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ORIGINAL RESEARCH

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)

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ABSTRACT

Introduction Tumour necrosis factor inhibitor (TNFi) agents are most often the first-choice biological treatment for patients with psoriatic arthritis (PsA). When their discontinuation is needed, a switch to another TNFi or to another therapeutic class may be considered. However, data supporting one approach over another are lacking.

Objective To compare the long-term persistence of classes of biologics in PsA patients with prior TNFi exposure.

Methods This nationwide cohort study involved the administrative healthcare database of the French health insurance scheme linked to the hospital discharge database. We included all adults with PsA starting a second-line biological after discontinuing a TNFi during 2015–2020. Persistence was defined as the time from biological initiation to discontinuation and was estimated by the Kaplan-Meier method. Comparison of persistence by biological class was performed with Poisson regression models with time divided into 6-month intervals.

Results We included 2975 patients: 1580 (53%) initiating a second TNFi, 426 (14%) an interleukin 12/23 inhibitor (IL-12/23i) and 969 (33%) an IL-17 inhibitor (IL-17i). Overall, 1-year and 3-year persistence rates were 42% and 17%, respectively. After adjustment, persistence was associated with treatment with an IL-17i (adjusted relative risk (RR_a) 0.79, 95% CI 0.71 to 0.87) or IL-12/23i (RR_a 0.69, 95% CI 0.61 to 0.79) vs a TNFi, with no significant difference between IL-12/23 and IL-17 inhibitors (RR_a 0.88, 95% CI 0.76 to 1.02).

Conclusions Overall, this real-life study shows low persistence for all biologics at 3 years in PsA patients previously exposed to a TNFi. However, persistence was higher with an IL-17i or IL-12/23i than a TNFi.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Current international recommendations for treating psoriatic arthritis (PsA) do not provide clear guidelines for the choice of second-line biologic after prior tumour necrosis factor inhibitor (TNFi) discontinuation.

⇒ Whether it is preferable to switch to another TNFi or to change the therapeutic class remains unclear.

WHAT THIS STUDY ADDS

⇒ We found better persistence of interleukin 17 (IL-17) and 12/23 (IL-12/23) inhibitors as compared with a TNFi as second-line therapy in PsA patients after previous TNFi exposure.

⇒ Persistence rates for all three therapeutic classes remained low at 3 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This first large comparative study suggests that long-term control of PsA requires multiple therapeutic lines, including molecules with different modes of action.

⇒ Predictors of biological persistence are needed to identify patient subgroups and optimise therapeutic sequences.

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory arthritis that combines articular and periarticular but also extra-articular manifestations. It affects 0.1%–0.2% of the general population and up to 20% of patients with psoriasis.[1–4] This disease can be severe, leading to irreversible joint damage and impaired quality of life.[5] With the rapid emergence of biologics and targeted therapies over the past two decades, treatments for PsA have evolved considerably. Tumour necrosis factor inhibitor (TNFi) agents but

also interleukin 12/23 inhibitor (IL-12/23i), IL-17 inhibitor (IL-17i) and Janus kinase inhibitor (JAKi) agents are now recommended for moderate to severe PsA when conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) fail to control disease or are not tolerated.[6–9] Currently, except in a few cases in which an extra-articular manifestation (very active psoriasis, inflammatory bowel disease, severe or repeated acute anterior uveitis) guides the prescriber's choice, no factor likely to influence the prescription of one therapeutic class over another is known at the population level. Nevertheless, owing to the longer time of use and cost of the treatments, TNFi agents are most often the first choice among biological treatments for patients with PsA.[6–9]

These treatments have been found effective and safe in various studies but can be discontinued because of primary or secondary failure or adverse events.[10] When discontinuation of the first-line TNFi is necessary, switching to another TNFi or to another therapeutic class may be considered.[6–9] Previous studies have shown that a second biologic, after a first TNFi, can achieve sustained improvements, although the proportion of responders is lower than with the first-line therapy.[11–13] In case of primary lack of effectiveness of the first TNFi, it seems logical to change targets and switch to another therapeutic class; in case of secondary loss of efficacy to the first TNFi, an alternative TNFi or another therapeutic class may be proposed.[9] However, data supporting one approach over the other are lacking.

