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Original Article

Evaluation of the Risk of Psoriatic Arthritis in Patients With Psoriasis Undergoing Biological Treatment. Global Population Study (TRINETX)

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ABSTRACT

Introduction: Psoriatic arthritis (PsA) is an inflammatory condition associated with psoriasis (PsO), with variable prevalence ranging from 6% to 42%. Despite the known link between PsO and PsA, reliable biomarkers for predicting PsA onset remain elusive. Recent research has identified risk determinants including obesity, onychopathy, PsO severity, and familial predisposition. Detecting PsO patients at risk of developing PsA is crucial given the disparity in treatment efficacy post-PsA establishment.
Objective: This study evaluates the rate of PsA among PsO patients undergoing targeted biologic therapy as first- or second-line therapy.
Material and methods: We conducted a retrospective cohort study utilizing TriNetX database and identified PsO patients receiving biologic therapy. Propensity score matching was applied to adjust for potential confounders. Patients were followed for 5 years, and the incidence rate of PsA was determined. Statistical analyses were performed to estimate relative risks and hazard ratios.
Results: Among 1,175,000 PsO patients, 41,990 received first-line biologic therapy. Following matching, patients initiating IL12/23i or IL23i exhibited a lower PsA incidence rate vs TNFi. Second-line IL12/23i and IL23i treatment also showed a lower PsA risk vs TNFi. IL17i did not significantly differ from TNFi in PsA risk.
Conclusion: This study highlights differential PsA risk among PsO patients on biologic therapy, suggesting potential benefits of IL12/23i and IL23i in PsA prevention. Prospective studies are needed to confirm these findings and optimize PsA prevention strategies.

Introduction

Psoriatic arthritis (PsA) is an inflammatory arthropathy intricately linked with psoriasis (PsO). The prevalence of PsA exhibits notable variability from 6% to 42%, with an incidence rate of 2.7 per 100 patient-years.[1] PsO stands as the foremost predisposing factor for PsA development, with 70–80% of PsA patients having exhibited PsO a decade prior to onset, on average.[2]

Despite advances in understanding the pathophysiology of PsA, identifying reliable biomarkers to predict its onset remains challenging. Zabotti et al.[3] reviewed evidence on risk determinants for PsA, including obesity, onychopathy, PsO severity, and a family history of PsA. Additionally, the presence of unexplained joint pain and subclinical inflammation observed in the imaging modalities (ultrasound or magnetic resonance) can indicate a heightened risk of transitioning to PsA within a shorter timeframe, within 1–3 years.

The importance of identifying PsO patients at elevated risk of progressing to PsA arises from the observed disparity in treatment efficacy vs cutaneous signs, wherein fewer than 50% of patients achieve clinical remission once PsA has been established.[4] These circumstances drive research into the feasibility of preventing PsA development or intercepting its progression.[5] Given the established correlation between PsO severity and PsA risk,[3] several investigations have explored the prospect of aggressive systemic therapies, such as biologic therapies, as potential preventive measures vs PsA development.[1,6–13] In the current landscape, biologic therapies represent some of the most effective therapies for PsO. However, their capacity to prevent PsA onset and whether all mechanisms exert uniform effects, remain areas of active investigation.

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The objective of this study was to compare the incidence of PsA among patients with PsO treated with targeted biologic agents, stratified by drug class and by use as first- or second-line therapy.

Material and methods

We conducted a retrospective cohort study and examined data from the TriNetX Global Collaborative Network that provided access to electronic health records from 120 health care organizations spread across 17 countries.[14] The analysis included data from 2010 (or before) up to December of 2023, selecting patients diagnosed with PsO (ICD-10-CM code L40) on biologic drugs. Exclusion criteria included prior biologic therapy or documented history of PsA (ICD-10-CM code L40.5) before the index date. The index date, which marks the beginning of the observation, was established when the patient started the first biologic agent after the diagnosis of psoriasis. Patients with failed cohort treatment and switched to a new therapy were not included in the final analysis.

