Retrospective evaluation of patient profiling and effectiveness of apremilast in an Italian multicentric cohort of psoriatic arthritis patients

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Abstract

Objective

We aimed to evaluate the baseline characteristics, the reasons for prescription, and the effectiveness/safety profile of real-life apremilast for the treatment of psoriatic arthritis (PsA).

Methods

PsA patients treated with apremilast were retrospectively extracted from an Italian multicentric cohort. Baseline population characteristics and reasons for apremilast prescription were analysed. Clinical response was defined as the proportion of patients achieving Disease Activity in PSoriatic Arthritis (DAPSA) remission/low disease activity (LDA), minimal disease activity (MDA), and very low disease activity (VLDA). Six-month retention rate was computed by the Kaplan-Meier method, with a detailed analysis of reasons for discontinuation. Univariate and multivariate models were developed to examine predictors of clinical response and persistence.

Results

The study population included 131 patients mainly with oligoarticular PsA (58%), carrying at least one comorbidity (64.1%, in particular history of malignancies [25.9%] and latent tuberculosis [16.3%]) treated with apremilast as first-line targeted therapy (47.7%) or in biologics failures (52.3%). Contraindication to biologics (60.3%) and lack of poor prognostic factors (27.5%) were the most frequent reason for apremilast prescription. The 6-month retention rate was 72.1%. Inefficacy (n=7), diarrhoea (n=10), nausea (n=3), and headache (n=7) were the most frequent reasons for discontinuation. At 3 months DAPSA LDA/remission, MDA, and VLDA were observed in 40.3, 6.7, and 5.6% of patients, respectively. Female sex was a negative predictor of both retention rate and clinical response.

Conclusion

In our real-life analysis apremilast was mainly used in oligoarticular PsA carrying comorbidities leading to contraindications to biologics. Effectiveness and safety profiles were consistent with clinical trials.

Key words

apremilast, psoriatic arthritis, real-life, effectiveness, retention rate

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Introduction

Psoriatic arthritis (PsA) is a heterogeneous systemic inflammatory disease that affects peripheral joints, axial skeleton, and entheseal structures, occurring in up to 30% of patients with psoriasis (PSO) of the skin and nails (1). As a chronic and progressively disabling disorder, PsA is associated with impaired physical function, poor quality of life, several comorbidities, and increased mortality (2). According to international recommendations, the management of PsA should be based on a treat-to-target approach aiming to obtain an acceptable and comprehensive disease control (3). Conventional treatment usually begins with disease-modifying anti-rheumatic drugs (csDMARDs) and non-steroidal anti-inflammatory drugs, but in the last two decades the introduction of pathogenesis-based interventions has significantly improved the outcomes in patients with PsA (4). Nevertheless, despite this evident progress, not all patients respond to or tolerate the available biologics (5), thus in the management of PsA several clinical needs are still largely unmet, highlighting the importance of the development of additional treatments with novel mechanisms of action (6). Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor able to partially inhibit the secretion of proinflammatory cytokines such as tumour necrosis factor alpha (TNF), interleukin-17 (IL-17), and interleukin-23 (IL-23), and to increase the expression of anti-inflammatory mediators such as interleukin-10 (IL-10) (7).

The effect of apremilast on articular and extra-articular manifestations of PsA has been assessed in the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) phase III clinical trial programme, including four large multicentre randomised controlled trials (RCTs) conducted in patients with active PsA and different baseline characteristics (8-11). As a result, apremilast is now approved for the treatment of both PSO and PsA and is used in daily clinical practice as an alternative therapeutic option beside conventional and biologic DMARDs. Nevertheless, as usual the generalisability of RCT results to real-life populations can be significantly limited by stringent exclusion and inclusion criteria potentially affecting the external validity of this kind of studies (12).

Owing to this limitation and the previous similar experience encountered with bDMARDs (13), data from large population-based registries should be advocated to better evaluate the effectiveness and safety of apremilast in a real-life setting. Moreover, considering the peculiar mechanism of action, real-life information can be additionally useful to profile patients candidate to receive apremilast according to their baseline characteristics. However, to date observational data on the use of apremilast for the treatment of PsA are lacking, with the only exception of two brief reports of the preliminary experience of single centres (14, 15).

