Cycling versus swapping strategies in psoriatic arthritis: results from the rheumatic diseases Portuguese register

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Abstract

Objective: To compare the 2-year retention rate between a second tumor necrosis factor alpha inhibitor (TNFi) and secukinumab (SEK) or ustekinumab (UST), in Psoriatic Arthritis (PsA) patients with previous inadequate response to their first TNFi.

Methods: Prospective longitudinal cohort study with a follow-up period of 2 years using the Nationwide Portuguese Reuma.pt database. Patients with a clinical diagnosis of PsA who also fulfill the CASPAR classification criteria, with previous treatment failure to a first-line TNFi and having started a second biotechnological drug (TNFi, SEK or UST) were included. The Cycling group was defined as switching from a first TNFi to a second TNFi, and the Swapping group as switching from a first TNFi to SEK or UST. Sociodemographic data, disease characteristics, disease activity scores and physical function at baseline and after 6, 12 and 24 months were recorded. Cox-proportional hazards regression was used to compare retention rates between Cycling and Swapping groups. To obtain a predictor model of 2-year discontinuation, a multivariable Cox regression model was performed.

Results: In total, 439 patients were included, 58% were female, with a mean age (standard deviation) of 49 (12) years. Globally, 75.6% initiated a second TNFi (Cycling group), and 24.4% started SEK/UST (Swapping group). The retention rates after 6, 12 and 24 months were 72%/66%/59% in the Cycling group; and 77%/66%/59% in the Swapping group. There were no significant differences in retention rates between both strategies (HR: 1.06, 95% CI 0.72-1.16). After 2 years of follow-up, 34.4% of patients discontinued their second biologic, mainly due to inefficacy (72.8%), with no differences found between groups. Baseline treatment with glucocorticoids was the only predictor of discontinuation after 2 years of follow-up (HR:1.668, 95% CI 1.154-2.409).

Conclusions: After failure of a first TNF inhibitor, Cycling and Swapping strategies result in similar retention rates suggesting that both are acceptable in the management of patients with psoriatic arthritis.

Keywords: Inflammation; Biological therapies; DMARDs; Spondyloarthropathies (including psoriatic arthritis); Spondylarthritis.

Background

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory rheumatic disease characterized by a wide spectrum of articular and extra-articular manifestations, such as peripheral arthritis, spondylitis, enthesitis, dactylitis, psoriasis and uveitis[1]. This heterogeneity may explain the difficulty in the therapeutic approach and follow-up of these patients.

Treatment options for PsA have considerably changed in the last decades, and tumor necrosis factor alpha inhibitors (TNFi) dramatically improved the treatment of PsA[2,3]. However, a significant proportion of patients have an inadequate response and/or are intolerant to a first TNFi, requiring drug discontinuation and switching to other treatment options[2,4]. In fact, a recent Portuguese study based on the Rheumatic Diseases Portuguese Register (Reuma.pt) showed that more than one-third of the patients discontinued a first TNFi due to ineffectiveness or adverse event5. In the previous years, multiple treatments, with different modes of action (MoA), such as IL-176, IL-12/237, Janus Kinases (JAKS)8 and phosphodiesterase 4 inhibitors[9], were approved to be used in PsA patients, either in biologic naïve or experienced patients. As a result, the pharmacological armamentarium in PsA has increased as for the complexity of managing PsA patients regarding the number of drugs available and the lack of comparison studies.

Recent international guidelines stated that after an inadequate response to a first TNFi, in order to achieve a state of minimal disease activity in a treat-to-target strategy, the patient may receive a second TNFi (Cycling strategy) or a drug with a different MoA (Swapping strategy), depending on the clinical manifestations[10]. Several studies have shown the effectiveness of switching to a second TNFi, even though, generally the treatment response and drug survival significantly decreased[5,11–16]. Additionally, switching to a different MoA has also shown to be effective[6–8,17,18]. However, data about the comparative effectiveness of different switching strategies (Cycling versus Swapping) in daily clinical practice are scarce. While the 2018 ACR/NPF guidelines recommend switching from a first TNFi to a second TNFi, prior to switching to a different MoA19, the 2019 EULAR guidelines consider that there is a lack of evidence to prefer one strategy over another[10], placing this question on the research agenda.

A recently published head-to-head trial comparing secukinumab with adalimumab (EXCEED) reported similar efficacy on treatment response, nonetheless suggesting higher

retention rates for secukinumab[20]. However, patient populations in clinical trials are highly selected, and so there is a need for real-world evidence (RWE). A systematic literature review suggests that Swapping strategy may be superior, although it was mainly based on expert opinion[21]. Yet, a recent multicentric retrospective study found no significant difference in treatment retention or response between secukinumab and adalimumab, suggesting that both strategies may be equally effective after a first TNFi failure[22]. Nevertheless, the follow-up time was short (12 months) and did not consider the extra-articular manifestations and PsA subtypes. RWE on this matter is also limited.