The primary endpoint was defined as PsA diagnosis during follow-up, with patients censored upon this diagnosis or at follow-up termination without PsA, whichever occurred first. Statistical analysis employed Propensity Score 1:1 Matching (PSM) to adjust for sex, time since PsO diagnosis, obesity (BMI >30), alcohol/tobacco use, onychopathy, and prior conventional disease-modifying anti-rheumatic drugs (cDMARDs) use. All eligible TriNetX patients were included. Descriptive statistics were reported for clinical characteristics. Biologics were categorized into cohorts according to their mechanism of action [TNF inhibitors (TNFi), IL12/23 inhibitors (IL12/23i), IL17 inhibitors (IL17i) and IL 23 inhibitors (IL23i)], they were followed for 5 years and cumulative PsA incidence rate was calculated. The absolute risk reduction (ARR), expressed as the number of PsA cases avoided per 1000 patients, and the relative risk (RR) comparing PsA incidence rates between cohorts were calculated. The risk of developing PsA during follow-up was expressed as hazard ratios (HR) with 95% confidence intervals (CI), using first-line TNF inhibitor (TNFi) exposure as the reference.

Furthermore, the cumulative incidence rate of PsA was evaluated among the study cohorts (IL12/23i, IL23i and IL17i) in second-line patients (patients with previously failed TNFi), comparing them with the cohort of TNFi as first-line therapy. This analysis focused on the subsequent 3 years post-index date to maintain an adequate sample size.

Additionally, comparisons between the IL23i and IL17i cohorts, both naïve and second-line therapy, were conducted.

Our hospital records are reviewed to verify the accuracy of the data.

Initial cohort comparisons utilized the chi-square test (or Fisher's exact test) for categorical variables and *t*-Student test (or Wilcoxon's 2-sample rank sum test) for continuous variables. Time-to-event analysis employed Kaplan–Meier curves, with HRs calculated using multivariable Cox proportional analysis and significance assessed via the log-rank test.

Statistical analysis and data management were performed using SAS 9.4 software, with significance set at $p < 0.05$.

Results

Within the global network, 1,175,000 patients PsO were identified, of whom 928,200 had no prior diagnosis of PsA. Among this subgroup, 41,990 patients received first-line targeted biologic therapy: TNFi (24,700 patients, 58.82%), IL12/23i (6020 patients, 14.33%), IL23i (5830 patients, 13.88%), and IL17i (5440 patients, 12.95%). Following PSM, patients available for comparison with TNFi treatment were 5640 for iIL23, 5480 for IL12/23i, and 4910 for iIL17.

Table 1 illustrates the characteristics of adjusted and matched cohorts of patients with PsO initiating first-line biologic therapy who meet the selection criteria. Although patients show similarities in most variables, discrepancies in the incidence rate of liver disease and congestive heart failure are observed between the TNFi, IL12/23i, and IL17i cohorts.

Regarding the onset of PsA cases, naïve patients treated with IL12/23i and IL23i demonstrated lower PsA incidence compared to TNFi, with a RR of 0.66 (0.58–0.75) and 0.40 (0.35–0.46), an ARR of 64 and 33 cases of PsA avoided/1000 patients and HR 0.678 (0.593, 0.777) and 0.579 (0.496, 0.657 respectively. Conversely, the difference in PsA incidence between IL17i and TNFi was not significant (Figs. 1a and 2).

Regarding the onset of PsA, biologic-naïve patients treated with IL12/23 inhibitors (IL12/23i) or IL23 inhibitors (IL23i) demonstrated a lower rate of PsA vs those on TNF inhibitors (TNFi), with relative risks (RR) of 0.66 (95% CI, 0.58–0.75) and 0.40 (95% CI, 0.35–0.46), respectively. The corresponding ARRs were 64 and 33 PsA cases avoided per 1000 patients, and HR were 0.678 (95% CI, 0.593–0.777) and 0.579 (95% CI, 0.496–0.657), respectively. Conversely, the difference in PsA incidence between IL17i and TNFi was not statistically significant (Figs. 1a and 2).

Table 2 illustrates the characteristics of cohorts of PsO patients without arthritis initiating second-line therapy with IL12/23i, IL17i, or IL23i vs those on first-line TNFi. No significant differences were detected in baseline characteristics across these groups. The incidence rate of new cases of PsA during a 3-year follow-up was also lower in the IL12/23i and IL23i groups vs the TNFi group, with RR of 0.76 (0.62–0.93) and 0.60 (0.44–0.82), an ARR of 19 and 40 cases avoided/1000 patients and HR of 0.696 (0.565, 0.857) and 0.708 (0.506, 0.991), respectively (Figs. 1b and 3). This differentiation was not observed in the group of patients on iIL17, in which the risk of developing PsA was higher vs TNFi as first-line therapy (Fig. 3), with HR of 1.2 (1.039, 1.601).

