. No patients developed TB in Tofacitinib group, as it is a common threat with this drug, especially in Bangladesh. The most common AEs of Tofacitinib seen in most of the studies till now are nasopharyngitis, URTI and UTI; the most common SAEs are infections and infestations. The most common serious infections are pneumonia, HZ, UTI and cellulitis. Opportunistic infection like tuberculosis is one

of the major threats during treatment with Tofacitinib, and latent TB screening should be done before starting treatment. Other AEs are hypertension, headache, diarrhea, alterations in liver and/or renal function tests, anemia, skin melanoma, esophageal candidiasis, hyperlipidemia, and gastrointestinal perforation [31]. In previous studies, the most common AEs of MTX were GI-related and elevation of liver enzymes. GI AEs were the most common side effect (52–65%) and had similar incidence whatever the duration of MTX. Elevations of liver enzymes (>ULN) occurred especially during the first 4 years of treatment (69–88%).

References

1. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann. Rheum. Dis*. 64, 18-23 (2005).
2. Gladman DD, Antoni C, Mease P *et al*. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann. Rheum. Dis*. 64, 14-7 (2005).
3. Sherlock JP, Joyce-Shaikh B, Turner SP *et al*. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+ CD4– CD8– entheseal resident T cells. *Nat. Med*. 18, 1069-76 (2012).
4. Partsch G, Steiner G, Leeb BF *et al*. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J. Rheumatol*. 24, 518-23 (1997).
5. Ritchlin C, Haas-Smith SA, Hicks D *et al*. Patterns of cytokine production in psoriatic synovium. *J. Rheumatol*. 25, 1544-52 (1998).
6. Jandus C, Bioley G, Rivals JP *et al*. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. *Arthritis Rheum.* 58, 2307-17 (2008).
7. Gossec L, Smolen JS, Ramiro S *et al*. European League against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann. Rheum. Dis*. 75, 499-510 (2016).
8. Fraser AD, van Kuijk AW, Westhovens R *et al*. A randomised, double blind, placebo controlled multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann. Rheum. Dis*. 64, 859-64 (2005).
9. Coates LC, Helliwell PS. Methotrexate efficacy in the tight control in psoriatic arthritis study. *J. Rheumatol*. 43, 356-61 (2016).
10. Ghoreschi K, Jesson MI, Li X *et al*. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J. Immunol*. 186, 4234-43 (2011).
11. Maeshima K, Yamaoka K, Kubo S *et al*. The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-γ and interleukin-17 production by human CD4+ T cells. *Arthritis Rheum*. 64, 1790-8 (2012).
12. Rosengren S, Corr M, Firestein GS *et al*. The JAK inhibitor CP-690,550 (tofacitinib) inhibits TNF-induced chemokine expression in fibroblast-like synoviocytes: autocrine role of type I interferon. *Ann. Rheum. Dis*. 71, 440-7 (2012).
13. Mease P, Hall S, FitzGerald O *et al*. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N. Engl. J. Med*. 377, 1537-50 (2017).
14. Gladman D, Rigby W, Azevedo VF *et al*. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N. Engl. J. Med*. 377, 1525-36 (2017).
15. Kane D, Jensen LE, Grehan S *et al*. Quantitation of metalloproteinase gene expression in rheumatoid and psoriatic arthritis synovial tissue distal and proximal to the cartilage-pannus junction. *J. Rheumatol*. 31, 1274-80 (2004).
16. Baranauskaite A, Raffayová H, Kungurov NV *et al*. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. *Ann. Rheum. Dis*. 71, 541-8 (2012).
17. Kingsley GH, Kowalczyk A, Taylor H *et al*. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatol*. 51, 1368-77 (2012).
18. Dalrymple JM, Stamp LK, O'Donnell JL *et al*. Pharmacokinetics of oral methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum*. 58, 3299-308 (2008).
19. Fleischmann R, Wollenhaupt J, Takiya L *et al*. Safety and maintenance of response for tofacitinib monotherapy and combination therapy in rheumatoid arthritis: an analysis of pooled data from open-label long-term extension studies. *RMD open*. 3, e000491 (2017).
20. Van Vollenhoven RF, Wallenstein G, Lee EB *et al*. THU0151 Effects of tofacitinib (CP-690,550), an oral janus kinase inhibitor, or adalimumab on patient reported outcomes in a phase 3 study of active rheumatoid arthritis. *Ann. Rheum. Dis*. 71, 206 (2013).
21. Smolen JS, Aletaha D, Gruben D *et al*. Brief report: remission rates with tofacitinib treatment in rheumatoid arthritis: a comparison of various remission criteria. *Arthritis Rheum*. 69, 728-34 (2017).
22. Strober B, Teller C, Yamauchi P *et al*. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. *Br. J. Dermatol. Suppl*. 159, 322-30 (2008).
23. Gladman DD, Farewell VT. Progression in psoriatic arthritis: role of time varying clinical indicators. *J. Rheumatol*. 26, 2409-13 (1999).

24. Helliwell P, Coates LC, FitzGerald O *et al*. Disease-specific composite measures for psoriatic arthritis are highly responsive to a Janus kinase inhibitor treatment that targets multiple domains of disease. *Arthritis Res. Ther*. 20, 1-3 (2018).

25. Tsakok T, Jabbar-Lopez Z, Smith C. Subcutaneous methotrexate in patients with moderate-to-severe psoriasis: a critical appraisal. *Br. J. Dermatol.* 179, 50-53 (2018).

26. Paul C, Cather J, Gooderham M *et al*. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br. J. Dermatol.* 173, 1387-99 (2015).

27. Van Der Heijde D, Deodhar A *et al*. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. *Ann. Rheum. Dis*. 76, 1340-7 (2017).

28. Olivieri I, Giasi V, Scarano E *et al*. A brief course of anti-TNF-alpha therapy can cure recurrent episodes of HLA-B27-associated severe and refractory heel enthesitis. *Clin. Exp. Rheumatol*. 27, 1057-author (2009).

29. McInnes IB, Mease PJ, Kirkham B *et al*. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 386, 1137-46 (2015).

30. Kavanaugh A, Mease PJ, Gomez-Reino JJ *et al*. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. *J. Rheumatol*. 42, 479-88 (2015).

31. Cohen SB, Tanaka Y, Mariette X *et al*. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann. Rheum. Dis*. 76, 1253-62 (2017).