To fill this gap, we performed a retrospective analysis of the multicentric observational PsA cohort of the Real-life APremilast for Psoriatic arthritis Evaluation Registry (RAPPER) to evaluate in a real-life setting the population baseline characteristics, the reasons for prescription, and 3- and 6-month effectiveness and safety profile of apremilast.

Methods

Study population and treatment

The source of data was a multicentric population-based cohort approved by the Ethic Committee of the Gaetano Pini Institute (approval n. 138_1999), established with the aim of collecting demographic and clinical data of all rheumatoid arthritis, ankylosing spondylitis, and PsA patients ≥18 years treated with targeted (biologic and synthetic) DMARDs in twelve Italian tertiary Rheumatology Centres. As a part of this cohort, the RAPPER registry included all PsA patients treated with apremilast since January 2017, with the only exclusion of those previously enrolled in an apremilast RCT. The current analysis was performed on all the patients included in the registry, until the database lock on May 31st, 2018. Treatments were prescribed according to licensed regimen and concomitant csDMARDs and/or corticosteroids were administered if ordered by the referring rheumatologist.

Outcomes and statistical analyses

Demographic features (age, sex, body mass index [BMI], smoking, and PsA duration), pattern of PsA involvement, therapeutic data (previous and concomitant treatment with DMARDs and corticosteroids), and baseline prevalence of extra-articular manifestations and comorbidities were extracted. The impact of comorbid conditions was also computed by the Rheumatic Disease Comorbidity Index (RDCI) (16). Participant rheumatologists were asked to indicate one or more reasons leading to the prescription of apremilast for each patient according to a predefined list of potential options including age, the preference for the oral administration, the lack of poor prognostic factors (as defined by the 2015 EULAR recommendations for the management of psoriatic arthritis (4)), the presence of contraindication to the treatment with csDMARDs or bDMARDs, a previous history of malignancy, the coexistence of comorbidities, an elevated risk of serious infections, or other reasons. Main disease activity indices (Disease Activity in PSoriatic Arthritis [DAPSA], Leeds Enthesitis Index [LEI], psoriasis skin Body Surface Area [BSA], Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] were collected at baseline, 3 and 6 months (with a time range of ± 2 weeks for each timepoint). Clinical response was defined as the proportion of patients achieving DAPSA 3- and 6-month minor, moderate, or major clinical response and remission (DAPSA<4)/low disease activity (LDA; DAPSA between 4 and 14), minimal disease activity (MDA), and very low disease activity (VLDA). Patients who discontinued apremilast before the 3- and 6-month timepoints were considered as no-responders. Additional effectiveness analyses were performed by a paired *t*-test considering the mean change from baseline of swollen and tender joint count for articular involvement, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for axial subset, Leeds Enthesitis Index (LEI) for entheseal pattern, and Body Surface Area (BSA) for skin disease. Moreover, a multivariate logistic regression model was developed to examine the role of baseline factors as predictors of achieving 3-month DAPSA remission/LDA and major response, MDA, and VLDA. The results are presented as odds ratio (ORs) with 95% CI.

Three- and six-month drug survival were retrospectively calculated as the time period until the definitive treatment interruption after initiation of apremilast. Discontinuations were considered definitive when no consecutive re-introduction of treatment was reported or when indicated in the registry. All observations were right censored at the last registered visit before May 31st, 2018. Patients discontinuing apremilast because of inactive disease/remission or pregnancy were censored at the date of withdrawal and thus not considered as events in the survival analysis. The reasons for apremilast discontinuation were classified into three major categories: inefficacy, adverse events (AEs), and others (including desire for pregnancy, remission, and patient preference). Additionally, a Cox proportional hazard model was developed to analyse the role of baseline factors as predictors of apremilast persistence. Results are presented as hazard ratios (HRs) with 95% confidence intervals (95% CI). Both logistic regression model and Cox proportional hazard model included gender, oligoarticular pattern (≤4 involved joints), entheseal involvement, axial subset, use in bDMARD naïve, and concomitant MTX as categorical variables, whereas body mass index (BMI), age, and disease duration at the beginning of apremilast therapy were considered as continuous variables.

