**ORIGINAL ARTICLE**

# Apremilast retention rate in clinical practice: observations from an Italian multi-center study

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## Abstract

**Objective** There are few real-world setting studies focused on apremilast effectiveness (i.e., retention rate) in psoriatic arthritis (PsA). The main aim of this retrospective observational study is the assessment of apremilast 3-year retention rate in real-world PsA patients. Moreover, the secondary objective is to report the reasons of apremilast discontinuation and the factors related to treatment persistence.

**Methods** In fifteen Italian rheumatological referral centers, all PsA consecutive patients who received apremilast were enrolled. Anamnestic data, treatment history, and PsA disease activity (DAPSA) at baseline were recorded. The Kaplan–Meier curve and the Cox analysis computed the apremilast retention rate and treatment persistence-related risk factors. A $p$-value $< 0.05$ was considered statistically significant.

**Results** The 356 enrolled patients (median age 60 [interquartile range IQR 52–67] yrs; male prevalence 42.7%) median observation period was 17 [IQR 7–34] months (7218 patients-months). The apremilast retention rate at 12, 24, and 36 months was, respectively, 85.6%, 73.6%, and 61.8%. The main discontinuation reasons were secondary inefficacy (34% of interruptions), gastro-intestinal intolerance (24%), and primary inefficacy (19%). Age and oligo-articular phenotype were related to treatment persistence (respectively hazard ratio 0.98 IQR 0.96–0.99; $p = 0.048$ and 0.54 IQR 0.31–0.95; $p = 0.03$).

**Conclusion** Almost three-fifths of PsA patients receiving apremilast were still in treatment after 3 years. This study confirmed its effectiveness and safety profile. Apremilast appears as a good treatment choice in all oligo-articular PsA patients and in those ones burdened by relevant comorbidities.

**Key Points**
• *Apremilast retention rates in this real-life cohort and trials are comparable.*
• *The oligo-articular phenotype is associated with long-lasting treatment (i.e., 3 years).*
• *No different or more prevalent adverse events were observed.*

## Introduction

Apremilast is an inhibitor of the phosphodiesterase 4 that EULAR guidelines recommend to use in moderate active

psoriatic arthritis (PsA) [1, 2]. According to study based on data from three trials, PALACE 1, PALACE 2, and PALACE 3 [3–5], apremilast retention rate after 1, 2, and 3 years is respectively 72%, 62%, and 56% [6]. Even if retention rate is an extremely useful tool in order to describe the drugs' effectiveness in clinical practice, the investigated cohorts included only patients with characteristics fitting for trials. For example, severe comorbidities (i.e., cancer, chronic

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infection, etc.), less than three tender and swollen joints, and the use of more than two csDMARDs are exclusion criteria. So, it is reasonable to hypothesize that the above-mentioned studies do not replicate a real-world setting.

However, some observations, based on small clinical practice cohorts, suggest that apremilast has a lower effectiveness and higher adverse event prevalence [7, 8]. The largest one shows a 56% 6-month retention rate [9]. Even if the cohort included real-life PsA patients, some aspects remained unclear. The long-term effectiveness is unknown as only 20% of enrolled subjects had a 6-month assessment and the median observation period was less than 6 months. All these issues make the results quite hard to be considered as representative of a clinical practice scenario.

Even today the apremilast effectiveness in a real-world setting does not appear fully understood. In order to enlighten this issue, there is a need of studies about apremilast retention rate in patients not included in registries. The main aim of this study is the assessment of apremilast 3-year retention rate in clinical practice. Secondary objectives are the report of the apremilast interruption causes and the identification of most relevant factors related to treatment persistence.

## Materials and methods

As a part of the BIRRA (BIologics Retention Rate Assessment) project, this observational retrospective study is designed in order to assess the 3-year retention rate of apremilast. It is carried out following the Declaration of Helsinki principles and approved by the local Ethics Committees (the main is the Comitato Etico dell'Area Vasta Emilia Nord, protocol code 34,713, approved on 28 August 2019).

### Patients

All PsA consecutive patients from fifteen Italian rheumatological referral centers were screened. Inclusion criteria were as follows: (a) PsA diagnosis according to CASPAR criteria [1], (b) apremilast' prior or actual use, (c) availability of data about treatment beginning and discontinuation. Patients who received apremilast and bDMARDs at the same time or only for dermatologic indication (i.e., psoriasis (PsO)) were excluded.

The inclusion/exclusion criteria of the PALACE studies [3–5] divided the cohort into two groups. Subjects satisfying the criteria made up the PALACE-like subgroup (PLG); the other the real-world subgroup (RWG).

