BMC Rheumatology

https://doi.org/10.1186/s41927-025-00587-8

Article in Press

Comparative effectiveness of cycling versus swapping to UL-17 inhibitors after first TNF inhibitor failure in Psoriatic Arthritis: A real-world multicenter study

Received: 25 June 2025

Accepted: 10 October 2025

Published online: 24 November 2025

Cite this article as: Ariani A., Larosa M., Gullo A.L. *et al.* Comparative effectiveness of cycling versus swapping to UL-17 inhibitors after first TNF inhibitor failure in Psoriatic Arthritis: A real-world multicenter study. *BMC Rheumatol* (2025). https://doi.org/10.1186/s41927-025-00587-8

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Article type: **Original article**

Switching after the failure of the first TNF inhibitor: effectiveness of cycling versus swapping to IL-17 inhibitors in psoriatic arthritis. A multicenter retrospective observational study

Running header: **Effectiveness of cycling versus swapping to IL-17i in psoriatic arthritis**

Alarico Ariani[1], Maddalena Larosa[2], Alberto Lo Gullo[3], Olga Addimanda[4,5], Romina Andracco[6], Patrizia Del Medico[7], Marino Paroli[8], Maria Chiara Ditto[9], Bernd Raffeiner[10], Aurora Ianniello[11], Francesca Ometto[12], Marta Priora[13], Aldo Biagio Molica Colella[14], Elena Bravi[15], Viviana Ravagnani[16], Alessandra Bezzi[17], Rosetta Vitetta[18], Palma Scolieri[19], Alessandro Volpe[20], Federica Lumetti[21], Antonella Farina[22], Francesco Girelli[23], Elisa Visalli[24], Francesca Serale[25], Eleonora Celletti[26§], Veronica Franchina[27], Francesco Molica Colella[28], Giulio Ferrero[29], Fabio Mascella[17], Maria Cristina Focherini[17], Alessia Fiorenza[18], Guido Rovera[19], Cecilia Giampietro[12], Simone Bernardi[23], Natalia Mansueto[6], Dario Camellino[2], Rosalba Caccavale[8], Valeria Nucera[11], Myriam Di Penta[26], Emanuela Sabatini[26], Ilaria Platè[15], Adorni Giuditta[1], Eleonora Di Donato[1], Daniele Santilli[1], Gianluca Lucchini[1], Mirco Magnani[4], Gianluca Smerilli[7], Giorgio Amato[24], Francesco De Lucia[24], Ylenia Dal Bosco[24], Roberta Foti[24], Francesco Cipollone[26], Gerolamo Bianchi[2], Rosario Foti[24], Eugenio Arrigoni[15], Antonio Marchetta[20], Vincenzo Bruzzese[19], Gilda Sandri[30], Enrico Fusaro[9], Massimo Reta[4], Dilia Giuggioli[30], Antonio Marchesoni[30], Simone Parisi[9*], Andrea Becciolini[1]

*Co-last Author

1. Internal Medicine and Rheumatology Unit, University Hospital of Parma, Parma, Italy
2. Division of Rheumatology, Ospedale La Colletta-Azienda Sanitaria Locale 3, Genova, Italy
3. Rheumatology Unit, ARNAS Garibaldi di Catania, Catania, Italy
4. Rheumatology Unit, Azienda Unità Sanitaria Locale di Bologna, Bologna, Italy
5. Policlinico S.Orsola, Azienda Ospedaliera Universitaria-IRCCS di Bologna, Bologna, Italy
6. Internal Medicine Unit, Rheumatology Outpatient Clinic, Imperia Hospital, Imperia, Italy
7. Rheumatology outpatient clinic, Internal Medicine Unit, Civitanova Marche Hospital, Civitanova Marche, Italy
8. Department of Clinical, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Polo Pontino, Rome, Italy
9. Rheumatology Department, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
10. Rheumatology Unit, Department of Medicine, Bolzano Hospital, Bolzano, Italy
11. Rheumatology Outpatient Unit, ASL Novara, Novara, Italy
12. Rheumatology Outpatient Clinic, Azienda ULSS 6 Euganea, Padova, Italy
13. Rheumatology Day Hospital and Outpatient Clinic, ASL CN1, Cuneo, Italy
14. Rheumatology Unit, Azienda Ospedaliera Papardo, Messina, Italy
15. Rheumatology Unit, Ospedale G. da Saliceto, Piacenza, Italy
16. Rheumatology Unit, Santa Chiara Hospital APSS Trento, Trento, Italy
17. Internal Medicine and Rheumatology Unit, ASL Romagna Rimini, Rimini, Italy