Treatment persistence, defined as the time between initiation and discontinuation, is an important real-world outcome for assessing the total value of a drug and is a relevant indicator of the patient's level of interest. This criterion can be considered a composite of efficacy (a treatment considered ineffective is likely to be discontinued) and safety (a poorly tolerated treatment is likely to be discontinued) but also of patient satisfaction or preference and adherence.[14] Some studies have compared the persistence of biologics as first-line therapy in PsA,[15–17] but although this is an important issue, limited data are available on persistence of second-line treatment in real life, particularly after TNFi discontinuation.[18]

The current study aimed to compare the long-term persistence of second-line biologics in PsA patients with prior TNFi exposure.

METHODS
Data source and study design
This nationwide cohort study was based on data from the French national health insurance database (Système National des Données de Santé (SNDS)).[19] This database contains individualised anonymous health data and covers 98.8% of the French population (> 67 million individuals). Each person is identified by a unique anonymous number. The French healthcare system provides universal and mandatory coverage: all citizens have free, equal and universal access to healthcare for chronic diseases. As previously described, the SNDS contains exhaustive data for all reimbursements for health-related expenditure and outpatient medical care and nursing care prescribed or performed by health-care professionals, together with sociodemographic data (including year of birth, sex, area of residence, degree of social deprivation in the geographical area[20] and vital status). The database also includes data on all pharmacy-dispensed medications (number of units and date of reimbursed drug dispensation), date and nature of medical and paramedical interventions, information on patient eligibility for fully reimbursed care (long-term diseases) related to severe, costly chronic diseases, such as moderate to severe PsA, with codes assigned according to the International Classification of Diseases, 10th Revision (ICD-10) and detailed medical information concerning all admissions to French public-sector and private-sector hospitals (dates of hospital admission and discharge; ICD-10 code on discharge; medical procedures performed in hospital; and costly drugs, such as biologics, administered in hospital).[19 21] This large database has been used for several pharmacoepidemiological studies.[22 23]

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Study population and exposure definition
All adults (≥ 18 years old) with PsA registered in the SNDS were eligible for inclusion between 1 January 2015 and 31 December 2020. Adults with PsA were identified with a specific ICD-10 code (M07, except M07.4 and M07.5) according to an algorithm that was previously published.[2] Then, patients with at least one prescription of a biologic for PsA were identified. Next, we selected new users, defined as those who had not filled a prescription for one of these drugs for 1 year.[24] Finally, we included those starting a second-line biologic after discontinuing a TNFi (the most frequently prescribed class in first-line therapy). The drugs considered for second-line treatment included etanercept, infliximab, adalimumab, certolizumab and golimumab as the TNFi; ustekinumab as the IL-12/23i; secukinumab and ixekizumab as the IL-17i; and tofacitinib as the JAKi. Upadacitnib, a JAKi, and guselkumab, an IL-23i, available for PsA since late 2021, were not included as interventions. Drugs were identified in outpatient and hospital discharge databases. The index date was the date of the first reimbursement of a second-line biological during the study period. Treatment initiation was defined as delivery of one of the study molecules in the database between 1 January 2015 and 31 December 2020, in a patient who stopped a first-line TNFi during that period. The second therapeutic sequence differed from the first one. Only the second therapeutic sequence of biologic after discontinuing a first TNFi was considered in this analysis.

Outcome

The primary endpoint was persistence of a biologic (originator and biosimilar), defined as the time between second-line treatment initiation and discontinuation. We defined the discontinuation of treatment as a period of more than 60 days without filling a prescription for the same treatment after the period covered by the previous prescription, regardless of the molecule used. The period covered by a prescription was 30 days for most TNFi and IL-17i agents, 56 days for infliximab and 84 days for the IL-12/23i. These durations are periods on the frequency of administration of the different molecules.

Covariables

We collected data on basic demographics, including age, sex, complementary universal health coverage and French deprivation index (geographical indicator of social disadvantage specifically adapted to health studies of the French population,[20] inflammatory diseases associated with PsA (active skin psoriasis, inflammatory bowel disease, uveitis), variables used to calculate the Charlson Comorbidity Index adapted to the SNDS[25] and other comorbidities (essential hypertension, dyslipidaemia, dispensing of nicotine replacement therapy, varenicline or cytisine and other hospital discharge diagnoses related to tobacco, such as mental and behavioural disorders due to use of tobacco or problems related to tobacco use as a smoking proxy, morbid or complicated obesity, mood disorders). These covariables are defined in online supplemental table 1. Other drugs used as add-on therapies to biologics were studied: csDMARDs (methotrexate, leflunomide and sulfasalazine), non-steroidal anti-inflammatory drugs (NSAIDs) and prednisone. Exposure to drug combinations (combination of csDMARDs, NSAIDs or prednisone with a biologic) at baseline was defined as a period of ≤30 days between the reimbursements of the two treatments. We also collected the first-line TNFi molecule prescribed, the duration before discontinuation of this first line (early discontinuation if ≤6 months, late discontinuation if >6 months), the duration between discontinuation of the first line and prescription of the second line (initiation of second-line biological directly after first-line discontinuation or after a 'wash-out' period), and the number of consultations with a rheumatologist within the 2 years before the index date. During the follow-up, we compiled the vital status.

