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Treatment With Tofacitinib in Refractory Psoriatic Arthritis: A National Multicenter Study of the First 87 Patients in Clinical Practice

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ABSTRACT. ***Objective.*** Tofacitinib (TOF) is the first Janus kinase (JAK) inhibitor approved for psoriatic arthritis (PsA). It has shown efficacy in patients refractory to anti–tumor necrosis factor-α in randomized controlled trials (RCTs). Our aim was to assess efficacy and safety of TOF in clinical practice.

Methods. This was an observational, open-label multicenter study of PsA patients treated with TOF due to inefficacy or adverse events of previous therapies. Outcome variables were efficacy, corticosteroid dose-sparing effect, retention rate, and safety. A comparative study of clinical features between our cohort of patients and those from the OPAL Beyond trial was performed.

Results. There were 87 patients (28 women/59 men), with a mean age of 52.8 ± 11.4 years. All patients were refractory to biologic disease-modifying antirheumatic drugs (DMARDs) and/or to conventional synthetic DMARDs plus apremilast. TOF was started at 5 mg twice daily after a mean follow-up of 12.3 ± 9.3 years from PsA diagnosis. At first month, Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR) decreased from median 4.8 (IQR 4.1–5.4) to 3.7 (IQR 2.8–4.7, $P < 0.01$), Disease Activity Index for Psoriatic Arthritis from median 28 (IQR 18.4–34.1) to 15.5 (IQR 10.1–25.7, $P < 0.01$), and C-reactive protein from median 1.9 (IQR 0.3–5.0) to 0.5 (IQR 0.1–2.2) mg/dL ($P < 0.01$). Also, TOF led to a significant reduction in prednisone dose. Mild adverse effects were reported in 21 patients (24.13%), mainly gastrointestinal symptoms. TOF retention rate at Month 6 was 77% (95% CI 65.2–86.3). Patients in clinical practice were older with longer disease duration and received biologic agents more commonly than those in the OPAL Beyond trial.

Conclusion. Data from clinical practice confirm that TOF seems to be effective, rapid, and relatively safe in refractory PsA despite clinical differences with patients in RCTs.

Key Indexing Terms: biologic therapy, clinical practice, psoriatic arthritis, real-world data, tofacitinib

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Psoriatic arthritis (PsA) is a chronic inflammatory disorder comprising a wide spectrum of clinical domains, including skin and nail involvement, enthesitis, dactylitis, as well as axial and peripheral arthritis.[1] The recommended therapy depends on the clinical manifestations. It may include nonsteroidal antiinflammatory drugs (NSAIDs); conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); targeted synthetic (ts)DMARDs, such as phosphodiesterase-4 (PDE4) inhibitors; and biological (b)DMARDs, such as anti–tumor necrosis factor-α (anti-TNF-α), and interleukin (IL)-12/23 and IL-17 inhibitors.[2,3]

Anti-TNF-α are the current standard of care for PsA patients with an inadequate response to conventional therapy.[2,3] However, loss of efficacy is not uncommon in clinical practice.[4] In addition, the proportion of patients achieving minimal disease activity (MDA) across randomized controlled trials (RCTs) with anti-TNF-α is highly variable, ranging from 33% to 52% at 24 weeks.[5,6,7,8] The proportion of patients fulfilling MDA criteria at 12 months in observational studies and open-label cohorts ranged from 44% to 64%.[9,10,11,12]

IL-17 inhibitors seem to be especially useful for skin and musculoskeletal manifestations of PsA.[13] However, in patients with underlying inflammatory bowel disease, they are not useful, and can even be harmful. IL-12/23 inhibitor ustekinumab and PDE4 inhibitor apremilast have shown modest and slow joint response, with an American College of Rheumatology 20% (ACR20) response of 43.7% and 40.7% at 24 weeks, respectively.[14,15,16,17]

Tofacitinib (TOF) is the first Janus kinase (JAK) inhibitor approved for the treatment of PsA by the European Medicines Agency (EMA), in June 2018. TOF is a small-molecule inhibitor of JAK1, JAK3, and, to a lesser extent, JAK2,[18] which inhibits key immune triggers of both psoriasis and PsA.[19] In the OPAL Beyond trial, TOF showed to be more effective than placebo in active PsA patients with an inadequate response to anti-TNF-α.[20]

