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Treatment with Upadacitinib in Difficult-to-Treat (D2T) Psoriatic Arthritis (PsA): A National Multicenter Study of the First 134 Patients in Clinical Practice

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Abstract: Upadacitinib has demonstrated efficacy in psoriatic arthritis in clinical trials, but its real-world performance in difficult-to-treat PsA remains underexplored. This observational, multicenter, open-label study evaluated the efficacy and safety of upadacitinib in 134 patients with psoriatic arthritis (97 women, mean age 51.8 ± 11.2 years, mean disease duration 9.94 ± 7.72 years) who showed inadequate response to advanced therapies. Most patients (74.6%) had received at least two biological/targeted synthetic disease-modifying antirheumatic drugs with different mechanisms of action. Upadacitinib was initiated at 15 mg daily, and within one month, significant improvements were observed: DAS28-ESR decreased from 4.7 to 3.77 ($p < 0.001$), DAPSA from 25 to 17 ($p < 0.001$), and CRP from 2.90 to 1.50 mg/L ($p = 0.001$). These reductions persisted throughout the study. Prednisone dosage decreased significantly ($p = 0.049$). Adverse events led to upadacitinib discontinuation in 8.2% of patients, but no serious adverse events were reported. Compared to the SELECT-PsA 2 trial, our cohort had a higher proportion of females and greater prior exposure to biologic agents but showed comparable efficacy and safety outcomes. These findings suggest that upadacitinib is a rapid, effective, and relatively safe therapeutic option for

difficult-to-treat psoriatic arthritis under real-world conditions, supporting its use despite differing patient characteristics from clinical trial populations.

Keywords: biologic therapy; clinical practice; psoriatic arthritis; real-world data; upadacitinib; JAK inhibitor; difficult-to-treat PsA

1. Introduction

Psoriatic arthritis (PsA) is a chronic, immune-mediated, inflammatory arthropathy that affects 6–41% of patients with psoriasis [1] and has an overall prevalence of 0.2% in Europe [2]. PsA is a clinically heterogeneous condition with musculoskeletal involvement, such as arthritis, dactylitis, enthesitis, axial involvement, and skin and nail psoriasis [3]. The impact of PsA on quality of life is similar to that of rheumatoid arthritis (RA) and is associated with an increased risk of cardiovascular comorbidities and increased mortality [3].

PsA treatment addresses not only all of the disease domains but also has to take into account previous and concomitant therapies, as well as associated comorbidities (i.e., cardiovascular disease, metabolic syndrome, liver disease, mood, and anxiety disorders, chronic infections, malignancies, and fibromyalgia) all of which increase its complexity [4]. Pharmacological treatment of PsA includes conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), a broad group of biologics DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) such as apremilast and Janus kinase (JAK) inhibitors [4]. Despite the availability of these treatments, the proportion of patients who achieve the target of minimal disease activity (MDA) remains low. For example, in randomized clinical trials (RCT) where tumor necrosis factor (TNF) inhibitors were used to treat PsA patients, only 24 to 52% achieved MDA, with similar numbers observed in observational studies [5]. Evidence from the EuroSpA, DANBIO, and CORRONA registries, observations studies and clinical trials, shows that the American College of Rheumatology 70% improvement criteria (ACR70) responses and MDA are only achieved in 20% to 30% of PsA patients after 6 or more months of treatment with bDMARDs therapy [6–9]. This data highlights the need for additional therapeutic options beyond biological therapy.

The concept of difficult-to-treat (D2T) rheumatoid arthritis (RA) has recently been defined [10]. It describes patients who exhibit symptoms and/or signs of active disease despite treatment with at least two b/tsDMARDs with different mechanisms of action. Additionally, their disease management must be perceived as problematic by either the rheumatologist or the patient. In relation to PsA, it is known that a remarkable proportion of patients with this disease remain resistant to advanced therapeutic interventions and are labelled as D2T PsA. Several factors may contribute to inadequate response to treatments in these patients. The truth is that currently there is no consensus to what constitutes active disease and how many drugs a patient must fail to be classified as D2T PsA [11,12].

Upadacitinib (UPA) is an oral, selective and reversible JAK1, JAK2 inhibitor that preferentially inhibits JAK1 and has shown efficacy in patients with RA, with similar results in methotrexate-naïve patients or patients with inadequate response to methotrexate or bDMARDs [13]. In 2021 UPA 15 mg once daily was approved by the European Medicines Agency (EMA) for the treatment of active PsA in adult patients who have responded inadequately or are intolerant to one or more DMARDs, either as monotherapy or in combination with methotrexate [14]. The approval was based on two RCTs of UPA in patients with refractory PsA to non-biologic or biologic DMARDs (SELECT-PsA 1 and SELECT-PsA 2 trials) [15,16], which demonstrated greater efficacy regarding musculoskeletal manifestations, psoriasis, physical function, pain, and quality of life than placebo.