Statistical analyses

Categorical variables are reported as number (percentage). Quantitative variables are reported as median with IQR or mean±SD. There were no missing data in our database.

The main analysis was conducted on a per-protocol analysis. Patients were followed until biological switch, biological discontinuation, death or 31 December 2020, whatever came first.

Changes in treatment persistence over time were estimated for all biologics together, for each therapeutic class and for each molecule involved by using the Kaplan-Meier method. Therapeutic persistence overall, by therapeutic class and by molecule was also reported at 1, 2 and 3 years of follow-up. Poisson regression models with time split into 6-month intervals were used to estimate the adjusted relative risk (RR_a) and 95% CIs. Poisson regression is most often used for modelling count data and contingency tables; however, the extension to survival analysis via a piecewise exponential model can serve as an alternative approach to the Cox model,[26] which was not applicable here because of the violation of the proportional-hazards assumption. We adjusted for covariables collected at the index date and related to the primary endpoint at p<0.1 on univariate analysis but also for covariables known to be factors associated with the primary endpoint (age, sex, Charlson Comorbidity Index, smoking proxy, morbid or complicated obesity, treatments within 2 years such as csDMARDs and/or NSAIDs and/or prednisone).

We performed prespecified subgroup analyses of patients: (1) with and without active skin psoriasis (requiring topical therapies) at the index date; (2) with early (ie, ≤6 months) or late (ie, >6 months) first-line TNFi discontinuation and (3) with initiation of second-line biologic directly after first-line discontinuation (ie, switch) or after a 'wash-out' period.

To assess the sensitivity of the estimated RR_a with respect to several possible models, we performed the following additional analyses: (1) an intention-to-treat analysis: follow-up was censored at the time of treatment switch, death or 31 December 2020, whatever came first; (2) treatment discontinuation defined by >90 days without filling a prescription for the same treatment after the period covered by the previous prescription; and we added post hoc sensitivity analyses and (3) after excluding patients with no consultation with a rheumatologist within 2 years and within 6 months.

All tests were two tailed, and results were considered statistically significant at p<0.05. Analyses were performed with SAS Enterprise Guide V.7.1 (SAS Institute).

RESULTS

Description of the cohort population

During our study period, we identified 11 685 patients with PsA new users of biologics, including 8424 (72%) initiating a TNFi. Of these, 2975 patients started a second-line biologic (mean age 47.4±12.4 years; 35% men; median follow-up 229 days (IQR 113–501)), including 1580 (53%) initiating a second TNFi, 969 (33%) an IL-17i and 426 (14%) an IL-12/23i (table 1). Only 54 patients initiated the JAKi (tofacitinib), so they were not subsequently analysed.

The most frequently prescribed first-line TNFi was adalimumab (48% of patients), followed by etanercept (33% of patients). At initiation of the second-line biologic, 1035 (35%), 1076 (36%) and 477 (16%) patients had a coprescription of a csDMARD, NSAIDs