Furthermore, the incidence rate of PsA was compared between the IL17i and IL23i cohorts in both first- and second-line therapies. It was observed that the risk of developing PsA was significantly lower with IL23i than with IL17i in both therapy lines (Figs. 1c and 4).

All reviewed records had a correct diagnosis and treatment. The only error detected is in the treatment line: 13-15% records were actually posterior lines.

Discussion

Our investigation revealed a reduced risk of PsA development associated with IL12/23i and IL23i vs TNFi. Conversely, IL17i did not exhibit a significant difference in PsA risk compared to TNFi.

Although these findings are consistent with those reported by Singla et al.,[12] in a U.S. cohort, our study cohort is substantially larger. While they primarily investigated inflammatory arthritis in adult psoriatic patients initiating biologic therapy, including PsA in some sensitivity analyses, our study focused on patients diagnosed with PsO without arthritis initiating biologic therapy for the first time. We compared the risk of developing PsA across different classes of biologics, after adjusting for risk factors such as sex, time since PsO onset, obesity (BMI >30), alcohol/tobacco abuse, nail psoriasis, and cDMARDs.

Another single-center study with 1023 patients found no significant differences in PsA prevalence among different biologic classes. However, PsA was numerically lower in patients on IL17i (1.9%) and IL23i or IL12/23i (6.1%) vs TNFi (8.8%).[13]

Moreover, our investigation extended also to PsO patients without arthritis who initiated IL12/23i, IL17i, or IL23i as second-line therapy, contrasting them with individuals with TNFi as first-line. This methodological approach aligns more closely with real-world clinical practices, in regions such as Spain, where the public health system recommends initiating therapy with TNFi biosimilars for the management of moderate-to-severe PsO cases requiring biologic therapy. Even in the second-line scenario, we observed a diminished risk of developing PsA with IL12/23i and IL23i vs TNFi 3 years after starting first-line therapy.

These findings are consistent with the established understanding of IL23 in the pathogenesis of enthesitis, which marks the onset of PsA[15];

Table 1
Characteristics of adjusted and matched cohorts of patients with psoriasis without arthritis initiating first-line biological treatment.

