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Research Letter

Combination of Methotrexate and Leflunomide Is Safe and Has Good Drug Retention Among Patients With Psoriatic Arthritis

To the Editor:

Psoriatic arthritis (PsA) is a potentially progressive immune-mediated musculoskeletal disease with the involvement of synovium, enthesis, and axial structures (especially the cervical spine and sacroiliac joints), along with the involvement of skin and nails. Even a short delay in the diagnosis and commencement of antirheumatic therapy can cause long-term damage and disabilities.[1] However, there remains considerable confusion regarding the effectiveness of conventional synthetic (cs-) disease-modifying antirheumatic drugs (DMARDs), especially methotrexate (MTX), given the lack of high-level evidence to support its use in PsA.[2] The availability of biologic DMARDs (bDMARDs) and targeted synthetic DMARDs have revolutionized the management of psoriatic disease[3]; however, for Pakistani patients, it comes with a significant cost burden. Unfortunately, being in a resource-poor country, access to biologic therapies is extremely limited. Hence, in our practice, we are inclined to use a combination of potent DMARDs after MTX failure, prior to considering biologic therapies (except in the scenario of very active axial disease or skin disease). We believe that a combination of DMARDs, especially that of MTX and leflunomide (LEF), provides a valuable low-cost treatment option for patients with PsA after failure of MTX monotherapy. Little is known about the combined use of LEF and MTX in PsA, especially in the context of drug retention time and tolerability.[4] We aimed to review our PsA cohort data especially examining the drug retention of first-line csDMARD monotherapy and combination csDMARD therapy.

In our center, MTX is a preferred first-line csDMARD, unless contraindicated, and patients are followed up with a protocol on a 4- to 6-weekly basis unless complete remission is achieved. MTX is escalated to the maximum tolerated dose (up to 25 mg/week) if needed, and if PsA is still active at the end of 3 months, then preferably LEF is added (usual starting dose for add-on therapy is 10 mg/day, and escalated to 20 mg/day if needed, without any loading dose). Other csDMARDs, such as sulfasalazine (SSZ) are used as well, if necessary.

Ethical approval was obtained from the Fatima Memorial Hospital Institutional Review Board (approval no. FMH-08-2019-IRB-648-M), and informed written consent obtained from patients.

For this study, inclusion criteria were adult patients (aged ≥ 18 yrs) who had a follow-up of at least 6 months with our rheumatology services, and who fulfilled the Classification Criteria for Psoriatic Arthritis criteria. Moreover, only patients who were DMARD-naïve (no prior DMARD therapy for any cause, including psoriasis), and initiated DMARD as monotherapy after April 1, 2018, were included.

Apart from the standard disease activity assessments (68-joint tender joint count [TJC]/66-joint swollen joint count [SJC], presence of dactylitis, presence of enthesitis, and Psoriasis Area and Severity Index [PASI]), we also calculated whether the patient has achieved minimal disease activity (MDA) at the time of current assessment. We used MDA as a treatment target for patients with PsA. MDA in PsA was defined as SJC and TJC of ≤ 1, PASI ≤ 1 or body surface area of ≤ 3%, patient pain visual analog score ≤ 15, patient global assessment of disease activity score ≤ 20, Health Assessment Questionnaire–Disability Index ≤ 0.5, and tender entheseal points ≤ 1.[5] Data were represented as mean and SD for normally distributed data, and median and IQR for non-normally distributed data. We used independent samples *t* test (normally distributed data), Mann-Whitney *U* test (non-normally distributed data), or chi-square and Fisher exact test as appropriate.

Table 1. Descriptive characteristics and summary of patients who were commenced on MTX monotherapy compared to patients with combination MTX + LEF therapy.