Table 1 Characteristics of the cohorts by biological molecule

Characteristic	Total biologics n=2975	TNF inhibitors n=1580 (53.1)	IL-17 inhibitor n=969 (32.6)	IL-12/23 inhibitors n=426 (14.3)
Follow-up				
Median (IQR) of follow-up (days)	229 (113–501)	186 (98–457)	246 (126–506)	352 (174–642)
Death	22 (0.7)	10 (0.6)	5 (0.5)	7 (1.6)
Sociodemographic				
Age (mean±SD) (years)	47.4±12.4	47.6±12.5	47.7±12.1	46.4±13.0
Men	1028 (34.5)	503 (31.8)	371 (38.3)	154 (36.1)
Complementary universal health coverage	403 (13.5)	205 (13.0)	134 (13.8)	64 (15.0)
Associated inflammatory diseases (within 2 years)				
Active psoriasis	792 (26.6)	301 (19.0)	305 (31.5)	186 (43.7)
IBD	235 (7.9)	110 (7.0)	46 (4.7)	79 (18.5)
Uveitis	15 (0.5)	11 (0.7)	3 (0.3)	1 (0.2)
Charlson comorbidity index				
0 point (less comorbid)	1808 (60.8)	982 (62.1)	585 (60.4)	241 (56.6)
1–2 points	988 (33.2)	511 (32.3)	322 (33.2)	155 (36.4)
3–4 points	140 (4.7)	69 (4.4)	47 (4.8)	24 (5.6)
≥ 5 points (more comorbid)	39 (1.3)	18 (1.1)	15 (1.5)	6 (1.4)
Comorbidities				
Essential hypertension	455 (15.3)	247 (15.6)	144 (14.9)	64 (15.0)
Diabetes	273 (9.2)	273 (9.2)	87 (9.0)	53 (12.4)
Dyslipidaemia	163 (5.5)	92 (5.8)	54 (5.6)	17 (4.0)
Chronic pulmonary disease	408 (13.7)	212 (13.4)	137 (14.1)	59 (13.8)
Heart failure	27 (0.9)	17 (1.1)	7 (0.7)	3 (0.7)
Kidney failure	41 (1.4)	14 (0.9)	18 (1.9)	9 (2.1)
Liver disease	68 (2.3)	28 (1.8)	24 (2.5)	16 (3.8)
Therapies/codes related to tobacco	210 (7.1)	98 (6.2)	82 (8.5)	30 (7.0)
Morbid or complicated obesity	336 (11.3)	152 (9.6)	118 (12.2)	66 (15.5)
Mood disorders	203 (6.8)	109 (6.9)	70 (7.2)	24 (5.6)
First-line TNF inhibitor				
Adalimumab	1423 (47.8)	607 (38.4)	261 (61.3)	555 (57.3)
Certolizumab	250 (8.4)	129 (8.2)	28 (6.6)	93 (9.6)
Etanercept	969 (32.6)	653 (41.3)	101 (23.7)	215 (22.2)
Golimumab	312 (10.5)	178 (11.3)	34 (7.9)	100 (10.3)
Infliximab	21 (0.7)	13 (0.8)	2 (0.5)	6 (0.6)
TNF inhibitor first-line discontinuation				
Early discontinuation	1408 (47.3)	794 (50.2)	428 (44.2)	186 (43.7)
Late discontinuation	1567 (52.7)	786 (49.8)	541 (55.8)	240 (56.3)
Initiation of a second line bDMARD				
Directly after first-line discontinuation	2321 (78.0)	1294 (81.9)	736 (75.9)	291 (68.3)
After a 'wash-out' period	654 (22.0)	286 (18.1)	233 (24.1)	135 (31.7)
Non-biological therapies within 2 years				
csDMARDs	2140 (71.9)	1179 (74.6)	665 (68.6)	296 (69.5)
NSAIDs (on at least three occasions)	2258 (75.9)	1255 (79.4)	285 (66.9)	718 (74.1)
Prednisone (on at least three occasions)	1009 (33.9)	604 (38.2)	117 (27.5)	288 (29.7)

Continued

Table 1 Continued

Characteristic	Total biologics n=2975	TNF inhibitors n=1580 (53.1)	IL-17 inhibitor n=969 (32.6)	IL-12/23 inhibitors n=426 (14.3)
Co-therapies at second-line therapy initiation				
csDMARDs	1035 (34.8)	621 (39.3)	303 (31.3)	111 (26.1)
NSAIDs	1076 (36.2)	588 (37.2)	363 (37.5)	125 (29.3)
Prednisone	477 (16.0)	277 (17.5)	154 (15.9)	46 (10.8)
Co-therapies during follow-up				
csDMARDs	1433 (48.2)	853 (54.0)	410 (42.3)	170 (39.9)
NSAIDs (on at least three occasions)	1477 (49.6)	861 (54.5)	197 (46.2)	419 (43.2)
Prednisone (on at least three occasions)	602 (20.2)	384 (24.3)	69 (16.2)	149 (15.4)
Care consumption				
Rheumatologist consultation within 2 years				
mean±SD	4.1±3.5	4.6±3.6	3.9±3.5	2.7±3.0
0	529 (17.8)	194 (12.3)	190 (19.6)	145 (34.0)
1	291 (9.8)	137 (8.7)	109 (11.2)	45 (10.6)
≥ 2	2153 (72.4)	1247 (78.9)	670 (69.1)	236 (55.4)

Data are n (%) unless indicated.
bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; IBD, inflammatory bowel disease; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor.

and/or prednisone, respectively. These drugs were prescribed during follow-up for 48%, 49% and 20% of patients, respectively.