18. Unit of Rheumatology, ASL VC Ospedale S. Andrea, Vercelli, Italy
19. Department of Medical Specialties, “Nuovo Regina Margherita" Hospital, Roma, Italy
20. Unit of Rheumatology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella, Italy
21. Rheumatology Unit, Azienda USL of Modena and University Hospital "Policlinico di Modena", Modena, Italy
22. Internal Medicine Unit, Rheumatology Outpatient Clinic, Ospedale "A. Murri” di Fermo, Fermo, Italy
23. Rheumatology Unit, Ospedale GB Morgagni - L Pierantoni, Forlì, Italy
24. Rheumatology Unit, Policlinico San Marco Hospital, Zingonia, Italy
25. Rheumatology Day Hospital and Outpatient Clinic, ASL CN2, Cuneo, Italy
26. Rheumatology Unit, Ospedale "SS. Annunziata" di Chieti - Università "G. d'Annunzio" Chieti, Chieti, Italy
27. UOC Oncologia Medica, Azienda Ospedaliera Papardo, Messina, Italy
28. Internal Medicine Unit, Università Bicocca Milano, Milano, Italy
29. Unit of Diagnostic and IPrioranterventional Radiology, Santa Corona Hospital, Pietra Ligure, Italy
30. University of Modena and Reggio Emilia, Rheumatology Unit, Modena, Italy

§Corresponding Author

Eleonora Celletti

Rheumatology Unit, Ospedale "SS. Annunziata" di Chieti - Università "G. d'Annunzio" Chieti, Italy

cellettieleonora@gmail.com

DECLARATIONS

Ethics approval and consent to participate: The local Ethics Committees (the main one being the Comitato Etico dell'Area Vasta Emilia Nord, protocol code 34713) approved the study, which follows the Declaration of Helsinki principles. Informed consent was obtained from the patient prior to participation in the study.

Consent for publication: Not applicable.

Availability of data and materials: The data underlying this article will be shared upon reasonable request to the corresponding author.

Competing Interests: A. Ariani has received honoraria as a speaker and an advisory board member of Abbvie, Abiogen, Amgen, Bristol-Myers Squibb, Boeringher, Bruno farmaceutici, Stava EG, Janssen, Lilly, Novartis, Novo Nordisk, Sanofi and Zentiva. F. Lumetti has received honoraria as an advisory board member of Amgen. None of the other Authors have any potential conflicts of interest to disclose in relation to this work.

Funding: No specific funding was received from any bodies in the public, commercial, or not-for-profit sectors to carry out the work described in this article. Editorial assistance was supported by Novartis Farma Italy.

Author contributions:

Substantial contributions to the conception or design of the work: Maddalena Larosa, Alberto Lo Gullo, Olga Addimanda, Romina Andracco, Patrizia Del Medico, Marino Paroli, Maria Chiara Ditto, Bernd Raffeiner, Aurora Ianniello, Francesca Ometto, Marta Priora, Aldo Biagio Molica Colella, Elena Bravi, Viviana Ravagnani, Alessandra Bezzi, Rosetta Vitetta, Palma Scolieri, Alessandro Volpe, Federica Lumetti, Antonella Farina, Francesco Girelli, Elisa

Visalli, Francesca Serale, Eleonora Celletti, Alarico Ariani, Antonio Marchesoni, Simone Parisi, Andrea Becciolini.

