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Cycling versus swapping strategies with TNF-α inhibitors and IL-17 inhibitors in psoriatic arthritis in clinical practice

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The availability of a number of bDMARDs with different mechanism of action increases potential treatment pathways in psoriatic arthritis (PsA). In clinical practice, following the failure of one bDMARD, it is normal to consider which options are the best for switching strategy. In most cases this choice involves IL17i and TNFi. The main aim of this study was to compare the effectiveness of cycling (from TNFi to another TNFi) and swapping (from TNFi to IL17i or vice versa) strategies. In this monocentric retrospective observational study, all PsA patients treated with TNFi or IL17i between January 2016 and January 2022 were enrolled. The prescriptions were clustered in one cycling group (CG), and two swap groups: from TNFi to IL17i (SG1) and from IL17i to TNFi (SG2). The Kaplan–Meier method and Cox regression models were applied to compare the drug retention rates and to identify factors affecting treatment persistence. A total of 122 patients were enrolled. The CG, SG1 and SG2 2-years retention rates were 51%, 58% and 34% (p = 0.1), respectively. SG1 strategy (HR 0.53; CI 0.31–0.89; p = 0.02), age (HR 0.98; CI 0.96–0.99; p = 0.003), Disease Activity PsA (HR 1.11; CI 1.08–1.13; p < 0.0001), year of switch (HR 1.78; CI 1.39–2.22; p < 0.0001) influenced the retention rate. The findings of this real-world study, even if burdened by bias related to its observational nature, support the hypothesis that in PsA patients swapping from TNFi to IL17i might be more effective than cycling TNFis.

Keywords Psoriatic arthritis, Drug retention rate, Biologics

Abbreviations

PsA	Psoriatic arthritis
bDMARD	Biological disease modifying anti-rheumatic drug
csDMARD	Conventional synthetic disease modifying anti-rheumatic drug
tsDMARD	Target synthetic disease modifying anti-rheumatic drug
MoA	Mechanisms of action
TNFi	Tumor necrosis factor alpha inhibitor
IL17i	Interleukin 17 inhibitor
DAPSA	Disease activity index in PsA
CG	Cycling from TNFi to another TNFi
SG1	Swap from TNFi to IL17i
SG2	Swap from IL17i to TNFi
IQR	Interquartile range
nss	Not statistically significant

Psoriatic arthritis (PsA) is a chronic inflammatory autoimmune condition that affects joints, tendons, and entheses which may lead to progressive and destructive joint damage and functional disability[1]. In recent

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years the treatment of PsA has improved with the introduction of several biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) with different mechanisms of action (MoA)[2].

The first bDMARDs available were the tumor necrosis factor alpha inhibitors (TNFis), such as infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol. Subsequently, the arrival of inhibitors of interleukin (IL) 17 (secukinumab, ixekizumab, and bimekizumab), IL-12/23 (ustekinumab), IL-23 (guselkumab and risankizumab), cytotoxic T-lymphocyte antigen 4 (abatacept), phosphodiesterase-4 (apremilast) and Janus kinase (JAK) (upadacitinib and tofacitinib), has increased the number of therapeutic agents, granting the access to drugs with different MoAs[3].

According to all recommendations, the prescribed drugs for PsA treatment should be TNFis, owing to their biosimilars, which significantly reduce the economic burden. However, none of the recommendations from leading Scientific Societies on PsA treatment suggest which is the best strategy after the failure of a bDMARD[4–8].

Several trials investigated the efficacy of a single drug after the failure of first-line biological therapy (mainly TNFis). However, these trials are not conclusive, as they only compared two drugs at a time and did not specifically address the issue of switching drugs[9–11].

In clinical practice, the necessity to understand which bDMARD following the failure of a previous one, is even more pressing. Generally, the choice is between TNFi or IL17i. Therefore, the most common switching scenarios are the sequential strategy (from one TNFi to another TNFi) or the change of MoA (from TNFi to IL17i or vice versa)[12]. Preliminary observational studies suggested that the swap strategy is slightly better than cycling, even if no remarkable advantages emerged[13–16].

The main aim of this real-world study is to identify which of the most common switching strategies (cycling TNFi or swap between TNFi and IL17i) are better in clinical practice.