Statistical analyses were performed using SPSS statistical software, v. 20.0 (SPSS, Chicago, IL, USA). *p*-values equal to or less than 0.05 were considered statistically significant.

Results

Demographic and baseline characteristics

The overall study cohort included 131 patients with PsA treated with apremilast in the selected period. The baseline population characteristics are detailed in Table I. Briefly, 63.3% were women, the mean age (± standard deviation) was 57.5 (±12) years, and the mean disease duration 10.8 (±12.4) years. The majority of patients (n=105, 80%) showed articular involvement, with oligoarticular pattern (<5 affected joints) in 76 (58%) cases. Other PsA domains were represented as follow (Fig. 1): enthesitis 26.7% (n=35), axial disease 12.2% (n=12), dactylitis 8.4% (n=11), skin involvement 48% (n=63), and nail PSO 40.4% (n=53). A concomitant inflammatory bowel disease (IBD) was reported in 5 patients as previous history (n=2, both Crohn's disease [CD]) or current disease (1 CD and 2 ulcerative colitis [UC]), whereas uveitis was registered only in 4 patients previous history. About two thirds (n=84, 64.1%) of patients had at least one comorbidity (mean RDCI 1.20) and the prevalence of comorbid conditions is reported in Table II. In particular, 25.9% of patients had a previous history of malignancies and 16.3% a positive screening for latent tuberculosis.

Apremilast was prescribed as first-line targeted therapy in 62 patients (47.7%), who received apremilast as csDMARD naïve (n=4, 6.4%) or after the failure of one (n=14, 22.6%), two (n=24, 38.8%), three (n=16, 25.8%), or four and more (n=4, 6.4%) csDMARDs. In this subgroup, the most frequently csDMARDs failed before apremilast introduction were methotrexate (MTX, 49.2%), sulfasalazine (SSZ, 28.4%), cyclosporine (CyA, 12.1%), and leflunomide (LEF, 10.3%). In the remaining 53.3% of patients apremilast was administered after the failure of one (n=27, 20.8%; 25 anti-TNF and 2 ustekinumab), two (n=16, 12.3%; 15 anti-TNF and 1 ustekinumab), three (n=14, 10.8%; 9 anti-TNF, 2 ustekinumab, and 3 secukinumab), or four and more (n=11, 8.4%; 8 anti-TNF and 3 ustekinumab) previous bDMARDs. Eighty-four (64.1%) patients received apremilast as monotherapy, whereas 47 (35.9%) were treated with a concomitant csDMARD (MTX, n=25 [53.3%]; SSZ, n=13 [27.6%]; LEF, n=6 [12.7]; or CyA, n=3 [6.4%]). Treatment with corticosteroids was reported in 55 (41.9%) patients at a mean daily prednisone-equivalent dose of 5.82 mg.

Reasons for the choice of apremilast

Reasons for using apremilast in each patient were recorded according to a

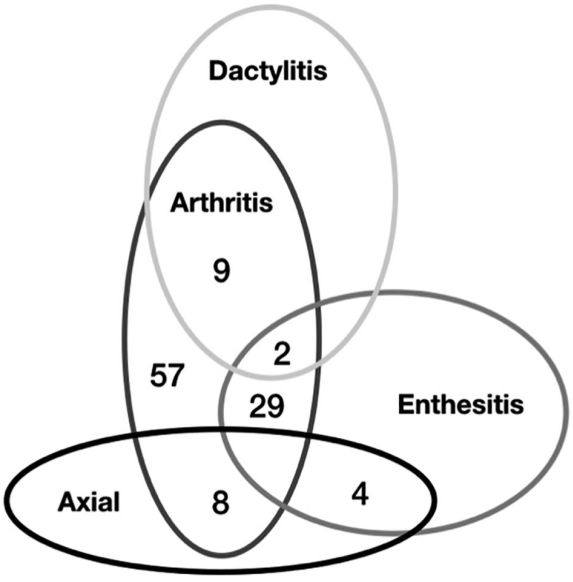
Table I. Clinical response at 3 and 6 months according to main endpoints.