RCTs are the best tool to assess the efficacy of therapeutic agents.[21] They are conducted under highly standardized design and strict inclusion criteria to ensure the reliability of results.[22,23] However, it is known that the demographic and clinical features of patients included in RCTs may differ from those of clinical practice. These differences may have an influence on the clinical outcomes when applied to patients seen in daily clinical practice.[24–30] In this regard, it is very important to carry out observational studies in order to obtain real-world evidence, which is needed to improve healthcare decision making and to assess the feasibility of evidence from RCTs.[24,25,30,31,32]

Taking all these considerations into account, our aim was to assess the efficacy and safety of TOF in patients with PsA from a real-world clinical setting with inadequate response and/or unacceptable side effects to conventional therapy. In addition, we aimed to compare the clinical profile of patients from our cohort with those included in the OPAL Beyond trial.[20]

METHODS

We conducted an open-label, multicenter study including 87 patients of clinical practice with refractory PsA treated with TOF.

Patients and enrollment criteria. We included all patients with PsA diagnosis who had received at least 1 dose of TOF at the Rheumatology Division of 25 national referral centers in Spain between January 1, 2015, and December 31, 2019. The ethical approval for the study protocol was originally obtained from the Institutional Review Committee at Hospital Marqués de Valdecilla in Santander, Spain (approval number: 2019.177) and was subsequently approved by the remaining participating centers.

PsA diagnosis was based on ClASsification for Psoriatic ARthritis (CASPAR) criteria.[33] Refractory PsA was defined when the patient did not achieve clinical low disease activity or remission despite the use of bDMARDs or apremilast.

All patients were refractory to at least 1 bDMARD or to csDMARDs in addition to apremilast. TOF was used at the standard dose of 5 mg taken orally twice daily. Since TOF therapy was an off-label indication for PsA before EMA approval in June 2018, written informed consent was requested and obtained for those patients.

Following the Spanish Biologic Treatment Administration National Recommendations, the presence of infectious diseases was ruled out before starting treatment with TOF.[34] To exclude latent tuberculosis, a tuberculin skin testing and/or an interferon assay (quantiFERON) as well as chest radiography were performed. In positive cases, prophylaxis with isoniazid was initiated for at least 4 weeks before using the biologic treatment and was maintained for 9 months. Patients with active malignancies were excluded.

Outcome variables. The outcome variables were efficacy, corticosteroid dose-sparing effect, retention rate, and safety of TOF therapy.

The main efficacy outcomes were improvement in the Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR)[35] and Disease Activity Index for Psoriatic Arthritis (DAPSA) score.[36] DAPSA is the result of the sum of the number of tender joints, number of swollen joints, C-reactive protein (CRP), patient global assessment (PtGA) of arthritis (as measured on a visual analog scale [VAS] ranging from 0 to 100 mm), and patient assessment of arthritis pain (as measured on a VAS).

The secondary outcome was skin efficacy, which was assessed by the improvement on the Psoriasis Area and Severity Index score (range 0–72, higher scores indicating more severe disease).[36,37]

For the purpose of comparing the clinical profile of our cohort of patients with those from RCTs, information was retrieved from the results of the TOF arm (5 mg/12 h) of OPAL Beyond RCT.[20]

Data collection and statistical analysis. Information was retrieved from the patient clinical records in each participating center according to a predefined protocol. To minimize entry error, all data was double-checked. Information was stored on a computerized database.

All continuous variables were tested for normality, and results were expressed as mean ± SD or as median and IQR as appropriate. The chi-square

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test and the *t* test or Mann-Whitney *U* test were used for comparison of qualitative and quantitative variables, respectively. For comparisons among quantitative follow-up data related to baseline, paired *t* tests or Wilcoxon signed-rank tests were used. Medians were compared by quantile regression analysis.

The outcome variables were assessed and compared between baseline (at TOF onset), and at 1 and 6 months. Retention rate at Month 6 was estimated using Kaplan-Meier nonparametric survival data analysis, in which the event was discontinuation of the drug due to inefficacy or toxicity.

Statistical significance was set at $P < 0.05$. Analyses were performed using SPSS 23.0 (IBM Corp.) and Stata SE 14.2 (StataCorp).