Persistence of biologics among the cohorts

During the follow-up, 2168 (73%) patients discontinued their second-line biologic. Kaplan-Meier survival analyses revealed overall persistence of 43% in the first year of treatment (table 2). The persistence decreased over time: 25% at the end of the second year and 17% at the end of the third year. Figure 1 summarises the Kaplan-Meier analyses for each biological class in the cohort.

Comparison of persistence between biological classes and sensitivity analyses

The results of the main analysis are in figure 2. The crude and adjusted RR are described in online supplemental table 2. After adjustment, therapeutic persistence was associated with treatment with an IL-17i (RR_a 0.79, 95% CI 0.71 to 0.87) or IL-12/23i (RR_a 0.69, 95% CI 0.61 to 0.79) vs a TNFi, with no significant difference between IL-12/23i and IL-17i treatment (RR_a 0.88, 95% CI 0.76 to 1.02).

Increased therapeutic persistence was associated with male sex and older age and decreased persistence with exposure to non-biological therapies (csDMARDs, NSAIDs, prednisone) within 2 years before the index date (data not shown).

Overall, the results did not differ between patients with and without active psoriasis, patients who stopped their first line early (ie, ≤6 months) or late (ie, >6 months), or patients who initiated their second-line directly after first-line discontinuation or after a 'wash-out' period (table 3).

Sensitivity analyses results were consistent with main analysis (online supplemental table 3).

Table 2 Persistence (%) for biological molecules at 1, 2 and 3 years of follow-up among the cohort (Kaplan-Meier)

Persistance rate (%)	1 year	2 years	3 years
Total (n=2975)	**42.6**	**25.0**	**17.2**
TNFi (n=1580)	**36.8**	**21.3**	**15.1**
Adalimumab (n=660)	39.9	23.1	16.4
Certolizumab (n=252)	33.2	20.0	13.1
Etanercept (n=428)	32.2	17.8	12.1
Golimumab (n=220)	38.0	22.2	18.7
Infliximab (n=20)	65.0	47.3	29.5
IL-17i (n=969)	46.3	28.0	19.0
Secukinumab (n=820)	46.4	27.4	18.4
Ixekizumab (n=149)	45.7	33.5	26.7
IL-12/23i (n=426)			
Ustekinumab	**56.0**	**31.9**	**20.6**

ILi, interleukin inhibitor; TNFi, tumour necrosis factor inhibitor.