	Mean ± SD	Mean ± SD	*p*-value	Mean ± SD	*p*-value
Overall population	Baseline (n=131)	3 months (n=65)		6 months (n=26)	
ESR, mm/h	23.2 ± 18.6	24.3 ± 20.2	0.69	25.4 ± 22.5	0.80
CRP, mg/dL	1.4 ± 3.6	1.3 ± 1.7	0.12	1.3 ± 2.1	0.56
PGA	6.3 ± 2.1	4.3 ± 2.5	<0.0001	6.1 ± 14.4	0.97
Pain VAS	6.4 ± 2.3	4.4 ± 2.7	<0.0001	5.9 ± 13.5	0.94
PhGA	5.3 ± 2.3	3.2 ± 2.1	<0.0001	2.7 ± 2.4	0.001
DAPSA	23.6 ± 12.3	14 ± 11.9	<0.0001	15.9 ± 31.1	0.13
Joint involvement	Baseline (n=105)	3 months (n=51)		6 months (n=18)	
Swollen joints, n	2.9 ± 2.6	1.2 ± 2.1	<0.0001	1.1 ± 1.7	0.07
Tender joints, n	9.1 ± 8.4	4.5 ± 7.3	<0.0001	4.2 ± 5.1	0.01
Axial involvement	Baseline (n=16)	3 months (n=9)		6 months (n=5)	
BASDAI	4.6 ± 3.1	5.1 ± 2.6	0.98	3.8 ± 2.7	1
Entheseal involvement	Baseline (n=35)	3 months (n=14)		6 months (n=6)	
LEI	2 ± 1.4	1 ± 1.1	0.09	0.2 ± 0.8	1
Skin involvement	Baseline (n=63)	3 months (n=28)		6 months (n=4)	
BSA	6 ± 11.2	1 ± 2.7	0.01	2 ± 2.2	0.04

SD: standard deviation; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAPSA: Disease Activity in PSoriatic Arthritis; PGA: Patient Global Assessment; VAS: visual analogue scale; PhGA: Physician Global Assessment; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; LEI: Leeds Enthesitis Index; BSA: body surface area.

predefined list of potential options. Contraindication to the treatment with bDMARDs (60.3%) was largely the most frequent driver toward apremilast prescription. Elevated risk of serious infections (35.1%), presence of comorbidities (28.4%), lack of poor prognostic factors for PsA progression (27.5%), and previous history of malignancy (23.6%) were also frequently reported. On the other hand, contraindication to the treatment with csDMARDs (12.2%), oral administration (6.1%), and age (5.3%) seemed to be less important in the choice of apremilast. Decision-making was driven by one, two, or three or more concomitant reasons in 35.9%, 32.8%, and 31.3% of patients, respectively.

Fig. 1. Distribution of study population according to the 4 PsA musculoskeletal domains.



Patient disposition and retention rate

Out of 131 patients enrolled, an effectiveness and safety analysis was conducted in the 89 and 58 with available 3- and 6-month data, respectively. The patient disposition is described in Figure 2. Apremilast withdrawal was observed in a total of 33 patients after a mean [±SD] period of 81.1±54.3 days. Twenty-four of 89 (26.9%) patients discontinued the drug within the first 3 months of therapy because of inefficacy (n=4, 4.5%), AEs (n=18, 20.2%) or other reasons (n=2, 2.2%), and other 9 of 58 (15.5%) patients between 3 and 6 months of treatment because of inefficacy (n=3, 5.1%), AEs (n=5, 8.6%) or other reasons (n=1, 1.7%). The most frequent AEs leading to discontinuation were gastrointestinal complaints (n=14, in particular diarrhoea [n=10], nausea/vomiting [n=3], and relapse of UC [n=1]), followed by headache (n=7), anaemia (n=1), and depression (n=1). Similarly, AEs not requiring drug withdrawal included diarrhoea (n=7), nausea (n=7), and headache (n=4). A detailed description of apremilast safety profile is reported in Table III.