	IL12/23i (5480)	TNFi (5480)	*p*-Value	IL17i (4910)	TNFi (4910)	*p*-Value	IL23i (5640)	TNFi (5640)	*p*-Value	IL23i (4730)	IL17i (4730)	*p*-Value
Primary outcome events/person-years	350	530	–	460	520	–	240	600	–	200	440	–
Cumulative incidence of arthritis, per 100 person-years	6.4	9.7	–	9.4	10.6	–	4.3	10.6	–	4.2	9.3	–
Current age, years	49 ± 19.2	49.9 ± 18.8	0.007	51.2 ± 17.0	54.5 ± 17.3	<0.001	50.8 ± 16.1	54.7 ± 16.5	<0.001	51.1 ± 16.0	51.3 ± 16.7	0.570
Age at index, years	44.1 ± 18.6	43.8 ± 18.3	0.355	48.2 ± 16.8	48.4 ± 16.8	0.495	48.7 ± 16.1	48.6 ± 16.2	0.884	48.9 ± 16.0	48.2 ± 16.5	0.032
Sex												
Male	2630 (48.0%)	2620 (47.8%)	0.848	2470 (50.3%)	2430 (49.5%)	0.419	2840 (50.4%)	2860 (50.7%)	0.706	2350 (49.7%)	2380 (50.3%)	0.537
Female	2790 (50.9%)	2810 (51.3%)	0.702	2360 (48.1%)	2410 (49.1%)	0.313	2730 (48.4%)	2720 (48.2%)	0.851	2320 (49.0%)	2290 (48.4%)	0.537
Race/ethnicity												
White	3930 (71.7%)	3920 (71.5%)	0.832	3210 (65.4%)	3480 (70.9%)	<0.001	3910 (69.3%)	3890 (69.0%)	0.683	3360 (71.0%)	3110 (65.8%)	<0.001
Black or African American	350 (6.14%)	420 (7.6%)	0.009	370 (7.5%)	390 (7.9%)	0.450	330 (5.9%)	410 (7.3%)	0.002	280 (5.9%)	350 (7.4%)	0.004
Asian	180 (3.3%)	160 (2.9%)	0.270	250 (5.1%)	130 (2.6%)	<0.001	280 (5.0%)	150 (2.7%)	<0.001	260 (5.5%)	240 (5.1%)	0.358
Other or not available	770 (14.1%)	760 (13.9%)	0.728	800 (16.3%)	660 (13.4%)	<0.001	670 (11.9%)	750 (13.3%)	0.023	580 (12.3%)	760 (16.1%)	<0.001
Comorbidities before the index date												
Overweight, obesity and other hyperalimentation	910 (16.6%)	880 (16.1%)	0.438	1010 (20.6%)	1010 (20.6%)	1	1270 (22.5%)	1250 (22.2%)	0.651	1000 (21.1%)	1000 (21.1%)	1
Obesity (body-max index >30 kg/m^2)	1090 (19.9%)	1050 (19.1%)	0.335	1180 (24.0%)	1200 (24.4%)	0.638	1210 (21.5%)	1190 (21.1%)	0.645	1090 (23.0%)	1090 (23.0%)	1
Tobacco use or tobacco use disorder	530 (9.7%)	530 (9.7%)	1	600 (12.2%)	570 (11.6%)	0.350	700 (12.4%)	680 (12.1%)	0.566	560 (11.8%)	570 (12.1%)	0.751
Alcohol related disorders	170 (3.1%)	190 (3.5%)	0.283	220 (4.5%)	200 (4.1%)	0.319	270 (4.8%)	230 (4.1%)	0.067	200 (4.2%)	210 (4.4%)	0.614
Onycholysis	50 (0.9%)	30 (0.5%)	0.024	40 (0.8%)	40 (0.8%)	1	60 (1.1%)	40 (0.7%)	0.045	30 (0.6%)	40 (0.8%)	0.230
Chronic obstructive pulmonary disease	190 (3.5%)	180 (3.3%)	0.597	220 (4.5%)	230 (4.7%)	0.629	220 (3.9%)	260 (4.6%)	0.062	180 (3.8%)	220 (4.7%)	0.041
Congestive heart failure	170 (3.1%)	120 (2.2%)	0.003	220 (4.5%)	150 (3.1%)	<0.001	230 (4.1%)	180 (3.2%)	0.012	180 (3.8%)	220 (4.7%)	0.041
