






Descriptive Comparisons of the Effect of Apremilast and Methotrexate Monotherapy in Oligoarticular Psoriatic Arthritis: The Corrona Psoriatic Arthritis/Spondyloarthritis Registry Results

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ABSTRACT. *Objective.* Therapeutic response was evaluated among new apremilast, methotrexate (MTX), or biologic disease-modifying antirheumatic drug (bDMARD) initiators with oligoarticular psoriatic arthritis (PsA). *Methods.* Patients with oligoarticular PsA in the Corrona PsA/Spondyloarthritis Registry initiating treatment with apremilast, MTX, or bDMARD, and completing 6-month follow-up were included. *Results.* In total, 150 patients initiated monotherapy (apremilast: n = 34; MTX: n = 15; bDMARD: n = 101). Apremilast initiators had higher baseline disease activity than MTX initiators. At follow-up, apremilast initiators experienced numerically greater disease activity improvements than MTX initiators and similar improvements to bDMARD initiators. *Conclusion.* Findings suggest apremilast monotherapy is an effective option for patients with oligoarticular PsA.

Key Indexing Terms: arthritis, methotrexate, psoriatic arthritis, TNF receptors

Oligoarticular psoriatic arthritis (PsA), defined as < 5 involved joints^{1,2}, affects ≈50% of patients with PsA³. Typical randomized controlled trials have not focused on this population, and on average, patients enrolled have swollen and tender joint counts of 12 and 21, respectively⁴. Despite the high prevalence of oligoarticular PsA, data are lacking in this population, and recommendations for management remain largely unaddressed^{4,5,6}.

Our study assessed baseline clinical characteristics of patients with oligoarticular PsA (≤ 4 swollen joints) to determine the

effect of apremilast or methotrexate (MTX) treatment on disease activity. Patients initiating biologic disease-modifying antirheumatic drug (bDMARD) monotherapy were examined as a point of reference.

MATERIALS AND METHODS

Study design. A cohort study was performed in the Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry, a multicenter registry that recruited patients among > 50 participating rheumatologists in the United States⁷. Adults (aged ≥ 18 yrs) were included if they had PsA and

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oligoarthritis (defined as ≤ 4 swollen joints); were enrolled in the Corrona PsA/SpA Registry; initiated apremilast, MTX, or bDMARD monotherapy as the first initiation within the registry between June 1, 2014, and March 1, 2018; and had a 6-month follow-up visit with a time window of 3 to 9 months within the same period. Patients were defined as having polyarticular or oligoarticular PsA at the time of therapy initiation. Patients defined as having oligoarticular PsA may have had polyarticular disease previously, as they may have had changing numbers of joints involved with therapy selection based on patient characteristics.

Outcomes. Outcomes at 6 months included assessments of disease activity and patient-reported outcome (PRO) measures. Included were the proportion of patients with > 1 swollen joint or > 1 tender joint at baseline achieving a swollen joint count (SJC) of 0 or 1 or a tender joint count (TJC) of 0 or 1, respectively; change from baseline in SJC and TJC; and change from baseline in the Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) score and the cDAPSA core components.

The cDAPSA score was calculated as SJC (0–66) plus TJC (0–68) plus the patient global assessment of disease activity–arthritis and psoriasis (PtGA-PsO) visual analog scale (VAS) score (0–10 cm) plus the overall pain VAS (0–10 cm) score. Additional PRO measures included the change from baseline in fatigue VAS (0–100 mm) score, proportion of patients achieving the minimal clinically important difference (MCID; ≥ 0.35 -point decrease) in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score, change from baseline in PtGA-arthritis (PtGA-PsA) VAS score (0–100 mm), and the proportion of patients without physician-reported clinical characteristics of nail psoriasis at 6 months.

Statistical analysis. Descriptive statistics were calculated for patient demographic, clinical, and treatment characteristics at the index visit and outcomes at the 6-month follow-up visit. The index visit was defined as the visit in which patients reported treatment initiation with apremilast, MTX, or bDMARD. All data were analyzed descriptively using means and SD for continuous variables and presented as counts and percentages of patients for categorical variables.

