Switching related to inefficacy in biologics and targeted synthetic therapies for psoriatic arthritis: a comparative real-life study

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Abstract

Background: Switching between therapies is a recommended strategy for psoriatic arthritis (PsA) patients who experience treatment failure; however, studies including real-life data are scarce.

Objectives: To assess the incidence rate (IR) of switching between biologics and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) due to inefficacy in PsA, and to compare the risk of switching due to inefficacy across different b/tsDMARDs groups.

Design: A longitudinal retrospective study, spanning from 2007 to 2022, was conducted on patients with PsA treated with b/tsDMARDs at an outpatient rheumatology clinic.

Methods: The primary outcome was switching between b/tsDMARDs due to inefficacy. The independent variable was the exposure to b/tsDMARDs during follow-up. As covariates, clinical, treatment-related, and sociodemographic variables were considered. Survival techniques were run to estimate the IR of switching due to inefficacy per 100 patients*year and confidence interval at 95% (95% CI). Cox multivariate regression analyses were run to assess the risk of b/tsDMARDs switching due to inefficacy, expressed as hazard ratio (HR) and 95% CI.

Results: In all, 141 patients were included, with 893.09 patients*year follow-ups. 52.48% of them were females in their fifties. In total, 262 courses of treatment were recorded. During the study period, 56 patients presented 121 switches and 103 related to inefficacy (IR: 11.53 (9.51–13.98)). Tumor necrosis factor-alpha inhibitors (TNFi) showed the lowest IR. In the bivariate analysis, all b/tsDMARDs had more risk of switching compared to TNFi (HR: anti-lL-17 vs TNFi: 2.26 (1.17–4.36); others vs TNFi: 3.21 (1.59–6.45)); however, this statistical significance was no longer present in the multivariate analysis once adjustments were made for the covariates. Still, the final model achieved statistical significance in the following variables: gender, clinical symptoms, prescription year, therapy courses, glucocorticoids, and sulfasalazine.

Conclusion: In this study, we did not find differences in the rate of switching due to inefficacy among different groups of b/tsDMARDs. Other concomitant treatments, sociodemographic, and clinical variables were identified as risk factors for switching due to inefficacy.

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Plain language summary

Changes due to drug failure between biologic therapies: a real-life study in psoriatic arthritis patients

Introduction: We wanted to evaluate how often patients with psoriatic arthritis change between different drugs because the drugs weren't working well enough. Additionally, we evaluated which factors could influence the change due to drug failure. The studied drugs are biological therapies that are arthritis-modifying drugs designed early in the last decade to prevent or reduce inflammation caused by the disease. Methods: We included patients from 2007 to 2022 in which their consultant rheumatologist had decided to commence them on biologic therapy. We studied the changes due to drug failure, we also included sociodemographic, clinical and treatments information. Results: The study comprised 141 patients. 52% were women in their fifties. We found that 56 patients change drugs 121 times, with 103 of those changes due to failure drug. This means about 11 out of every 100 patients change their biologic therapy each year. There was no difference in the risk of change between the different studied biologic therapies. Women, those with inflammatory back pain, and those who had tried many different drugs were more likely to change due to drug failure. Using additional therapies like glucocorticoids and sulfasalazine also increased the probability of biologic therapy change. Conclusion: Our work did not find differences in the risk of change due to drug failure among different biologic therapies.

Introduction

Psoriatic arthritis (PsA) is a chronic and inflammatory disease that variably affects synovial joints, tendons, entheses, and axial sites, and tends to be associated with psoriasis (both in the skin and nails).[1–3] Although the overall prevalence of PsA is low, it is more common among patients with psoriasis, affecting approximately 30% of them over the course of their lifetime.[2–4] Prognosis varies from a relatively mild form to a severe and destructive polyarticular form with progressive joint deformities. In addition to being related to other extra-articular manifestations such as uveitis or inflammatory bowel disease (IBD), PsA is also associated with several comorbidities (e.g., metabolic syndrome, depression, hypertension). Moreover, PsA patients suffer from fatigue, limited physical function, sleep disturbances, and reduced ability to work and engage in social activities. Together with other musculoskeletal symptoms represent a major burden for patients, with a severe impact on their quality of life that leads to an increased mortality rate.[5–7]

Because PsA is a heterogeneous and potentially serious disease, patient routine management should aim to achieve remission or low disease activity through regular assessment of disease activity and appropriate therapy adjustments.[8,9] Disease-modifier therapies include biologic disease-modifying anti-rheumatic drugs (bDMARDs) targeting tumor necrosis factor-alpha inhibitors (TNFi), interleukin (IL)-17A (ixekizumab, secukinumab); the p19 subunit of IL-23 (guselkumab, risankizumab); the co-stimulation molecule CD80/86 (abatacept). Furthermore, Janus kinase inhibitors (JAKi) have been assessed and approved in PsA.[8–11] All these therapies have deeply transformed the management of rheumatic diseases in the last decades. Biological agents and target synthetic drugs directly target the molecules and cells involved in the pathogenesis of inflammatory diseases and allow a better prognosis and clinical remission rate in patients.[1,12,13]

Switching between DMARDs is a recommended strategy for PsA patients who experience treatment failure; however, studies including real-life data about therapy selection and switching between the diverse biologics and targeted synthetic therapies