The overall retention rate was 72.1% and 56.9% at 3 and 6 months, respectively (Fig. 3). In the Cox proportional hazard model female sex was a strong predictor of apremilast discontinuation (HR=9.5, 95% CI 2.65–34.57; *p*=0.001) among the considered factors (Table IV).

Table II. Baseline prevalence of comorbidities.

Comorbidity	Prevalence (n=131)
Hypertension	35.1%
History of malignancy	25.9%
Fibromyalgia	17.9%
Latent tuberculosis	16.3%
Liver disease	12.2%
Lung disease	11.4%
Dyslipidaemia	16.8%
Diabetes	12.9%
Depression	13%
HBV/HCV infection	7.6%
Osteoporosis	9%
Haematological disorders	7%
Cardiovascular disease	7.6%
Gastrointestinal disorders	3%
Neurological disorders	3%

Effectiveness

Clinical response at 3 and 6 months according to all considered endpoints is reported in Table I. In the overall population, we found a significant decrease from baseline for PhGA at both 3 ($p<0.0001$) and 6 ($p=0.001$) months, whereas PGA, pain VAS, and DAPSA were statistically reduced only at 3 months ($p<0.0001$ for all). No statistical difference was observed for acute phase reactants (ESR and CRP) at both timepoints. The proportion of patients achieving DAPSA minor, moderate, or major response was 32.5%, 16.8% and 6.7% at 3 months and 22.4%, 17.2% and 10.3% at 6 months, respectively. DAPSA LDA and remission were observed in 26.9% and 13.4% of patients at 3 months, and 15.5% and 13.7% at 6 months, respectively. Only 6 patients achieved MDA and 5 VLDA at 3 months. In patients with peripheral arthritis swollen and tender joints counts decreased at 3 months ($p<0.0001$ for both) and 6 months ($p=0.07$ and $p=0.01$, respectively) as well as BSA in the subgroup with skin involvement ($p=0.01$ at 3 and $p=0.04$ at 6 months). A clear trend toward a favourable effect of apremilast, although statistically not significant, was observed in patients with enthesitis ($p=0.09$ at 3 months), while no significant effect in axial subset was found at both timepoints. In the logistic regression analysis, among the considered factors only male sex (OR=1.5, 95% CI 1.11–2.18; $p=0.04$) and the lack of previous exposure to a bDMARD (OR=8.05, 95% CI 1.28–36.4; $p=0.02$) were predictors of achieving 3-month DAPSA remission/LDA (Table IV).

Discussion

We report herein the baseline characteristics, short-term clinical response, and retention rate of apremilast in a multicentric cohort of real-world PsA patients. To our knowledge, this is the first extended report on real-life data of apremilast for this indication.

Considering the retrospective design of our study, the first endpoint was to evaluate the profile of PsA patients who were treated with a novel mechanism of action as PDE4 inhibition. Compared with the PALACE programme, we selected a cohort of older patients (mean age 49.9–51.4 *vs*. 55.7 years, respectively) with long-standing PsA (mean disease duration 6.8–8.1 *vs*. 10.8 years, respectively) and with a more frequent previous exposure to bDMARDs (17.3–26.2% *vs*. 53.3%, respectively). Moreover, our registry included subjects with a predominant oligoarticular joint involvement (58%). A similar proportion of oligoarthritis was reported in 503 patients enrolled in the GRACE cohort (53%) (17), and in 329 and 135 patients included in two observational studies from Norway (55%) (18) and Sweden (44%) (19), respectively, thus confirming our observations. Similarly, half of patients had active skin disease, a quarter entheseal involvement, and only 10% a predominantly axial subset. Beside the established effect on skin and musculoskeletal features, data on the potential role of apremilast in the management of extra-articular manifestations of PsA are still lacking. In vitro studies demonstrated the capability of PDE4 inhibitors to interfere at different levels with the pathway to gut tissue damage, emphasising the prospect of using apremilast to treat inflammatory bowel diseases (20). Accordingly, the preliminary results of the first RCT evaluating the use of apremilast for UC have recently showed clinically meaningful improvements in symptoms, endoscopy, biomarkers, and mucosal healing compared with PBO (21).