Ethical conduct. All participating investigators were required to obtain full board approval for conducting research involving human subjects. Sponsor approval and continuing review was obtained through a central investigational review board (New England Independent Review Board, NEIRB No. 120160610); there were > 50 study sites. For academic investigative sites that did not receive a waiver to use the central investigational review board, full board approval was obtained from the respective governing investigational review boards and documentation of approval was submitted to the sponsor before initiating any study procedures. All registry patients were required to provide written informed consent before participating.

RESULTS

Index visit: patient demographics and clinical characteristics. A total of 1593 patients with oligoarticular PsA were listed in the Corrona PsA/SpA Registry between June 2014 and March 2018. Of these patients, 150 had initiated monotherapy with apremilast ($n = 34$), MTX ($n = 15$), or bDMARD ($n = 101$) as the first initiation during follow-up for oligoarticular PsA (Supplementary Figure 1, available with the online version of this article). Patient demographic, clinical, and treatment characteristics at the index visit are presented in Table 1. Patients who initiated MTX monotherapy were slightly older and a higher proportion were female compared with patients in the apremilast and bDMARD monotherapy groups. More than half of patients in all 3 monotherapy groups were obese. Mean disease duration was generally similar among monotherapy groups.

Overall, treatment and clinical characteristics of apremilast

initiators were suggestive of more refractory oligoarticular PsA compared with MTX initiators (Table 1). Among apremilast and MTX initiators, 79% and 20% received ≥ 1 prior bDMARD, respectively. Patients who initiated apremilast had higher levels of disease activity at baseline, measured by a cDAPSA score > 13 (moderate or high disease activity), and fewer had minimal disease activity (MDA) at baseline compared with patients who initiated MTX or bDMARD. Patients initiating apremilast monotherapy also reported numerically higher mean scores of PRO measures at baseline, including PtGA-PsA and fatigue VAS scores; likewise, the proportion of patients with a HAQ-DI score > 0.5 was also higher with apremilast monotherapy.

Disease activity assessments. A numerically greater proportion of patients with an SJC > 1 or TJC > 1 at baseline who received apremilast monotherapy achieved an SJC ≤ 1 or TJC ≤ 1 at 6 months than those who received monotherapy with MTX or bDMARD (Figure 1). Achievement of an SJC ≤ 1 or TJC ≤ 1 in the apremilast monotherapy group was more similar to the bDMARD monotherapy group than to the MTX monotherapy group (Figure 1). Mean changes in SJC and TJC, respectively, from baseline were numerically greater with apremilast monotherapy (-0.4 and -0.4) compared with MTX (0.1 and -0.3) or bDMARD (0.2 and -0.1) monotherapy. A numerically greater proportion of apremilast monotherapy initiators who were in a moderate or high disease activity cDAPSA category at baseline achieved low disease activity (LDA) or remission (REM) at 6 months compared with MTX and bDMARD monotherapy initiators (Figure 2). Achievement of LDA or REM in the apremilast monotherapy initiators was more comparable to bDMARD monotherapy initiators than to MTX monotherapy initiators (Figure 2). Of those patients who did not have MDA at initiation, 8.7% (2/23) in the apremilast monotherapy group, 0% (0/7) in the MTX group, and 17.9% (10/56) in the bDMARD monotherapy group achieved MDA at the 6-month visit. None of the patients receiving apremilast monotherapy or MTX who did not have very LDA (VLDA) at initiation achieved VLDA at the 6-month visit; 4.8% (4/84) initiating bDMARD monotherapy achieved VLDA. The mean improvement from baseline in cDAPSA score was numerically greater in patients receiving apremilast monotherapy (-1.5) compared with those receiving MTX (-0.2) or bDMARD (-0.1) monotherapy.

