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BRIEF REPORT

Use of FDA-Approved Medications: Biologics for Psoriatic Arthritis in Patients at an Urban Outpatient Rheumatology Clinic

Ira Khanna, Orysia Kozicky, and Harry Fischer

Objective. Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis that manifests as peripheral arthritis, dactylitis, enthesitis, and spondylitis. Biologics, particularly tumor necrosis factor inhibitors (TNFis) and some interleukin 17 (IL-17) and interleukin 23 (IL-23) inhibitors, are the only US Food and Drug Administration (FDA)–approved treatments shown to limit joint damage in clinical trials for PsA. Conventional synthetic disease-modifying antirheumatic drugs have also been adapted to PsA treatment. Current 2018 American College of Rheumatology (ACR) guidelines regard TNFis as first-line therapy in treatment-naïve patients. The aim of this project is to review the prescribing practices for patients with PsA at an urban rheumatology office, with a focus on biologic prescribing.

Methods. A retrospective chart review was performed to search for patients seen from June 1, 2017, to June 1, 2018, using *International Classification of Diseases, 10th Revision* codes for PsA. A log of prescribing practices listed the use of biologics versus oral small molecules (OSMs) (methotrexate, sulfasalazine, leflunomide, and apremilast) across different ages, sex, and disease severity.

Results. This study included a total of 97 patients (40 women and 57 men), and 66% were on biologics (60% of women and 70% of men). There was no sex bias in biologic prescribing ($P = 0.59$). Use of biologics was highest in the 38 to 57 years age group and lowest in the 78 to 97 years age group, although, statistically, there was no age bias in biologic prescribing ($P = 0.22$). Biologics provided superior disease control (84.37%) compared with nonbiologics (66.6%) ($P = 0.0016$). OSMs provided slightly better control (69.5%) over apremilast monotherapy (61.5%) ($P = 0.016$).

Conclusion. There is no age or sex bias in prescribing practices for PsA. In accordance with the ACR, patients with controlled symptoms on OSMs are being appropriately maintained. Although apremilast is allocated as an add-on therapy, 13.4% of patients were on apremilast monotherapy. This quality improvement project reveals that in most instances, biologics are being appropriately initiated as the primary mode of therapy for patients with PsA at our outpatient practice; however, treatment modifications can be made regarding patients who are managed with apremilast alone.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis that mostly manifests as peripheral arthritis, dactylitis, enthesitis, and spondylitis. Its incidence is 6 per 100 000 a year, and its prevalence is 1 to 2 per 1000 in the general population (1). Among patients with psoriasis, the annual incidence of PsA is 2.7% (2), and prevalence ranges from 6% to 41% (1). PsA may present even before skin symptoms in 10% to 15% of patients (2). It affects men and women equally, although women mostly present with peripheral disease with greater functional impairment, whereas men mostly present with axial disease (3). Early diagnosis and treatment of PsA is imperative to decrease associated morbidity. Biologics, particularly tumor necrosis factor inhibitors (TNFis) and some interleukin 17 (IL-17) and interleukin 23 (IL-23) inhibitors, are the only US Food and Drug Administration (FDA)–approved treatments shown to limit joint damage in clinical trials for PsA (4). Nevertheless, there are other immune-modulating therapies, such as methotrexate, sulfasalazine, leflunomide, and apremilast, that have been adapted

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to PsA treatment. Current American College of Rheumatology (ACR) 2018 guidelines regard TNFis as first-line therapy in treatment-naïve patients. The aim of this quality improvement (QI) project is to review the prescribing practices for patients with PsA at an urban rheumatology office, with a focus on biologic prescribing.

MATERIALS AND METHODS

A retrospective chart review of the electronic medical record (Epic Systems Corporation) was performed to search for patients with PsA seen in the office between June 1, 2017, and June 1, 2018, using *International Classification of Diseases, 10th Revision* codes for PsA (L40.50, L40.51, L40.52, L40.53, and L40.59). A log of prescribing practices listed the use of biologics versus oral small molecules (OSMs) (methotrexate, sulfasalazine, leflunomide, and apremilast) across different ages, sex, and disease activity. Disease activity was deduced by documentation of regions of joint involvement, joint pain, swelling or active synovitis, or dactylitis under a review of systems or physical examination at the latest documented visit during the study period. The project aim was to determine the percentage of patients being prescribed biologics versus OSMs, whether there was a sex or age bias in prescribing biologics, and whether there is better disease control with biologics compared with OSMs and apremilast monotherapy. For those individuals who might have qualified for biologics but remained on OSMs, charts were reviewed for contraindications or barriers to biologic prescribing. Pearson's χ^2 test, Fisher's exact test, and the unpaired *t* test were used for the statistical analysis.