Reuma.pt provides an excellent source of RWE on this subject that has not been studied so far. In Portugal, the most frequently used drugs after TNFi failure are a second TNFi, secukinumab and ustekinumab, depending on the clinical presentation. Although tofacitinib has also been recently approved for PsA patients, there are few Portuguese PsA patients on this treatment, thus being excluded from this endeavor. Also, although approved for PsA, the implementation of apremilast and abatacept in Portugal is scarce, so they will also not be included in this study.

The primary objective of this study was to compare the effectiveness of a second TNFi versus switching to secukinumab or ustekinumab, measured by retention rates during 2 years of follow-up, in PsA patients with previous inadequate response to their first TNFi. Secondly, we aimed to compare the remission rates of the patients who remained on secukinumab/ustekinumab, or a second TNFi after 6, 12 and 24 months of treatment; and finally, to describe the frequency and reasons for treatment discontinuation and predictors thereof.

Material and methods

Study design and population

Prospective longitudinal cohort study, with a 2-year period of follow-up, using real-world anonymous patient-level data from the Reuma.pt Portuguese nationwide database. Reuma.pt (www.reuma.pt), became active in 2008 and includes patients with varied rheumatic diseases[23,24]. Adult patients with a clinical diagnosis of PsA who also fulfill the CASPAR classification criteria with a previous treatment failure to a first-line TNFi and who started a second biotechnological (TNFi or secukinumab/ustekinumab) treatment were included.

Data collection

Sociodemographic data [(gender, age, ethnicity), comorbidities (smoking habit, alcohol consumption, hypertension, dyslipidemia, diabetes), body mass index (BMI)], disease characteristics [age of diagnosis, type of involvement (axial, peripheral and both axial and peripheral), extra-articular manifestations (enthesitis, dactylitis, uveitis, psoriasis, inflammatory bowel disease - IBD)], and concomitant treatment (nonsteroidal anti-inflammatory drugs - NSAIDs -, glucocorticoids, methotrexate, sulfasalazine and leflunomide) were assessed at baseline.

Disease activity scores [tender joint count (TJC68); swollen joint count (SJC66); patient global/pain visual analogue scales (VAS); physician VAS; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); Disease Activity Index for Psoriatic Arthritis (DAPSA) and Disease activity score-28 4 variables-CRP (DAS-28 4vCRP) for peripheral disease; Ankylosing Spondylitis (AS) Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for axial disease; Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), psoriasis VAS; number of fingers with dactylitis] and physical function scores [Health Assessment Questionnaire (HAQ) for peripheral disease and Bath Ankylosing Spondylitis Functional Index (BASFI)] were collected at baseline and after 6, 12 and 24 months of follow-up. The discontinuation date and reasons for discontinuation were also recorded.

Data was extracted from the Reuma.pt database on the 2nd of august 2022.

The cycling group was defined as switching from a first TNFi to a second TNFi, excluding changes between original biologic to a biosimilar. The swapping group was defined as switching from a first TNFi to a biologic with a different MoA (secukinumab or ustekinumab).

Follow-up occurred at 4 different timepoints: baseline, 6, 12 and 24 months. Baseline was defined as the starting date of the second biologic. Drug retention was defined as the time until treatment discontinuation, such as: the end of treatment registered by the physician; occurrence of any switch to a different biologic (excluding switching from an original drug to a biosimilar) or 90-day continuous gap of treatment without a posterior biological treatment. Temporary discontinuations (less than 90 days), after which the patient resumed the same biological agent, were considered as continuous use of the drug.

Remission was defined as DAPSA ≤4 or DAS-28 4vCRP ≤2.6, for peripheral disease; and ASDAS <1.3 or BASDAI <4, for axial disease.

Drug discontinuation due to inefficacy was defined as a primary or secondary failure if occurring during the first or after 6 months, respectively.

Statistical analysis

Continuous data were presented as mean (standard deviation) for normally distributed data or median (interquartile range) for variables with skewed distribution, and categorical variables as absolute number/percentage. Univariate analysis was performed using Chi-square/Fisher exact tests for comparisons of categorical variables and Student's t-test or One Way-ANOVA/Mann-Whitney U test for comparisons between categorical and continuous variables with/without normal distribution, respectively.

Persistence of TNFi and secukinumab/ustekinumab was estimated using Kaplan-Meier analysis, where follow-up time was measured as time in months from initiation of each therapy until discontinuation/ switch of therapy and last follow-up visit up to 2 years. Univariable Cox-proportional hazards regression was used to compare retention rates between Cycling and Swapping groups. A multivariable analysis was used to adjust for the following confounders: age, gender, number of comorbidities, reason for discontinuation of the first TNFi, extra-musculoskeletal manifestations (EMM), such as skin and nail psoriasis, uveitis, and IBD, baseline methotrexate, baseline glucocorticoids and baseline DAPSA.