### Data

For each patient, the following data were recorded: general characteristics (age, sex, body mass index (BMI), smoke habit, presence of the human leukocyte antigen (HLA) class I molecule B27, PsA and PsO onset, and diagnosis date), PsA phenotype (oligo-articular, poli-articular, enthesitic, axial, and dactylics subtype), apremilast-related information (date of the first and last intake), other PsA treatments' history (both csDMARDs and bDMARDs), PsA disease activity (number of tender/swollen joints, painful enthesis and fingers affected by dactylitis, C-reactive protein, pain Visual Analog Scale, and patient global assessment values) at baseline (i.e., the visit after which patients started the apremilast treatment), the cause of interruption, and the presence of comorbidities.

The definition of oligo-articular phenotype was the presence of less than five affected joints [2]. Disease Activity index for PSoriatic Arthritis (DAPSA) and Leeds enthesitis index (LEI) assessed the PsA disease activity [10, 11].

Cancer, HBV, HCV, latent tuberculosis (TB), and other chronic infections were considered as relevant comorbidities. The classification of apremilast treatment interruptions included primary or secondary failure, gastro-intestinal intolerance, neurologic side effects, infection, and cancer.

## Statistical analysis

The D'Agostino-Pearson test verified the variables' normal distribution. Continuous variables were reported as median value and interquartile range (IQR); categorical values as percentage.

The Kaplan–Meier curve represented the percentage of baseline patients still in treatment with apremilast. The Cox analysis verified if there were factors (such as age, sex, BMI, smoke habit, relevant comorbidity, PsA disease duration, baseline disease activity, oligo-articular phenotype, concomitant csDMARDs treatment) related to apremilast treatment persistence.

The Mann–Whitney and chi-squared tests assessed the difference between PLG and RWG, as appropriate. A $p$-value $< 0.05$ was considered statistically significant. Statistical analysis was performed using an online application (www.statskingdom.com, last visit 28 February 2022) and R (http://www.r-project.org, V.3.3.3).

## Results

The PsA patients enrolled were three-hundred fifty-six; the median observation period was 17 (IQR 7–34) months (in total 7218 patients-months). Their main baseline characteristics are in Table 1. In general, about three-quarters of patients (268; 75.3%) had at least one csDMARDs before apremilast, one-fifth (74; 20.1%) did not receive any DMARDs, and more than one-quarter (100; 28.1%) had at least one bDMARDs. The DAPSA score at baseline (median 24.6; IQR 19.2–32.3) was suggestive of moderate

disease activity. Relevant comorbidities affected 44.4% patients.

The apremilast retention rate at 12, 24, and 36 months was, respectively, 85.3%, 73.6%, and 61.8% (Fig. 1). The main discontinuation reasons were secondary inefficacy (34% of 94 interruptions), primary inefficacy (24%), and gastro-intestinal intolerance (19%). Other causes, like relapsing infections, neurological side effects (e.g., depression, insomnia), and cancer onset during treatment, made about one-quarter of patients to discontinue the treatment. The decrease of treatment interruption risk is related to older age (hazard ratio 0.98 IQR 0.96–0.99; $p < 0.05$) and oligo-articular phenotype (hazard ratio 0.54 IQR 0.31–0.95; $p < 0.05$). Sex, BMI, smoke habit, relevant comorbidity, PsA disease duration, baseline disease activity, and concomitant csDMARDs treatment did not modify the risk of treatment discontinuation.

In the PLG, there was the 20.2% of enrolled patients. The main statistically significant differences with RWG were in terms of disease duration (higher), PsA or PsO duration (lower), and PsA phenotype (oligo-articular was more common in RWG while poli-articular in PLG) (for details, see Table 1).

The retention rates at 12, 24, and 36 months in RWG and PLG were respectively 83.4% vs 93.7%, 72.4% vs 78.3%, and 60.7% vs 65.1% without any statistically significant difference ($p = 0.2$) (Fig. 2).