RCTs are the main research tool for evaluating the effects and value of interventions [17]. However, the restrictive selection criteria and other characteristics of RCTs, such as closer follow-up of the patients, limit the external validity of these studies, and overall, they cannot fully elucidate the benefits and risks of interventions in clinical practice [18]. Therefore, the assessment of an intervention also requires evaluation in a practical real-world setting [19].

The aim of this observational study was to assess the efficacy and safety of UPA in patients with PsA with an inadequate response to previous therapies and unacceptable side effects treated under real-world conditions. In addition, we aimed to compare the clinical profiles of patients from our cohort with those included in the SELECT-PsA 2 trial [16].

2. Materials and Methods

This observational, retrospective, open-label study was conducted on patients from clinical practice. The study was conducted in 29 rheumatology units throughout Spain during a period of two years (Figure 1). This study was approved by the Ethics Committee of the Hospital Universitario Marqués de Valdecilla (code: 2022.006; Santander, Spain). Informed consent was not required for this study, as the intervention did not modify routine clinical practice.

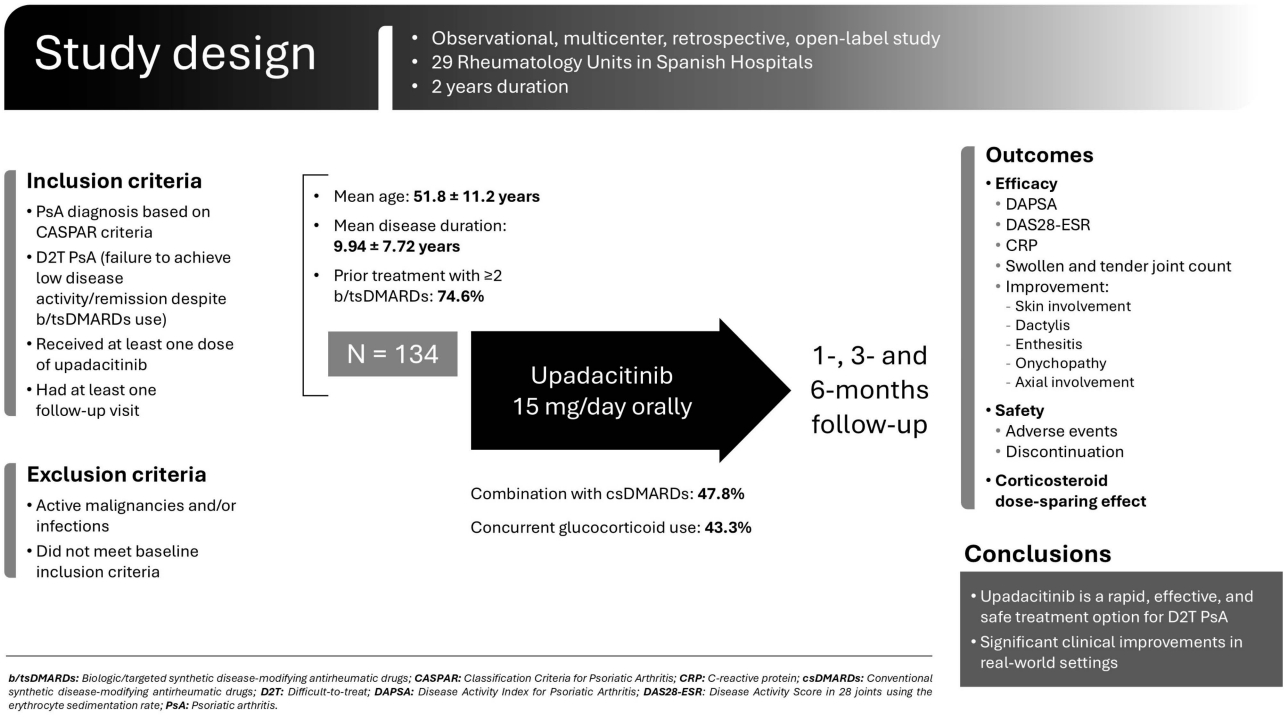


Figure 1. Overview of the study.

2.1. Patients and Enrollment Criteria

Patients had to meet the following inclusion criteria to be enrolled in the study: PsA diagnosis according to the Classification Criteria for Psoriatic Arthritis (CASPAR) [20]; PsA categorized as D2T following failure to achieve clinical low disease activity or remission despite the use of bDMARDs or tsDMARDs; having received at least one dose of UPA and having at least one follow-up visit before the enrollment. UPA treatment during the study followed a standard dose of 15 mg taken orally daily, as stated in the recommendations in the summary of product characteristics. The presence of infectious diseases was ruled out before starting treatment with UPA, as recommended by the Spanish Biologic Treatment Administration National Recommendations [21]. Tuberculin skin testing, interferon assay

(quantiFERON), and chest radiography were performed to exclude latent tuberculosis. In positive cases, prophylaxis with isoniazid was initiated for at least 4 weeks before treatment and was maintained for 9 months. Patients with active malignancies and/or infections were excluded from the study (Figure 1).