PRO measures. At 6 months, patients in all 3 monotherapy groups experienced minimal changes from baseline in mean PtGA-PsA VAS, overall pain VAS, fatigue VAS, and PtGA-PsO VAS scores. Changes from baseline in the apremilast, MTX, and bDMARD monotherapy groups were -0.2 , 2.5 , and 0.4 for mean PtGA-PsA VAS scores; 0.2 , -0.1 , and 0.1 for overall pain VAS scores; -1.4 , 0.3 , and -0.3 for mean fatigue VAS scores; and -2.3 , 1.7 , and -2.0 for PtGA-PsO VAS scores, respectively. The proportions of patients achieving at least a 0.35-point improvement in HAQ-DI MCID were similar in the apremilast, MTX, and bDMARD monotherapy groups (Supplementary Figure 2, available with the online version of this article). A numerically greater proportion of patients with physician-reported nail psoriasis at baseline were without physician-reported nail psoriasis at

Table 1. Baseline patient characteristics.

| | Apremilast, n = 34 | MTX, n = 15 | bDMARD, n = 101 |
|------------------------------------------------------|-----------------------|---------------------|----------------------|
| Age, yrs | 55.7 (12.6), n = 33 | 61.5 (16.6), n = 15 | 52.9 (11.5), n = 99 |
| Female, n (%) | 20 (58.8), n = 34 | 10 (71.4), n = 14 | 59 (59.0), n = 100 |
| BMI, kg/m ² | 34.4 (9.3), n = 34 | 30.6 (8.1), n = 14 | 32.7 (6.8), n = 96 |
| Obese ^a , n (%) | 22 (64.7), n = 34 | 8 (57.1), n = 14 | 58 (60.4), n = 96 |
| Duration since PsA diagnosis, yrs | 8.0 (6.7), n = 33 | 5.4 (7.8), n = 14 | 9.7 (9.4), n = 96 |
| Prior non-bDMARD use, n (%) | 23 (67.6), n = 34 | 2 (13.3), n = 15 | 73 (72.3), n = 101 |
| Prior biologic use (≥ 1), n (%) | 27 (79.4), n = 34 | 3 (20.0), n = 15 | 76 (75.2), n = 101 |
| SJC ^b (0–66) | 1.5 (1.5), n = 34 | 1.0 (1.1), n = 15 | 0.8 (1.3), n = 101 |
| SJC > 1, n (%) | 17 (50.0), n = 34 | 4 (26.7), n = 15 | 26 (25.7), n = 101 |
| TJC (0–68) | 2.7 (3.9), n = 34 | 2.5 (3.3), n = 15 | 3.1 (5.9), n = 101 |
| TJC > 1, n (%) | 17 (50.0), n = 34 | 8 (53.3), n = 15 | 39 (38.6), n = 101 |
| SPARCC enthesitis > 0, n (%) | 6.0 (17.6) | 2.0 (13.3) | 20 (19.8) |
| Dactylitis count > 0, n (%) | 6.0 (17.6) | 2.0 (13.3) | 6.0 (5.9) |
| Axial disease, n (%) | 6 (17.6) | 3 (20.0) | 22 (21.8) |
| MDA, n (%) | 6 (20.0), n = 30 | 4 (36.4), n = 11 | 35 (37.2), n = 94 |
| VLDA, n (%) | 3 (10.0), n = 30 | 1 (9.1), n = 11 | 7 (7.4), n = 94 |
| cDAPSA score (0–154) | 14.0 (8.5), n = 34 | 11.5 (4.9), n = 11 | 12.3 (9.1), n = 98 |
| cDAPSA category, n (%) | | | |
| Remission (≤ 4) | 5 (14.7), n = 34 | 1 (9.1), n = 11 | 17 (17.3), n = 98 |
| Low disease activity (> 4 to ≤ 13) | 12 (35.3), n = 34 | 7 (63.6), n = 11 | 45 (45.9), n = 98 |
| Moderate disease activity (> 13 to ≤ 27) | 14 (41.2), n = 34 | 3 (27.3), n = 11 | 30 (30.6), n = 98 |
| High disease activity (> 27) | 3 (8.8), n = 34 | 0 (0.0), n = 11 | 6 (6.1), n = 98 |
| PtGA-PsA VAS score (0–100 mm) | 47.1 (29.8), n = 34 | 32.5 (26.3), n = 13 | 42.9 (27.7), n = 99 |
| Patient-reported overall pain VAS score (0–100 mm) | 50.5 (31.1), n = 34 | 46.7 (26.5), n = 14 | 42.7 (29.6), n = 99 |
| Patient-reported fatigue VAS score (0–100 mm) | 55.9 (30.0), n = 34 | 37.8 (31.9), n = 15 | 41.2 (29.0), n = 101 |
| HAQ-DI score | 1.0 (0.7), n = 34 | 0.5 (0.4), n = 14 | 0.7 (0.6), n = 100 |
| HAQ-DI score > 0.5, n (%) | 21 (61.8), n = 34 | 6 (42.9), n = 14 | 45 (45.0), n = 100 |
| Psoriasis-affected BSA, % | 7.1 (17.6), n = 30 | 4.8 (9.4), n = 14 | 4.1 (7.8), n = 97 |
| PtGA-PsO VAS score (0–100 mm) | 47.1 (29.4), n = 34 | 28.4 (16.6), n = 12 | 41.2 (26.8), n = 99 |
| Presence of physician-reported nail psoriasis, n (%) | 8 (23.5), n = 34 | 3 (20.0), n = 15 | 25 (24.8), n = 101 |