RESULTS

This study included a total of 97 patients (40 women and 57 men); 23.7% were in the 18 to 37 years age group, 39.2% were in the 38 to 57 years age group, 33% were in the 58 to 77 years age group, and 4.1% were in 78 to 97 years age group; 66% of the patients were on biologics monotherapy or combination therapy (60% of women and 70% of men) (Figures 1 and 2). Of the patients on biologics, 84.4% were on TNFis and 15.6% were on IL-17 inhibitors. We found no sex bias in biologic prescribing ($P = 0.59$). Use of biologics was highest in the 38 to 57 years age group (75% of women and 81% of men) and lowest in the 78 to 97 years age group (0% of women and 33% of men) (Figures 1 and 2), although, statistically, there was no age bias in biologic prescribing ($P = 0.22$; $P = 0.22$ in men and $P = 0.12$ in women).

Based on encounter documentation of examination findings and subjective symptoms, biologics provided superior disease control (84.37%) compared with nonbiologics (66.6%) ($P = 0.0016$). OSMs provided slightly better control (69.5%) over apremilast monotherapy (61.5%) ($P = 0.016$). One woman stopped her biologic therapy because of pregnancy. Among the patients with active symptoms on OSMs (n = 7), three (at the initial visit) had plans to start biologics at the follow-up visit, two were not amenable to taking biologics, one had stopped his medication with plans to resume, and one had just received apremilast as an add-on therapy. The remaining patients on OSMs had documented contraindications or barriers to biologics, such as untreated latent tuberculosis, hepatitis B, malignancy, congestive heart failure, and insurance limitations, and others had inhibitions to biologic side effects.

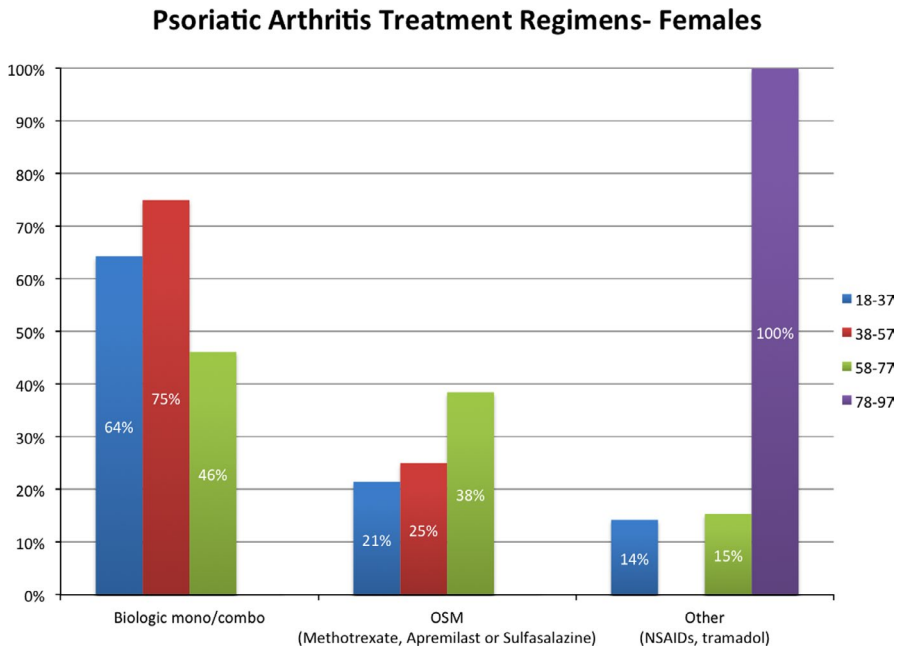

Figure 1. Psoriatic arthritis treatment regimens (women). mono/combo, monotherapy or combination therapy; NSAID, nonsteroidal anti-inflammatory drug; OSM, oral small molecule.