Diabetes mellitus	640 (11.7%)	630 (11.5%)	0.765	740 (15.1%)	740 (15.1%)	1	790 (14.0%)	870 (15.4%)	0.033	660 (14.0%)	720 (15.2%)	0.081
Liver disease	280 (5.1%)	370 (6.8%)	<0.001	320 (6.5%)	370 (7.5%)	0.048	410 (7.3%)	420 (7.4%)	0.718	330 (7.0%)	310 (6.6%)	0.413
Renal disease	170 (3.1%)	190 (3.5%)	0.248	170 (3.5%)	190 (3.9%)	0.283	190 (3.4%)	220 (3.9%)	0.131	160 (3.4%)	160 (3.4%)	1
DMARDs before the index date												
Methotrexate	650 (11.9%)	630 (11.5%)	0.552	480 (9.8%)	470 (9.6%)	0.733	450 (8.0%)	440 (7.8%)	0.727	410 (8.7%)	420 (8.9%)	0.716
Cyclosporine	210 (3.8%)	150 (3.5%)	0.308	210 (4.3%)	200 (4.1%)	0.614	200 (3.5%)	180 (3.2%)	0.297	180 (3.8%)	170 (3.6%)	0.586
Acitretin	170 (3.1%)	130 (2.4%)	0.019	170 (3.5%)	120 (2.4%)	0.003	130 (2.3%)	90 (1.6%)	0.006	130 (2.7%)	130 (2.7%)	1
Apremilast	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Upadacitinib	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Tofacitinib	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Deucravacitinib	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
DMARDb after the index date												
TNF inhibitor												
Adalimumab	0 (0%)	3450 (63.0%)	<0.001	0 (0%)	3190 (65.0%)	<0.001	0 (0%)	3710 (65.8%)	<0.001	0 (0%)	0 (0%)	–
Etanercept	0 (0%)	1340 (24.5%)	<0.001	0 (0%)	1150 (23.4%)	<0.001	0 (0%)	1270 (22.5%)	<0.001	0 (0%)	0 (0%)	–
Infliximab	0 (0%)	810 (14.8%)	<0.001	0 (0%)	630 (12.8%)	<0.001	0 (0%)	710 (12.6%)	<0.001	0 (0%)	0 (0%)	–
Certolizumab	0 (0%)	120 (2.2%)	<0.001	0 (0%)	120 (2.4%)	<0.001	0 (0%)	140 (2.5%)	<0.001	0 (0%)	0 (0%)	–
Golimumab	0 (0%)	70 (1.3%)	<0.001	0 (0%)	80 (1.6%)	<0.001	0 (0%)	80 (1.4%)	<0.001	0 (0%)	0 (0%)	–
IL12/23 inhibitor												
Ustekinumab	5480 (100%)	0 (0%)	<0.001	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
IL17 inhibitor												
Secukinumab	0 (0%)	0 (0%)	–	2750 (56.0%)	0 (0%)	<0.001	0 (0%)	0 (0%)	–	0 (0%)	2670 (56.4%)	<0.001
Ixekizumab	0 (0%)	0 (0%)	–	2160 (44.0%)	0 (0%)	<0.001	0 (0%)	0 (0%)	–	0 (0%)	2070 (43.8%)	<0.001
Brodalumab	0 (0%)	0 (0%)	–	70 (1.4%)	0 (0%)	<0.001	0 (0%)	0 (0%)	–	0 (0%)	70 (1.5%)	<0.001
IL23 inhibitor												
Guselkumab	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	2130 (37.8%)	0 (0%)	<0.001	1790 (37.8%)	0 (0%)	<0.001
Tildrakizumab	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	210 (3.7%)	0 (0%)	<0.001	190 (4.0%)	0 (0%)	<0.001
Risankizumab	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	3330 (59.0%)	0 (0%)	<0.001	2780 (58.8%)	0 (0%)	<0.001