The following information was collected at the time of UPA prescription (baseline): demographic data, disease duration, presence of dactylitis, enthesitis, axial involvement, nail involvement, painful and swollen joint count, the Health Assessment Questionnaire Disability Index (HAQ-DI) score [22], the Psoriasis Area Severity Index (PASI) score [23], treatment history (current use of oral glucocorticoids, use of previous bDAMRDs and tsDMARDs) and the prescription of UPA in monotherapy or combined treatment with csDMARDs. At baseline, 1 month, 3 months, and 6 months, we recorded information on the number of swollen and tender joints, improvement in dactylitis, enthesitis, and onychopathy and axial involvement; levels of C-reactive protein (CRP), the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) [24] and the Disease Activity Index for Psoriatic Arthritis (DAPSA) [25] score; as well as treatment-emergent adverse reactions, as recorded from clinical reports. Instruments used to measure dactylitis, enthesitis, and nail and axial involvement are described in the study outcomes section (Figure 1).

2.2. Study Outcomes

The outcomes of the study were efficacy, corticosteroid dose-sparing effect and safety of the UPA therapy. The main efficacy outcomes were improvement in the DAS28-ESR [24] and DAPSA scores [26] (considered statistically significant when $p < 0.05$ compared to baseline). DAPSA is the result of the sum of the number of tender joints, number of swollen joints, CRP, global patient evaluation and patient assessment of pain [26].

Other effectiveness outcomes included skin efficacy, assessed by the improvement in the PASI [26,27]; the mean change from baseline in CRP levels (mg/L); and the proportion of patients with clinical improvement (defined as a decrease relative to baseline) in dactylitis (assessed by presence/absence and acute vs. chronic status), enthesitis (assessed by the Maastricht Ankylosing Spondylitis Enthesitis Score [MASES]) [26], nail involvement (measured by the number of affected nails) and axial involvement (assessed by the Ankylosing Spondylitis Disease Activity Score with CRP [ASDAS-CRP] and the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]) [28,29] (Figure 1).

To compare the clinical profiles of our cohort of patients with those from RCTs, information was retrieved from the results of the UPA arm (15 mg/24 h) of the SELECT-PsA 2 trial [16].

2.3. Data Collection and Statistical Analysis

Data was collected at each participant center from patient's clinical records. To reduce errors during data entry, a specific protocol was developed, and all data was double-checked. Once the data was collected, it was stored in a computerized database.

Continuous outcomes were tested for normality, and the results are presented as the mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Binary outcomes are presented as absolute and relative frequencies. Mann-Whitney test of t-test for quantitative variables and chi-square tests for qualitative variables were used to compare the demographic and clinical characteristics of our study sample with those of the RCT of UPA in patients with PsA and an inadequate response to bDMARDs (SELECT-PsA 2) [16].

The outcomes were assessed and compared between baseline and at 1, 3 and 6 months. Changes from baseline in quantitative outcomes were compared using the paired t-tests or Wilcoxon signed-rank tests.

Besides, we performed a subgroup analysis of the patients who exhibit symptoms and/or signs of active disease despite treatment with at least two b/tsDMARDs with different mechanisms of action.

All analyses were performed using SPSS version 29 and Stata version 18. All tests were two-tailed and considered significant at $p < 0.05$.

3. Results

3.1. Baseline Main Clinical Features at UPA Onset

One hundred and thirty-four patients were recruited during a period of two years. The mean age of the participants was 51.8 ± 11.2 years, and they were predominantly females (n = 97, 72.4%) (Table 1). Enrolled patients displayed the following cardiovascular comorbidities: smoking (24,7%), obesity (26%), high blood pressure (20%) and type 2 diabetes mellitus (8%). Moreover, 2% of the patients had a history of heart failure, and 2% had a history of deep vein thrombosis.

Table 1. Baseline characteristics.