DISCUSSION

In this nationwide study involving 2975 patients with PsA, we sought to compare the long-term persistence
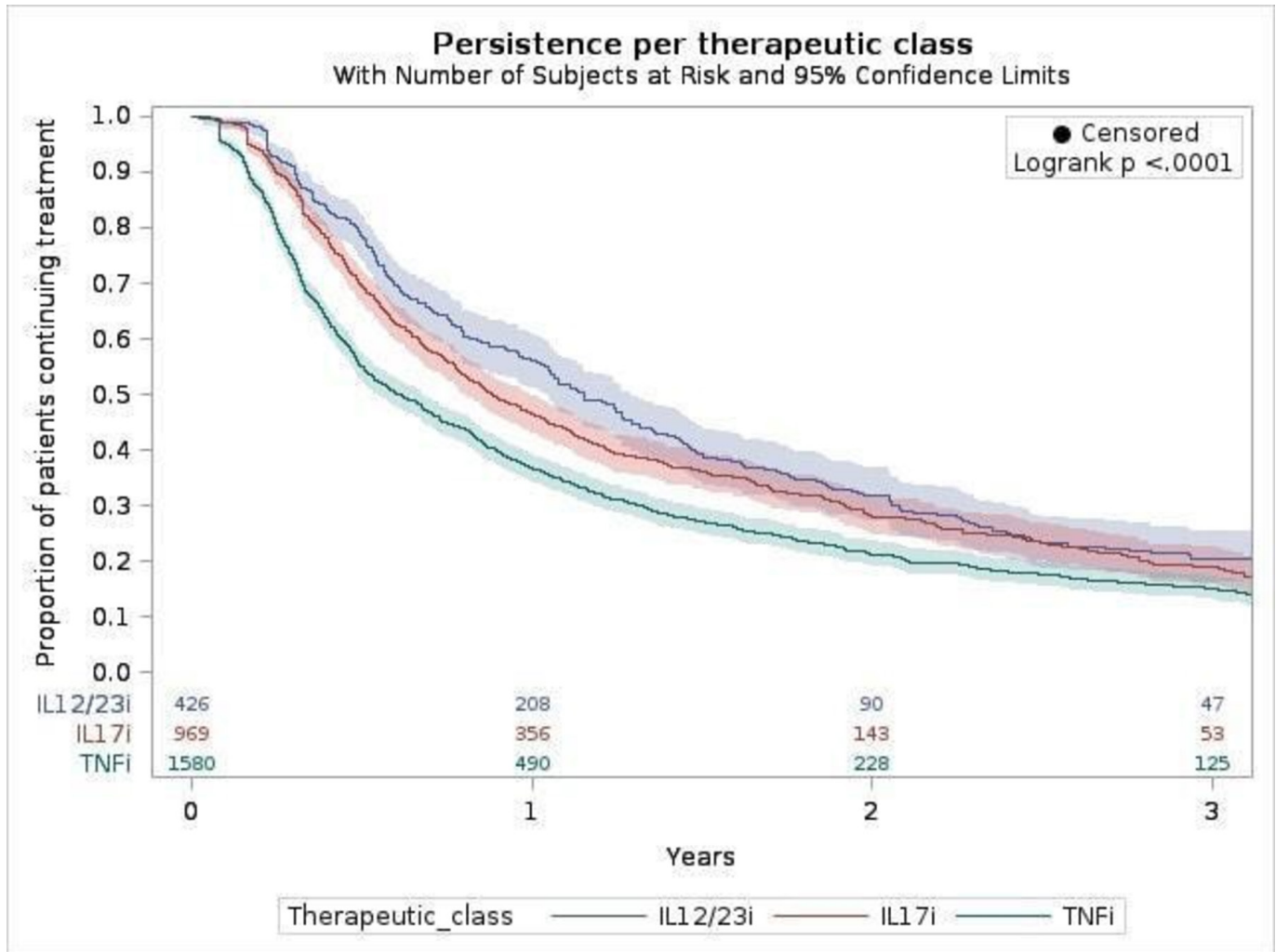
Figure 1 Kaplan-Meier estimates of biological treatment persistence in the cohort. ILi, interleukin inhibitor; TNFi, tumour necrosis factor inhibitor.

of second-line biologics in an unselected population of patients with prior TNFi exposure. In the first year, the overall persistence of biologics was 43% and decreased markedly over time, to 25% at the end of the second year and 17% at the end of the third year. After adjustment, IL-17i and IL-12/23i treatment was associated with higher persistence as compared with TNFi treatment, with no significant difference between IL-17i and IL-12/23i treatment.

Comparison of current biological persistence rates with previously reported results is complicated by the diversity of study methods, definition used, healthcare settings and patient populations.[14] Nonetheless, studies seem to agree that biologics are less effective and that therapeutic persistence is lower with second-line treatment than in treatment-naive patients.[10 27] The 1-year persistence rates reported in the literature are highly variable but seem to be consistent (although in the low range) with those measured here: 35%–75% for TNFi,[11 27–31] 60%–80% for IL-17i[32 33] and 50%–71% for IL-12/23i[34] in biologic-experienced patients. In our study, persistence was 37%, 46% and 56%, respectively. In addition, longer-term persistence rates are less frequently reported and show even more considerable heterogeneity. This observation may be due to small sample sizes and potential selection bias, which could limit the extrapolation of literature data. As has been reported for randomised clinical trials, for registries and national cohorts, the representativeness of patients included may be questioned. Indeed, these studies have several inclusion and exclusion criteria that may lead to a particular selection of the study population.[35] Moreover, they are also subject to bias related to lost to follow-up (persistence is probably lower in patients lost to follow-up than in those still followed), the country's healthcare organisation, and the physician–patient relationship. In contrast, our study was based on a large-scale, exhaustive analysis of reimbursement data from a non-selected population, with no lost to follow-up, which avoids these biases.