(b/tsDMARDs) in PsA are limited.[14] Rheumatologists are now able to choose between different therapies for PsA with different chemical structures, pharmacokinetic properties, dosing regimens, immunogenicity, safety profiles, and mechanisms of action.[9,10] However, data to guide clinicians on the best switching strategy between different b/tsDMARDs are limited. The switching between TNFi can be effective for many patients; however, biologic or target synthetic drugs with different mechanisms of action may be superior alternatives.[15] Over the last decade, after two or more anti-TNF failures, swapping to a different mode of action was recommended.[16] At present, several factors must be considered in deciding which drug to switch to, including disease characteristics, activity, comorbidities, treatment sequence, and patient preferences. Switching has become a widespread practice not only among anti-TNFs but also with alternative biologics or JAKi that have different mechanisms of action. If none of the available b/tsDMARDs in this setting present a clear benefit, the choice of the second agent is personalized, depending on factors such as reasons for discontinuing the first TNFi, previous agents used, concomitant therapies, and comorbidities. The severity of psoriasis, the articular involvement, and the predominance of enthesitis and/or dactylitis may drive the choice.[16] Therefore, clinicians are increasingly familiar with the clinical profiles of different biological agents and the evidence of their benefits in halting disease progression.

Many of these new drugs have been well studied in short-term randomized controlled trials with placebo as a comparator for drug approval reasons. Nevertheless, comparative studies of different drugs relevant to clinical practice are lacking, and clinicians need some guidance in decision-making. Therefore, well-designed studies are needed to learn more about switching during the follow-up of this heterogeneous disease and to analyze the impact of different comorbidities as well as disease aspects. This study aims to obtain real-world clinical practice and long-term information on PsA treatment with b/tsDMARDs in the Rheumatology Outpatient Unit of the Hospital Clínico San Carlos (HCSC) in Madrid. This research is framed in the study of switching between b/tsDMARDs in PsA patients.

Therefore, the aim is to explore the incidence rate (IR) and causes of switching between b/tsDMARDs, to assess the IR of switching between b/tsDMARDs due to inefficacy, and to analyze the role of various b/tsDMARDs groups and other potential factors in the risk of switching due to inefficacy.

Materials and methods

Setting, study design, and patients

The study was conducted in the HCSC, a public tertiary hospital in Madrid, Spain, with a catchment area of nearly 400,000 subjects.

We performed an observational retrospective longitudinal study. Patients seen at the HCSC rheumatology outpatient clinic from January 2007 to April 2021, whose data were recorded in the departmental electronic health record (EHR), were included in the study. The study was set from the date of the first b/tsDMARDs, and patients were followed until the end of the study (i.e., September 30, 2022) or until loss of follow-up.

In this study, patients were selected according to the following criteria: (1) visit our outpatient clinic during the study inclusion period; (2) 16 years of age or older; (3) had at least two medical claims with an International Classification of Diseases (ICD), Ninth or Tenth Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) diagnosis of PsA (ICD-9-CM code 696.0/ICD-10-CM code L40.5) in our outpatient clinic (Supplementary Table S1), fulfilled the PsA diagnosis according to The CASPAR criteria[17] (classification criteria for psoriatic arthritis), and reviewed by three clinical researchers of the group; (4) at least two registered consecutive consultations during the study period; and (5) had to be on b/tsDMARDs treatment in the inclusion period. Patients with a concomitant diagnosis of IBD were excluded.

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. HCSC Ethics Review Board approval was obtained as a retrospective study (approval code 17/300-E) and waiver of informed consent was granted for the use of de-identified clinical records. This research is executed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[18]

Data source

Data were obtained from our departmental EHR. It included (1) sociodemographic and administrative data that were integrated from the hospital information system; (2) clinical analysis data that were integrated into the hospital laboratory information system; and (3) clinical data including comorbidity, clinical disease activity, and prescribed drugs (using the Spanish Drug and Medical Device Agency codification system). These variables were recorded by the rheumatologist at each visit to the EHR.

Variables

Dependent variable. Our main outcome was the switching between ts/bDMARDs due to inefficacy. Inefficacy events were registered according to the rheumatologist's criteria from the clinical chart.

Independent variables. The independent variables included exposure to various types of b/tsDMARDs during follow-up, encompassing the following groups: (1) TNFi (infliximab, adalimumab, etanercept, certolizumab, golimumab); (2) other biologics: CTLA4–Ig (abatacept); anti-IL17 (ixekizumab, secukinumab); anti-IL12/23 (Ustekinumab); anti-IL-23, (guselkumab); and (3) JAKi (tofacitinib, baricitinib, upadacitinib).