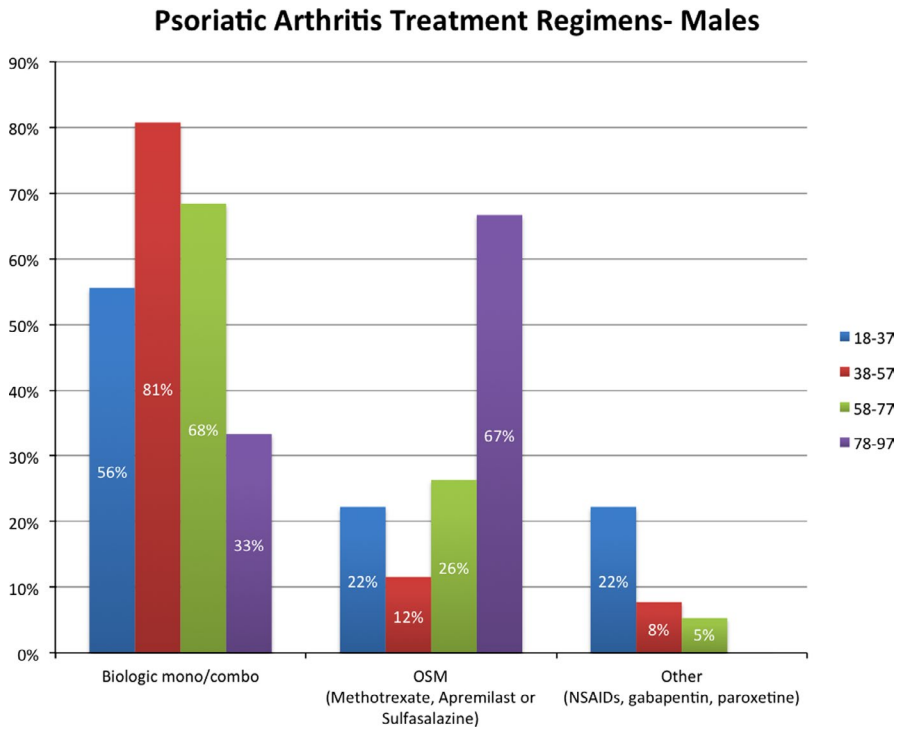

Figure 2. Psoriatic arthritis treatment regimens (men). Mono/combo, monotherapy or combination therapy; NSAID, nonsteroidal anti-inflammatory drug; OSM, oral small molecule.

DISCUSSION

Biologics, mostly TNFis and IL-17 and IL-23 inhibitors, are the only FDA-approved treatment for PsA shown to limit joint damage in various clinical trials and meta-analyses (4). Infliximab efficacy was evaluated in the Infliximab Multinational Psoriatic Arthritis Controlled Trial 2 (IMPACT 2 trial) and, at week 24, showed significantly better response rates for American College of Rheumatology 20% Improvement Response Criteria (ACR20), the Psoriatic Arthritis Response Criteria (PsARC), the Psoriasis Area Severity Index (PASI), enthesitis, and dactylitis, as well as radiographic progression at week 54, compared with a placebo (5). Similar results were seen for other TNFis, such as etanercept (6), Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT trial) (7), golimumab GO-REVEAL trial (A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody) (8), and certolizumab RAPID-PsA trial (Certolizumab Pegol in Subjects With Adult Onset Active and Progressive Psoriatic Arthritis) (9). The PSUMMIT 1 and PSUMMIT 2 trials (Study of the Safety and Effectiveness of Ustekinumab in Patients with Psoriatic Arthritis) showed improvement in ACR20 and radiographic progression in patients with PsA on ustekinumab (interleukin 12 and IL-23 inhibitors) who both were biologic naïve and had treatment failure of previous TNFis (10,11).

There is no significant difference in efficacy among TNFis based on results of one randomized, nonblinded study and two indirect meta-analyses (12–14). The IL-17 inhibitor secukinumab showed greater improvements in ACR20, the PASI, dactylitis and enthesitis scores, and radiographic progression compared with a placebo in the FUTURE 1 and FUTURE 2 trials (Efficacy at 24 weeks and Long Term Safety, Tolerability and Efficacy up to 2 years of Secukinumab in Patients with Active Psoriatic Arthritis), although it seemed to work better in biologic-naïve patients (15,16).

Apremilast was also approved by the FDA for use in PsA in 2014 on the basis of the PALACE-1, PALACE-2 and PALACE-3 trials (Psoriatic Arthritis Long-term Assessment of Clinical Efficacy), which revealed that patients receiving apremilast with or without disease-modifying antirheumatic drugs (DMARDs) showed greater improvement in signs and symptoms of PsA compared with those receiving a placebo with or without DMARDs (17,18). However, in these studies, 65% of patients were on concomitant DMARDs and 14% were on concomitant steroids; hence, per the current PsA ACR guidelines, apremilast is recommended for use as an add-on therapy.