	Clinical Practice n = 134	**SELECT-PsA 2 n = 211**	***p*-Value**
Demographics			
Age (years), mean ± SD	51.82 ± 11.22	53.0 ± 12.0	0.362
Sex (female), n (%)	97 (72.4)	113 (53.6)	<0.001
Clinical characteristics			
Duration since PsA diagnosis (years), mean ± SD	9.94 ± 7.72	9.5 ± 8.4	0.625
Swollen joint count, mean ± SD	4.33 ± 5.01	11.3 ± 8.2	<0.001
Tender joint count, media ± SD	6.10 ± 5.6	24.9 ± 17.3	<0.001
Enthesitis, n (%)	29 (21.6) (MASES)	172 (81.5) (SPARCC)	<0.001
Dactylitis, n (%)	14 (10.5)	55 (26.1)	<0.001
CRP (mg/L), mean ± SD	8.36 ± 14.47	11.2 ± 18.5	0.133
HAQ-DI, mean ± SD	1.00 ± 0.63	1.10 ± 0.6	0.140
PASI score, mean ± SD	0.95 ± 1.65	10.1 ± 9.2	<0.001
Glucocorticoid use, n (%)	58 (43.28)	22 (10.4)	<0.001
Prior biologic DMARDs			
Prior biologic DMARD use, n (%)	123 (91.8)	195 (92.4)	0.833
Number of prior biologic DMARD, n (%)			
0	11 (8.2)	18 (8.5) *	0.916
1	22 (16.4)	135 (63.7)	<0.001
2	21 (15.7)	35 (16.5)	0.822
≥3	80 (59.7)	24 (11.3)	<0.001
Upadacitinib at baseline			
Monotherapy, n (%)	70 (52.24)	113 (53.6)	0.811
In combination with csDMARDs, n (%)	64 (47.76)	98 (46.4)	0.811

* Patients with intolerance but not inadequate response to biologic DMARDs. CRP: C-reactive protein; csDAMARDs: conventional synthetic disease-modifying antirheumatic drugs; DMARDs: disease-modifying antirheumatic drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score (MASES > 0); PASI: Psoriasis Area Severity Index; SD: standard deviation; SPARCC: Spondyloarthritis Research Consortium of Canada (SPARCC > 0).

The mean ± SD time from PsA diagnosis to UPA onset was 9.94 ± 7.72 years. The most common phenotype was peripheral PsA (n = 83, 61.9%), followed by mixed PsA (n = 41, 30.6%) (peripheral and axial PsA) and axial PsA (n = 10, 7.5%) (assessed by radiog-

raphy and/or magnetic resonance). Most patients had received at least two b/tsDMARDs with different mechanisms of action (n = 100, 74.6%).

At the time of inclusion, the main clinical manifestations were arthritis (n = 105, 78.4%), skin involvement (n = 34, 25.4%), enthesitis (n = 29, 21.6%), nail involvement (n = 15, 11.3%), and dactylitis (n = 14, 10.5%) (Table 1).

Prior to the UPA, 93 (69.4%) patients had received oral prednisone or the equivalent (maximum mean dose 13.4 ± 9.3 mg/d), at least 1 csDMARD (mean no. 1.8 ± 1.0) and 1 bDMARD (mean no. 3.3 ± 2.2). The previous csDMARDs used were methotrexate (n = 113), leflunomide (n = 63), and sulfasalizine (n = 50). The previous bDMARDs used were adalimumab (n = 101), etanercept (n = 53), certolizumab (n = 37), infliximab (n = 30), golimumab (n = 26), secukinumab (n = 66), ixekizumab (n = 44), ustekinumab (n = 44), guselkumab (n = 2), abatacept (n = 2), and brodalumab (n = 1). Patients also received the following tsDMARDs: apremilast (n = 27), tofacitinib (n = 29), and filgotinib (n = 1).

3.2. UPA Treatment and Efficacy

UPA was administered at a standard dose of 15 mg daily. Concomitant glucocorticoid therapy was administered to 58 patients (43.3%), with a mean prednisone dose of 8.3 ± 5.6 mg/d. UPA in combination with csDMARDs was used in 64 patients (47.8%): methotrexate (n = 39), leflunomide (n = 19), and sulfasalazine (n = 10). Seventy patients (52.2%) received UPA monotherapy (Table 1). The mean follow-up was 6.0 ± 5.1 months.

Rapid and sustained improvement in the disease activity indices (DAS28-ESR and DAPSA) was observed (Table 2 and Figure 2). The DAS28-ESR score decreased from a median (IQR) of 4.7 (3.97; 5.38) at baseline to 3.77 (2.87; 4.76) ($p < 0.001$) in the first month, and the DAPSA score decreased from a median of 25 (18.06; 30.60) to 17 (10.10; 22.60) ($p < 0.001$). Improvements were also observed in patients with axial, skin, and nail involvement, and those with enthesitis and dactylitis (Table 2). CRP levels decreased significantly from a median (IQR) at baseline of 2.90 (1.00; 8.95) mg/dL to 1.50 (0.43; 4.90) mg/dL ($p = 0.001$) in the first month, and the reduction was maintained until month 6 (Table 2). UPA also had a prednisone dose-sparing effect, with a reduction from a mean of 8.26 (5.58) mg/d to 7.73 ± 4.18 mg/d ($p = 0.049$) in the first month (Table 2).