The covariates considered were as follows: (1) demographic (age and sex at birth (both codified)); (2) disease-related (date of PsA symptoms onset (clinical notes collected from the EHR) and diagnosis (codified)); calendar time: dividing the starting time of each b/tsDMARDs into year intervals based on treatment strategies and the commercialization, anti-IL-17 or JAKi (cutoff dates: January 2015 and January 2019); (3) musculoskeletal manifestations (presence of peripheral arthritis, inflammatory low back pain, enthesitis and dactylitis (all collected from the clinical notes)); (4) extra-articular manifestations recorded by the rheumatologist (presence of active cutaneous or nail psoriasis, uveitis and IBD (clinical notes collected from the EHR)); (5) comorbidities (arterial hypertension, dyslipidemia, diabetes mellitus, obesity, ischemic heart disease, cerebrovascular disease, depression, cognitive impairment, sleep disorders, malignancy, fibromyalgia, osteoporosis, osteoporotic fracture, hyperuricemia, interstitial lung disease, chronic obstructive pulmonary disease, restrictive pulmonary disease, renal disease, liver disease, peptic ulcer, thyroid disease, and a previous diagnosis or history of cutaneous psoriasis (all collected from the comorbidity section of the EHR)); (6) laboratory parameters at baseline: erythrocyte sedimentation rate, C-reactive protein (CRP), rheumatoid factor, and HLA B27; (7) treatment-related (current use of corticosteroids (whether or not during at least 6 months from every b/tsDMARDs and regardless the dosage), non-steroidal anti-inflammatory drugs (NSAIDs) (taken for at least 3 months since the start of every b/tsDMARDs)), and (8) previous use of DMARDs (at least in the previous 6 months) and also concomitant conventional synthetic DMARDs (csDMARDs) during the whole follow-up of the study (methotrexate, sulfasalazine, leflunomide, or antimalarials).

Statistical analysis

The statistical analysis included descriptive assessments of the sociodemographic factors, clinical characteristics, comorbidities, disease activity measures, and treatment details for all patients included in the study. A detailed description of the clinical course, treatment switches to biological agents, and outcomes were carried out, both globally and stratified by treatment courses. Frequency distributions were used for qualitative variables, while means and standard deviations or medians and percentiles were reported for quantitative variables. For the study of bivariate associations, the student's *t*-test was used for the analysis of continuous variables with normal distribution. Continuous variables with non-normal distribution were analyzed with the Mann–Whitney test or the Kruskal–Wallis test if there are more than two categories. The categorical variables were analyzed with Chi-square or the Fisher test.

To explore switching between b/tsDMARDs due to inefficacy, we included all the patients with PsA. The time of exposure comprised the period from the baseline visit (i.e., starting date of first b/tsDMARDs therapy) until the occurrence of any of the following cutoff points: loss of follow-up, the main outcome, or the end of the study. Kaplan–Meier curves were set to account for switching over time. IRs of total switching and switching due to inefficacy were estimated by survival techniques (allowing for multiple failures per patient), expressing the IR per 100 patient-years with their respective 95% confidence interval (CI). Cox bivariate analyses were conducted to assess the differences between demographic,

clinical covariates, and the risk of switching due to inefficacy. Cox multivariate regression analyses were run to assess the role of the different groups of b/tsDMARDs in switching due to inefficacy. Other covariates were also investigated. In the multivariate analysis, we included age, sex, calendar time, other related factors previously identified, and all variables with a *p*-value <0.2 in the bivariate analysis. It is important to note that how drug prescription was done in real-life conditions hampered the categorization of therapeutic options including csDMARDs, NSAIDs, and glucocorticoids, being analyzed in a time-dependent manner (at the beginning of every b/tsDMARDs). Clinical symptoms and CRP were analyzed in a time-dependent manner. The analysis was divided into periods according to the retention rate of every b/tsDMARDs that determined the presence or not of an event in that time frame. In each period, a patient was deemed exposed if they had been on any b/tsDMARDs for a duration exceeding 6 months. Patients were classified as exposed to glucocorticoids and NSAIDs if they had been receiving these medications for a minimum of 3 months within the analyzed period.

The results of the regression models were expressed by hazard ratio and 95% CI. We considered the influence of covariates if the prevalence was >10%. When the frequency was lower, as observed with some comorbidities and treatments, they were grouped based on affinity. We limited the number of variables in the multivariate model following the rule of Freeman[19] and the value of 10 events per variable.[20,21] Variables with more than 10% of missing values were not used in the multivariate analysis. The proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. A two-tailed *p*-value under 0.05 was considered to indicate statistical significance. Statistical analyses were performed using STATA software (Stata Corp, College Station, TX, USA).

Results

Patient characteristics

A total of 141 patients were included, with a total follow-up of 893.1 patient-years, a median of 4.9 (1.6–10.9) years, and a maximum follow-up of 16 years. Table 1 outlines the baseline demographic and clinical characteristics of the included patients. Half of them were women and the mean age at the first biologic agent prescription was 48.1 ± 13.2 years. The median lag time from symptoms to PsA diagnosis and from diagnosis to the first b/tsDMARDs was 1 (0.25–4.7) year and 1.1 (0.27–2.8), respectively. Regarding comorbidities, 57% of the patients had at least one at the baseline visit and 50.37% (*n* = 68) of them presented cardiovascular risk factors, with dyslipidemia and arterial hypertension as the most prevalent. Interestingly, obesity, depression, and thyroid disease were present in more than 10% of the patients. As expected, a previous history of psoriasis was present in 108 patients (80.6%) of the patients.