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RESULTS

Baseline main clinical features at TOF onset. We studied 87 patients (28 women/59 men) with a mean age of 52.8 ± 11.4 years (Table 1). All patients fulfilled CASPAR criteria for PsA diagnosis. The pattern of joint involvement of PsA was peripheral (n = 60), mixed (n = 26), and axial (n = 1).

The mean ± SD time from PsA diagnosis to TOF onset was 12.3 ± 9.3 years. The main clinical features at the time of TOF onset were arthritis (95.4%), skin involvement (48.3%), enthesitis (32.2%), nail involvement (19.5%), and dactylitis (18.4%; Table 1).

Before TOF, all patients had received at least 1 csDMARD (mean no. 2.26 ± 0.86) and 1 bDMARD (mean no. 3.6 ± 1.9). Previous csDMARDs were methotrexate (MTX; n = 72), leflunomide (LEF; n = 48), and sulfasalazine (SSZ; n = 39). Previous bDMARDs were etanercept (n = 58), adalimumab (n = 54), secukinumab (n = 54), ustekinumab (n = 39), golimumab (n = 37), infliximab (n = 31), certolizumab (n = 30), and ixekizumab (n = 2). Apremilast was used in 17 patients. Also, 44 (50.6%) patients had received oral prednisone or the equivalent (max mean dose 15.8 ± 13.9 mg/d).

TOF treatment and efficacy. TOF was initiated at the standard dose of 5 mg twice daily. Concomitant glucocorticoid therapy was administered to 44 cases (50.6%) with a mean dose of prednisone of 7.8 ± 4.9 mg/d. Combined therapy with MTX (n = 30), LEF (n = 15), and SSZ (n = 6) was used in 48 cases (55.2%). In the remaining 39 patients (44.8%), TOF was used as monotherapy (Table 1).

Following TOF therapy, patients experienced rapid and maintained joint improvement (Table 2). The main outcomes (DAS28-ESR, DAPSA) showed significant improvement in the first month of TOF therapy that was longer maintained (Figure 1). Likewise, the PASI score showed a trend for improvement throughout follow-up, although no statistically significant differences were achieved (Table 2).

Table 1. Baseline characteristics of 87 patients with refractory PsA of clinical practice and the standard TOF therapy arm (5 mg/12 h) of the OPAL Beyond clinical trial.

	Clinical Practice, n = 87	RCT[20], n = 131	*P*
Baseline demographics			
Age, yrs, mean ± SD	52.8 ± 11.4	49.5 ± 12.3	0.047
Sex, M/F, n (%)	59/28 (67.8/32.2)	67/64 (51.1/48.9)	0.02
Disease characteristics			
PsA duration, yrs, mean ± SD	12.3 ± 9.3	9.6 ± 7.6	0.02
HAQ-DI[a], mean ± SD	1.4 ± 0.7 (n = 26)	1.3 ± 0.7	0.51
Swollen joint count, mean ± SD	5.7 ± 5.8	12.1 ± 10.6	< 0.001
Tender joint count, mean ± SD	8.0 ± 6.6	20.5 ± 13.0	< 0.001
Enthesitis, n (%)[b]	28 (32.2)	83 (63)	< 0.001
Dactylitis, n (%)[c]	16 (18.4)	66 (50)	< 0.001
PASI score, median [IQR][d]	5.0 [1–14]	7.6 [0.6–32.2]	–
Elevated CRP, n (%)[e]	55 (63.2)	85 (65)	0.002
Oral glucocorticoid use, n (%)	44 (50.6)	37 (28.0)	0.001
Concomitant csDMARD, n (%)	48 (55.2)	131 (100)	< 0.001
Methotrexate	30 (34.4)	98 (75)	–
Leflunomide	15 (17.2)	12 (9)	–
Sulfasalazine	6 (6.9)	21 (16)	–
Other	0 (0)	2 (2)	–
Previous use of anti-TNF-α, mean ± SD	2.4 ± 1.4	1.7 ± 1.0	< 0.001
Previous use of other non–anti-TNF-α biologics, n (%)	68 (78.2)	11 (8)	< 0.001
TOF monotherapy, n (%)	39 (44.8)	0 (0)	< 0.001

[a] Scores on HAQ-DI range from 0 to 3, with higher scores indicating greater disability. [b] Leeds Enthesitis Index > 0 indicated presence of enthesis. [c] Dactylitis Severity Score > 0 indicated presence of dactylitis. [d] PASI scores range from 0 to 72, with higher scores indicating more severe disease. [e] CRP > 0.5 mg/dL in clinical practice and > 0.287 mg/dl in the OPAL Beyond trial. CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire–Disability Index; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; RCT: randomized controlled trial; TNF: tumor necrosis factor; TOF: tofacitinib.