Materials and methods

Study design and patients

This single-center, retrospective, observational study was approved by the local Ethics Committee (ref. 192/2021). We included all PsA patients diagnosed according to the CASPAR criteria[17] and aged > 17, treated with TNFi and/or IL17i between January 2016 and January 2022. Patients who received bDMARDs for concomitant psoriasis were excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki. All the patients provided written informed consent.

Data collection

For each patient included in the study, main baseline characteristics (age, sex, disease duration, HLA-B27 presence, value of Disease Activity index in PsA (DAPSA) and a range of information regarding PsA treatment were collected. In particular, the following data were considered: treatment duration (time interval between the first and last prescription or failure of bDMARDs), line of treatment, concomitant conventional synthetic (cs) DMARDs and/or steroids and reason for suspending bDMARDs, if applicable.

The different pharmacological prescriptions, and the subsequent switch, allowed to identify three subgroups according to the therapeutic strategy: Cycling from TNFi to another TNFi (CG), Swap from TNFi to IL17i (SG1) or from IL17i to TNFi (SG2).

Statistical analysis

The three subgroups (CG, SG1, and SG2) were compared for effectiveness, expressed as survival on treatment, which was estimated with Kaplan–Meier curves. The Log-rank test was used to verify whether the differences between curves were significant. In addition to the treatment strategy, it seems reasonable to hypothesize that the following factors may also influence the retention rate: age, sex, disease duration, line of treatment (considering only bDMARDs, targeted synthetic (ts) DMARDs and apremilast), year of switch, disease activity (i.e. DAPSA), and concomitant csDMARDs treatment. The Cox analysis (stepwise) was used to reveal which factors were independently associated with treatment discontinuation.

All variable values were reported as prevalence (in %) or median with its 95% confidence interval, as appropriate. Chi-squared or Kruskal–Wallis tests investigated the differences between baseline characteristic of the three subgroups.

Medcalc, version 18.2.1 (Medcalc Software Ltd. Ostend Belgium) was the statistical software used for the analysis. Values of $p < 00.05$ were considered statistically significant.

Results

In the chosen period (from January 2016 to January 2022), 122 patients met the inclusion criteria. The number of prescriptions in CG, SG1 and SG2 were 100 (1752 patient-months), 59 (1103 patient-months) and 13 (103 patient-months), respectively. The baseline characteristics of these patients are reported in Table 1.

The main cause of failure was lack of response in CG and SG2 and loss of response over time in SG1 (Table 1). The 1-year retention rates in CG, SG1 and SG2 were 67%, 71.8% and 45.5%, respectively. After two years the retention rate in SG1 (58%) was still better than in the other subgroups (51% in CG and 34% in SG1). These differences, however, were not statistically significant (p-value = 0.1) (Fig. 1).

The Cox analysis showed that the SG1 strategy (i.e. from TNFi to IL-17i) and the patients' age increasing were associated with a longer treatment persistence. Factors associated with a reduced retention rate were higher baseline DAPSA value and the year in which the treatment was prescribed. More details are provided in Table 2.

		Cycling Group	Swap Group 1	Swap Group 2	p-value
M:F		43:57	26:33	4:9	nss
Age, median (IQR), yrs		50 [44–63]	55 [47–66]	45 [39–52]	0.03 (SG1 vs SG2)
PsA duration, median (IQR), months		45 [34–54]	48 [37–56]	40 [31–43]	0.03 (SG1 vs SG2)
DAPSA (IQR)		5.6 [2.5–12.5]	6.0 [4.0–14.5]	13.5 [4.8–15.1]	nss
HLAB27 presence, n (%)		3 (3)	0 (0)	1 (8)	nss
Concomitant csDMARDs, n (%)		39 (39)	23 (39)	2 (17)	nss
Line of treatment, n (%)	2 3 4 5 or more	57 (57) 30 (30) 11 (11) 2 (2)	21 (36) 19 (32) 14 (24) 5 (8)	3 (23) 5 (39) 3 (23) 2 (15)	0.01 (CG vs SG1) 0.02 (CG vs SG2)
Cause of failure, n (%)	Lack of response Loss of response Infection Cancer Adverse event	10 (10) 31 (31) 3 (3) 0 (0) 1 (1)	5 (8) 10 (17) 0 1 (2) 3 (5)	3 (23) 1 (8) 0 0 1 (8)	0.045 (CG vs SG2)
Period of observation, median (IQR), months		13,1 [6.9–26.8]	12,2 [4.8–34.6]	2,6 [0.9–14.8]	0.02 (SG1 vs SG2) 0.005 (CG vs SG2)

Table 1. Characteristics of cycling and swap groups.