The primary musculoskeletal manifestation at baseline was peripheral arthritis, followed by inflammatory low back pain and enthesitis. Only one patient presented at baseline with an extracutaneous and extra-articular manifestation (uveitis). Several patients had more than one PsA feature present (18.57%), being the presence of arthritis and inflammatory back pain, the most frequent combination followed by peripheral arthritis and enthesitis. HLA B27 determination resulted in positive in almost 20% of the patients and the median C-reactive protein value was 0.31 (p25–p75: 0.29–0.83).

In the year before starting the first b/tsDMARDs, 80 patients (56.74%) received at least one csDMARD, the most common being methotrexate, either as monotherapy or in combination. At the starting date of first b/tsDMARDs, 38 patients were on monotherapy and most of them progressed through combination therapy later. Twenty-nine patients, at the time of diagnosis, started with two csDMARDs: methotrexate–sulfasalazine (*n* = 13) and methotrexate–leflunomide (*n* = 12), the most frequently used.

Regarding therapy, at the beginning of the study, 72 (51.06%) patients were prescribed with NSAIDs, and 53 (37.59%) were prescribed with oral glucocorticoids. The most frequent drugs used as first b/tsDMARDs were TNFi with 125 (88.65%) patients (mainly adalimumab and etanercept), followed by anti-IL-17 (mostly secukinumab with 11 patients). Interestingly, 73% (*n* = 103) of the patients used csDMARDs associated with b/tsDMARDs, 89 (63.1%) were combined with one csDMARDs (mainly methotrexate), and the remaining 14 in combination with two csDMARDs: methotrexate–sulfasalazine, the most frequently used).

Table 1. Description of baseline (at first ts/bDMARD) demographic and clinical characteristics of psoriatic arthritis patients.

Variable	141 (110)
Sex at birth, women; n (%)	74 (52.48)
Age; n (%) in years	
<40	43 (30.50)
41–50	34 (24.11)
51–60	37 (26.24)
61–70	16 (11.35)
>71	11 (7.80)
Smoking habit (n = 106); n (%)	
Current	31 (29.25)
No	69 (65.09)
Former	6 (5.66)
Lag time from symptoms to diagnosis; mean ± SD	3.64 ± 5.65
Lag time from diagnosis to first ts/bDMARD; mean ± SD	2.38 ± 3.21
Comorbidity (n = 135); n (%)	
Dyslipidemia	53 (39.26)
Arterial hypertension	25 (18.52)
Diabetes mellitus	7 (5.19)
Obesity	18 (13.33)
Ischemic heart disease	2 (1.48)
Ischemic cerebrovascular disease	4 (2.96)
COPD	3 (2.22)
ILD disease	0
Liver disease	6 (4.44)
Thyroid disease	16 (11.85)
Peptic ulcer disease	5 (3.70)
Cancer history	4 (2.96)
Depression	14 (10.37)
Psoriasis history	108 (80.60)
Clinical symptoms; n (%)	
Inflammatory back pain (n = 141)	22 (15.60)

(Continued)

Table 1. (Continued)

Variable	141 (110)
Anterior uveitis	1 (0.71)
Peripheral arthritis	105 (74.47)
Enthesitis	12 (8.51)
Dactylitis	8 (5.67)
HLA B27+ (n = 56); n (%)	10 (17.86)
Rheumatoid factor+ (n = 103); n (%)	7 (6.80)
C-reactive protein (n = 129); mean ± SD, mg/dL	1.28 ± 2.79
Concomitant glucocorticoids; n (%)	53 (37.59)
Concomitant NSAIDs; n (%)	72 (51.06)
Previous csDMARDs (12 months)	
None	61 (43.26)
Monotherapy	44 (31.21)
Methotrexate	40
Leflunomide	1
Sulfasalazine	2
Azathioprine	1
Combined 2 csDMARDs	29 (20.57)
Combined 3 csDMARDs	6 (4.26)
Combined 4 csDMARDs	1 (0.71)
ts/bDMARDs; n (%)	
TNFi	125 (88.65)
Adalimumab	63
Etanercept	25
Certolizumab	21
Golimumab	8
Infliximab	8
Anti-IL17	12 (8.51)
Secukinumab	11
Ixekizumab	1
Anti-IL12/IL23	1 (0.71)
Ustekinumab	1
JAKi	3 (2.12)

(Continued)

Table 1. (Continued)

Variable	141 (110)
Tofacitinib	2
Baricitinib	1
Therapeutic regimen; *n* (%)	
ts/bDMARDs in monotherapy	38 (27)
ts/bDMARDs combined with 1 csDMARDs	89 (63.1)
ts/bDMARDs combined with 2 csDMARDs	14 (9.9)
Concomitant csDMARDs; *n* (%)	
Methotrexate	82 (58.16)
Sulfasalazine	15 (10.64)
Antimalarials	2 (1.42)
Leflunomide	14 (9.93)

Anti-IL12/IL23, anti-interleukin-12/23 biological agent; anti-IL17, anti-interleukin17 biological agent; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; JAKi, Janus kinase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; TNFi, tumor necrosis factor-alpha inhibitors; ts/bDMARDs, targeted synthetic and biologic disease-modifying anti-rheumatic drugs.

During the study period, patients received 262 courses of b/tsDMARDs therapy, and 85, 25, and 16 patients received one, two, and three consecutive b/tsDMARDs, respectively. Thus, 56 patients had a second course, and 31 had a third course of b/tsDMARDs (Figure 1).