Values are expressed as mean (SD) unless otherwise indicated. ^a BMI ≥ 30 kg/m². ^b Patients had oligoarticular PsA, defined as ≤ 4 swollen joints. bDMARD: biologic disease-modifying antirheumatic drug; BSA: body surface area; cDAPSA: Clinical Disease Activity Index for Psoriatic Arthritis; HAQ-DI: Health Assessment Questionnaire–Disability Index; MDA: minimal disease activity; MTX: methotrexate; PtGA-PsA: patient global assessment of disease activity-arthritis; PtGA-PsO: patient global assessment of disease activity-arthritis and psoriasis; PsA: psoriatic arthritis; SJC: swollen joint count; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC: tender joint count; VAS: visual analog scale; VLDA: very low disease activity.

6 months in the apremilast monotherapy group compared with the MTX and bDMARD monotherapy groups (Supplementary Figure 3). Improvement in nail psoriasis in the apremilast monotherapy group was more similar to the bDMARD monotherapy group than to the MTX monotherapy group (Supplementary Figure 3).

DISCUSSION

Although oligoarticular PsA, by definition, involves fewer joints than polyarticular PsA, the 2 subgroups had comparable disease burden^{8,9,10}. Oligoarticular PsA, while common^{11,12,13,14,15,16}, remains understudied and identification of effective management of this PsA phenotype is warranted. Despite use in a more often treatment-refractory patient population, the

apremilast monotherapy group experienced improvements in disease activity and PRO measures; improvements were also experienced in the MTX group. The improvements observed with apremilast monotherapy in this population were comparable with bDMARD monotherapy. Our comparison of the 3 groups was descriptive, without statistical testing, because we cannot fully address confounding by indication when comparing different therapy classes across different lines of therapy. Of note, in many cases, patients included in this study were receiving apremilast shortly after its approval. As is generally observed, due to physician comfort with a new medication and payer preference, new-to-market therapies are often used in a more recalcitrant patient population. Over time, apremilast has been more commonly used earlier in the disease course¹⁷.