Reasons for discontinuing therapy were summarized using descriptive statistics and stratified by the treatment.

To obtain a predictor model of discontinuation, a multivariable Cox regression analysis was used, including variables of interest such as age and gender, together with variables with a p-value <0.20 in the univariable analysis. This univariable analysis included the following variables: type of involvement, baseline glucocorticoids, smoking history, baseline DAS-28 4vCRP, baseline DAPSA, baseline ASDAS-CRP, baseline BASDAI, reason of discontinuation of the first TNFi. Collinear variables were excluded. Thereafter, variables losing significance or with a high number of missing data were excluded stepwise.

Baseline DAS-28 4vCRP and ASDAS-CRP and after 6, 12 and 24 months of treatment were compared according to the biologic class using the Chi-square test for categorical variables and T-student or Mann-Whitney tests for continuous variables.

The proportion of patients achieving remission, after 6, 12 and 24 months, was evaluated. LUNDEX adjustment, in which the fraction of responders is multiplied by the fraction of patients remaining in the study, was used to account for the fraction of patients discontinuing the treatment.

The SPSS v25 was used to analyze the data collected from this study. P-value was considered significant at <0.05.

Ethical considerations

This study was conducted according to the Declaration of Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies. This study received approval from the Coordinator and Scientific Board of Reuma.pt and the Unidade Local de Saúde do Alto Minho Health Ethics Committee (Nº62/2021).

Results

A total of 439 patients with PsA who discontinued a first TNFi (Supplementary Table I) were included, with a mean disease duration until the use of the second biologic of 8.5 ± 7.5 years. 58.1% were female, with a mean age of 49.4 ± 11.6 years old.

The main reason for discontinuation of the first TNFi was ineffectiveness (73.1%), mainly secondary (82.2%), followed by the occurrence of an adverse event (17.8%). The remaining patients discontinued due to other reasons (pregnancy, refusal of treatment, surgery). After the first TNFi discontinuation, 332 (76.6%) initiated a second TNFi and 107 (24.4%) a drug with a different MoA (68 secukinumab and 39 ustekinumab). Considering the second TNFi, adalimumab was started in 149 (44.9%) patients, etanercept in 102 (30.7%), golimumab in 39 (11.4%), infliximab in 39 (8.7%), and certolizumab in 13 (3.9%) patients (Supplementary Table I). About half of the patients (48.1%) were also on concomitant methotrexate. The patient and

disease characteristics at baseline are described in Table I. There are some differences in characteristics between groups at baseline: patients from the Cycling group were younger at diagnosis (40.1 ± 12.1 *VS* 44.6 ± 12.3, *p*=0.003), had a higher number of comorbidities (0.9 ± 0.1 *VS* 0.4 ± 0.1, *p*<0.001), longer disease duration (9.0 ± 7.5 *VS* 6.8 ± 7.2, *p*=0.028), lower prevalence of isolated spondylitis (4.0% *VS* 9.9%, *p*=0.031), and were more frequently co-medicated with methotrexate (53.2% *VS* 32.4%, *p*<0.001) and glucocorticoids at baseline (38.5% *VS* 24.0%, *p*=0.010). Disease activity according to DAPSA, DAS-28 4vCRP (and their components); ASDAS, BASDAI, but also MASES and physical function are described in Table I.

Drug retention

The overall cohort retention rates at 6, 12 and 24 months of follow-up were 73%, 66% and 59%, respectively. After 6 months of starting a second TNFi (cycling group), 72% of the patients maintained the same treatment, decreasing to 66% and 59% after 12 and 24 months, respectively. In the Swapping group, the retention rates at 6, 12 and 24 months of follow-up were 77%, 66% and 59%, respectively.

During the first 2 years, the overall mean drug retention of the second biologic was 18.7 ± 0.4 (95% CI 17.3-19.5) months. There were no significant differences in drug retention rates between Cycling and Swapping groups (HR: 1.06, 95% CI 0.72-1.16). Even after adjustment for possible confounders, such as age, gender, number of comorbidities, reason for discontinuation of the first TNFi, EMM, baseline methotrexate and glucocorticoids and baseline DAPSA, there were still no differences between both groups (HR: 1.28, 95% CI 0.61-2.71 p=0.52) (Figure 1A and 1B).

Reasons for drug discontinuation

From the initial 439 patients, 151 (34.4%) discontinued their second biologic in the first 2 years of follow-up. The proportion of patients discontinuing therapy in the Cycling and Swapping group was 35.2% and 31.8% (RR=1.11, 95%CI 0.81-1.52). The main reason for discontinuation was inefficacy (72.8%), mainly secondary (68.8%), in both groups (Supplementary Table II). There were no differences regarding the reason for second drug discontinuation, yet, there was a non-significant higher proportion of patients discontinuing their second drug due to primary inefficacy in the Cycling group (34.9% VS 16.6%, p=0.11).