Table 2. Improvement in efficacy outcomes at Months 1 and 6 after tofacitinib therapy in 87 patients with refractory PsA.

	Baseline, n = 87	Month 1, n = 77	Month 6, n = 52
Swollen joint count	4 (2–8)	1 (0–4)*	0 (0–2)*
Tender joint count	6 (3–10)	3 (1–5)*	1 (0–3)*
DAS28-ESR	4.82 (4.14–5.40)	3.71 (2.82–4.67)*	2.88 (2.24–3.85)*
DAPSA	28 (18.41–34.05)	15.5 (10.1–25.7)*	9 (6.07–15)*
PASI	5.0 (1–14)	1.45 (0–7)	0 (0–4)
CRP, mg/dL	1.90 (0.34–5)	0.5 (0.1–2.24)*	0.5 (0.3–1.24)*
Prednisone dose, mg/d	7.83 ± 4.93	6.67 ± 3.77*	5.39 ± 2.24*

Values are expressed as median (IQR) or mean ± SD. * $P < 0.01$ vs baseline (Wilcoxon signed-rank test). CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28-ESR: Disease Activity Score in 28 joints based on erythrocyte sedimentation rate; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis.

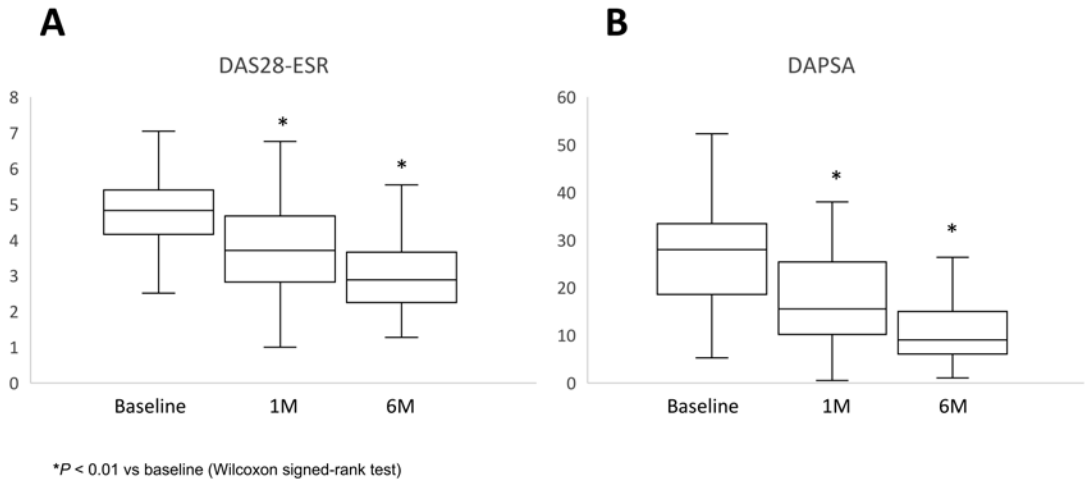

Figure 1. Improvement in disease activity indexes in 87 patients with refractory psoriatic arthritis following tofacitinib therapy. (A) Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR). (B) Disease Activity in Psoriatic Arthritis Score (DAPSA). Bars represent median values with 95% CI.

CRP decreased from median 1.90 (IQR 0.34–5) mg/dL to 0.5 (IQR 0.1–2.24; $P = 0.004$) mg/dL at the first month. A corticosteroid dose-sparing effect was also observed. TOF led to a reduction of the prednisone dose from 7.83 ± 4.93 mg/d to 6.67 ± 3.77 mg/d ($P = 0.006$) at the first month (Table 2).

Regarding concomitant use of csDMARDs, there were no changes in their mean dose throughout the study (data not shown).