Switches between ts/bDMARDs during the study period

Through the study period, 56 patients (40%) presented 121 switches between b/tsDMARDs. The IR of total switching was estimated at 13.54 (11.33–16.19) per 100 patient-years and 50% of the events were at 4 years. As we illustrated in Figure 2, the main cause of switching was related to inefficacy ($n = 103$), followed by adverse events.

Switches due to inefficacy

We found 103 events with an IR of 11.53 (9.51–13.98) per 100 patient-years with 8%, 20%, and 31% of failures at 6 months, in the first year and the second year, respectively; and 50% of the events were at 5.12 years.

Table 2 shows the IR of switching due to inefficacy by different variables. Regarding the b/tsD-MARDs, TNFi was the drug with the lowest incidence, specifically adalimumab (IR: 7.94 (5.61–11.23)), followed by infliximab (IR: 9.93 (5.16–19.90)), golimumab (IR: 10.78 (4.84–24.00), and etanercept (IR: 11.16 (7.03–17.71)). Concerning other covariables, IR was lower in those on methotrexate or in those using NSAIDs. In the case of the presence of baseline comorbidity, peripheral arthritis, HLA B27 positive, and concomitant use of leflunomide, IR was similar between categories. Focusing on the first course, the IR was estimated in 8.38 (6.33–11.08), and it was increasing in the subsequent courses. Interestingly, IR was higher in women, smoking habits, the presence of inflammatory back pain or enthesitis, and concomitant use of sulfasalazine (IR: 22.83 (14.38–36.23)). The calendar time effect was lower in the first two periods, increasing from 2019.

Factors associated with switching related to inefficacy during follow-up

Bivariate analyses for switching due to inefficacy are detailed in Table 3. Regarding the type of ts/bDMARDs, all drugs had more risk of switching compared to TNFi. These differences were statistically significant. As expected, sex, year of b/tsD-MARDs prescription, courses of b/tsDMARDs, and some domains of the disease (enthesitis, inflammatory back pain, or use of glucocorticoids) were associated with switching due to inefficacy. Baseline comorbidity, age, or concomitant csD-MARDs did not, although the use of sulfasalazine almost achieves statistical significance.

To examine the impact of therapeutic b/tsD-MARDs alternatives on switching due to inefficacy, independent of additional factors, a final model showed that no specific type of b/tsD-MARDs had more risk of switching (Table 4). The analysis was adjusted for age, sex, year of b/tsDMARDs prescription, and comorbidity. Comorbidity had no impact and was excluded from the final model. In the model, we presented the effect of sex on switching and we also showed other interesting findings such as (1) the effect of the year of prescription, increasing the risk over 2019 compared to previous years; (2) the more courses of b/tsDMARDs, the greater the risk of switching; and (3) the negative influence of glucocorticoids on switching. Regarding csD-MARDs, sulfasalazine increased the risk, whereas
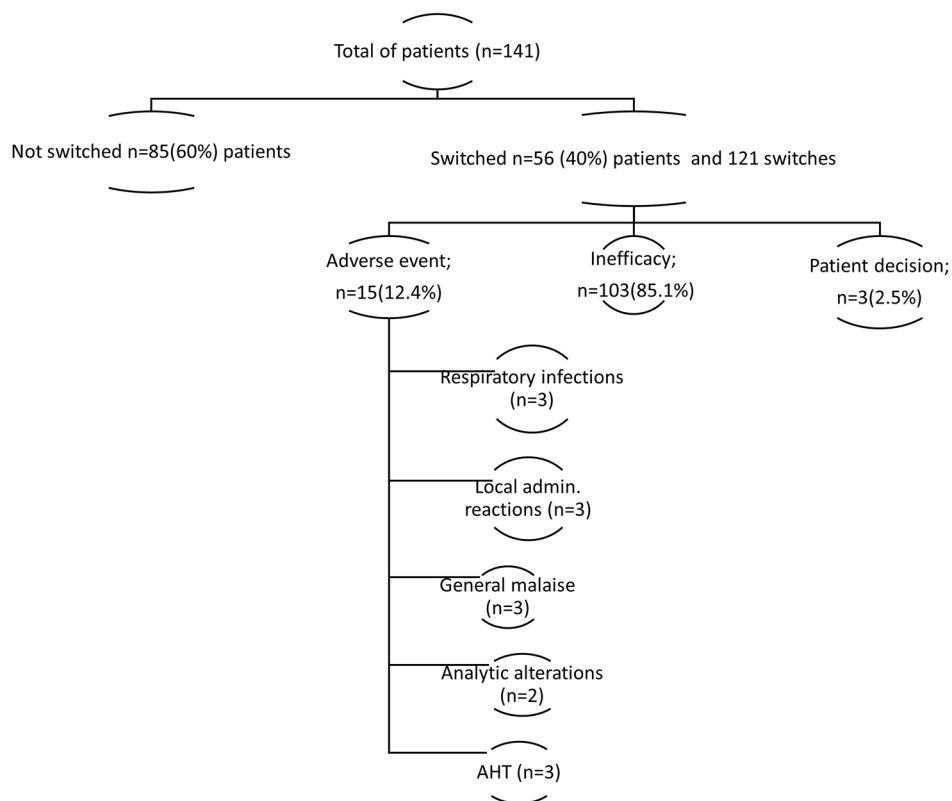
Figure 1. Treatment switching courses in psoriatic arthritis patients.