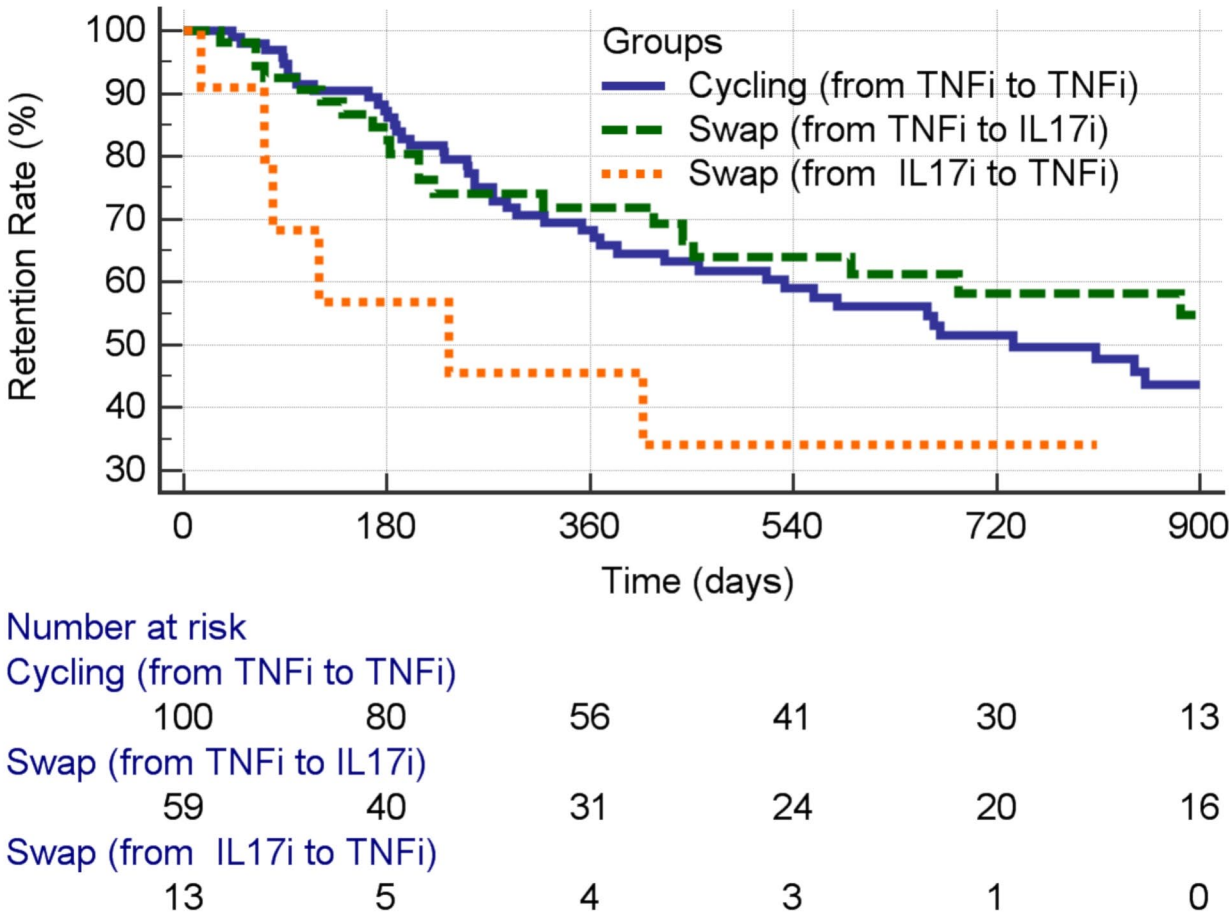

Fig. 1. Kaplan–Meier curve of the three strategy groups

Variable	HR	95% CI	p-value
Age*	**0.98**	**0.96–0.99**	0.003
Sex	0.68	0.53–1.50	nss
Disease duration	1.02	0.97–1.08	nss
Line of treatment	0.97	0.46–2.06	nss
Year of switch	**1.78**	**1.39–2.22**	< 0.0001
Swap strategy (from TNFi to IL17i) **	**0.53**	**0.31–0.89**	0.02
Swap strategy (from IL17i to TNFi) **	2.06	0.79–5.3	nss
Concomitant csDMARD	0.79	0.48–1-31	nss
DAPSA (baseline)	**1.11**	**1.08–1.13**	< 0.0001