There are some data comparing biologics after first-line discontinuation in axial spondyloarthritis[18 36]; nevertheless, few studies have focused on PsA. Our results are important because, to our knowledge, this is the largest study comparing the persistence of second-line biologics
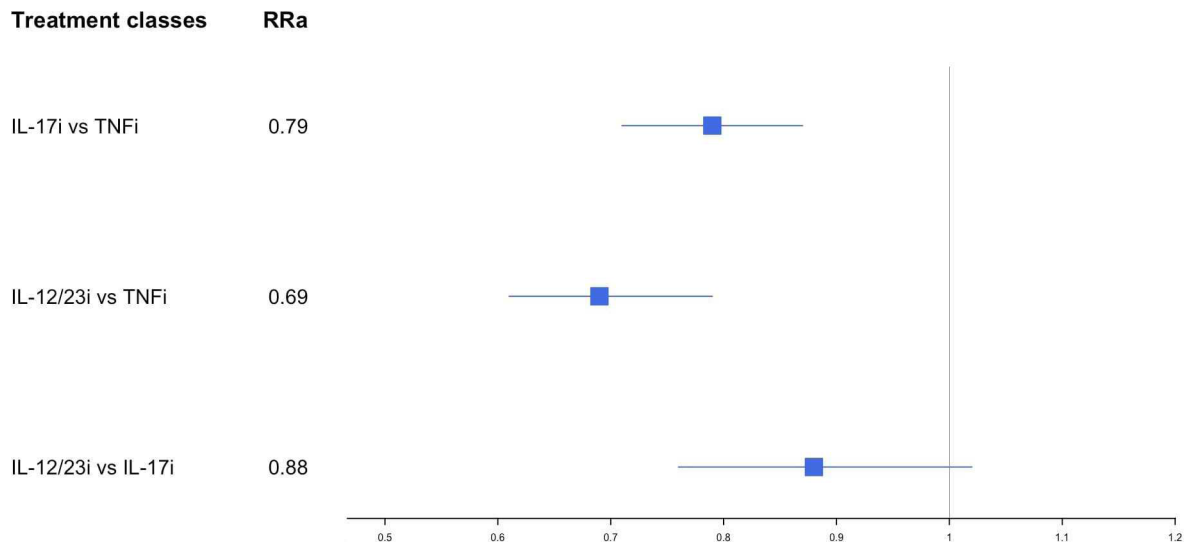
Treatment classes	RRa

Figure 2 Forest plot of comparison of treatment persistence by treatment classes analysed using poisson regression models with time split into 6-month intervals (main analyses) analyses adjusted for age, sex, Charlson Comorbidity Index, smoking proxy, morbid or complicated obesity, non-biological therapies within 2 years (csDMARDs and/or NSAIDs and/or prednisone). csDMARDs, conventional synthetic biologial disease-modifying anti-rheumatic drug; ILi, interleukin inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; RRa, adjusted relative ratio; TNFi, tumour necrosis factor inhibitor.

in PsA patients with prior TNFi exposure in a real-world setting. Our findings suggest higher persistence of IL-17i and IL-12/23i than TNFi agents, with no difference between IL-17i and IL-12/23i agents. These results are consistent with smaller observational studies in which biologic-experienced patients initiating secukinumab (an IL-17i)[28 37] or ustekinumab (the IL-12/23i)[38] showed better persistence than those initiating a TNFi. Similarly, subgroup analyses from PSOLAR (a registry including patients with psoriasis receiving systemic therapy) among patients with concurrent PsA confirmed by a rheumatologist found better persistence of ustekinumab than a TNFi.[39] Of note, Lindström *et al* found no significant difference in treatment retention between secukinumab and adalimumab (a TNFi) in PsA, regardless of the treatment line.[40]

However, only 1-year persistence was assessed, and few patients were second-line users (430 for adalimumab and 282 for secukinumab). Finally, the results of a recent study comparing secukinumab with ustekinumab in PsA did not find any difference in persistence between these two molecules after prior exposure to one biologic (subgroup analysis).[15] Nevertheless, of note, the long-term persistence of all biologics remained low in our study.

This study has limitations. First, although we adjusted on baseline characteristics known to affect treatment persistence, we cannot exclude residual confounding. Indeed, our analyses are limited by the availability of data for some factors, in particular, information on disease activity, precise weight of potential psoriasis itself at the time of prescription and the absence of directly available

Table 3 Comparison of treatment persistence by treatment classes in subgroup analyses using poisson regression models with time split into 6-month intervals