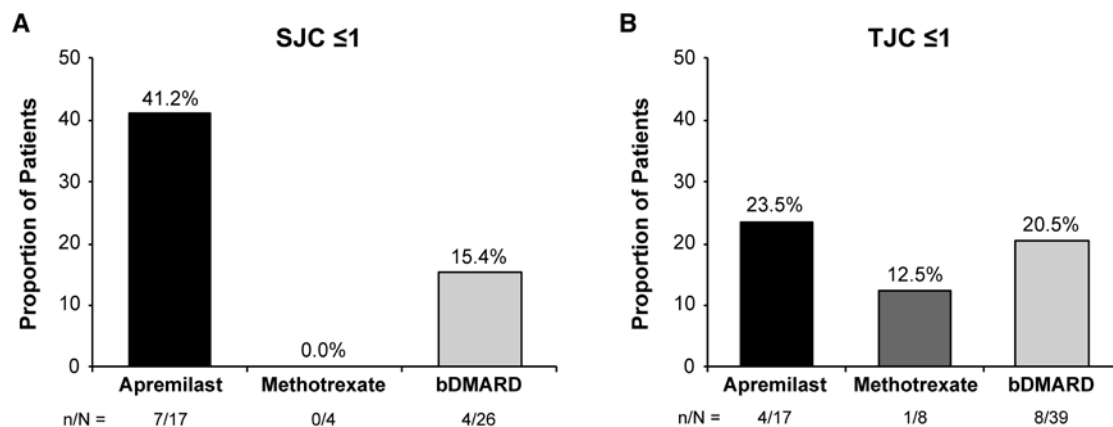


Figure 1. The proportions of patients with > 1 swollen joint or > 1 tender joint at baseline achieving (A) swollen joint count (SJC) ≤ 1 and (B) tender joint count (TJC) ≤ 1 at 6 months. bDMARD: biologic disease-modifying antirheumatic drug; n/N: number of responders/patients with sufficient data for evaluation.

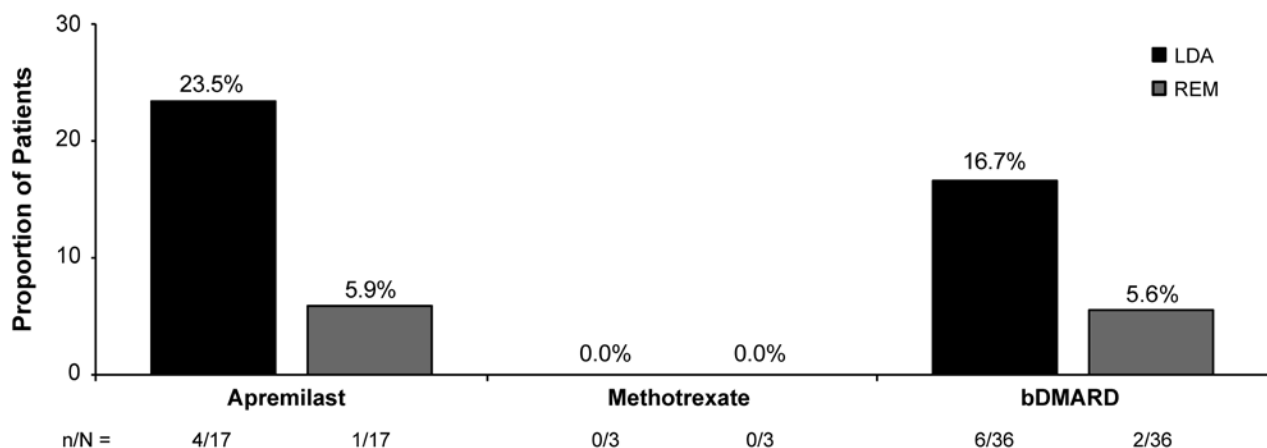


Figure 2. Achievement of low disease activity (LDA)/remission (REM). Proportions of patients in moderate or high Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) categories at baseline achieving cDAPSA LDA or REM categories at 6 months. bDMARD: biologic disease-modifying antirheumatic drug; n/N: number of responders/patients with sufficient data for evaluation.

A limitation of this study is the small sample size and therefore statistical testing was not performed. Further, only patients who completed the 6-month follow-up visit were analyzed, which can introduce selection bias. A larger phase IV, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (ClinicalTrials.gov: NCT03747939) is currently assessing the efficacy of apremilast in patients with early oligoarticular PsA despite initial stable treatment with either nonsteroidal antiinflammatory drugs and/or 1 conventional synthetic DMARD. Overall, findings from this exploratory analysis suggest that apremilast monotherapy is an effective treatment option for oligoarticular PsA.

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DATA SHARING

The Corrona dataset is based on a large US multicenter study adhering to a number of institutional review boards, with complex logistics. Patients did not provide consent to raw data sharing during the data collection for this purpose, and the Corrona data sharing policies do not permit raw data sharing for this purpose. An aggregated limited dataset from the current analyses is available to qualified investigators with an approved protocol. Data requests may be sent to Corrona, represented by Dr. Jeffrey Greenberg; email: jgreenberg@corrona.org.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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