Table 2
Characteristics of adjusted and matched cohorts of psoriatic patients without arthritis initiating second-line treatment with iIL12/23, iIL17, or iIL23 compared to those receiving first-line iTNF.

	IL12/23i (2580)	TNFi (2580)	*p*-Value	IL17i (1700)	TNFi (1700)	*p*-Value	IL23i (1010)	TNFi (1010)	*p*-Value	IL23i (1010)	IL17i (1010)	*p*-Value
Primary outcome events/person-years	160	210	–	180	160	–	60	100	–	60	110	–
Cumulative incidence of arthritis, per 100 person-years	6.2	8.1	–	10.6	9.4	–	5.9	9.9	–	5.0	10.9	–
Current Age, years	44.8 ± 18.8	45.8 ± 18.7	0.058	50.7 ± 16.5	53.5 ± 16.7	<0.001	50.3 ± 15.1	54.4 ± 16.0	<0.001	50.3 ± 15.1	51.0 ± 16.3	0.330
Age at index, years	39.7 ± 18.0	39.6 ± 17.9	0.857	47.0 ± 16.1	47.4 ± 16.1	0.467	47.8 ± 15.1	48.1 ± 15.4	0.599	47.8 ± 15.1	47.2 ± 16.0	0.382
Sex												
Male	1110 (43.0%)	1100 (42.6%)	0.778	770 (45.3%)	780 (45.9%)	0.731	520 (51.5%)	520 (51.5%)	1	520 (51.5%)	510 (50.5%)	0.656
Female	1450 (56.2%)	1470 (57.0%)	0.574	920 (54.1%)	920 (54.1%)	1	490 (48.5%)	490 (48.5%)	1	490 (48.5%)	500 (49.5%)	0.656
Race/ethnicity												
White	1930 (74.8%)	1880 (72.9%)	0.113	1190 (70.0%)	1260 (74.1%)	0.007	740 (73.3%)	740 (73.3%)	1	740 (73.3%)	720 (71.3%)	0.320
Black or African American	210 (8.1%)	220 (8.5%)	0.614	140 (8.2%)	140 (8.2%)	1	70 (6.9%)	80 (7.9%)	0.396	70 (6.9%)	80 (7.9%)	0.396
Asian	60 (2.3%)	80 (3.1%)	0.087	70 (4.1%)	50 (2.9%)	0.063	60 (5.9%)	40 (4.0%)	0.281	60 (5.9%)	50 (5.0%)	0.327
Other or not available	280 (10.9%)	330 (12.8%)	0.031	220 (12.9%)	200 (11.8%)	0.297	110 (10.9%)	140 (13.9%)	0.043	110 (10.9%)	140 (13.9%)	0.043
Comorbidities before the index date												
Overweight, obesity and other hyperalimentation	530 (20.5%)	530 (20.5%)	1	480 (28.2%)	500 (29.4%)	0.449	280 (27.7%)	300 (29.7%)	0.325	280 (27.7%)	270 (26.7%)	0.617
Obesity (body-max index >30 kg/m^2)	1270 (49.2%)	1220 (47.3%)	0.040	490 (28.8%)	520 (30.6%)	0.260	220 (21.8%)	220 (21.8%)	1	220 (21.8%)	210 (20.8%)	0.587
Tobacco use or tobacco use disorder	370 (14.3%)	340 (13.2%)	0.225	310 (18.2%)	310 (18.2%)	1	160 (15.8%)	160 (15.8%)	1	160 (15.8%)	150 (14.9%)	0.027
Alcohol related disorders	80 (3.1%)	60 (2.3%)	0.087	110 (6.5%)	110 (6.5%)	1	60 (5.9%)	60 (5.9%)	1	60 (5.9%)	60 (5.9%)	1
Onycholysis	40 (1.6%)	30 (1.2%)	0.229	30 (1.8%)	10 (0.6%)	0.001	20 (2.0%)	20 (2.0%)	1	20 (2.0%)	10 (1.0%)	0.066
Chronic obstructive pulmonary disease	80 (3.1%)	90 (3.5%)	0.435	90 (5.3%)	90 (5.3%)	1	40 (4.0%)	40 (4.0%)	1	40 (4.0%)	50 (5.0%)	0.281
Congestive heart failure	70 (2.7%)	60 (2.3%)	0.374	50 (2.9%)	60 (3.5%)	0.332	30 (3.0%)	40 (4.0%)	0.224	30 (3.0%)	30 (3.0%)	1