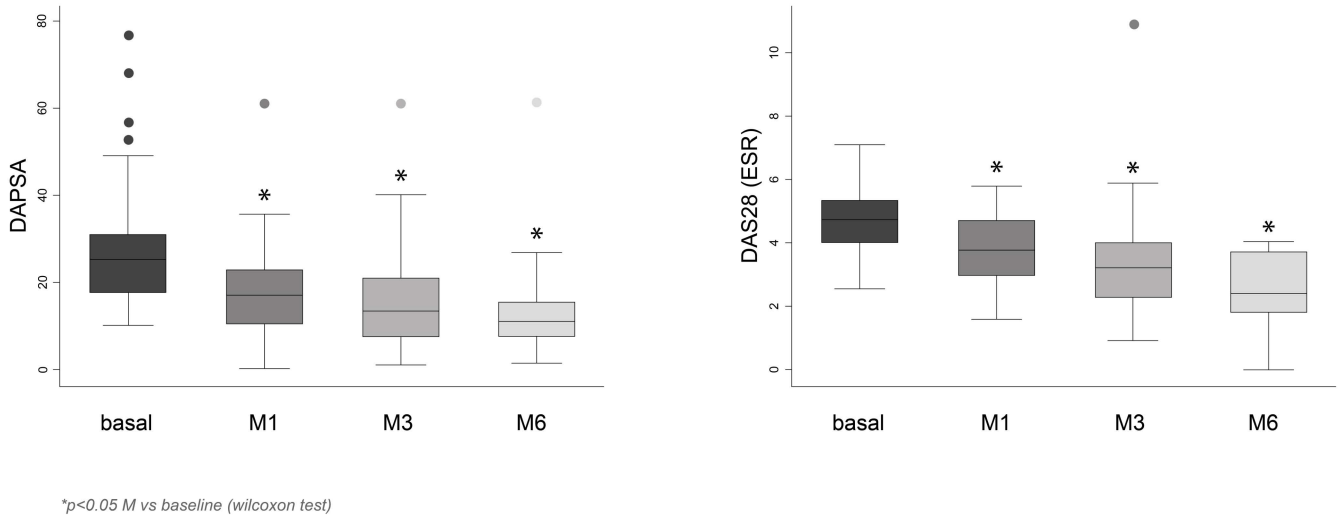


Figure 2. Improvement in disease activity indices with upadacitinib in patients with D2T PsA at baseline, 1, 3 and 6 months (M1, M2 and M6 respectively). DAPSA: Disease Activity in Psoriatic Arthritis; DAS28-ESR: Disease Activity Score in 28 joints using erythrocyte sedimentation rate.

There were no changes in the mean dose of concomitant csDMARDs throughout the study.

Table 2. Course of efficacy outcomes.

	Baseline n = 134	Month 1 n = 89	Month 3 n = 84	Month 6 n = 55
Swollen joint count				
Median [IQR]	3 [1.00;6.00]	1 [0.00; 4.00]	0 [0.00; 2.00]	0 [0.00; 2.00]
p-value vs. baseline		$p < 0.001$	$p < 0.001$	$p < 0.001$
Tender joint count				
Median [IQR]	5 [2.00; 8.00]	2 [0.00; 4.00]	2 [0.00; 6.00]	1 [0.00; 2.00]
p-value vs. baseline		$p < 0.001$	$p < 0.001$	$p < 0.001$
DAS28-ESR				
Median [IQR]	4.7 [3.97; 5.38]	3.77 [2.87; 4.76]	3.17 [2.16; 4.06]	2.38 [1.73; 3.68]
p-value vs. baseline		$p < 0.001$	$p < 0.001$	$p < 0.001$
DAPSA				
Median [IQR]	25 [18.06; 30.60]	17 [10.10; 22.60]	13.29 [7.32; 21.27]	12 [7.27; 16.00]
p-value vs. baseline		$p < 0.001$	$p < 0.001$	$p < 0.001$
Axial involvement (ASDAS-CRP and BASDAI)				
Improvement *, n (%)	-	9 (52.94)	10 (45.45)	5 (35.71)
Skin involvement (PASI)				
Improvement *, n (%)	-	10 (52.63)	14 (87.50)	9 (69.23)
Nail involvement (number of affected nails)				
Improvement *, n (%)	-	2 (20)	4 (57.14)	0 (0.0)
Enthesitis (MASES)				
Improvement *, n (%)	-	9 (64.29)	10 (50)	7 (53.85)
Dactylitis (presence/absence)				
Improvement *, n (%)	-	7 (77.78)	4 (66.67)	4 (80)
CRP (mg/dL)				
Median [IQR]	2.90 [1.00; 8.95]	1.50 [0.43; 4.90]	2.02 [0.59; 5.12]	1.00 [0.3; 5.60]
p-value vs. baseline		$p = 0.001$	$p = 0.235$	$p < 0.001$
Prednisone dose (mg/day)				
Mean ± SD	8.26 ± 5.58	7.73 ± 4.18 $p = 0.049$	5.60 ± 3.41 $p = 0.003$	6.16 ± 3.52 $p = 0.031$

* Improvement was defined as a decrease relative to the baseline and was calculated based on the proportion of patients showing improvement at each study visit. ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with CRP; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28-ESR: Disease Activity Score in 28 joints using erythrocyte sedimentation rate; IQR: interquartile range; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; PASI: Psoriasis Area and Severity Index; SD: standard deviation.