Yet, as expected, in a subgroup analysis considering only patients who withdrawn their first TNFi due to inefficacy, there was a significant higher proportion of patients discontinuing their second drug due to primary inefficacy in the Cycling group (24% VS 4.5%, p=0.04)

Predictors of drug discontinuation

In the univariable analysis, there were some factors associated with a higher risk of discontinuation after 2 years of follow-up, namely the use of glucocorticoids at baseline (HR 1.60 95% CI 1.56-2.215), higher baseline ASDAS-CRP (HR 1.33 95% CI 1.03-1.74) and baseline BASDAI (HR 1.16 95%CI 1.01-1.34). In addition, gender, type of involvement, smoking history, baseline DAS-28 4vCRP and DAPSA, and reason for discontinuation of the first TNFi presented a *p*-value <0.20 in the univariate analysis and thus were also included in the multivariate Cox Regression model. After excluding variables, that lost statistical significance or presented a high number of missing data, the final multivariable model included the following variables age, gender, therapeutic group, type of involvement and use of baseline glucocorticoids, where only treatment with glucocorticoids was found to be an independent predictor of discontinuation (HR 1.67 95% CI 1.15-2.41) (Table II).

Remission rates

Considering patients with peripheral disease, the proportion of patients in remission according to DAS-28 4vCRP at 6, 12 and 24 months were, respectively, 42.2%/50.0%/60.0% in the Cycling group, and 46.2%/52.9%/63.5% in the Swapping group. After LUNDEX adjustment, remission rates were, respectively, 30.8%/33.0%/35.4% in the Cycling group and 34.0%/33.0%/34.0% in the Swapping group (Figure 2A).

CRUDE and LUNDEX adjusted remission rates according to ASDAS-PCR after 6, 12 and 24 months, in patients with axial disease were 25.7%/20.7%/30.0% and 18.3%/13.7%/17.7% for the Cycling group, respectively; and 0.0%/20.0%/20.0% and 0.0%/10.8%/10.0% for the Swapping group, respectively (Figure 2B).

There were no significant differences in the remission rates between Cycling and Swapping strategies (Figure 2).

Discussion

Drug persistence has been widely used in real-world studies to compare biological drug performance. It represents a composite measure of overall effectiveness, safety, tolerability and global satisfaction with a specific treatment. In this cohort, the overall treatment retention rates after 6, 12 and 24 months of follow-up were 73%, 66% and 59%, respectively, similar to what has been reported in other studies[22,25,26].

While several studies on comparative effectiveness between Cycling and Swapping strategies in rheumatoid arthritis favoured the Swapping strategy after a first TNFi failure, in PsA this data is scarce and controversial. In our cohort, the 2-year retention rates were similar between both strategies, even after adjustment for possible confounders, suggesting that Cycling and Swapping strategies are both acceptable in patients with psoriatic arthritis after a first TNFi. Data from the five Nordic countries registers (DANBIO, ROB-FIN, ICE-BIO, NOR-DMARD and ARTIS/SRQ) also reported similar retention rates between second-line secukinumab and adalimumab, with a 1-year retention rate of 64% and 66% for adalimumab and secukinumab, respectively. Cohort characteristics were similar to ours, except for higher use of methotrexate in both groups in our study[22]. Zhan *et al.*, using an American retrospective cohort, reported similar effectiveness between TNFi, secukinumab and ustekinumab in biologic-experienced patients, but lower for apremilast[27]. Additionally, a network meta-analysis using randomized controlled trials reported similar ACR responses in a biologic-experienced population, except for certolizumab which showed superiority compared to ustekinumab[20]. Yet, there are conflicting data on this subject. In fact, a recent review from Merola *et al.* highlighted that Cycling can be effective for many patients, but Swapping strategy may be a better therapeutic strategy[28]. Also, a real-work study from the Israeli national registry reported higher retention rates for secukinumab compared to TNFi, in biologic-experienced patients[29]. However, in this study, the patient's characteristics are slightly different from our cohort, with a higher prevalence of axial disease, enthesitis and methotrexate use. Also, they reported statistical differences between secukinumab and TNFi patient's characteristics concerning the type of involvement and EMM, which might influence the results. On the contrary, Merola *et al.* reported a higher 5-year retention rate for TNFi than ustekinumab and secukinumab[25]. Also, Geale K *et al.* reported higher persistence of ustekinumab compared to TNFi and secukinumab in biologic-experienced patients[30].

Psoriatic arthritis is a highly heterogeneous disease, which may explain the differences found across studies. In fact, most authors pointed out the importance of evaluating the comparative effectiveness in specific subgroups of patients, to find the best drug for a specific patient.