Acquisition, analysis, or interpretation of data for the work: Veronica Franchina, Francesco Molica Colella, Giulio Ferrero, Fabio Mascella, Maria Cristina Focherini, Alessia Fiorenza, Guido Rovera, Cecilia Giampietro, Simone Bernardi, Natalia Mansueto, Dario Camellino, Rosalba Caccavale, Valeria Nucera, Myriam Di Penta, Emanuela Sabatini, Ilaria Platè, Giuditta Adorni, Eleonora Di Donato, Daniele Santilli, Gianluca Lucchini, Mirco Magnani, Gianluca Smerilli, Giorgio Amato, Francesco De Lucia, Ylenia Dal Bosco, Roberta Foti, Francesco Cipollone, Gerolamo Bianchi, Rosario Foti, Eugenio Arrigoni, Antonio Marchetta, Vincenzo Bruzzese, Gilda Sandri, Enrico Fusaro, Massimo Reta, Dilia Giuggioli.

Drafting the work or revising it critically for important intellectual content: Alarico Ariani, Antonio Marchesoni, Simone Parisi, Andrea Becciolini, Maddalena Larosa, Alberto Lo Gullo, Olga Addimanda, Romina Andracco, Patrizia Del Medico, Marino Paroli, Maria Chiara Ditto, Bernd Raffeiner, Aurora Ianniello, Francesca Ometto, Marta Priora, Aldo Biagio Molica Colella, Elena Bravi, Viviana Ravagnani, Alessandra Bezzi, Rosetta Vitetta, Palma Scolieri, Alessandro Volpe, Federica Lumetti, Antonella Farina, Francesco Girelli, Elisa Visalli, Francesca Serale, Eleonora Celletti, Veronica Franchina, Francesco Molica Colella, Giulio Ferrero, Fabio Mascella, Maria Cristina Focherini, Alessia Fiorenza, Guido Rovera, Cecilia Giampietro, Simone Bernardi, Natalia Mansueto, Dario Camellino, Rosalba Caccavale, Valeria Nucera, Myriam Di Penta, Emanuela Sabatini, Ilaria Platè, Giuditta Adorni, Eleonora Di Donato, Daniele Santilli, Gianluca Lucchini, Mirco Magnani, Gianluca Smerilli, Giorgio Amato, Francesco De Lucia, Ylenia Dal Bosco, Roberta Foti, Francesco Cipollone, Gerolamo Bianchi, Rosario Foti,

Eugenio Arrigoni, Antonio Marchetta, Vincenzo Bruzzese, Gilda Sandri, Enrico Fusaro, Massimo Reta, Dilia Giuggioli.

Final approval of the version to be published: All authors.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

Clinical trial number: not applicable

Acknowledgments: Editorial assistance in the preparation of the manuscript was provided by Simonetta Papa, PhD, Valentina Attanasio and Aashni Shah (Polistudium SRL, Milan, Italy), with financial support from Novartis Farma Italy. The authors are fully responsible for the content of this manuscript, including data collection, analysis, interpretation, and the decision to submit for publication, which were made independently of the sponsor.

Counts

Words (abstract): 249

Words (main text): 2295

Table: 1

Figure: 1

References: 29

ABSTRACT

Objective

The increase in biological disease-modifying antirheumatic drugs for psoriatic arthritis (PsA) made it possible to consider different mechanisms of action (MoA) after the failure of the first advanced-line therapy. However, there is still a lack of real-world evidence comparing the cycling (re-administration of a similar MoA) and the swap strategy. This retrospective observational study aims to evaluate the retention rate, as a proxy for effectiveness, of second-line therapeutic options after the failure of a TNF inhibitor (TNFi) by comparing cycling versus swap strategies.