3.3. Adverse Effects

No serious adverse events (AEs) were reported. Mild adverse reactions, including viral infections, headache, and gastrointestinal disorders, were reported in 23 (17.2%) patients.

Upadacitinib was discontinued in 44 (32.8%) patients due to lack of efficacy (n = 28, 20.9%) (measured by DAPSA and activity and outcome measurements), adverse events (n = 11, 8.2%), and patient decision (n = 5, 3.7%). The AEs leading to UPA discontinuation were infection (n = 4), anterior uveitis (n = 2), thrombosis (n = 1), surgery (n = 1), pregnancy (n = 1), urticaria (n = 1), and diarrhea (n = 1).

The mean levels of hemoglobin, lymphocytes, neutrophils, platelets, lipids, and transaminases remained stable throughout the follow-up period (Table 3). It is worth noting that the increase in total cholesterol, LDL and HDL cholesterol levels after upadacitinib treatment during follow-up is a known effect of the drug and has been described in the summary of products characteristics [14].

Table 3. Laboratory findings at baseline and at months 1 and 6 after upadacitinib therapy.

	Baseline n = 134	Month 1 n = 89	Month 6 n = 55
Hemoglobin, g/dL	13.82 ± 1.53	13.65 ± 1.47	13.44 ± 1.35
Neutrophils, count/µL	4516.8 ± 1960.8	4138.9 ± 1816.3	4759.5 ± 1871.1
Lymphocytes, count/µL	2388.1 ± 885.5	2359.9 ± 893.9	2438.6 ± 934.9
Platelets, count/µL	273,593.8 ± 77,868.4	259,372.7 ± 80,370.8	266,084.4 ± 64,475.4
Creatinine, mg/dL	0.77± 0.18	0.80 ± 0.19	0.78 ± 0.22
AST, U/L	22.7 ± 9.64	24.9 ± 10.6	25.7 ± 9.3
ALT, U/L	23.7 ± 13.2	25.2 ± 12.8	25.8 ± 11.8
Cholesterol, mg/dL	193.7 ± 37.4	207.2 ± 45.2	207.3 ± 45.5
HDL, mg/dL	64.8 ± 25.1	63.1 ± 22.0	67.5 ± 17.0
LDL, mg/dL	116.0 ± 37.4	127.3 ± 39.3	132.2 ± 42.4

The values are expressed as the means ± SDs. ALT: alanine transaminase; AST: aspartate transaminase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

3.4. Subgroup Analysis of Patients with at Least Two b/tsDMARDs with Different Mechanisms of Action

Most patients in our study (n = 100, 74.6%) had received at least two b/tsDMARDs with different mechanisms of action. The mean time from PsA diagnosis to UPA initiation was 9.16 ± 8.61 years. The DAS28-ESR score decreased from a median of 4.72 (IQR 3.94; 5.51) at baseline to 2.27 (IQR 1.8; 3.0, $p < 0.001$) in the sixth month, and the DAPSA score decreased from a median of 26 (IQR 18.12; 30.60) to 11.6 (IQR 7.55; 14.84, $p < 0.001$). The proportion of patients with improvement in other manifestations of PsA at month 6 was as follows: dactylitis 75%, enthesitis 53.8%, skin involvement 75%, and arthritis 78.1%.

3.5. Comparative Study of a Clinical Practice Cohort and SELECT-PsA 2

Patient characteristics were compared between our clinical practice cohort (n = 134) and the standard UPA therapy (15 mg daily) arm of the SELECT-PsA 2 (n = 211) (Table 1).

There was a greater proportion of females among patients from clinical practice (72.4% vs. 53.6%, $p < 0.001$). The mean age was similar in both groups (51.82 ± 11.22 vs. 53.0 ± 12.0, $p = 0.362$). The tender and swollen joint counts, PASI score, and the proportion of patients with enthesitis and dactylitis were greater in patients from SELECT-PsA 2 (Table 1). A non-significant higher functional disability HAQ-DI score was observed in patients from the SELECT-PsA 2 trial (1.00 ± 0.63 vs. 1.10 ± 0.6, $p = 0.140$).

Prior exposure to bDMARDs was greater among the patients in this real-world study. Thus, the proportion of patients who had received 3 or more bDMARDs in our study was 59.7% vs. 11.3% in the SELECT-PsA 2 trial ($p < 0.001$) (Table 1). Patients in clinical practice more frequently received corticosteroids (43.3% vs. 10.4%; $p < 0.001$), while the proportion of patients receiving UPA in combination with csDMARDs was similar in both groups (Table 1).