Diabetes mellitus	260 (10.1%)	310 (12.0%)	0.026	300 (17.6%)	300 (17.6%)	1	160 (15.8%)	180 (17.8%)	0.234	160 (15.8%)	160 (15.8%)	1
Liver disease	230 (8.9%)	170 (6.6%)	0.002	160 (9.4%)	160 (9.4%)	1	100 (9.9%)	100 (9.9%)	1	100 (9.9%)	90 (8.9%)	0.446
Renal disease	120 (4.7%)	90 (3.5%)	0.035	80 (4.7%)	80 (4.7%)	1	50 (5.0%)	50 (5.0%)	1	50 (5.0%)	40 (4.0%)	0.281
DMARDs before the index date												
Methotrexate	780 (30.2%)	790 (30.6%)	0.762	440 (25.9%)	440 (25.9%)	1	220 (21.8%)	200 (19.8%)	0.273	220 (21.8%)	220 (21.8%)	1
Cyclosporine	150 (5.8%)	140 (5.4%)	0.546	100 (7.1%)	100 (5.9%)	0.163	50 (5.0%)	40 (4.0%)	0.281	50 (5.0%)	50 (5.0%)	1
Acitretin	150 (5.8%)	140 (5.4%)	0.546	90 (5.3%)	90 (5.3%)	1	60 (5.9%)	50 (5.0%)	0.327	60 (5.9%)	60 (5.9%)	1
Apremilast	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Upadacitinib	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Tofacitinib	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Deucravacitinib	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
DMARDb after the index date												
TNF inhibitor												
Adalimumab	1700 (65.9%)	1620 (62.8%)	0.020	1370 (80.6%)	1140 (67.1%)	<0.001	840 (83.2%)	660 (65.3%)	<0.001	840 (83.2%)	830 (82.2%)	0.557
Etanercept	710 (27.5%)	630 (24.4%)	0.011	430 (25.3%)	390 (22.9%)	0.109	210 (20.8%)	240 (23.8%)	0.109	210 (20.8%)	250 (24.8%)	0.034
Infliximab	660 (25.6%)	430 (16.7%)	<0.001	100 (5.9%)	250 (4.7%)	<0.001	40 (4.0%)	130 (12.9%)	<0.001	40 (4.0%)	60 (5.9%)	0.040
Certolizumab	170 (6.6%)	70 (2.7%)	<0.001	50 (2.9%)	40 (2.4%)	0.285	40 (4.0%)	20 (2.0%)	0.009	40 (4.0%)	30 (3.0%)	0.224
Golimumab	30 (1.2%)	40 (1.6%)	0.229	40 (2.4%)	20 (1.2%)	0.009	10 (1.0%)	20 (2.0%)	0.066	10 (1.0%)	30 (3.0%)	0.001
IL12/23 inhibitor												
Ustekinumab	2580 (100%)	0 (0%)	<0.001	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
IL17 inhibitor												
Secukinumab	0 (0%)	0 (0%)	–	1060 (62.4%)	0 (0%)	<0.001	0 (0%)	0 (0%)	–	0 (0%)	630 (62.4%)	<0.001
Ixekizumab	0 (0%)	0 (0%)	–	650 (38.2%)	0 (0%)	<0.001	0 (0%)	0 (0%)	–	0 (0%)	390 (38.6%)	<0.001
Brodalumab	0 (0%)	0 (0%)	–	20 (1.2%)	0 (0%)	<0.001	0 (0%)	0 (0%)	–	0 (0%)	10 (1.0%)	<0.001
IL23 inhibitor												
Guselkumab	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	340 (33.7%)	0 (0%)	<0.001	340 (33.7%)	0 (0%)	<0.001
Tildrakizumab	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	40 (4.0%)	0 (0%)	<0.001	40 (4.0%)	0 (0%)	<0.001
Risankizumab	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	650 (64.4%)	0 (0%)	<0.001	640 (63.4%)	0 (0%)	<0.001