Methods

PsA patients who failed the first-line TNFi and subsequently received either a TNFi or IL-17i were retrospectively selected from 25 centers. We collected demographic and disease-related data (disease duration, clinical phenotype, Disease Activity in Psoriatic Arthritis score), concomitant use of conventional synthetic disease-modifying antirheumatic drugs. Patients were categorized into cycling (second TNFi) (CG) or swapping (switch to IL-17i) (SG) groups. Kaplan-Meier survival curves were used to evaluate the retention rate, and a Cox regression analysis was performed to identify risk factors influencing treatment retention.

Results

In CG and SG there were 275 and 177 patients, respectively. Retention rate in SG was higher than in CG ($p<0.001$). Treatment interruption predictors were cycling strategy ($p<0.001$), Disease Activity in Psoriatic Arthritis ($p=0.013$), prescription year ($p=0.016$), axial ($p=0.013$), mixed involvement ($p=0.001$).

Conclusion

The swap strategy showed higher treatment retention than cycling in PsA patients who failed the first-line TNFi. This finding supports the hypothesis that changing MoA may improve the chances of selecting the most effective PsA treatment.

Clinical trial number: not applicable

Keywords

Psoriatic arthritis, TNFi, IL-17i, drug retention rate, bDMARDs, switch, cycling strategy, swap strategy.

Abbreviations

ASDAS: Ankylosing Spondylitis Disease Activity Score

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

bDMARDs: biological disease-modifying antirheumatic drugs

BIRRA: BIologics Retention Rate Assessment

CASPAR: ClASsification criteria for Psoriatic ARthritis

CG: cycling group

csDMARD: conventional synthetic DMARD

DAPSA: Disease Activity in Psoriatic Arthritis

EULAR: European Alliance of Associations for Rheumatology

HLA: human leukocyte antigen

IL-17i: interleukin-17 inhibitor

MoA: mechanisms of action

SG: swap group

TNFi: TNF inhibitor

BACKGROUND

In the last decade, the pharmacological treatment options for psoriatic arthritis (PsA) have dramatically increased [1]. The availability of new biological disease-modifying antirheumatic drugs (bDMARDs) with different mechanisms of action (MoA) presents the rheumatologist with a choice between sequential (re-administration of a similar MoA) or swap (switching to a different MoA) strategies after the failure of a bDMARD [2]. The potential advantages of these strategies have not been widely explored in clinical practice and remain an unmet need [3,4], even according to the European Alliance of Associations for Rheumatology (EULAR) guidelines [5].

TNF inhibitors (TNFis), the first class of bDMARDs effective in PsA, are still widely used, especially their biosimilars. Both guidelines and stakeholders recommend considering them as the first-line treatment after conventional synthetic DMARD (csDMARD) failure [5–7]. Since 2016, the availability of interleukin-17 inhibitor (IL-17i) has provided an alternative MoA that is not inferior to TNFi in clinical practice [8,9]. However, after the eventual failure of the first-line TNFi, it remains unclear which treatment offers the highest effectiveness between the two aforementioned classes.

Some attempts have been made to fill this gap. Retrospective observational studies have suggested that a change in MoA could be beneficial [2,10]. Moreover, some sequences are likely better than others. For example, in a monocentric cohort, Sandri et al. showed that switching from TNFi to IL-17i resulted in a better retention rate than cycling TNFi [11]. However, these observations refer to patients in different treatment lines and do not take into account all previous bDMARDs. In fact, for those who have already failed two or three TNFis, using yet another bDMARD with the same MoA could be unfavorable

[12]. There are some analyses of insurance claims regarding the best bDMARD choice between cycling (from TNFi to TNFi) versus swapping (from TNFi to IL-17i) strategies in second-line PsA patients [10]. However, their findings cannot be easily applied to clinical practice. Observation from a real-world cohort of PsA patients who failed the first-line bDMARD and switched to another with the same or different MoA could provide new insights into the strategy with the greatest likelihood of treatment effectiveness (i.e., retention rate).

The main aim of this retrospective real-life study is to compare the retention rate, intended as a proxy for effectiveness [13], of TNFi versus IL-17i after the failure of the first TNFi in PsA patients. Secondary objectives involve detecting the most relevant factors related to treatment persistence and the causes of failure.