Methotrexate is the most commonly used DMARD in PsA and is prescribed off label given its ease of use, tolerability, and proven efficacy in skin psoriasis. However, the MIPA trial (Methotrexate in Psoriatic Arthritis Trial), which was the largest randomized, placebo-controlled trial for methotrexate use in PsA, failed to show superiority of methotrexate over a placebo, although it was limited by the fact that only the efficacy of low-dose methotrexate was considered (15 mg) (19). The LEF trial (Efficacy and Safety of Leflunomide in the Treatment of Psoriatic Arthritis and Psoriasis) (2004) showed that leflunomide significantly improved swollen and tender joint counts over a placebo;

however, it is still not approved by the FDA for PsA treatment because it does not have much effect on skin psoriasis. (20)

The SEAM trial (Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis) evaluated the efficacy of etanercept and methotrexate as monotherapies and as a combination therapy in subjects with active PsA. Results from February 2019 revealed that etanercept monotherapy and combination therapy showed greater efficacy than methotrexate monotherapy in ACR 20/50/70 criteria (20%, 50%, 70% improvement in the American College of Rheumatology Criteria), minimum disease activity scores, dactylitis and enthesitis scores, and radiographic progression, with no major benefit of combination therapy except for some skin end points (21). This was the first head-to-head randomized control trial (RCT) to examine the comparative efficacy of a TNFi and the most commonly prescribed conventional synthetic DMARD in PsA early in the course of a disease (22).

To date, there is no RCT with an aim to assess efficacy on axial joint manifestation in PsA, and as for ankylosing spondylitis, there is no evidence of efficacy of conventional synthetic DMARDs on axial PsA. Only one observational study reported the effect of etanercept in patients with axial PsA, revealing a significant improvement of the Bath Ankylosing Spondylitis Disease Activity Index and the Bath Ankylosing Spondylitis Functional Index (23). Thus, per the European League Against Rheumatism (EULAR) guidelines, biologics are initiated in patients with axial PsA if they have treatment failure of nonsteroidal anti-inflammatory drugs.

The 2015 EULAR guidelines for PsA still recommend use of methotrexate prior to use of biologics, especially in patients with skin manifestations, because of its known efficacy in skin psoriasis; however, the EULAR guidelines also recommend switching to a biologic if there is no improvement in symptoms in 3 months of therapy. However, the 2018 ACR guidelines recommend starting TNFis as first-line therapy in treatment-naïve patients with PsA, the order of preference being TNFis, then OSMs, then IL-17 inhibitors, then IL-23 inhibitors. In patients with active PsA despite use of OSMs, the order of preference is TNFis, then IL-17 inhibitors, then IL-23 inhibitors. In patients with active PsA despite use of TNFis, the order of preference is to first switch to a different TNFi, then use IL-17 inhibitors, then IL-23 inhibitors. Patients well controlled on OSMs must be continued on OSMs (24).

Biologics are usually contraindicated in patients with active infections, history of untreated tuberculosis, hepatitis B, congestive heart failure, malignancy, demyelinating diseases, and blood dyscrasias. Biologics are also Category B medications; however because of limited data on use in late pregnancy, these medications are usually discontinued in early pregnancy (25).

Our rheumatology division's prescribing practices had largely been derived from a combination of EULAR guidelines and the aforementioned pivotal trials for PsA. However, the results generally align with the recently released formal ACR guidelines. Although we are pleased to report this congruity, our study did have several limitations. Most clinical studies reference validated scores of disease activity, which was not possible in our study given the lack of regular implementation in the documentation and retrospective chart review. For each visit, the patient's signs and symptoms under a review of systems and physical examination were extrapolated to gauge disease activity. Encounter notes were fairly detailed, including the extent of joint involvement, the joint and skin examinations, and any other extra articular concomitant symptoms. Furthermore, disease activity was only noted for the latest documented visit within the year of observation; disease activity was not monitoring beyond that encounter given the infrequent follow-up visits for most of our patients. Also, there was incomplete gathering of data on prior medication regimens prior to biologic prescribing. Only 10 of 64 (15.6%) patients on biologics had documentation of prior medication regimens. Four patients were on combination therapy with OSMs, and five patients were on biologic monotherapy, all having treatment failure of prior biologic monotherapies. There was a case of need for transition from methotrexate to a TNFi due to concern for lung toxicity rather than PsA symptom control. Lastly, the elderly contingent was underrepresented, limiting the statistical significance.

Based on our results, it seems that biologics are being used consistently at our rheumatology practice, with the exception of use in the elderly, possibly secondary to comorbidities, including heart failure, malignancies, etc. Nevertheless, statistically, there is no age or sex bias in prescribing practices toward biologics. This may also be due to the fact that our practice has a designated person to facilitate prior authorizations, which helps our patient population obtain insurance authorization to be on biologics. In accordance with the ACR, patients with controlled symptoms on OSMs are being appropriately maintained on them. Although apremilast is allocated as an add-on therapy, 13.4% of patients were on apremilast monotherapy, given a more favorable side-effect profile. This QI project reveals that in most instances, biologics are being appropriately initiated as the primary mode of therapy for patients with PsA at our outpatient practice; however, treatment modifications can be made regarding patients managed with apremilast alone.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, approved the final version to be published, and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Khanna, Fischer
Acquisition of data. Khanna, Kozicky, Fischer
Analysis and interpretation of data. Khanna, Kozicky, Fischer

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