	MTX Monotherapy, n = 71 (88%)[a]	MTX + LEF, n = 45 (55.5%)[a]	*P*
Age, yrs, mean ± SD	44.6 ± 11	45.2 ± 11.3	0.77
Sex, male	37 (52.1)	26 (57.8)	0.57
Treatment failure during			
Follow-up	56 (78.8)	7 (15.5)	< 0.001
Ineffective	51 (71.8)	4 (8.8)	
Adverse events	5 (7.0)	3 (6.6)	
Hepatotoxicity (ALT ≤ 3× ULN[b]	7 (9.8)	6 (13.3)	0.76
Hepatotoxicity (ALT ≥ 3× ULN)[b]	2 (2.8)	3 (6.6)	0.37
GI symptoms (nausea, vomiting, or diarrhea)	3 (4.2)	0	0.28
TJC, maximum[c]	12.4 ± 6.9	13.3 ± 7.8	0.53
SJC, maximum[c]	9.1 ± 5.1	8.9 ± 5.8	0.80
MDA achieved[d]	14 (19.7)	29 (64.4)	< 0.001
Ongoing treatment[e]	15 (21.1)	38 (84.4)	< 0.001

Values are expressed as n (%) unless otherwise indicated. [a] 88% (n = 71) of the PsA cohort was started on MTX monotherapy (as first-line DMARD). However, 79% (n = 56 out of 71) of these patients failed this monotherapy during follow-up, and 45 out of these 56 patients were started on combination therapy of MTX + LEF. [b] Normal range: 10–40 IU/L. [c] SJC and TJC were measured at the time of commencement of MTX monotherapy and combination MTX + LEF therapy. [d] MDA described here was assessed at the time of either enrollment in this study (for those who successfully continued MTX monotherapy or combination MTX + LEF), or switching to MTX monotherapy or combination MTX + LEF. [e] Ongoing treatment refers to the number of patients continuing medications at the time of study enrollment. ALT: alanine aminotransferase; GI: gastrointestinal; MDA: minimal disease activity; MTX: methotrexate; LEF: leflunomide; SJC: swollen joint count; TJC: tender joint count; ULN: upper limit of normal.