PATIENTS AND METHODS

This retrospective observational study derives from the BIologics Retention Rate Assessment (BIRRA) project. The local Ethics Committees (the main one being the Comitato Etico dell'Area Vasta Emilia Nord, protocol code 34713) approved the study, which follows the Declaration of Helsinki principles.

Patients

Secukinumab, the first IL-17 inhibitor available in Italy, was introduced in January 2016. Accordingly, all consecutive PsA patients from January 2016 to March 2024 at 25 Italian rheumatology referral centers were retrospectively screened. Inclusion criteria were: a) PsA diagnosis according to the ClASsification criteria for Psoriatic ARthritis (CASPAR) [14], b) failure of the first-line TNFi, c) subsequent treatment with another TNFi or IL-17i started after 31 December 2015, and d) availability of data on treatment initiation and discontinuation.

Patients who interrupted or started bDMARD treatment solely for reasons unrelated to joint involvement (e.g., psoriasis, inflammatory bowel disease, uveitis) or switched from bDMARD originator to its biosimilar were excluded.

The switching strategy adopted in the second-line bDMARD clustered the cohort into two groups: cycling group (CG; from TNFi to another TNFi) and swap group (SG; from TNFi to IL-17i).

Data

All participating centers used the same standardized case report form and retrospectively extracted clinical data from medical records. Data collected included general characteristics (age, sex, presence of human leukocyte antigen (HLA) class I molecule B27), disease duration at the time of switching, PsA involvement (categorized as peripheral, axial or mixed), time interval between initiation and discontinuation of the second-line bDMARD, reasons for withdrawal, baseline concomitant use of csDMARDs, and baseline disease activity. Disease activity in peripheral PsA was assessed using the Disease Activity in Psoriatic Arthritis (DAPSA) score, while in patients with axial involvement, clinimetric assessments were performed using the Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Originators and their biosimilars were grouped together.

Reasons for treatment discontinuation included lack or loss of efficacy, adverse events, or death. Patients lost to follow-up or those who discontinued second-line bDMARDs due to dermatological reasons were censored. Only baseline data were collected, with no standardized follow-up time points. There was no minimum follow-up duration.

Study measures

The primary outcome was treatment retention, defined as the time from initiation (i.e., baseline) to the last visit or discontinuation of the second-line bDMARD (either TNFi or IL-17i). Secondary outcome measures included predictors of treatment discontinuation, such as baseline disease activity, PsA phenotype (peripheral, axial, or mixed), and the presence of HLA-B27.

Statistical analysis

Continuous variables were reported as median value and interquartile range (IQR), and categorical variables as percentages.

The Kaplan-Meier curve and log-rank test were used to evaluate the retention rate of the two strategies. Cox analysis was conducted to verify if factors, such as age, sex, switch strategy, PsA phenotype, PsA disease duration, DAPSA, year of prescription and concomitant csDMARD treatment influenced the treatment persistence.

The Mann-Whitney and chi-squared tests assessed the difference between subgroups as appropriate. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using Jamovi (https://www.jamovi.org, v 2.3).

RESULTS

A total of 452 PsA patients satisfied the inclusion criteria. The median observation period was 13 months (IQR 6–31), for a total of 9,905 patients/months. The main baseline characteristics are in Table 1.

The CG comprised 275 patients (60.8%), while the remaining 177 (39.2%) were in the SG. At baseline, there were no differences between the two groups except for the HLA-B27 assessment (it was investigated more often in SG, $p<0.01$). According to baseline DAPSA, the majority of patients in both groups had

moderate disease activity (Table 1). Prescriptions were not homogeneously distributed during the study period. In CG, half of prescriptions occurred between 2018 and 2022, while in SG, the same number took place between 2019 and 2022 (p=0.002).