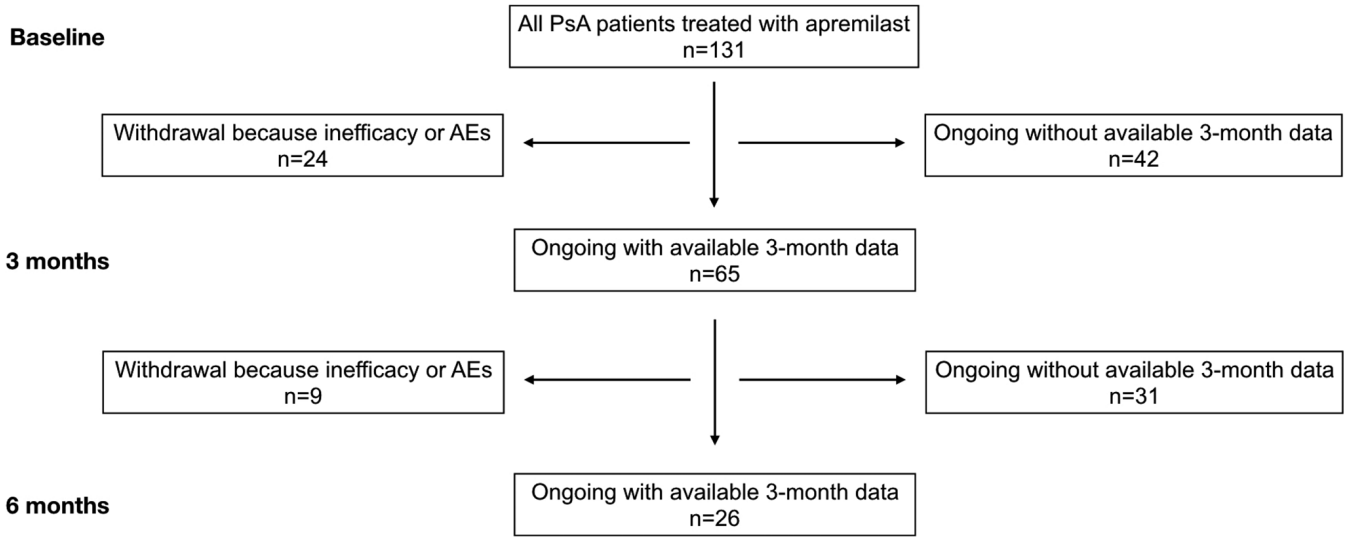


Fig. 2. Patient disposition over the 6-month follow-up period. PsA: psoriatic arthritis; AEs: adverse events.

Table III. Incidence of adverse events reported over the 6-month follow-up period.

Reported AEs	0-3 months (n=89)	3-6 months (n=34)	0-6 months (n=58)
Overall			
Diarrhoea	12	7	19
Headache	9	3	12
Nausea/vomiting	6	4	10
Depression	1	0	1
UC relapse	1	0	1
Weight loss	1	1	2
Upper respiratory tract infection	4	2	6
Rash	1	0	1
Abdominal pain	4	3	7
H. Zoster infection	1	0	1
AEs leading to discontinuation			
Diarrhoea	7	3	10
Headache	6	1	7
Nausea/vomiting	2	1	3
Depression	1	0	1
UC relapse	1	0	1
Anaaemia	1	0	1