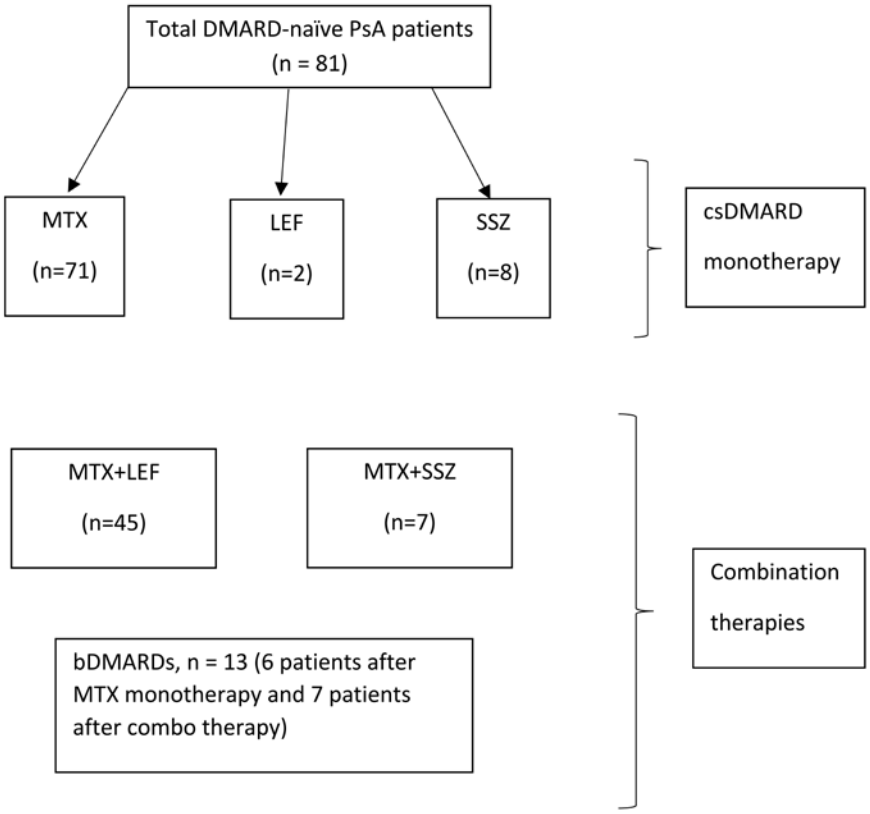

Figure 1. Breakdown of first-line and second-line csDMARD and bDMARD therapies of the studied cohort. Of 71 patients commenced on MTX monotherapy, 56 patients failed this monotherapy and 15 patients were successfully using this monotherapy after a median follow-up of 22 months. Out of the 56 patients failing MTX monotherapy, 45 were commenced on MTX + LEF; 5 patients were commenced on MTX + SSZ; and 6 patients were added a biologic agent. Of the 45 patients commenced on MTX + LEF, 38 successfully managed to continue this therapy, and 3 had severe hepatotoxicity; this therapy was clinically ineffective in 4 patients, requiring addition of a biologic agent. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine.

A total of 81 patients with PsA (mean age 45.6 ± SD 6 yrs, 52% male, mean PsA disease duration 9 ± 4 yrs, 35% with dactylitis, 42% with enthesitis, 17% with sacroiliitis, median current PASI 2.6, median SJC 8.0 [IQR 5.0–11.0], and median TJC 11.0 [IQR 8.0–15.0]) fulfilled the inclusion and exclusion criteria. Regarding first-line csDMARD monotherapy, 88% (n = 71) of patients were commenced on MTX (Table 1). The other 10 patients were not commenced on MTX due to pregnancy planning, concomitant fatty liver, or gastrointestinal symptoms.

Further breakdown of first-line and second-line csDMARD and bDMARD therapies are described in Figure 1. In total, 79% (n = 56 of 71) of patients who were started on MTX as their first-line csDMARD therapy failed this monotherapy during follow-up (51 = ineffective, 5 = intolerant). After a median follow-up of 22 months, MTX median drug retention among all MTX monotherapy users (n = 71) was only 7 months (IQR 5–7); and among MTX failures (n = 56), MTX monotherapy median drug retention was 6.0 months (IQR 4–8). There were 21% (15 of 71 patients) of patients in whom psoriatic disease was well controlled with MTX monotherapy. Eighty percent (n = 45 of 56) of the MTX monotherapy failure cohort was started on combination therapy of MTX and LEF (MTX + LEF); among them, only 7 patients needed escalation of therapy to bDMARDs (4 = ineffective, 3 = hepatoxicity), and the rest are still using MTX + LEF (Table 1)It was noted that to date, median drug retention time of MTX + LEF is 8 months (IQR 7–11), and 84% (n = 38 of 45) of these patients are still using this combination therapy. Significantly more patients managed to continue the MTX + LEF therapy compared to MTX monotherapy (84% vs 21%, $P < 0.001$, chi-square).

We conclude that among csDMARD-naïve patients with PsA, 79% of patients failed MTX monotherapy with median drug retention time of only 6 months. We observed much shorter drug retention times compared to previous studies,[6,7] and one plausible explanation is the close and regular follow-up of these patients in a treat-to-target fashion (target = achieving MDA). The combination of MTX and LEF was well tolerated and had good drug retention time, with 84% of patients having ongoing treatment to date. In low-income countries, where bDMARD availability is limited, financial arguments significantly influence the decision-making process,[8] and our data provide initial evidence that MTX + LEF combination therapy could be an effective treatment option for PsA. Further studies are required to confirm these findings.

Muhammad Haroon[1], PhD, MSc, MB, FRCPI, FFSEM, FACR
Shabnam Batool[1], MBBS, FCPS (Medicine), FCPS (Rheumatology)
Sadia Asif[1], MBBS, FCPS (Medicine), FCPS (Rheumatology)
Farzana Hashmi[1], MBBS, FCPS (Medicine)
Saadat Ullah[1], MBBS, FCPS (Medicine)
[1]Department of Rheumatology, Fatima Memorial Hospital & FMH College of Medicine and Dentistry, Lahore, Pakistan.

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Address correspondence to Dr. M. Haroon, Department of Rheumatology, Fatima Memorial Hospital & FMH College of Medicine and Dentistry, Lahore, Pakistan.
Email: mharoon301@hotmail.com.

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