Treatment retention

The retention rates at 12, 36, and 60 months were 68.3%, 39.3%, and 28.8% in the CG and 78.0%, 59.6%, and 53.5% in the SG, respectively (Figure 1A). This difference between the two study groups was statistically significant (p=0.00024). The gap in the retention rate curves emerged after 2 years and then remained stable at around 10%.

Predictors of treatment discontinuation

The swap strategy was the only factor significantly associated with longer treatment persistence. In contrast, axial or mixed involvement, higher baseline DAPSA values, and year of switch prescription were associated with shorter retention rates. A negative trend (although not significant) was found for the presence of concomitant csDMARDs. The hazard ratios and IQRs of all considered risk factors are reported in Figure 1B.

Overall, the prevalence of discontinuation due to lack of efficacy, loss of efficacy, and adverse events were 19%, 72%, and 9%, respectively. There was no statistically significant difference between the two groups (18%, 75%, and 7% in CG vs 21%, 66%, and 13% in SG, respectively). No deaths occurred.

DISCUSSION

The retention rate assessment and the factors influencing it are considered the best tools to evaluate bDMARD effectiveness [13]. In fact, persistence in therapy, an obvious consequence of an acceptable clinical state (remission or low disease

activity), entails a lower use of healthcare resources than when treatment fails [15,16]. Therefore, identifying the most effective switch strategy is a pivotal issue for developing a more cost-effective approach to managing severe chronic arthritis.

Some head-to-head trials have demonstrated no differences in efficacy and safety between TNFi and IL-17i [8,17]. However, these types of studies measure bDMARD efficacy under standardized conditions and in cohorts of patients with specific (and sometimes uncommon) characteristics [18]. For these reasons, their findings are difficult to apply to clinical practice [18]. In addition, they did not specifically address the switching issue.

Insurance registries provide interesting insights into drug persistence. Observations focused on second-line bDMARDs show that the difference between cycling and swap may not emerge in the short term [19]. On the other hand, in long-term observations, changing MoA (both IL-17i and IL-12/23) after TNFi failure appears to be the best strategy [10]. This difference is even more evident when short and homogeneous prescription periods are considered [20]. Selecting periods before the market introduction of IL-17i likely provides a biased advantage to the TNFi cycling strategy [21]. Although insurance claims are very informative, studies based on them have an intrinsic bias because they do not assess the impact of disease activity or ascertain why patients withdraw from therapy [22].

Data from real-world evidence are still not consistent. It is not yet entirely clear whether the line of treatment significantly impacts the retention rate of all drugs [23] or whether some bDMARDs are unaffected [24,25]. Our results are opposite to those of Takami et al. In a small cohort enrolled between 2010 and 2020, they observed that cycling was the better choice [26]. They confirmed that the line of

treatment significantly influences the retention rate, but they neglected the role of PsA involvement and the year of prescription. Moreover, the lack of alternatives or a prolonged marketing period may have extended the persistence of TNFi [26,27]. The year of prescription also affects the retention rate. In particular, it seems that prescriptions before 2015 were longer-lasting than those made afterward [28].

Some studies did not highlight differences between the two second-line strategies [29,30]. In particular, the Portuguese registry did not highlight differences between the two second-line strategies in patients observed for 2 years [29]. They reported retention rate values similar to those observed in our SG. However, the swap strategy they considered was heterogeneous because more than a third of the subjects received ustekinumab. Furthermore, they did not consider how relevant the year of prescription was, as the period studied was very extended (from 2008 to 2022).

The largest observational study showed a certain, but not statistically significant, positive trend toward the use of secukinumab [31]. However, the finding is difficult to interpret because second- and third-line patients were clustered together (despite using an adjustment factor), and no data on previously failed bDMARDs were collected.