AEs: adverse events; UC: ulcerative colitis

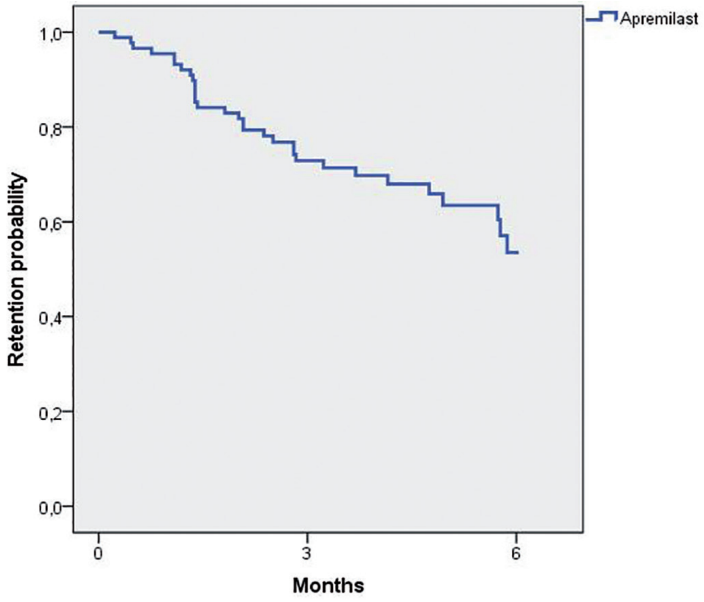


Fig. 3. 6-month retention rate of apremilast in the whole population

The prevalence of active or previous IBD in our cohort was very low (3.8%), and one patient with history of UC experienced a flare of disease during the 6-month follow-up period. Similarly, only 3% of enrolled patients had a history of previous uveitis, as expected since no published data are available regarding the effect of apremilast on uveitis either in animal studies or in the cohorts of patients with PsA and PSO (22).

The main finding regarding baseline population characteristics is the high prevalence of comorbidities in patients receiving apremilast compared with general population and PsA treated with different drugs (23). A quarter of patients included in our cohort had a previous history of malignancy and about 15% of latent tuberculosis, much higher as usually reported in the cohorts of PsA patients receiving conventional or biologic DMARDs (24). The selection of such a complex population can be the result of the favourable long-term safety profile of apremilast reported in both PsA and PSO RCTs (25). In particular, apremilast did not induce cancers in mice treated with oral doses up to 8.8-times the Maximum Recommended Human Dose; moreover, the drug seems to exhibit a marginal immunosuppressive activity, leading to non-specific recommendations for pre-treatment laboratory testing or exclusion of latent infections such as tuberculosis (26). On the other hand, despite warnings of a potential increase in adverse reactions of depression reported in the product label (26), 13% of subjects in our cohort had a history of minor depression without suicidal thoughts or behaviour and only one patient discontinued apremilast because of a worsening of depression. Indeed, the presence of comorbid conditions leading to contraindications to the use of conventional or biologic DMARDs along with the lack of poor prognostic factors for PsA progression were the most frequently reported reasons for prescribing apremilast. Considering the lack of data on the prevention of radiographic progression in the PALACE program, in our cohort apremilast was preferentially prescribed to patients without high risk of joint damage worsening. The route of administration was expected to be a key driver in the choice of apremilast as the drug is the first oral targeted therapeutic option proposed for PsA. However, oral administration was the reason for choosing apremilast only in a very small proportion of patients (6.7%).

The safety profile observed in our cohort was consistent with the 6-month results reported in RCTs on apremilast (30 mg) in both PSO (27) and PsA (8-11): no case of infection (including tuberculosis) or malignancy has been reported, while diarrhoea, nausea, and headache were the most frequently observed AEs. However, in RCTs the incidence of diarrhoea (ranging from 11.3 to 18.8%) and headache (ranging from 8.6 to 13.6%) was apparently lower compared with the ones observed in our cohort (32.7 and 20.7%, respectively). Moreover, the rate of discontinuations due to gastrointestinal events was higher in our population (22.4%) compared with PSO and PsA RCTs (<2%) (28), consistently with the high incidence reported in an observational study conducted on 208 real-life PSO patients receiving apremilast (13.9%) (29) and in a previous single-centre experience of 71 PsA patients (26.7%) (14).

Table IV. Predictors of 3 months DAPSA remission/LDA and of 6-month discontinuation of apremilast.