In this cohort, the main reason for discontinuing the second bDMARD was inefficacy (72.8%), followed by adverse events (15.2%), as previously reported. However, other studies reported a higher proportion of adverse events (24-35%) and lower inefficacy (49-61%)22,29. We found no differences between Cycling and Swapping strategies regarding the reason for discontinuation. Yet, a higher proportion of patients in the Cycling group discontinued the second bDMARD due to primary inefficacy, as expected, since several studies showed lower effectiveness of a second TNFi after a first TNF failure[5,31].

Baseline glucocorticoids was the only predictor of discontinuation after 2 years of the second biologic, even when including activity scores in the prediction model. Since glucocorticoids are usually reserved for patients with peripheral disease activity, allowing earlier control of inflammation while waiting for bDMARDs' effectiveness, we might question whether this result may actually represent a "masked" higher disease activity.

Overall, the proportion of patients achieving remission after 6 months was 43% and 22% for peripheral and axial disease, respectively, decreasing to 31.8% and 14.8%, after LUNDEX adjustment. These results are higher than the ones reported (10-15% CRUDE *VS* 8-9% LUNDEX adjusted) by Lindström *et al.*[22]. Some differences exist between studies, namely the different activity scores used to evaluate disease activity (DAS-28 4vCRP VS DAPSA) and the fact that our study separates peripheral and axial disease, contrary to Lindström *et al*.

This study presents some limitations. As with other real-world studies, the number of missing data is greater than in clinical trials. This has limited our predictor model of discontinuation and the analysis regarding CRUDE and LUNDEX adjusted remission rates due to the high number of missing information regarding DAPSA, DAS-28 4vCRP, ASDAS-CRP and BASDAI at baseline and during the follow-up. Additionally, this study does not account for the severity of some of the EMM, such as psoriasis and dactylitis which are important confounders[31]. The unbalanced size between the Cycling and Swapping groups and the number of missing data constrained a reliable subgroup analysis concerning type of involvement, which would be an additional data on this subject, giving the heterogenous nature of PsA. Also, there was a small

number of patients on ustekinumab, which may be due to constrains on its prescription to patients with isolated peripheral disease, regarding its lack of effectiveness on axial disease. This has limited our analysis, making it impossible to perform a three-group analysis, one for each different drug.

Notwithstanding, this study has several strengths. It represents a real-world study on a subject where literature is controversial, adding knowledge on comparative effectiveness between Cycling and Swapping strategies after a first TNF. Finally, this is the first national study comparing treatment strategies in PsA, which could guide future studies on this matter, with longer follow-up, individualized analysis by each drug, and including newer drugs, such as JAKi.

More real-world studies, with larger cohorts and longer follow-up on newer drugs, are needed to confirm these results. Also, subgroup analysis concerning EMM, namely dactylitis and enthesitis, is needed, to provide knowledge and allow personalized switching strategies in PsA patients.

Conclusion

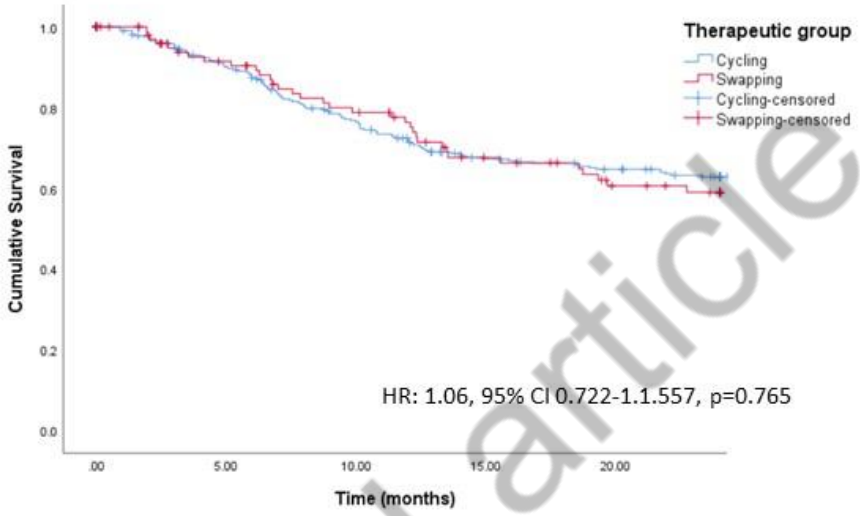
In conclusion, our study has not found any difference in the 2-year retention rates between a second TNFi and ustekinumab or secukinumab, after a first TNFi failure in PsA patients. The main reason for discontinuation of the second biologic DMARD is inefficacy, mainly secondary. Baseline use of glucocorticoids is an independent predictor of discontinuation of the second biologic DMARD.

Our study suggests that Cycling and Swapping strategies are both acceptable in PsA patients after a first TNFi failure, although other domains of PsA may influence the decision of the second biologic DMARD.