The results of this study are consistent with a better performance of the swap strategy (from TNFi to IL-17i) than the cycling of TNFi. The Kaplan-Meier curves clearly showed a higher retention rate for the SG, and the multivariate analysis revealed that swapping was the only factor associated with longer persistence on treatment. Moreover, no significant differences in safety were observed, making even more evident that the differences in retention rates between the two groups were primarily due to effectiveness. Since the difference in retention

between the two study groups emerged after 2 years, the advantage of swapping may not be immediately visible in clinical practice. In this study, higher baseline disease activity and axial involvement (mixed or alone) were associated with shorter treatment persistence. These results fit into an unclear context where these variables have appeared either as negative or positive risk factors [13,26,28,32].

We cannot speculate on concomitant baseline csDMARDs because whether these drugs were continued or suspended after the switch was not evaluated. Moreover, there was no record of possible dosage changes.

In our study, the year of prescription had a significant impact on the retention rate. It is not easy to explain this finding, although the application of tight control and the wide range of bDMARDs available probably played a role. Some of the inconsistencies between our study and previous ones may be related to the different intervals of years of prescription. Moreover, the majority of the Authors did not consider them in their analysis [29].

In addition to the limitations inherent in multicenter observational studies, this study is also burdened by other limitations. First of all, only a limited number of risk factors were evaluated. In particular, we did not consider smoking, body mass index, type of concomitant csDMARDs, or which TNFi failed in the first line. The reason for the failure of the first TNFi was also not taken into account, although there are convincing observations that it does not influence the persistence [28]. Lastly, the characteristics of the general pool of screened patients were not analyzed.

The SG retention rate may have been increased by the rheumatologists' lower propensity to return to a class of DMARDs (i.e., TNFi) that the patient had

previously failed. However, this is likely only until 2018, when the available alternatives increased significantly.

Phenotypes were approximated as peripheral or axial (mixed if both were present). This simplification may have led to an impoverishment of the analysis. In addition, the definition of axial involvement in PsA was far from standardized. In fact, we did not verify whether it was based on the rheumatologist's opinion or validated criteria (e.g., Assessment of Spondyloarthritis International Society criteria). However, the potential confounding effect was very limited, as the prevalence of axial or mixed involvement was almost the same in the two groups. To minimize this bias, we took into consideration the presence of HLA-B27. The prevalence of patients tested for HLA-B27 was comparable to the overall prevalence of subjects with axial and mixed involvement (i.e., in the total cohort, 41% vs 38%). Therefore, it seems reasonable to assume that clinicians made efforts to achieve an accurate diagnosis of axial involvement.

The assessment tool for disease activity was the DAPSA, which does not directly score axial or mixed involvement. For this reason, we considered both BASDAI and ASDAS, but it was not possible to include them in the Cox analysis. Moreover, we did not evaluate the presence of certain conditions, such as spine osteoarthritis or fibromyalgia. Although these comorbidities are not related to PsA itself, it is well known that they can affect treatment persistence, patients' quality of life, clinimetric measures, and the classification of involvement [33].

As our cohort was recruited exclusively from rheumatology centers, patient selection was inherently guided by articular rather than cutaneous disease activity. This likely explains why all participants received a TNFi as first-line therapy, with no patients starting an IL-17i, as recommended by international guidelines for those with predominant moderate-to-severe psoriasis.

Consequently, we cannot exclude a potential bias related to the lack of systematically collected data on psoriasis severity (e.g., PASI scores), which represents an additional limitation of our study. Thus, potential source of confounding by indication is the presence of severe psoriasis, which may have guided the rheumatologist's decision toward an IL-17i in the second line, despite the lack of systematically collected PASI scores or other standardized measures of skin disease activity in our cohort. In addition, the reason for the failure of the first TNFi was also not taken into account. Although there are convincing observations that it does not influence the persistence [28], it cannot be ruled out that the reason for treatment failure influenced the choice of the mechanism of action utilized in the second line, thereby introducing a baseline selection bias. The large number of participating centers represents both a strength and a weakness. While it allows for a broad national overview comparable to registry data, it also entails potential heterogeneity in the strategies employed to prolong treatment before switching. Although we believe this effect is randomly distributed across centers and partly mitigated by adherence to national and international guidelines, it cannot be entirely excluded. In addition, the representativeness of the cohort has minor limitations. As this was not a prevalence or registry study, the total number of eligible patients across all centers remains unknown, including those who may have pursued alternative treatments. Thus, although multi-center involvement enhances diversity, the initial population size from which the study cohort was drawn remains undefined. Finally, we did not investigate whether changing MoA from IL-17i to TNFi is equally effective. Since the results cannot be applied to other types of swaps or cycling (e.g., between IL-17i or IL-23i), it still remains unclear which strategy is

superior. However, this is the first step toward the most rational use of bDMARDs in PsA.