Table 2. Cox analysis (stepwise) of variables influencing treatment retention rate. *For every 1-year increasing. **Compared to cycling strategy. Significant values are in [bold].

Discussion

The aim of this study was to better understand which is the best therapeutic choice in real-life PsA patients, after the failure of a bDMARD. The growing availability of bDMARDs/tsDMARDs with different MoAs makes this issue increasingly important for achieving a personalized therapy for patients as well as a careful management of economic resources[18]. Since 2016, IL17i represents the most common alternative MoA to TNFi[12]. Even if cycling and swapping are two strategies that can be used in clinical practice, there is little evidence supporting either of them.

It has been shown that in PsA the failure of one (or more) TNFi decreases the effectiveness of another TNFi. Data from the CORRONA registry highlighted that subjects treated with a second TNFi showed overall a lower retention rate, compared to naive patients[19]. A similar trend was also observed in the British Society for Rheumatology Biologics Registry and the DANBIO Registry, where a subsequent TNFi showed lower treatment persistence[20,21].

Results from insurance database comparing cycling (i.e. TNFi after TNFi failure) and swapping (i.e. another biologic after TNFi failure) strategies are conflicting and not conclusive. On the one hand, retrospective analysis showed that in patients suffering from chronic inflammatory diseases (including PsA) cycling and swapping were similar[22]. On the other, according to two national insurance registries, IL17i or IL12/23i appeared to be the best choice in PsA patients with TNFi failure[23,24].

Other registry-based studies did not show any advantage in changing MoAs[15,25], in particular, from the 4th line of advanced treatment[26].

Studies based on clinical practice provided a glimpse of some advantages in changing MoA[13]. For example, secukinumab was helpful in PsA patients previously exposed to one or two different classes of biologics (TNFis, IL12/23is)[27] and there was no difference in effectiveness between the first and subsequent lines[28].

In this practice-oriented study, we explored in more depth the possibility that the swap strategy (with IL17i and TNFi) provides some advantages compared to TNFi cycling. Regardless of the strategy, failure was mostly due to the lack and loss of efficacy. Adverse events were observed in few cases. The swapping of TNFi with IL17i emerged as a factor which increased the persistence as well as younger age and lower disease activity at baseline. As the majority of these swaps (from TNFi to IL17i) occurred in the 2nd and 3rd lines, it is plausible that this advantage is more relevant in these phases, but further studies are required to confirm this hypothesis. Year of switch was another factor influencing drug persistence. This finding can be linked to differences in disease activity at the start of the therapy, or to the adoption of new treatment strategy (such as the treat-to-target method), or to more therapeutic choices being available as time progressed[29].

Finally, our study did not allow to establish whether swapping from IL17i to TNFi was better that cycling TNF with TNFi because of the low number of patients in the SG2 subgroup.

In addition to the limitations related to the observational, retrospective and mono-centric nature of the study (e.g. the selection bias due to the enrollment of patients with complete data), there are other issues to consider. The same patient may have contributed to more than one group or more than once n in the same group. To slightly limit this bias, we took into account the number of therapy changes (i.e. the line of therapy). Although most of the switches were made in the second and third lines, in the swap groups almost 1/3 occurred from the fourth line onwards. Some patient characteristics, such as age or disease severity may have affected the MoA choice (i.e. cohort assignment). In order to decreased the impact of this bias, the Cox analysis encompassed some variables like age, disease duration and DAPSA). However it is still possible that some influent variable was neglected. We did not consider other factors which could influence therapy suspension such as smoking, obesity and the type of PsA. In particular, we did not record whether there was axial involvement. We recorded presence of HLAB27) but it was found in a few patients. However, it should be taken into account that both TNFi and IL17i are equally effective in axial PsA[30]. The reduced number of swaps from IL17i to TNFi derive from the Italian regional guidelines, which require starting with TNFi biosimilars whenever possible. Moreover, there are not records about why some patients started with IL17i rather than TNFi or the clinicians chose one MoA instead of the other. Finally, we considered the class effect, so findings are not attributable to individual molecules.

