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Cycling or swap biologics and small molecules in psoriatic arthritis

Observations from a real-life single center cohort

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Abstract

During the last years there has been an increasing availability of drugs (biologics and small molecules) with different mechanisms of action (MoA) in psoriatic arthritis (PsA). New issues about treatment strategies have arisen. The main aim of this study is to verify if there is a difference in terms of clinical efficacy (i.e. retention rate) between cycling (i.e. treating patients with the same MoA after the failure of the previous one) or swap (i.e choosing drugs with a MoA different from the failed previous one) strategies in PsA.

In this mono-centric medical records review study, PsA patients treated with biologics, apremilast or tofacitinib were enrolled. Every prescription was clustered in three groups: cycling (CG), swap (SG) or first line group (1LG). Kaplan-Meier analysis and Cox test estimated and compared drugs' retention rate in CG, SG and 1LG. $P < .05$ was considered statistically significant.

One hundred eighty-three PsA patients were enrolled (9967 patient-months). In CG and 1LG the more prescribed drugs were tumor necrosis factor inhibitor (respectively 99% and 89%), in SG interleukin 17 inhibitor (60%). There were no differences in terms of sex, age, disease duration, and retention rate between CG and SG. The 18-months retention rate of 1LG, SG and CG was 77%, 60%, and 51% respectively. The CG retention rate was lower than in 1LG ($P = .03$).

The findings of this study suggest that in PsA the swap strategy gives no remarkable advantage compared to cycling. However, patients undergoing swap strategy may experience the same failure rate observed in naives.

Abbreviations: 1LG = first line group, bDMARD = biologic disease modifying anti-rheumatic drug, CG = cycling group, IL = interleukin, MoA = mechanisms of action, nss = not statistically significant, PsA = psoriatic arthritis, SG = swap group, TNFi = tumor necrosis factor inhibitor, tsDMARD = targeted synthetic disease modifying anti rheumatic drugs.

Keywords: biological products, psoriatic arthritis, therapeutics, treatment outcome

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Key points

- The increasing availability of new drugs (biologics and small molecules) increases the possible treatment strategies in PsA.
- The main strategies are cycling and swap, using drugs with either the same or different MoA after the failure of the previous one).
- In this study, swap strategy was not more remarkably favorable respect to cycling.

1. Introduction

During the last twenty years the treatment of psoriatic arthritis (PsA) has dramatically improved with the introduction of biologic disease modifying anti-rheumatic drugs (bDMARDs).[1,2] Up to 5 years ago, the only bDMARDs were tumor necrosis factor alfa inhibitors (TNFis): infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol. The subsequent introduction of inhibitors of interleukin (IL) 12/23 (ustekinumab), IL17 (secukinumab, ixekizumab) and cytotoxic T-lymphocyte antigen 4 (abatacept), as well as new small molecules, the targeted synthetic disease modifying anti rheumatic drugs (tsDMARDs), such as apremilast and tofacitinib, has extended the number of therapeutic

agents granting the access to drugs with different mechanisms of action (MoA).[3,4]

Both bDMARDs and tsDMARDs have showed a comparable efficacy and safety in the treatment of psoriatic arthritis. According to the most recent recommendations TNFis should be used in routine clinical practice. However, IL-12/23- or IL-17-inhibitors or tsDMARDs may be used as first line treatment.[5–8] On the other hand, the management of a first line bDMARD failure may consist in switching to a second bDMARD with a similar (i.e. cycling) or a different (swap) MoA.[9]

As there are not definitive evidences about the best strategy after a bDMARDs or tsDMARDs failure in PsA, European League against Rheumatism, and American College of Rheumatology recommendations do not suggest any specific treatment path.[5,6] In particular, the choice between cycling and swap has never been explored.

The main aim of this paper is to investigate the more effective strategy for real-life PsA patients, either cycling or swap.

2. Methods

This medical records review study was carried out following the Declaration of Helsinki principles and approved by local Ethic Committee (PROT 34713).

2.1. Patients

We included all peripheral PsA patients aged >17, treated with bDMARDs or tsDMARDs between January 2004 and July 2019 in our Rheumatology Unit. All patients provided written and informed consent.