CONCLUSION

Our findings support the notion that in PsA patients who have failed a TNFi, choosing an IL-17i in second-line can be more effective than a TNFi in terms of treatment retention. However, these results specifically apply to the TNFi/IL-17i sequence and should not be interpreted as evidence of improved outcomes across all PsA domains, which were not systematically assessed in this study. Thus, this study strengthens the hypothesis that a swap strategy offers PsA patients a better chance of achieving satisfying, long-lasting disease control.

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623 **TABLES**

624 **Table 1: Baseline characteristics of PsA patients**

	Total cohort (n=452, 100%)	Cycling group (n=275, 60.8%)	Swap group (n=177, 39.2%)	p-value
Male:Female	167:285	96:179	71:106	Nss
Age (years), median (IQR)	55 (46–62)	55 (46–62)	55 (46–62)	Nss
PsA duration (months), median (IQR)	52 (19–96)	52 (15–96)	54 (24–97)	Nss
PsA involvement, n (%):				Nss
▯ Peripheral	280 (62%)	165 (60%)	115 (65%)	
▯ Axial	70 (15%)	47 (17%)	23 (13%)	
▯ Both	102 (23%)	63 (23%)	39 (22%)	
DAPSA, median (IQR)	22.0 (15.1–28.0)	22.1 (15.1–28.0)	22.0 (15.3–28.0)	Nss
BASDAI*, median (IQR)	5.7 (3.8–7.0)	5.4 (4.2–7.0)	6.0 (2.1–6.6)	Nss
ASDAS**, median (IQR)	3.2 (2.5–3.8)	3.6 (2.5–4.0)	2.9 (2.3–3.6)	Nss

	Total cohort (n=452, 100%)	Cycling group (n=275, 60.8%)	Swap group (n=177, 39.2%)	p-value
Concomitant csDMARDs, n (%)	202 (45%)	126 (46%)	76 (43%)	Nss
HLA-B27, n (%)				<0.01
▯ Positive	27 (6%)	18 (7%)	9 (5%)	
▯ Negative	158 (35%)	81 (29%)	77 (44%)	
▯ Unknown	267 (59%)	176 (64%)	91 (51%)	
Second-line bDMARD, n (%)				-
▯ Adalimumab	92 (20.0%)	92 (33.5%)	–	
▯ Bimekizumab	1 (0.2%)	–	1 (0.6%)	
▯ Certolizumab	42 (9.3%)	42 (15.3%)	–	
▯ Etanercept	84 (19.0%)	84 (30.6%)	–	
▯ Golimumab	37 (8.2%)	37 (13.4%)	–	
▯ Infliximab ev	19 (4.2%)	19 (6.9%)	–	
▯ Infliximab sc	1 (0.2%)	1 (0.4%)	–	
▯ Ixekizumab	46 (10.0%)	–	46 (26.0%)	

	Total cohort (n=452, 100%)	Cycling group (n=275, 60.8%)	Swap group (n=177, 39.2%)	p-value
▯ Secukinumab	130 (29%)	–	130 (73.4%)	

Data missing in 92 (*) and 75 (**) patients.

IQR: interquartile range; DAPSA: Disease Activity Index for Psoriatic Arthritis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; Nss: not statistically significant.

629 **Figure 1**

630 Cycling and swap strategies comparison of **(A)** retention rate and **(B)** hazard

631 regression plot of the selected explanatory variables.