4. Discussion

Our series showed a greater exposure to previous biological treatments and a higher proportion of women compared to the SELECT-PsA 2 trial. Despite these differences, UPA was effective in bDMARD-experienced patients with PsA in real-world settings, improving clinical manifestations, disease activity, and non-specific markers of active inflammation without the emergence of new safety signals. These findings are consistent with those of previous RCTs.

The UPJOINT study, an observational clinical practice study, has been reported regarding UPA use in patients with PsA. This study was not specifically focused on patients with an inadequate response to bDMARDs or tsDMARDs but rather included those meeting the local summary of product characteristics [30]. Among the participants, 74.3% had previously received bDMARDs or tsDMARDs. The study analysis included 296 patients at baseline and 192 patients who completed the 24-week follow-up. The proportion of patients achieving MDA increased from 2.7% at baseline to 39.1% at week 24 (95% CI: 32.1–46.3). Similarly, the number of patients in DAPSA remission rose from none at baseline to 32 (16.7%) by week 24. At the same time point, 59.4% of patients were either in DAPSA remission or had low disease activity (DAPSA $\leq$ 14). Additionally, improvements were noted in extra-articular manifestations, including psoriasis, onychopathy, dactylitis, and enthesitis [30].

In our study, a significant reduction in the number of swollen and tender joints was also observed. UPA demonstrated effectiveness in improving disease activity measures, including DAS28-ESR and DAPSA. Notably, these improvements were clinically significant as early as the first month after treatment and were sustained throughout the study. For instance, the median DAPSA score decreased from 25 (18.06–30.60) at baseline to 17 (10.10–22.60) by the first month ($p < 0.001$) and continued to decline significantly over the follow-up period (Table 2). Similarly, DAS28-ESR scores improved from a baseline median of 4.70 (3.97–5.38) to 3.77 (2.87–4.76) at month one ($p < 0.001$), with further reduction to 2.38 (1.73–3.68) by month 6 ($p < 0.001$, Table 2).

As previously mentioned the concept of D2T RA has recently been defined [10]. Although some aspects of this definition are specific to RA, others can be translated and adapted for PsA [31]. D2T PsA may arise from intrinsic treatment resistance, potentially driven by immune escape mechanisms enabled by the plasticity of the cytokine and cellular networks involved in PsA [32]. Additionally, therapeutic failure can be attributed to various factors, including comorbidities that sustain inflammation, increase pain and disability, or complicated disease management, as well as coexisting rheumatologic conditions and resistance in specific disease domains [31]. Lubrano et al. [11] propose dividing refractory PsA into two categories: refractory disease secondary to persistent inflammation ('refractory to treatment' PsA) and non-remission due to pre-existing comorbidities ('D2T' PsA). However, it must be noted that a clear consensus on the precise definition of D2T PsA among physicians has yet to be reached [12]. Consequently, in clinical practice, the concept of D2T PsA should be viewed as dynamic rather than static, reflecting the evolving nature of the disease and its management [11].

The majority of patients in our study had received at least two b/tsDMARDs with different mechanisms of action. The efficacy outcomes observed in this subgroup were consistent with those of the overall sample, highlighting the effectiveness of UPA in this challenging population.

In comparison to the SELECT-PsA 2 trial, and despite the use of different outcome measures, our findings align with those of the trial. The SELECT-PsA 2 trial reported a statistically significant difference in the proportion of patients achieving MDA with 15 mg UPA compared to placebo (25.1% vs. 2.8%, $p \leq 0.05$) [16]. Notably, patients in our observational study were more experienced with bDMARDs than those in the SELECT-PsA 2 trial. In our cohort, 59.7% of patients had received three or more bDMARDs, compared to only 11.3% in the SELECT-PsA 2 trial ($p < 0.001$). These findings are similar to the evidence showing that patients with RA refractory to bDMARDs generally have poorer outcomes compared to those refractory to csDMARDs [33,34].

Consistent with the SELECT-PsA 2 trial, UPA showed a good safety profile in our study. The proportion of patients who discontinued UPA due to AE (8.2%) was similar to that reported in the SELECT-PsA 2 trial (7.1%) [16] and lower than in the UPJOINT study

(15%) [30]. Moreover, in our study, no serious AEs were reported. UPA was discontinued in 44 (32.8%) patients, primarily due to a lack of effectiveness (n = 28, 20.9%).

Although we did not analyze UPA persistence rate, there is substantial evidence supporting drug survival in real life settings. In a cohort of more than 2000 PsA patients treated with biologics from Israel's largest healthcare provider, Haddad et al. [35] reported a persistence rate of approximately 40% after 20 months of treatment; notably, in the Israeli National Healthcare Drug Plan, treatment with biologic therapy for PsA is indicated after the failure of two csDMARDs. Similarly, in a French study of nearly 3000 PsA patients treated with bDMARDs after failure of a TNF inhibitor, the persistence rate at one year was 42% [36]. Notably, both of these studies used survival analysis to estimate persistence rates.