TOF retention rate and adverse effects. TOF retention rate at Month 6 was 77% (95% CI 65.2–86.3). No serious adverse events (AEs) were observed after a mean follow-up of 6.5 ± 5.69 months. Twenty-one (24.13%) patients experienced at least 1 mild AE, including gastrointestinal (GI) symptoms (n = 17), upper respiratory tract infection (n = 4), urinary tract infection (n = 2), headache (n = 2), cutaneous infection (n = 1), and sleep disturbances (n = 1). TOF was discontinued in 29 of 87 patients (33.33%) due to inefficacy in most cases. No thrombotic events were observed, and the mean levels of hemoglobin, lymphocyte, neutrophils, platelets, lipids, and transaminases were stable throughout the follow-up (Table 3). However, mild lymphopenia was reported in 3 patients and worsening of lipid profile in 3 other patients.

Comparative study of clinical practice cohort and OPAL Beyond. Patients from our clinical practice cohort (n = 87) were compared to those included in the arm with standard TOF therapy (5 mg twice daily) of the OPAL Beyond trial (n = 131; Table 1).

There was a higher proportion of men in patients from clinical practice (67.8% vs 51.1%, $P = 0.02$). Also, they were older (52.8 ± 11.4 vs 49.5 ± 12.3 yrs, $P = 0.047$) and had a longer PsA duration (12.3 ± 9.3 vs 9.6 ± 7.6 years, $P = 0.02$). A nonsignificant increased functional disability (Health Assessment Questionnaire–Disability Index [HAQ-DI] 1.4 ± 0.7 vs 1.3 ± 0.7, $P = 0.51$) was observed in patients from clinical practice. In our series, patients had received a higher number of bDMARDs

Table 3. Laboratory findings at baseline, and at Months 1 and 6 after tofacitinib therapy, in 87 patients with refractory PsA.

	Baseline, n = 87	Month 1, n = 77	Month 6, n = 52
Hemoglobin, g/dL	13.3 ± 1.7	13.3 ± 1.4	13.3 ± 1.4
Neutrophils, count/μL	4826 ± 2462.4	5193 ± 3030.6	4711.5 ± 2317
Lymphocytes, count/μL	2443 ± 1151.7	2608 ± 1188.1	2500 ± 1577.5
Platelets, count/μL	258,127 ± 106,843.7	273,864 ± 92,855.9	272,868 ± 95,190
Creatinine, mg/dL	0.79 ± 0.3	0.79 ± 0.3	0.75 ± 0.2
AST, U/L	20.1 ± 10.4	19.9 ± 6.8	22 ± 9.0
ALT, U/L	21.2 ± 15.3	21.0 ± 13.2	20.3 ± 10.5
Cholesterol, mg/dL	197.6 ± 31.8	199.6 ± 42.6	206.3 ± 65.1
HDL, mg/dL	59.3 ± 15.8	64.1 ± 18.6	65.8 ± 17.0
LDL, mg/dL	114.4 ± 31.3	111.0 ± 38.3	113.8 ± 40.9

Values are expressed as mean ± SD. ALT: alanine transaminase; AST: aspartate transaminase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PsA: psoriatic arthritis.

prior to TOF than patients from the OPAL Beyond trial (Table 1).

The tender and swollen joint counts, PASI score, as well as the proportion of patients with enthesitis and dactylitis, were higher in patients from the OPAL Beyond trial (Table 1).

Regarding treatment, patients in clinical practice required more frequent corticosteroids (50.6 vs 28.0%, $P = 0.001$) but less frequent concomitant csDMARDs ($P < 0.001$). In the OPAL Beyond trial, all patients received combined therapy with a stable dose of a single csDMARD, whereas TOF was used as monotherapy in 39 (44.8 %) patients in our series (Table 1).

Besides the clinical differences shown above, there was good response both in the RCT and in clinical practice.

DISCUSSION

We present the first series published of patients with PsA treated with TOF in clinical practice, to our knowledge. Our series had a longer evolution of the disease and were more commonly refractory to conventional therapy when compared to patients from the OPAL Beyond trial. Despite these differences, TOF showed clinical efficacy and was well tolerated, making it a promising new agent for the comprehensive treatment of PsA.