Conclusions

This study focused on a clinical unmet need, which is not properly covered by the leading recommendations in PsA management. Based on our results, we suggest that in real-world clinical practice PsA patients swapping from TNFi to IL17i might be more effective than cycling TNFis. On the other hand, the results of this study are not conclusive. Further studies should be encouraged to confirm our results.

Availability of data and materials

The dataset used during the current study is available from the corresponding author on reasonable request.

Received: 24 April 2024; Accepted: 3 October 2024
Published online: 22 October 2024

References

1. Coates, L. C. & Helliwell, P. S. Psoriatic arthritis: State of the art review. *Clin. Med. R. Coll. Phys.* **17**, 65–70 (2017).
2. da Silva, M. R. R., Santos Dos, J. B. R., Almeida, A. M., Guerra Júnior, A. A., Alvares Teodoro, J., & Acurcio F de, A. Biological therapy in the treatment of psoriatic arthritis: Economic and epidemiological considerations. *Expert Rev. Clin. Immunol.* **15**, 879–87 (2019).
3. Ruyssen-Witrand, A., Perry, R., Watkins, C., Braileanu, G., Kumar, G., & Kiri, S., et al. Efficacy and safety of biologics in psoriatic arthritis: A systematic literature review and network meta-analysis. *RMD Open BMJ Specialist J.* **6**, e001117 (2020).
4. Coates, L. C. et al. Group for research and assessment of psoriasis and psoriatic arthritis (GRAPPA): Updated treatment recommendations for psoriatic arthritis 2021. *Nat. Rev. Rheumatol.* **18**, 465–479 (2022).
5. Gossec, L., Baraliakos, X., Kerschbaumer, A., de Wit, M., McInnes, I., & Dougados, M., et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann. Rheum. Dis.* 700–712 (2020).
6. Marchesoni, A. et al. Recommendations for the use of biologics and other novel drugs in the treatment of psoriatic arthritis: 2017 update from the Italian Society of Rheumatology. *Clin. Exp. Rheumatol.* **35**, 991–1010 (2017).
7. Tucker, L. et al. The 2022 British Society for Rheumatology guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs. *Rheumatology (Oxford)* **61**, e255–e266 (2022).
8. Singh, J. A. et al. 2018 American college of rheumatology/national psoriasis foundation guideline for the treatment of psoriatic arthritis. *Arthritis Care Res.* **71**, 2–29 (2019).
9. McInnes, I. B. et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. *N. Engl. J. Med.* **384**, 1227–1239 (2021).
10. Mease, P. J. et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. *Ann. Rheum. Dis.* **79**, 123–131 (2020).
11. McInnes, I. B. et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. *Lancet* **395**, 1496–1505 (2020).
12. Perrone, V., Losi, S., Filippi, E., Sangiorgi, D. & Degli, E. L. Pattern of drug use in patients with psoriatic arthritis in Italy: Study in a real-world setting. *Expert Rev. Pharmacoecon Outcomes Res.* **21**, 721–727 (2021).
13. Ariani, A. et al. Cycling or swap biologics and small molecules in psoriatic arthritis: Observations from a real-life single center cohort. *Medicine (Baltimore)* **100**, e25300 (2021).
14. Takami, K. et al. Long-term retention rates of anti-tumour necrosis factor and anti-interleukin-17 antibodies for patients with psoriatic arthritis. *Mod. Rheumatol.* **34**, 1013–1018 (2023).
15. Guimarães, F., Ferreira, M., Soares, C., Parente, H., Matos, C. O., & Costa, R., et al. Cycling versus swapping strategies in psoriatic arthritis: Results from the rheumatic diseases Portuguese register. *ARP Rheumatol.* (2023).
16. Lorenzin, M. et al. Predictive factors for switching in patients with psoriatic arthritis undergoing anti-TNFα, anti-IL12/23, or anti-IL17 drugs: A 15-year monocentric real-life study. *Clin. Rheumatol.* **40**, 4569–4580 (2021).
17. Taylor, W. et al. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. *Arthritis Rheum.* **54**, 2665–2673 (2006).