This study has several limitations, including its relatively small sample size, lack of a comparison group, relatively short follow-up period (6.0 $\pm$ 5.1 months), and retrospective design. Regarding the comparison group, in a subgroup analysis of a recent systematic review of JAK inhibitors for PsA, UPA 15 mg was superior to tofacitinib in several efficacy outcome measures [37]. It would be interesting to compare UPA 15 mg with other JAK inhibitors for the treatment of PsA in a real-world setting. Another limitation is the use of DAS28-ESR, which is primarily used for RA. However, we included DAPSA as an additional measure to address this limitation. Despite these limitations, this study supports the efficacy and tolerability of UPA in patients with PsA who show an inadequate response to bDMARDs.

5. Conclusions

In conclusion, our data suggest that UPA is effective with a rapid onset of action and is relatively safe for use in daily clinical practice for D2T PsA. Our study supports the findings of the SELECT-PsA 2 trial, confirming that UPA remains an effective and safe therapy for D2T PsA, despite some clinical differences between the study populations.

Real-word evidence studies like ours are essential for understanding how treatments perform in diverse, real-world settings, extending the insights from controlled clinical trials to broader patient groups. Our research reinforces that UPA is not only an effective therapeutic option but also well-tolerated, providing physicians with a reliable tool for managing D2T PsA. This confirms UPA's role as an important option in clinical practice, offering both rapid symptom relief and sustained efficacy for patients.

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Informed Consent Statement: Patient consent was waived with the approval of the Ethics Committee, which determined that consent was not required due to the observational nature of the study, the use of anonymized data, and the fact that the intervention did not alter routine clinical practice.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

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Conflicts of Interest: E. G-A. has been speaker and/or received grants for congress from Abbvie, Amgen, Jonhson & Johnson, Lilly, MSD, Novartis, Pfizer, UCB. D. P-P. has received speaker and/or grants for congress from Abbvie, Jannsen, Lilly, MSD, Novartis, Pfizer, Roche, UCB, Amgen, GSK, Astrazeneca. ML. G-V. has been speaker and/or received grants for congress from Abbvie, Amgen, Astrazeneca, Jonhson &Johnson, Lilly, MSD, Novartis, Pfizer, UCB. B. J-I. works as a consultant for Amgen, UCB, Abbvie, Janssen, Novartis; has collaborated as speaker at events for Abbvie, Janssen, Lilly, Amgen; has participated in studies/trials/research projects for Janssen, BMS, Abbvie, Lilly; and has received support to attend congresses from Novartis, Pfizer, UCB, Abbvie, Janssen. R. G-V. reports research or educational grants to her institution from Abbvie, BMS, Galapagos, GSK, Janssen, Lilly, MSD and Sanofi; have received personal fees for participating on advisory boards or delivering presentations sponsored by Abbvie, Biogen, Galapagos, GSK, Janssen, Pfizer, Sandoz and Sanofi; all outside of the submitted work. A. M-F. has received fees for attending congresses from Abbvie, Jannsen, Lilly, MSD, Novartis, Pfizer, UCB conferences; has received lectures from Abbvie, Jannsen, Lilly, MSD, Novartis, Pfizer, UCB. M. MM-L. has received consultancy/speaker fees from Abbvie, Boehringer Ingelheim, Johnson & Johnson, Lilly, Novartis, Pfizer, UCB; has received grants for congress from Abbvie, Johnson & Johnson, Novartis; has grants for investigation from UCB, Novartis. T. G-H. has received consultancy/speaker fees from Abbvie, Lilly, Novartis, Pfizer, Theramex; has received grants for congress from Abbvie, Lilly, Novartis, Pfizer, Gedeon. R. A-G. has received fees for lectures, training activities, scientific consultancy and research work from other pharmaceutical companies during the last 5 years: Abbvie, Almirall, Amgen, Bristol Myers Squibb, Galápagos, Gebro, Johnson & Johnson, Lilly, MSD, Nordic, Novartis, Pfizer, UCB. A. U-A. has received support from Abbvie, Galápagos, Novartis, GSK, AstraZeneca, Janssen, Pfizer y Amgen. C. M-V. has received consultancy/speaker fees from Abbvie, BMS, Jannsen, Lilly, MSD, Novartis, Pfizer, Roche, UCB; has received grants for congress from Abbvie, Janssen, Lilly, Novartis, Pfizer, UCB; has received grants for investigation from UCB. R. B-A. has received grants/research supports from AbbVie, MSD, and Roche, and had consultation fees/participation in company-sponsored speakers bureaus from AbbVie, Lilly, Pfizer, Roche, BMS, UCB Pharma, Jonhson & Johnson and MSD. JM. B-O, C. V., M. P-P., I. U-O., L. V-A., MA. P-L., C. R-G., V. J-C. and I. G-H., declare no conflict of interest.

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