Diagnosis of PsA is often delayed, resulting in significantly worse outcomes, including radiographic damage and impaired functional status.[38,39] Fortunately, during the last 15 years, a range of new treatment options have been developed that have improved outcomes for patients with PsA.[40] These therapeutic agents are directed toward different specific disease pathways.[41,42,43] As therapeutic options evolve, tailored therapies can be used, depending on the most PsA-affected domain.[44] However, there is a striking similarity regarding joint involvement efficacy for most current therapies, with only 50–60% of patients meeting the primary outcome measure (ACR20) regardless of the mechanism of action.[43]

As previously mentioned, TOF has shown efficacy in RCT for PsA refractory to csDMARD (OPAL Broaden)[45] and to TNF inhibitors (OPAL Beyond).[20] In the OPAL Beyond trial, at 3 months, the rates of ACR20 response with the 5 mg of TOF were significantly higher compared to placebo ($P < 0.001$), as well as the mean changes from baseline in HAQ-DI score ($P < 0.001$). The 10-mg dose of TOF, but not the 5-mg dose, was superior to placebo with respect to the rate of PASI75 response ($P < 0.001$) and the mean changes. Improvement in enthesitis and dactylitis could not be tested for statistical significance but were in the same direction as the findings for the primary endpoints. In the OPAL Balance[46] posthoc analysis of pooled data from 2 phase III studies, a significantly greater proportion of TOF-treated patients achieved PASI75 response at Month 3 compared to placebo (32.1–43.7% vs 14.3%, $P \leq 0.05$), and significant improvements in enthesitis and dactylitis were also observed. The efficacy across various PsA disease domains, including ACR, HAQ-DI, PASI75, Leeds Enthesitis Index, Dactylitis Severity Score, and pain response, were maintained up to 30 months.[46]

Like in the OPAL Beyond trial,[20] our patients experienced a rapid and maintained improvement in joint activity indexes (DAS28, DAPSA). A trend toward improvement of PASI score was also observed. In addition, a corticosteroid dose-sparing effect was achieved.

TOF has also shown a good safety profile in phase III trials and in the long-term extension study. At 36 months, AEs were reported in 79.6% patients, but only 13.8% patients had serious AEs. TOF was discontinued in 8.6% patients due to AEs.[46] Burmester *et al*[47] have recently published a study including 5799 patients, comparing the incidence rates of AEs in TOF clinical trials and real-world observational data of patients receiving csDMARDs, bDMARDs, or apremilast. TOF showed a similar safety profile to that of other systemic therapies in real-world settings, except for the increased risk of herpes zoster.[47] Of note, we observed a lower frequency of minor AEs in our study in comparison to the OPAL Beyond trial, and no serious AEs were reported. In this regard, AEs occurred in 55% of the patients from the OPAL Beyond trial, whereas they were reported in 24.13% of the patients from our clinical practice. The types of AEs were similar to those observed in TOF clinical trials, with GI symptoms (n = 17) and upper respiratory tract infection (n = 4) being the most commonly reported. Mild lymphopenia was reported in 3 patients. The fact that TOF was administered in monotherapy in almost half of the patients in our series, whereas all patients from the OPAL Beyond trial received TOF

along with csDMARDs, may explain the lower frequency of AEs in our clinical practice.

We observed a retention rate to TOF of 77% (95% CI 65.2–86.3) at 6 months. Of note, most of our patients had previously received at least 1 anti-TNF-α or other (non–anti-TNF-α) bDMARD; this may reflect that these patients had a more aggressive disease.

This study has certain limitations derived from the retrospective design. In addition, the follow-up period was relatively short (6.5 ± 5.69 months), mainly because TOF could not be prescribed until September 2019 in Spain. Further, this is a single-arm study, so in the absence of comparative data, it is purely descriptive. Another limitation of this study was the use of DAS28-ESR, as this is an outcome measure in rheumatoid arthritis. However, we have included DAPSA to address this limitation. Moreover, we are aware that retention rates may be artificially higher in patients with refractory disease who have fewer therapeutic options.

In conclusion, our data support that TOF is effective, rapid, and relatively safe in daily clinical practice for refractory PsA, despite the clinical differences with patients included in the OPAL Beyond trial.

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