Predictor	3-month DAPSA remission/LDA (Multivariate logistic regression model)			6-month discontinuation (Cox proportional hazard model)		
	OR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	0.96	0.88-1.04	0.32	1.05	0.96-1.05	0.81
Disease duration	1.04	0.94-1.16	0.39	0.99	0.95-1.04	0.94
BMI	1.02	0.88-1.18	0.76	0.95	0.89-1.02	0.16
Female sex	0.21	0.05-0.95	**0.04**	9.72	2.70-35.1	**0.001**
bDMARD naïve	3.16	0.72-13.9	0.13	0.60	0.27-1.34	0.21
Concomitant MTX	1.90	0.20-18.2	0.57	0.31	0.07-1.40	0.13
Oligoarticular subset*	0.54	0.08-3.62	0.52	1.22	0.37-3.99	0.74
Entheseal involvement	3.81	0.45-31.8	0.21	0.60	0.24-1.52	0.28
Axial involvement	1.70	0.20-14.2	0.62	2.51	0.56-11.3	0.23

BMI: body mass index; bDMARD: biologic disease-modifying anti-rheumatic drug; MTX: methotrexate; DAPSA: Disease Activity in PSoriatic Arthritis; LDA: low disease activity; OR: odds ratio; 95% CI: 95% confidence interval; HR: hazard ratio.
*Oligoarticular subset: ≤4 affected joints.

Accordingly, the 6-month retention rate was lower than expected (56.9%) as a consequence of poor tolerability rather than inefficacy. Indeed, in our cohort the overall clinical response was generally favourable with about 40% of patients achieving 3-month DAPSA remission or LDA. Of note, the use of apremilast in bDMARD naïve patients was associated with a higher probability of achieving remission/LDA compared with the prescription of the drug in multi-failure patients. Moreover, female sex was a strong negative predictor of response and drug continuation, as previously reported in other PsA cohorts treated with different drugs (30). The rate of more ambitious clinical response measures such as MDA and VLDA was poor, as the result of the better effectiveness of apremilast observed on articular than entheseal involvement and the partial effect on patient reported outcomes included in MDA criteria. These findings are consistent with the clear effect of apremilast on swollen and tender joints count reported by Abignano *et al*. (14) and the significant improvement in PsA joint inflammatory status detected by ultrasonography in a small group of 13 Italian PsA patients (15). A comparison with RCTs is difficult since no study in the PALACE programme used DAPSA or MDA/VLDA as efficacy primary endpoints. In addition, the differences in the efficacy and tolerability profile could be explained by the diversity in the baseline characteristics (including comorbidities) of real-life cohorts compared with clinical trials.

As in all observational registry studies, the major limitation of the present study is the retrospective design. Moreover, we could consider the entire cohort only for the analysis of baseline characteristics and reasons for prescription, but we had to limit the effectiveness/safety analysis to a lower number of patients with available data at 3 and especially 6 months, leading to a potential limitation of the generalisability of our findings. Furthermore, the RAPPER registry included patients coming from tertiary rheumatology centres only, potentially limiting the generalisability of our results to the whole Italian population of PsA patients. Finally, it is important to consider that in Italy the use of apremilast is conditioned by treatment rules which could partially drive the choice toward the preferential prescription in patients who previously failed at least two csDMARDs and with limitations to the use of bDMARDs. On the other hand, the most important strength is the opportunity to evaluate the profile of PsA patients treated with apremilast in real-life clinical practice for the first time.

Conclusions

In conclusion, our real-life analysis allows to demonstrate that apremilast has been mainly used in PsA with oligoarticular and entheseal pattern, mild skin involvement, and low risk of damage progression, carrying comorbidities (especially history of infections and malignancies) with contraindications to the use of biologic drugs. In this very complex setting of patients and with the limitation of the small sample size, effectiveness of apremilast was higher in bDMARD naïve subjects and the safety profile was consistent with what has been reported by main RCTs. However, we found lower tolerability compared with RCTs, similarly to previously published observational studies in PSO and PsA cohorts, with a higher incidence of gastrointestinal events leading to drug discontinuation. Additional analyses conducted in greater cohorts should be advocated for confirming our findings.

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