**Table 1** Baseline characteristics of PsA patients

| | | Total cohort | PLG | RWG | *p*-value |
|---|---|---|---|---|---|
| *N* | | 356 | 72 | 284 | - |
| M:F | | 152:204 | 27:45 | 125:159 | Nss |
| Age, median (IQR), yrs | | 60 (52–67) | 59 (50–66) | 60 (52–68) | Nss |
| Smokers: yes/former/no* | | 55:43:254 | 13:11:46 | 42:32:208 | Nss |
| Body mass index, median (IQR) kg/m²** | | 26.0 (23.5–29.2) | 25.4 (23.4–29.0) | 26.0 (23.6–29.3) | Nss |
| PsA duration, median (IQR), months | | 48 (17–95) | 23 (12–60) | 53 (20–100) | <0.001 |
| PsA phenotype | Oligo-articular | 158 (44.4) | 21 (29.2) | 137 (48.2) | <0.05 |
| | Poli-articular | 198 (55.6) | 51 (70.1) | 147 (51.8) | |
| | Enthesitic | 168 (47.2) | 28 (38.9) | 140 (49.3) | |
| | Dactylitis | 122 (34.3) | 26 (36.1) | 96 (33.8) | |
| | Axial | 44 (12.4) | 10 (13.9) | 34 (12.0) | |
| SJC, median (IQR) | | 3 (2–4) | 4 (4–6) | 2 (1–4) | <0.00001 |
| TJC, median (IQR) | | 6 (3–10) | 7 (4–12) | 6 (3–10) | <0.001 |
| LEI, median (IQR) | | 0 (0–2) | 0 (0–2) | 0 (0–2) | Nss |
| Dactylitis, median (IQR), fingers | | 0 (0–1) | 0 (0–1) | 0 (0–1) | Nss |
| CRP, median (IQR), mg/dl | | 2.0 (0.7–4.8) | 3.1 (1.0–6.2) | 1.9 (0.6–4.3) | <0.01 |
| DAPSA*, median (IQR) | | 24.6 (19.2–32.3) | 30.0 (23.6–38.2) | 23.9 (18.0–31.2) | <0.00001 |
| PsO duration, median (IQR), months | | 63 (20–129) | 26 (15–108) | 69 (28–131) | <0.05 |
| Prior csDMARDs use, *n* (%)* | MTX | 222 (62.4) | 40 (56.6) | 182 (64.1) | Nss |
| | LFN | 58 (16.3) | 9 (12.5) | 49 (17.3) | |
| | SSZ | 94 (26.4) | 19 (26.4) | 75 (26.4) | |
| | CYA | 33 (9.3) | 3 (4.2) | 30 (10.6) | |
| Prior tsDMARDs use, *n* (%) | | 0 | 0 | 0 | - |
| Prior bDMARDs use, *n* (%) | TNFi | 90 (25.3) | 0 | 90 (31.6) | - |
| | IL17i | 26 (7.3) | 0 | 26 (9.1) | |
| | IL12/IL23i | 21 (5.9) | 0 | 21 (7.4) | |
| | Abatacept | 2 (0.6) | 0 | 2 (0.7) | |
| Concomitant csDMARDs, *n* (%) | | 67 (18.8) | 13 (18.1) | 54 (19.0) | Nss |
| Concomitant relevant disease, *n* (%) | Cancer | 99 (27.8) | 0 | 99 (34.7) | - |
| | HCV/HBV | 23 (6.5) | 0 | 23 (8.1) | |
| | Latent TB | 17 (4.8) | 0 | 17 (6.0) | |
| | Other infections | 26 (7.3) | 5 (7.0) | 21 (7.4) | |

Data missing in 4 (*) and 36 (**) patients

*PLG* PALACE-like group, *RWG* real-world group, *IQR* interquartile range, *SJC* swollen joint count, *TJC* tender joint count, *LEI* Leeds enthesitis index, *CRP* C-reactive protein, *DAPSA* Disease Activity index for PSoriatic Arthritis, *Nss* not statistically significant