	IL-17i vs TNFi		IL-12/23i vs TNFi		IL-12/23i vs IL-17i	
	RR$_a$ (95% CI)	P value	RR$_a$ (95% CI)	P value	HR$_w$ (95% CI)	P value
Psoriasis						
Active (n=792)	0.85 (0.69 to 1.03)	0.10	**0.68 (0.54 to 0.85)**	<10^{-3}	0.80 (0.63 to 1.02)	0.07
Inactive (n=2183)	**0.77 (0.69 to 0.87)**	<10^{-4}	**0.73 (0.62 to 0.86)**	<10^{-4}	0.95 (0.79 to 1.13)	0.54
TNFi first-line discontinuation						
Early discontinuation (n=1408)	**0.79 (0.69 to 0.91)**	<10^{-3}	**0.67 (0.55 to 0.81)**	<10^{-4}	0.85 (0.69 to 1.05)	0.13
Late discontinuation (n=1567)	**0.79 (0.69 to 0.91)**	<10^{-3}	**0.73 (0.61 to 0.87)**	<10^{-4}	0.91 (0.75 to 1.11)	0.35
Initiation of a second line bDMARD						
Directly after first-line discontinuation (ie, switch) (n=2321)	**0.79 (0.71 to 0.88)**	<10^{-4}	**0.72 (0.62 to 0.84)**	<10^{-4}	0.91 (0.77 to 1.08)	0.28
After a 'wash-out' period (n=654)	**0.75 (0.61 to 0.93)**	<10^{-3}	**0.61 (0.46 to 0.79)**	<10^{-4}	0.81 (0.61 to 1.06)	0.14

Values in bold correspond to significant results.
bDMARD, biological disease-modifying anti-rheumatic drug; HR$_w$, weighted HR; ILi, interleukin inhibitor; RR$_a$, adjusted relative ratio; TNFi, tumour necrosis factor inhibitor.

data on smoking and obesity (although proxies for severe forms were used). In addition, the information on the hospital prescriber is incomplete, which could partly explain why some patients did not have a consultation with a rheumatologist. Nevertheless, the sensitivity analysis after excluding these patients showed stable results. Second, we defined drug exposure based on healthcare reimbursement data, which are not necessarily equivalent to days of use. However, adherence rates are typically higher for biologics than for other treatment categories.[41] New users would ideally be those using a treatment for the first time (ie, naive patients). To assess this parameter, lifetime treatment use data would be necessary, however this framework is most often not available, and in pharmacoepidemiology a wash-out window (period without delivery of the studied treatment) of 6–12 months is usual.[42] It must be borne in mind that some of the new user patients defined above may have received a bDMARD at an undocumented moment before the start of the study. In addition, some of the drugs studied were on the market years ago and others only recently, which may account for a change in persistence. However, our study period was restricted to a recent time frame (2015–2020), and to avoid channelling bias (ie, a confounding effect of assessing certain treatments in specific subgroups), we limited our analyses to a second therapeutic biological sequence after discontinuing a first TNFi. In addition, the drugs within each class were not analysed separately. Nevertheless, despite fluctuations due to small numbers in some treatment groups (notably for infliximab for which the numbers did not allow for reliable persistence rates to be estimated), persistence was similar between the different molecules of each therapeutic class. Finally, the database analysed in this study did not specify why a patient stopped filling prescriptions for a biologic: loss of efficacy, occurrence of a side effect, presence of comorbidities or extrinsic factors such as a wider range of treatment options.[43] Nevertheless, most patients (78%) initiated a second line of biologics directly after stopping the first-line, resulting in a low probability of discontinuation of the first-line due to an adverse event. In this subgroup, the results were stable: a better persistence of IL-17i and IL-12/23i vs TNFi was still observed. It should be noted, however, that there are many possible reasons for the gap between the two lines, and that a number of adverse events would still allow for a minimal interval between treatments.

This study has several strengths. Our cohort included a large number of patients from a national exhaustive database providing health-insurance data with a quality and consistency plan ensuring homogeneous data processing.[19] This framework minimises selection bias. Furthermore, we adjusted our analyses for several confounders to accurately estimate the persistence of biologics and to control for channelling bias. Of note, TNFi, IL-12/23i and IL-17i agents are recommended second-line therapies for moderate to severe disease[8] and in France, each physician is free to choose the biologics labelled for PsA; no discontinuation of biologics was related to cost sharing. We also limited classification bias by using a reproducible,

well-accepted definition of drug persistence.[27] Finally, several sensitivity analyses were performed and supported the integrity of our results.

CONCLUSIONS

This real-life study shows low persistence for all three therapeutic classes at 3 years in PsA patients receiving second-line therapy after TNFi exposure. It highlights that long-term control of PsA most often requires multiple therapeutic lines, including molecules with different modes of action. However, these persistence rates seem higher with IL-17i or IL-12/23i than TNFi treatment. Further studies, including head-to-head randomised trials, would be useful to confirm these findings and identify patient subgroups that may benefit from one management strategy over another.

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