Tables and Figures

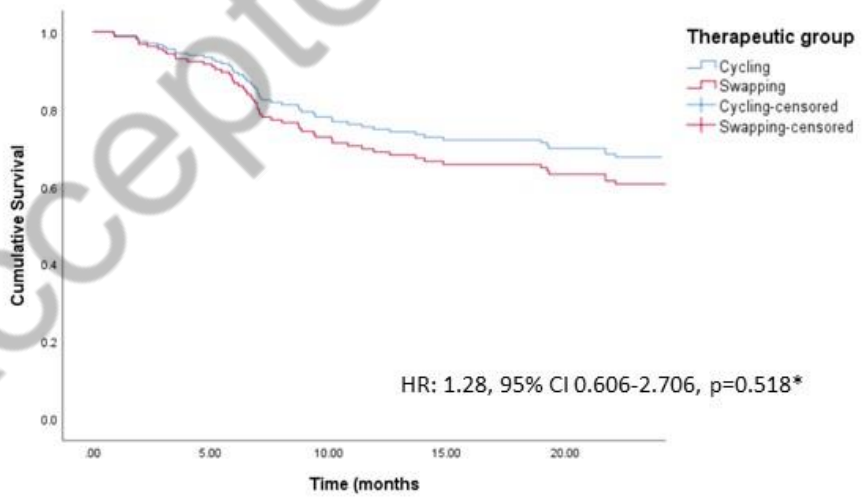
Figure 1. Comparison of the retention rates between Cycling and Swapping strategies. 1A. Non-adjusted analysis. 1B. Adjustment for possible confounders *age, gender, number of comorbidities, reason for discontinuation of the first TNFi, EEM, baseline MTX, baseline glucocorticoids, baseline DAPSA.

1A



Months	0	6	12	24
Cycling	331	267	210	165
Swapping	107	79	62	36

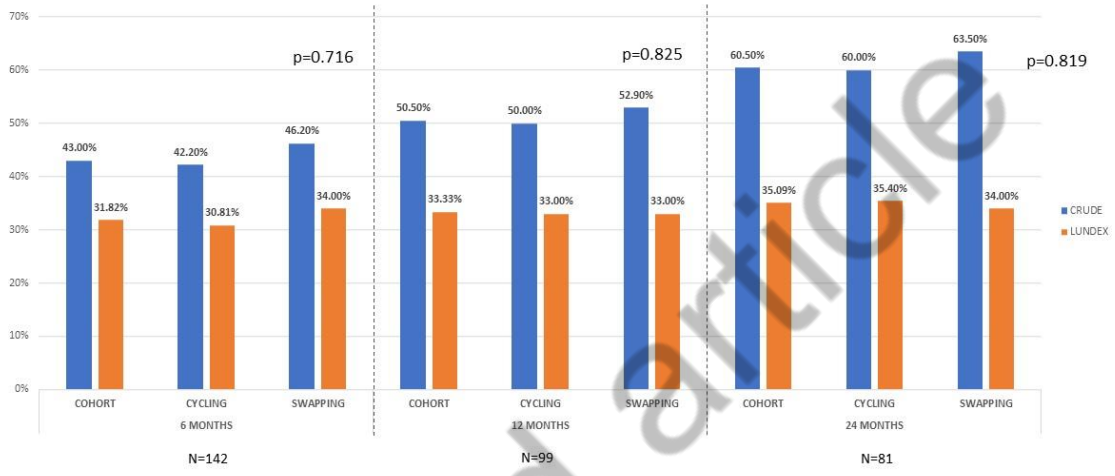
1B



Months	0	6	12	24
Cycling	131	107	84	69
Swapping	29	23	18	14

Figure 2. CRUDE and LUNDEX adjusted remission rates after 6,12 and 24 months, according to DAS-4v-CRP in peripheral disease (2A) and the ASDAS-CRP in axial disease (2B)

2A. Proportion of patients with PERIPHERAL INVOLVEMENT in remission according to DAS-4V-CRP



2B. Proportion of patients with AXIAL INVOLVEMENT in remission according to ASDAS-CRP