Figure 2. Treatment switches between ts/bDMARDs during the study period in psoriatic arthritis patients.

Table 2. IR of switching related to inefficacy by sociodemographic and clinical variables of the patients.

Variable	Patient-years	Events	IR per 100	CI (95%)
Global inefficacy	893.10	103	11.53	9.51–13.98
Sex at birth				
Male	460.90	26	5.64	3.84–8.28
Female	432.20	77	17.81	14.24–22.27
Age, years				
<40	228.12	18	7.89	4.97–12.52
41–50	262.77	37	14.08	10.20–19.43
51–60	222.03	26	11.70	7.97–217.19
61–70	129.67	18	13.88	8.74–22.03
≥71	50.49	4	7.92	2.97–21.10
Smoking habit				
Current	215.45	37	17.17	12.44–23.70
No/former	477.45	46	9.63	7.21–12.86
Comorbidity				
Yes	518.56	58	11.18	8.64–14.46
No	333.77	36	10.78	7.78–14.95
Cardiovascular comorbidity				
Yes	484.43	49	10.11	7.64–13.38
No	367.98	45	12.22	9.13–16.37
History of psoriasis				
Yes	607.01	63	10.37	8.10–13.28
No	231.81	29	12.51	8.69–18.00
Calendar time, years				
2007–2014	532.43	42	7.88	5.82–10.67
2015–2018	208.34	20	9.59	6.19–14.87
≥2019	152.33	41	26.9	19.81–36.55
Clinical symptoms				
Inflammatory back pain				
Yes	147.73	26	17.44	11.88–25.62
No	745.37	77	10.33	8.26–12.91

(Continued)

Table 2. (Continued)

Variable	Patient-years	Events	IR per 100	CI (95%)
Anterior uveitis				
Yes	12.15	2	16.46	4.11–65.84
No	880.94	101	11.46	9.43–13.93
Peripheral arthritis				
Yes	571.89	70	12.24	9.68–15.47
No	304.21	28	9.20	6.35–13.33
Enthesitis				
Yes	51.94	15	28.87	17.41–47.90
No	840.78	87	10.34	8.38–12.76
Dactylitis				
Yes	14.14	5	35.38	14.72–85.01
No	878.96	98	11.15	9.14–13.59
HLA B27				
Positive	67.85	1	1.47	0.20–10.46
Negative	228.93	36	15.72	11.34–21.80
Rheumatoid factor				
Positive	61.37	9	14.66	7.62–28.18
Negative	572.96	66	11.51	9.04–14.66
C-reactive protein				
$\leqslant 1$ mg/dL	681.43	87	12.76	10.94–15.75
>1 mg/dL	147.14	9	6.11	3.18–11.75
Concomitant glucocorticoids				
Yes	393.36	63	16.01	12.51–20.50
No	499.74	40	8.00	5.87–10.91
Concomitant NSAIDs				
Yes	544.21	51	9.37	7.12–12.33
No	348.88	52	14.90	11.35–19.56
ts/bDMARDs				
TNFi	793.00	77	9.47	7.55–11.87
Anti-IL17	69.66	16	23.00	14.09–37.54

(Continued)

Table 2. (Continued)

Variable	Patient-years	Events	IR per 100	CI (95%)
Anti-IL23	10.28	5	48.59	20.22–116.7
JAKi	14.05	4	28.45	10.67–75.81
Abatacept	5.91	1	16.94	2.38–120.28
Concomitant csDMARDs				
Methotrexate				
Yes	606.35	61	10.05	7.82–12.92
No	286.75	42	14.66	10.83–19.84
Sulfasalazine				
Yes	78.84	18	22.83	14.38–36.23
No	814.26	85	10.43	8.43–12.91
Leflunomide				
Yes	82.26	10	12.12	6.54–22.59
No	810.84	93	11.46	9.36–14.05
ts/bDMARDs courses of treatment				
First course	584.67	49	8.38	6.33–11.08
Second course	160.31	24	14.97	10.3–22.33
Third or more courses	148.11	30	20.25	14.16–28.96

Anti-IL12/IL23, anti-interleukin-12/23 biological agent; anti-IL17, anti-interleukin17 biological agent; C-reactive protein, cut point 90 percentile.; CI, confidence interval; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; IR, incidence rate; JAKi, Janus kinase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumor necrosis factor-alpha inhibitors; ts/bDMARDs, targeted synthetic and biologic disease-modifying anti-rheumatic drugs.

methotrexate dropped from the model ($p = 0.46$). Interestingly, the model shows that patients with inflammatory low back pain as the main musculo-skeletal manifestation had a worse treatment response, favoring switching due to inefficacy. Other variables such as smoking habit ($p = 0.7$) or use of NSAIDs ($p = 0.31$) dropped from the model. The proportionality of this regression model was tested with a p value $= 0.58$.

Discussion

This study provides a contemporary picture of therapeutic sequencing among PsA treated with b/tsDMARDs in real-life conditions, suggesting that long-term control of PsA requires different therapeutic switching mainly due to inefficacy. Our results offer useful information on the comparative efficacy of b/tsDMARDs, finding no statistical differences in switching due to inefficacy between different groups of b/tsDMARDs in the multivariate analysis. This study also confirms previously identified risk factors of switching and proposes new ones.