2.2. Effectiveness evaluation

The retention rate estimates drugs' efficacy, so each patient underwent a meticulous pharmacological anamnesis. In particular, for every drug we recorded: treatment duration (time interval between the first and last prescription), disease duration (from the prescription onwards), line, and suspension reason, if applicable. bDMARDs and tsDMARDs were gathered according their MoA: TNFi (golimumab, certolizumab pegol, etanercept, adalimumab, infliximab and their biosimilars), inhibitors of IL12/23 (ustekinumab), IL17 (secukinumab, ixekizumab), cytotoxic T-lymphocyte antigen 4 (abatacept) and the two small molecules (apremilast and tofacitinib). Each prescription was clustered considering the previous one: if they had the same MoA, it was included in the cycling group (CG); otherwise it was added to the swap group (SG). Baseline prescriptions made up the First line Group (1LG).

2.3. Statistical analysis

Descriptive variables were reported as median value with its 95% confidence interval. Chi-squared and Kruskal-Wallis tests investigated the differences between CG, SG, and 1LG, as appropriate. Kaplan-Meier estimator tested the groups' effectiveness; Cox proportional hazards model identified factors associated with treatment discontinuation. $P<.05$ was considered statistically significant.

3. Results

One hundred eighty-three (183) patients (9967 patient-months) were enrolled. On the whole, they received 322 prescriptions. We chose the cycling and swap strategies, respectively 87 and 52 times. The characteristics of the above mentioned groups are listed in Table 1.

The disease duration observed in SG and CG was similar, and, as expected, higher than in 1LG. The main reason of discontinuation was the loss of response over time in all groups.

In CG and 1LG we included almost all TNFis (respectively 86/87 and 163/183); in SG IL17- inhibitors were the most recurrent ones (31/52).

The Kaplan-Meier estimator does not show any significant difference between SG vs CG (HR 0.95, 95% CI 0.52-1.74) and between SG vs 1LG (HR 1.45, 95%CI 0.83–2.52). Retention rate in CG was lower than in 1LG (HR 1.52, 95%CI 1.05–2.20 $P=.03$) (Fig. 1). None of the covariates (age, sex, disease duration, change of MoA, line of treatment and drug prescribed) were retained in the Cox proportional hazards model.

4. Discussion

As far as we know this is the first study comparing the cycling and swap strategies in a real-life cohort of PsA patients. The increasing availability of drugs bDMARDs and tsDMARDs with different MoA makes this issue more and more preeminent as times goes by.

Recommendations do not face this point yet.[6–8] So, medical records review studies on real-life PsA patients can help to outline some preliminary answers. In our cohort, we did not observe any statistical difference between cycling and swap strategies.

However, the swap strategy shows an effectiveness not dissimilar to that one observed in the first line group. It is therefore possible that the MoA change can bring some minimal improvement in treatment effectiveness.

It is remarkable that there was a predominance of TNFis in CG (99%). This suggests that TNFi cycling could be less effective than swap to another MoA. Moreover, we observed that first line treatment is the most effective one. This finding, considering the high TNFi prevalence in 1LG (89%), is consistent with other studies. In particular, data from the Corrona registry pointed out that patients treated with a second TNFi showed an overall lower retention rate when compared to TNFi-naive.[10] A similar trend was observed in the British Society for Rheumatology Biologics Register and in the DANBIO registry, where subsequent TNFi lines showed a lower treatment persistence.[11,12]

Our analysis presents all the typical limitations of the medical records review studies. Furthermore, other limits must be taken into consideration. Firstly, the SG group is not homogeneous because it includes drugs with very different MoA. The impact of a specific MoA on the retention rate of the next treatment was not investigated for the small number of observations. Moreover, due to prescriptive limitations, we used apremilast only as first-line treatment. During the observation period (from 2004 to 2019) disease activity was not assessed with the same score, so it is not possible to verify if this issue could have affected the results. However, all treatments with bDMARDs or tsDMARDs were prescribed only in patients with a high grade of disease activity according to clinical opinion. For the same reason, it was not possible to analyze the predictive value of disease activity (in combination with gender, sex, smoke, concurrent conventional synthetic disease modifying anti rheumatic drugs therapy, psoriasis activity and comorbidities) as other Authors did in prospective studies.[13,14] Finally, the therapeutic possibilities' increasing in PsA and the pushing objectives to achieve through

Table 1

First line, cycling, and swap groups' characteristics (Other reasons of drug interruption are: pregnancy, remission or lost at follow-up).