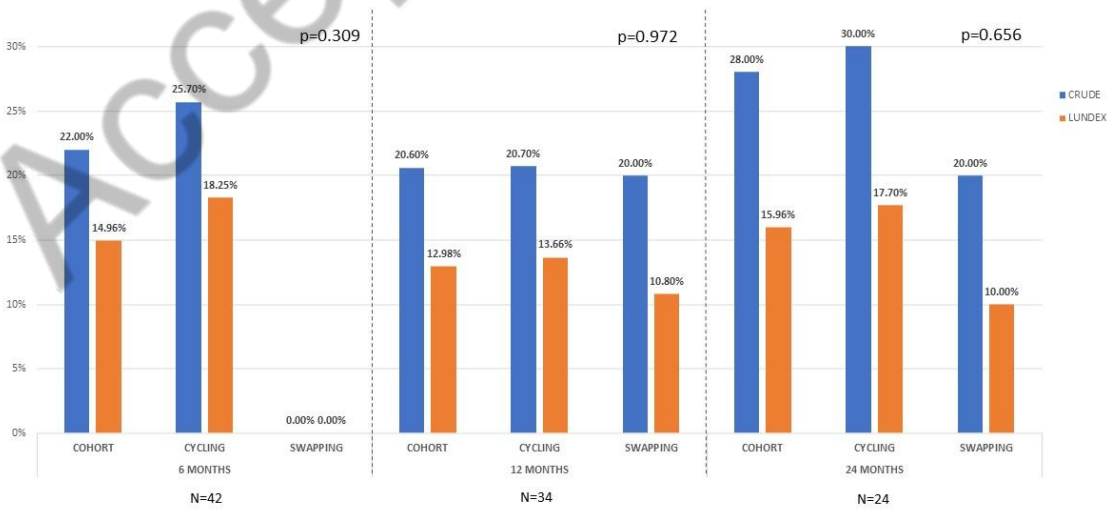


Table I. Patient and disease characteristics at baseline and comparison between therapeutic groups				
	All patients **N=439**	**Cycling** **N=332**	**Swapping** **N=107**	***p*-value**
Sociodemographic characteristics				
Age (years)	49.4 ± 11.4	49.1 ±11.4	50.4 ± 12.5	NS
Gender (Female)	255/439 (58.1)	193/332 (58.1)	62/107 (57.9)	NS
Race (White European origin)	311/323 (96.3)	248/259 (95.8)	63/64 (98.4)	NS
Disease characteristics				
Age at diagnosis (years), n=384	41.0 ± 12.2	40.1 ± 12.1	44.6 ± 12.3	**0.003**
Discontinuation of the 1st TNFi due to ineffectiveness	319/439 (72.7)	237/342 (71.4)	82/107 (76.6)	NS
Disease duration until 2nd biologic (years), n=370	8.5 ± 7.5	9.0 ± 7.5	6.8 ± 7.2	**0.028**
Axial disease	20/368 (5.4)	11/277 (4.0)	9/91 (9.9)	**0.031**
Peripheral disease	241/368 (65.5)	182/277 (65.7)	59/91 (64.8)	NS
Axial and peripheral disease	107/368 (29.1)	84/277 (30.3)	23/91 (25.3)	NS
Enthesitis	103/305 (33.8)	87/241 (36.1)	16/64 (25.0)	NS
Psoriasis	293/321 (91.3)	228/251 (90.8)	65/70 (92.9)	NS
Nail psoriasis	88/297 (29.6)	69/235 (29.4)	19/62 (30.6)	NS
Dactylitis	97/302 (32.1)	72/238 (30.3)	25/64 (39.1)	NS
Uveitis	22/305 (7.2)	21/242 (8.7)	1/63 (1.6)	NS
HLAB27 (positive)	44/205 (21.5)	38/160 (23.8)	6/45 (13.3)	NS
IBD	3/301 (1.0)	3/240 (1.3)	0/64 (0.0)	NS
EMM	301/327 (92.0)	236/257 (91.8)	65/70 (92.9)	NS
Comorbidities				
BMI (Kg/m^2), n=180	28.5 ± 5.6	28.6 ± 5.51	28.1 ± 6.3	NS
Smoking status (Never smoked)	186/300 (62.0)	155/245 (63.3)	31/55 (56.4)	NS
Alcohol consumption (occasional/never consumed)	230/282 (81.6)	188/230 (81.7)	42/52 (80.8)	NS
Number of comorbidities	0.8 ± 0.1	0.9 ± 0.1	0.4 ± 0.1	**<0.001**
DMARDs therapy				
Methotrexate	208/432 (48.1)	174/327 (53.2)	34/105 (32.4)	**<0.001**
Sulfasalazine	32/432 (7.4)	26/327 (8.0)	6/105 (5.7)	NS
Leflunomide	24/432 (5.6)	18/327 (5.5)	6/105 (5.7)	NS
Glucocorticoid	152/432 (34.6)	126/327 (38.5)	26/105 (24.8)	**0.010**
NSAIDs	133/432 (30.8)	107/326 (32.7)	26/104 (25.0)	NS
Baseline disease activity				
Tender joints 68 (n= 331)	7.8 ± 8.5	7.9 ± 8.5	7.6 ± 8.7	NS
Swollen joints 66 (n=329)	3.9 ± 5.0	3.8 ± 4.9	4.1 ± 5.1	NS
ESR (mm/1st hour) (n=306)	27.3 ± 24.1	28.1 ± 24.7	24.7 ± 22.2	NS
CRP (mg/dL) (n=305)	1.4 ± 2.2	1.5 ± 2.3	1.1 ± 2.0	NS
Patients VAS (n=292)	60.2 ± 26.1	60.4 ± 26.4	59.5 ± 29.9	NS
Pain VAS (n=228)	59.5 ± 25.8	59.4 ± 25.8	59.9 ± 26.2	NS
Physician VAS (n=268)	43.8 ± 23.8	42.8 ± 24.1	47.3 ± 22.5	NS
DAS 28 4V CRP (n=222)	4.0 ± 1.3	4.0 ± 1.3	4.1 ± 1.4	NS
DASPSA (n=205)	25.6 ± 13.8	25.2 ± 13.4	27.6 ± 15.5	NS
HAQ (n=207)	1.1 ± 0.7	1.1 ± 0.7	1.2 ± 0.8	NS
BASDAI (n=122)	5.7 ± 2.5	5.6 ± 2.6	5.9 ± 2.4	NS
ASDAS-CRP (n=113)	3.3 ± 1.2	3.3 ± 1.2	3.3 ± 1.2	NS
BASFI (n=101)	5.3 ± 2.8	5.3 ± 2.9	5.5 ± 1.8	NS
MASES (n=182)	1.4 ± 2.6	1.5 ± 2.8	1.2 ± 2.0	NS