18. Song, Y. et al. Economic burden of switching to different biologic therapies among tumor necrosis factor inhibitor-experienced patients with psoriatic arthritis. *Rheumatol. Ther.* **6**, 285–297 (2019).
19. Mease, P. J. et al. Discontinuation and switching patterns of tumour necrosis factor inhibitors (TNFis) in TNFi-naive and TNFi-experienced patients with psoriatic arthritis: An observational study from the US-based Corrona registry. *RMD Open* **5**, e000880 (2019).
20. Fagerli, K. M., Kearsley-Fleet, L., Watson, K. D., Packham, J., & Contributors Group, B-R, Symmons, D. P. M., et al. Long-term persistence of TNF-inhibitor treatment in patients with psoriatic arthritis. Data from the British Society for Rheumatology Biologics Register. RMD Open BMJ Specialist J. **4**, 596 (2018).
21. Glintborg, B. et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: Results from the Danish Nationwide DANBIO Registry. *Arthritis Rheum.* **65**, 1213–1223 (2013).
22. Asante, K., Racsa, P., Bloomfield, A., Cornett, D. & Schwab, P. Comparison of a second TNFi vs other biologic or targeted synthetic DMARD following an initial TNFi. *J. Manag. Care Spec. Pharm.* **29**, 1109–1118 (2023).
23. Oelke, K. R. et al. Persistence and adherence of biologics in US patients with psoriatic arthritis: Analyses from a claims database. *J. Comp. Eff. Res.* **8**, 607–621 (2019).
24. Pina Vegas, L., Hoisnard, L., Bastard, L., Sbidian, E., & Claudepierre, P. Long-term persistence of second-line biologics in psoriatic arthritis patients with prior TNF inhibitor exposure: A nationwide cohort study from the French health insurance database (SNDS). *RMD Open BMJ Specialist J.* **8**, e002681 (2022).
25. Walsh, J. A., Cai, Q., Lin, I., Pericone, C. D. & Chakravarty, S. D. Treatment persistence and adherence among patients with psoriatic arthritis who initiated targeted immune modulators in the US: A retrospective cohort study. *Adv. Ther.* **38**, 2353–2364 (2021).
26. Glintborg, B. et al. Uptake and effectiveness of newer biologic and targeted synthetic disease-modifying antirheumatic drugs in psoriatic arthritis: Results from five Nordic biologics registries. *Ann. Rheum. Dis.* **82**, 820–828 (2023).
27. Klavdianou, K. et al. Real life efficacy and safety of secukinumab in biologic-experienced patients with psoriatic arthritis. *Front. Med. (Lausanne)* **7**, 288 (2020).
28. Ramonda, R., Lorenzin, M., Carriero, A., Chimenti, M. S., Scarpa, R., & Marchesoni, A., et al. Effectiveness and safety of secukinumab in 608 patients with psoriatic arthritis in real life: A 24-month prospective, multicentre study. RMD Open BMJ Specialist J. **7**, e001519 (2021).
29. Becciolini, A. et al. bDMARDs retention rate in the biosimilar era: A real-life monocentric study. *Eur. J. Rheumatol.* **8**, 109 (2020).
30. Lubrano, E. et al. Management of axial disease in patients with psoriatic arthritis: An updated literature review informing the 2021 GRAPPA treatment recommendations. *J. Rheumatol.* **50**, 279–284 (2023).

Acknowledgements
We thank Dr Ottavio Secchi for the English revision.

Author contributions
F.L., D.G. and G.S. contributed to acquisition of data. A.A., A.M. and A.B. performed the statistical analysis. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Funding
None.

Declarations

Competing interests
A Ariani has received honoraria as a speaker and an advisory board member of Abbvie, Amgen, Bristol-Myers Squibb, Jannsen, Novartis and Sanofi. A Marchesoni has received honoraria from Abbvie, Eli Lilly, Janssen, Novartis, UCB None of the other authors have any potential conflicts of interest to disclose in relation to this work.

Ethics approval and consent to participate
This single-center, retrospective, observational study was approved by the local Ethics Committee (ref. 192/2021 - Comitato Etico Area Vasta Emilia Nord). All patients provided written informed consent.

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