	1st Line Treatment Group (1LG)	Cycling Group (CG)	Swap Group (SG)	*P*-value
N	183	87	52	–
Sex (M:F)	97:86	35:52	23:29	.57
Age, median (CI95%); yr	52 (49–54)	55 (53–58)	55 (50–57)	.61
Disease duration, median (CI95%); mo	48 (38–62)	96 (64–117)	112 (65–152)	1LG vs CG 1LG vs SG ($P<.01$)
Line of treatment, IQR	1–1	2–3	2–4	–
Failure				
Loss of response over time; %	11,5	36,8	23,1	1LG vs CG ($P<.001$) 1LG vs SG ($P=.04$)
Lack of response; %	2,7	2,3	1,9	.96
Adverse event; %	4,4	4,6	5,8	.94
Other reason; %	10,9	6,9	5,8	.91
TNF inhibitors				
Infliximab, %	13.7	13	6	–
Etanercept, %	28.9	32	6	–
Adalimumab, %	41.5	31	0	–
Golimumab, %	3.3	10	4	–
Certolizumab, %	1.6	13	2	–
IL 12/23 inhibitors				
Ustekinumab, %	0.6	0	12	–
IL17 inhibitors				
Secukinumab, %	3.8	0	60	–
Ixekizumab, %	0	1	0	–
CTLA4 inhibitors				
Abatacept, %	0	0	2	–
tsDMARDs				
Apremilast, %	6.6	0	4	–
Tofacitinib, %	0	0	4	–

CI95% = 95% interval of confidence, CTLA4 = cytotoxic T-lymphocyte antigen 4, IL = interleukin, IQR = inter-Quantile Range, nss = not statistically significant, TNF = tumor necrosis factor.

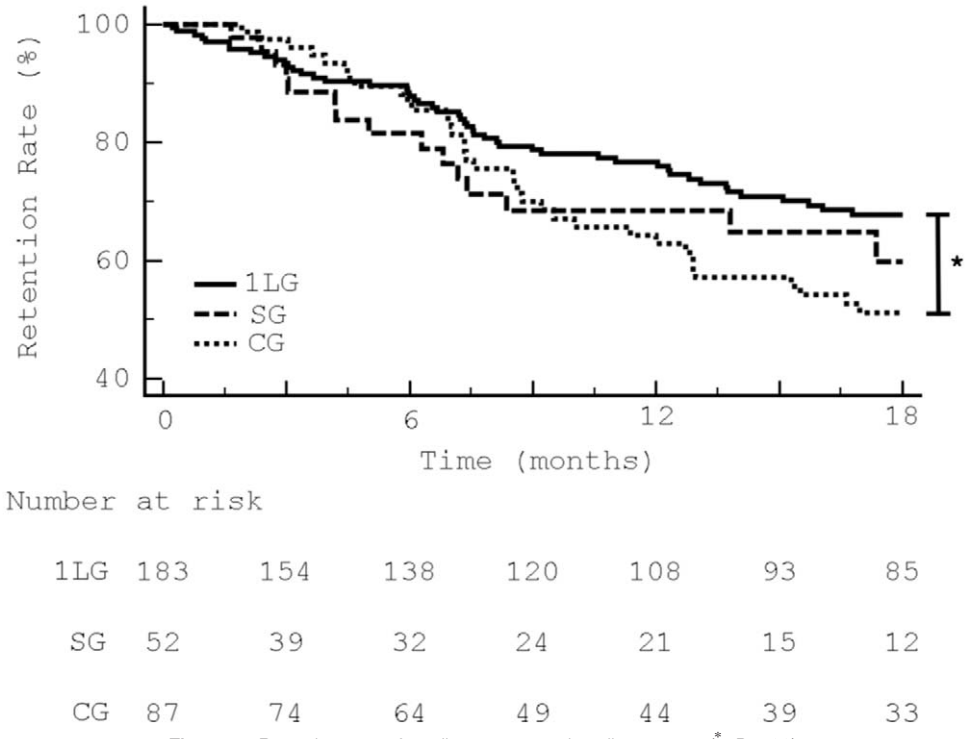

Figure 1. Retention rate of 1st line, swap, and cycling groups (*: $P=.03$).

"treat-to-target" strategies, may have had an influence on prescriptive attitudes.[15]

In conclusion, we observed that, even if swap strategy is slightly better than cycling, none of them brings about remarkably advantages in PsA treatment.

Author contributions

AA and AB designed the study. All the Authors collected data. AA and AB analyzed the data. AA wrote the paper with input from all authors.

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