This study was carried out from a long-term retrospective group of patients with PsA using all available b/tsDMARDs indicated for PsA in Madrid from 2007 until 2021. Sociodemographic and clinical data were comparable with other national PsA populations studied.[22–26] Despite the importance and advances of the PsA treatment, patients may experience treatment failure and switch to another treatment. Switching found in this study was around 40%, and as in most publications, our study involved switching from

Table 3. Factors associated with switching related to inefficacy in psoriatic arthritis patients: bivariate analysis.

Variable	HR	CI (95%)	*p*
Gender, female	3.02	1.58–5.78	0.001
Age at 1st ts/bDMARDs, years	1.008	0.98–1.02	0.4
Smoking habit			
No/former	1	—	—
Current	1.80	0.97–3.32	0.06
Lag time from diagnosis to first ts/bDMARD	0.99	0.89–1.11	0.9
Baseline comorbidity	1.12	0.63–1.98	0.69
Baseline cardiovascular comorbidity	0.91	0.51–1.60	0.73
History of psoriasis	0.77	0.43–1.40	0.4
Calendar time, years			
2007–2014	1	—	—
2015–2018	1.08	0.61–1.91	0.7
≥2019	2.79	1.49–5.24	0.001
Clinical symptoms			
Inflammatory back pain	1.85	1.04–3.26	0.034
Peripheral arthritis	1.24	0.68–2.23	0.47
Enthesitis	2.58	1.11–6.02	0.03
Concomitant glucocorticoids	2.16	1.35–3.45	0.001
Concomitant NSAIDs	0.65	0.40–1.06	0.088
ts/bDMARDs			
TNFi	1	—	—
Anti-IL17	2.26	1.17–4.36	0.014
Others: anti-IL23, JAKi, Abatacept	3.21	1.59–6.45	0.001
Therapeutic regimen combined	1.33	0.87–2.05	0.184
Concomitant csDMARDs			
Methotrexate	0.76	0.46–1.25	0.28
Sulfasalazine	2.11	0.96–4.64	0.06
Leflunomide	1.04	0.51–2.12	0.9
Courses of ts/bDMARDs	2.07	1.57–2.74	0.000

Anti-IL12/IL23, anti-interleukin-12/23 biological agent; anti-IL17, anti-interleukin17 biological agent; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; JAKi, Janus kinase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumor necrosis factor-alpha inhibitors; ts/bDMARDs, targeted synthetic and biologic disease-modifying anti-rheumatic drugs.

Table 4. Factors associated with switching related to inefficacy in psoriatic arthritis patients: multivariate analysis.

Variable	HR	CI (95%)	*p*
Sex, female	2.57	1.55–4.26	0.000
Age at 1st ts/bDMARDs	0.99	0.98–1.01	0.6
Calendar time, years			
<2019	1	—	—
2019–2022	2.49	1.49–4.18	0.000
Inflammatory back pain	1.49	1.02–2.17	0.039
Concomitant glucocorticoids	2.05	1.36–3.10	0.001
ts/bDMARDs			
TNFi	1	—	—
Anti-IL17 agents	1.05	0.54–1.99	0.88
Others: anti-IL12/23, JAKi, abatacept	1.55	0.69–3.48	0.28
Concomitant sulfasalazine	2.25	1.26–4.01	0.006
Courses of ts/bDMARDs	1.22	1.04–1.43	0.010

Anti-IL12/IL23, anti-interleukin-12/23 biological agent; anti-IL17, anti-interleukin17 biological agent; JAKi, Janus kinase inhibitors; TNFi, tumor necrosis factor-alpha inhibitors; ts/bDMARDs, targeted synthetic and biologic disease-modifying anti-rheumatic drugs.

one TNFi to another both as first- and second-line treatments, as TNFi has been the most widely used drug. Consistent with findings reported in the literature,[15] 85% of the switches in our study were due to treatment failure (IR of 11.53 per 100 patient-years) Interestingly and regarding drug survival over time, 20% switched due to treatment failure in the first year, increasing to 32% at the second year, with a median survival time of b/tsDMARDs almost 5 years. Retention rate was reduced in patients who received a second or third course of treatment,[25,27–30] increasing the IR of switching related to inefficacy in subsequent courses, achieving statistical significance in the final model as well.

During the long follow-up study period, we observed the application in clinical practice of the different guidelines and recommendations for the management of PsA according to the period. In this context, guidelines were developed addressing switching strategies when all available bDMARDs were TNFi and therefore did not include other agents with different mechanisms of action.[31] These guidelines recommended switching to a second TNFi.[32–34] In recent GRAPPA and EULAR recommendations for the management of PsA based on new evidence, a switch to an alternative biologic within a drug class or a drug with a different mode of action is recommended for patients who failed biologic therapy.[10,35] In this sense, we observe how in recent years prescription by rheumatologists has adapted to the new evidence, tailoring treatment according to the dominant manifestation, in our results opting for anti-IL17 drugs as the second most prescribed drug.