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BMI: Body mass index; CRP: C-reactive protein; DAS: Disease Activity Score; DAPSA: Disease Activity Index for Psoriatic Arthritis; DMARD: Disease Modifying Antirheumatic Drug; EMM: Extra-articular manifestations (including skin and nail psoriasis, uveitis and IBD); ESR: Erythrocyte Sedimentation Rate; HAQ: Health Assessment Questionnaire; IBD: inflammatory bowel disease; MASES: Maastrich Ankylosing Spondylitis Enthesitis Score; NS: not significant; NSAIDs: Non-steroidal anti-inflammatory drugs;; VAS: visual analogue scale.Categorical variables are presented as number/total population (percentage); continuous variables are presented as mean ± standard deviation.

Table II. Predictor model of discontinuation after 2 years of follow up, in the overall cohort			
	Univariate analysis **HR (95%CI)**	***p*-value**	**Multivariate analysis** **HR (95% CI)** **N= 350**
Gender (ref: female)	0.72 (0.51-1.01)	0.054	0.70 (0.47-1.01)
Age, n=415	1.00 (0.99-1.01)	0.861	1.00 (0.98-1.01)
Type of involvement (peripheral only: ref), n=368		0.106	
Only axial	0.57 (0.21-1.55)	0.268	0.60 (0.22-1.66)
Both axial and peripheral	1.36 (0.94-1.96)	0.102	1.48 (1.01-2.17)
Baseline glucocorticoids, n=414	1.60 (1.56-2.22)	0.005	**1.67 (1.1542.41)***
Smoking history, n=291	0.76 (0.50-1.15)	0.198	α
Baseline DAS4vCRP, n=215	1.17 (0.99-1.39)	0.068	ǂ
Baseline DAPSA, n=199	1.01 (1.00-1.03)	0.089	α
Baseline ASDAS-CRP, n=110	1.33 (1.03-1.74)	0.032	¥
Baseline BASDAI, n=119	1.16 (1.01-1.34)	0.033	ǂ
Reason of discontinuation 1st TNFi (ref: primary inefficacy), n=415		0.103	
Secondary inefficacy	0.64 (0.41-1.01)	0.056	α
Adverse event	0.68 (0.39-1.19)	0.174	
Other	0.41 (0.19-0.88)	0.022	
Therapeutic group (ref: cycling)	1.06 (0.722-1.56)	0.765	1.40 (0.92-2.13)

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; CRP: C-reactive protein; DAS: Disease Activity Score; DAPSA: Disease Activity Index for Psoriatic Arthritis; HR: Hazard ratio.

α: non including in the final model due to loss of significance

ǂ: non included in the final model due to correlation with other variables

¥: non included in the final model due to high number of missing value (more than 1/3)

*$p<0.05$

Supplementary Table I. Distribution of the 1st and 2nd iTNF by drug.

	Etanercept	Adalimumab	Golimumab	Infliximab	Certolizumab	Total
1st iTNF	191 (43.5)	123 (28.0)	63 (14.5)	58 (13.2)	-	439
2nd iTNF	102 (30.7)	149 (44.9)	39 (11.7)	29 (8.7)	13 (3.9)	332

iTNF: tumor necrosis factor alpha inhibitor

Supplementary Table II. Reason for discontinuation of the 2nd biologic drug

	All patients N=439	Cycling N=332	Swapping N=107	*p*-value
Discontinuation of the 2nd biologic	151 (34.4)	117 (35.2)	34 (31.5)	NS
Adverse event	23 (15.2)	16 (13.7)	7 (20.6)	NS
Ineffectiveness	110 (72.8)	86 (73.5)	24 (70.6)	NS
Primary	34 (30.9]	30 (34.9)	4 (16.6)	NS
Secondary	76 (69.1)	56 (65.1)	20 (83.3)	NS
Other reason*	18 (11.9)	15 (12.8)	3 (8.8)	NS

*Malignancy, pregnancy, refusal of treatment, remission.
NS: non-significant

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