**Fig. 1** Apremilast retention rate
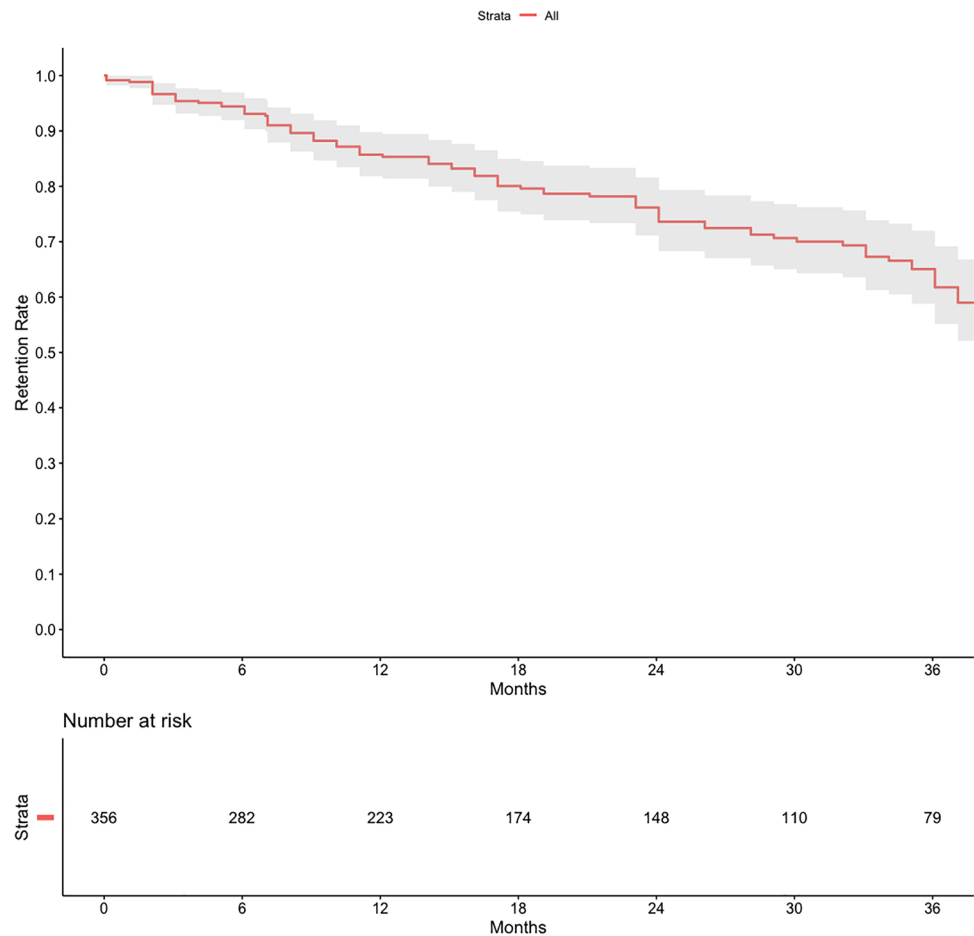
## Discussion

As far as we know, this is the largest study about apremilast retention rate in real-world setting PsA cohort. Findings from previous studies showed a lower retention rate than those one reported in trials [7, 9]. In general, the small sample size, the high prevalence of comorbidity, and the short period of follow-up (no more than 6 months) are major biases. In this study, we observed the 3-year retention rate of a PsA patients' cohort that is comparable to those enrolled in trials. Although the data does not derive from a national register, it is reasonable to think that it is quite representative of the Italian scenario as fifteen centers, fairly evenly distributed from a geographical point of view, participated. This element should also reduce any bias in the use of the drug since, in Italy, in addition to the guidelines, rheumatologists must also comply with regional provisions which can be very different from center to center.

In this study, many PsA subjects had a moderate disease and relative contraindications to bDMARDs. Most of them had HBV/HCV chronic infections, latent TB, or cancer. On the other hand, only one-fifth of patients satisfied the inclusion/exclusion criteria of PALACE studies [3–5].

Our findings suggest that apremilast has a higher retention rate than those reported in trials. This trend is much more pronounced in the first 2 years of therapy, but in the third, this gap narrows. The subgroups' analysis shows that there is the same trend both in RWG and PLG. However, in our opinion, these observations are not sufficient to assume that apremilast has a retention rate higher than expected.

In fact, this study's cohort includes patients not to be included in trials. In these patients, comorbidities and the reduced therapeutic opportunities may have led the rheumatologists to avoid any therapy change. Furthermore, although the PLG was selected according to the same PALACE inclusion/exclusion criteria, it is hard to directly compare the different groups' baseline characteristics. However, the lower number of affected joints observed in the PLG compared to those reported in trials can have had a relevant role. Similarly, BMI is lower than those ones observed in PALACE (which are near the obesity) and RAPPER [6, 9]. It is widely known that in PsA weight affects disease activity [12, 13]. It is therefore possible that in groups of predominantly overweight subjects the treatment is less effective. Moreover, in PALACE and RAPPER, PsA disease durations are much longer than in this