Another important effect observed in this long follow-up study has been the change in the management of these diseases. To control this issue, the study was analyzed by the calendar time variable, showing that the incidence of inefficacy increased in 2016, with a peak in 2019, achieving statistical significance in the final model as well. This reflects quite well not only the release of new

therapeutic options but also the emergence, application, and establishment of tight control of PsA in our cohort.[36]

Evidence on the comparative efficacy of b/tsDMARDs for the treatment of PsA in the real world is scarce.[32] This study found that although all drugs had a higher risk of switching compared to TNFi, with statistical significance in the bivariate analysis, after adjustment for confounders, none b/tsDMARDs presented more risk of switching due to inefficacy. It seems that TNFi and IL-17 are similar in terms of efficacy in real life and independently of the course and other clinical variables. It is important to recognize that TNFi were approved years ago and the others were authorized more recently, explaining the small number of patient-years in the remaining groups of b/tsDMARDs. Therefore, all these had to be combined for statistical analysis, precluding individual comparisons and further studies would be necessary to support separate comparisons.

Our study investigated other potential predictors of switching due to inefficacy in b/tsDMARDs. Regarding sociodemographic factors, previous studies have reported a higher rate of discontinuation of first- and second-line biologics among females in different rheumatic diseases including PsA.[37–41] Our study goes one step further and corroborates this finding in all treatment courses. PsA pathophysiology and its burden have been reported to differ by sex.[39,40] Whereas PsA is similarly prevalent in both sexes, rheumatoid arthritis and axial spondylarthritis are more common in women and men, respectively.[37] Although physiological differences might influence the response to pharmacotherapy in men and women, differences in coping mechanisms between sexes could also influence the response to treatment.[39]

Clinical trials involving specific groups of b/tsDMARDs suggest that patients with PsA might suffer noticeably different clinical domain responses to some pharmacological classes. In this sense, this study assessed those aspects.[42]

In line with the GRAPPA and EULAR recommendations,[16] our data reflect the recommendations of the working group, considering the early escalation of methotrexate therapy and eventually switching to another csDMARDs.[10,35] Other authors have analyzed the effect of concomitant csDMARDs on the discontinuation of b/tsDMARDs due to inefficacy.[43,44] In this scenario, we were able to show that patients receiving sulfasalazine or glucocorticoids associated with biological treatment were those with a greater risk of inefficacy during follow-up, while those with methotrexate decreased the risk, although without statistical significance. Data concerning dosages would be necessary to support all these findings.

The presence of inflammatory low back pain was significantly and independently associated with switching due to inefficacy during follow-up in our study. Assuming the study period, the first years of the study period guides recommended the use of TNFi for the management of axial PsA, according to the treatment guidelines for axial spondyloarthritis.[45,46] However, if axial disease predominates, in addition to TNFi, associated with the GRAPPA and EULAR recommendations, a lot of new data suggests that JAKi, IL-23, and IL-17 are also targets for the treatment of axial PsA.[10,35,45] Inflammatory low back pain could reflect a loss of efficacy due to the development of neutralizing antibodies, and these patients might particularly benefit from switching to another agent with lower immunogenicity.[47]

The main limitations of this study are those that affect any retrospective observational study. Other limitations are that the musculoskeletal manifestations assessment consisted of a clinical evaluation reported by the rheumatologist, and we did not use any standardized index to identify and quantify them, but all these patient features could be analyzed as different musculoskeletal manifestations, providing added value to the final model. In addition, we did not report parameters of disease activity in PsA, but the use of glucocorticoids could be considered as a variable of disease activity. The main strength of this study lies in the long-term use of mostly codified sociodemographic or clinical real-world data, including a broad patient spectrum and a wide variety of treatment options in PsA management. In addition, all these data were available for analysis, allowing adjustment by confounders including calendar time to avoid possible bias.

In summary, this real-life study provides valuable data on the course of treatment in patients with

PsA, as well as on the long-term switch pattern of b/tsDMARDs. We corroborate that switching between b/tsDMARDs is a common issue over time, with inefficacy being the main cause. Focusing on b/tsDMARDs, we were able to compare switching due to inefficacy between different groups of b/tsDMARDs, suggesting that they might have similar global efficacy regardless of other factors. We consider these findings useful for the management of patients with PsA. The presence of certain baseline clinical manifestations in patients represents a greater predictor than the different groups of ts/bDMARDs themselves in the risk of switching due to inefficacy. Sulfasalazine appears to be not effective as a concomitant treatment in these patients. The effect of glucocorticoids may reflect the disease activity, although further studies would be necessary including dosages. It is important to consider sex-specific differences and the number of previous courses of treatment in PsA daily management.

Conclusion

We did not find differences in the risk of switching between ts/bDMARDs groups after adjusting for confounders, allowing specific comparisons between TNFi and IL-17. In PsA patients, inflammatory low back pain, female sex, and the number of previous courses of ts/bDMARDs implied more switching due to inefficacy. Regarding concomitant therapies, glucocorticoids and sulfasalazine independently increased the risk of switching due to inefficacy.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Hospital Clinico San Carlos Ethics Review Board approval was obtained as a retrospective study (approval code 17/300-E) and waiver of informed consent was granted for the use of de-identified clinical records.

Consent for publication
Not applicable.

Author contributions
Dalifer Freites-Nuñez: Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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