**Fig. 2** The apremilast retention rate in real-world group (red) and PALACE-like group (green)
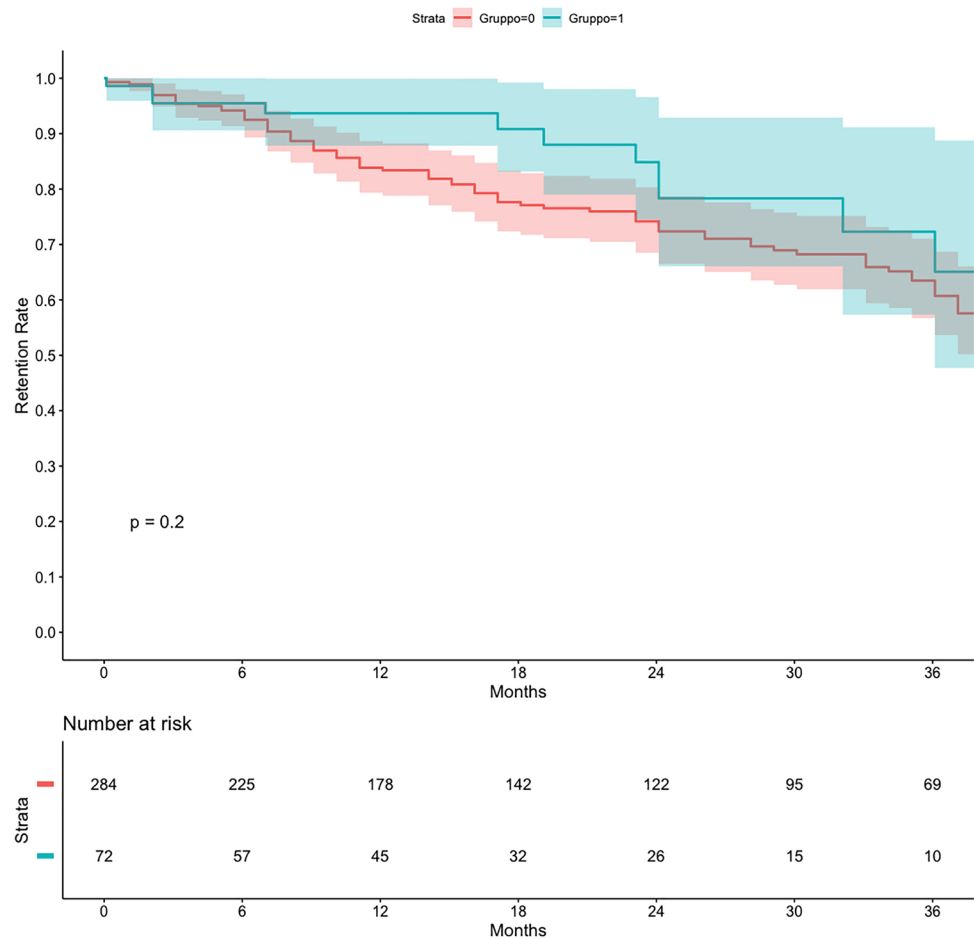


study (respectively 7.5 and 10.8 versus 4 years). Therefore, in these studies, the included population had more persistent and severe disease. This hypothesis is supported by the different therapeutic history. For example, the ratio of patients with previous use of bDMARDs in the RAPPER is 70% higher than that one reported in our cohort. In addition, the concomitant csDMARDs prevalence was more than three times higher in the three PALACE trials. In this study, the PsA disease duration had no effect on apremilast retention rate. It is likely that placing apremilast earlier in PsA treatment algorithm can improve the clinical response [7]. Finally, it should be highlighted that, in our cohort, the 3-year retention rate confidence interval includes those ones reported in trials. However, in PsO real settings, apremilast showed slightly better outcomes than in trials [14, 15].

The main reasons for discontinuation are the same reported in literature. It is worthy that in patients with relevant comorbidities there is no greater risk of treatment failure. In fact, we do not identify any discontinuation risk factors among sex, BMI, smoke habit, relevant comorbidity, PsA disease duration, baseline disease activity, and concomitant csDMARDs treatment. The oligo-articular phenotype influences the apremilast retention rate. Even if the poli/oligo-articular clinical classification is a critical issue [16, 17], some authors suggested that apremilast is more effective in the latter phenotype [18, 19]. In fact, Ogdie et al. showed that apremilast monotherapy decreases PsA disease activity more than methotrexate and bDMARDs [20]. This improvement is relevant from both a clinical and musculoskeletal ultrasound point of view [21].

In addition to the inherent limitations of a multi-center retrospective study, we believe that the results should be viewed with caution for the following reasons. First, the disease activity is not evaluated at 24 or 36 months. Only this outcome can actually clarify if the high retention rate observed is due to a therapeutic alternative lack. Second, no baseline radiological findings, which may allow a better patients' classification, were taken into account. Psoriasis severity and previous treatment were not assessed. Therefore, it is unknown how much they affected the decision to start or discontinue the treatment.

In conclusion, the apremilast retention rate in a large real-life cohort is comparable to that observed in trials. The oligo-articular phenotype is associated with long-lasting treatment (i.e., 3 years) even in cohorts of patients burdened

by relevant comorbidities. Finally, there were no different or more prevalent adverse effects than already known.

## Declarations

## References

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