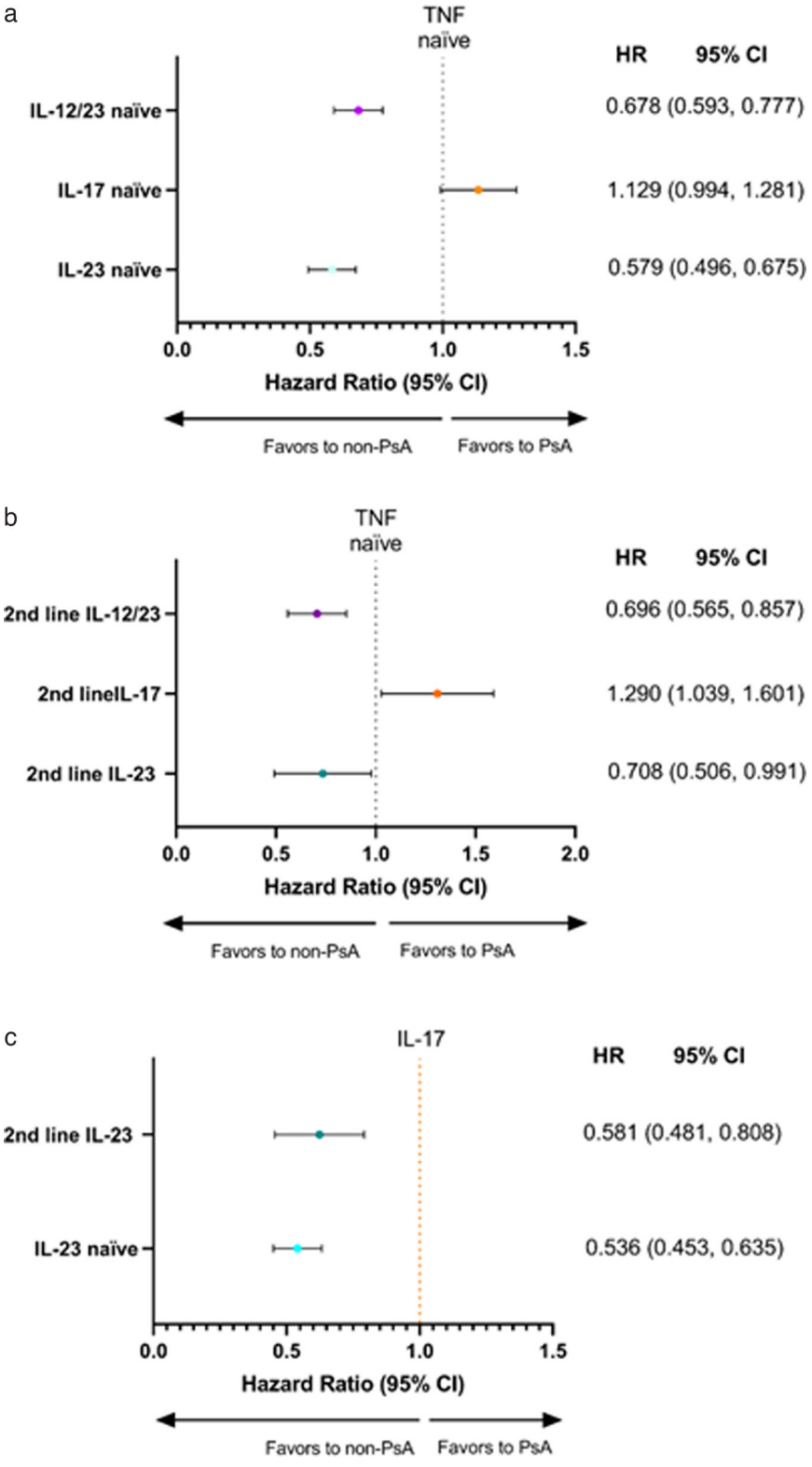
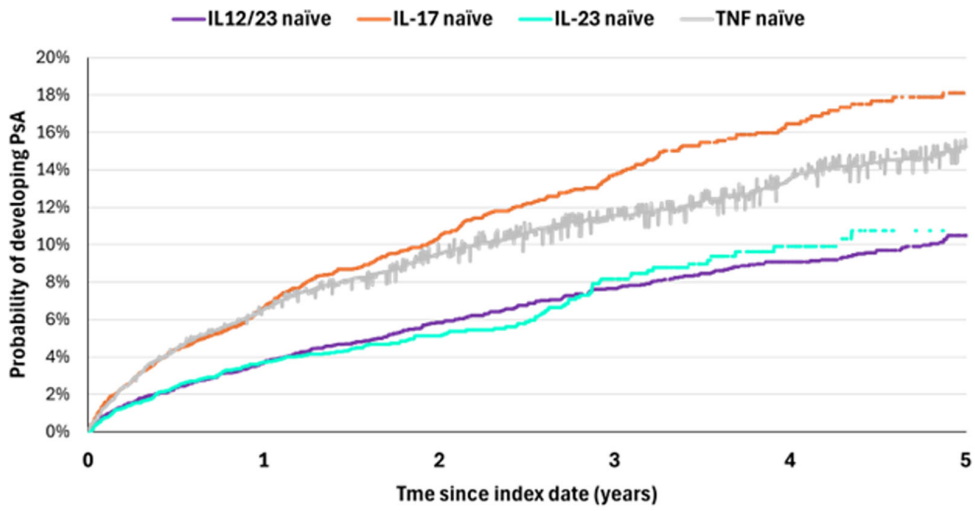
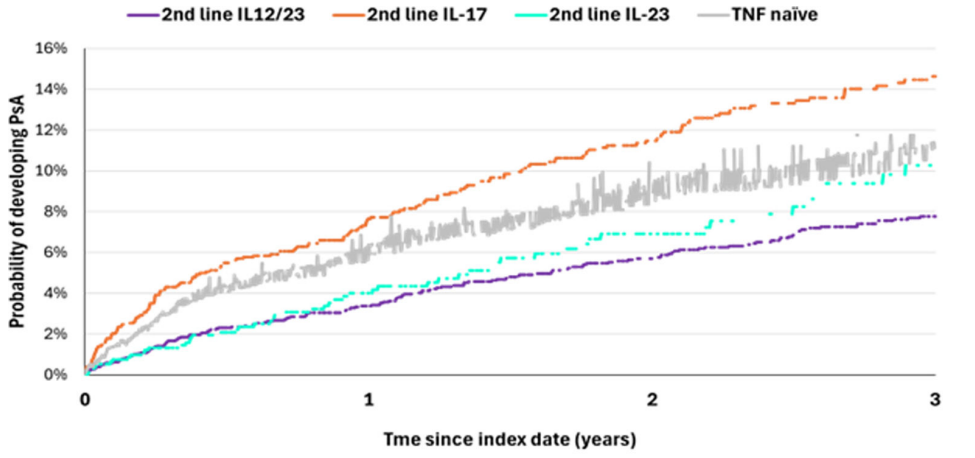


Fig. 1. Forest plot depicting adjusted HRs for time to psoriatic arthritis for patients with psoriasis without arthritis initiating some first-line biologic therapy (a), patients with psoriasis without arthritis initiating treatment with IL12/23i, IL17i, or IL23i as second-line therapy vs those on TNFi as first-line therapy (b) and patients with psoriasis without arthritis initiating treatment with IL17i and IL23i as both first- and second-line therapies.



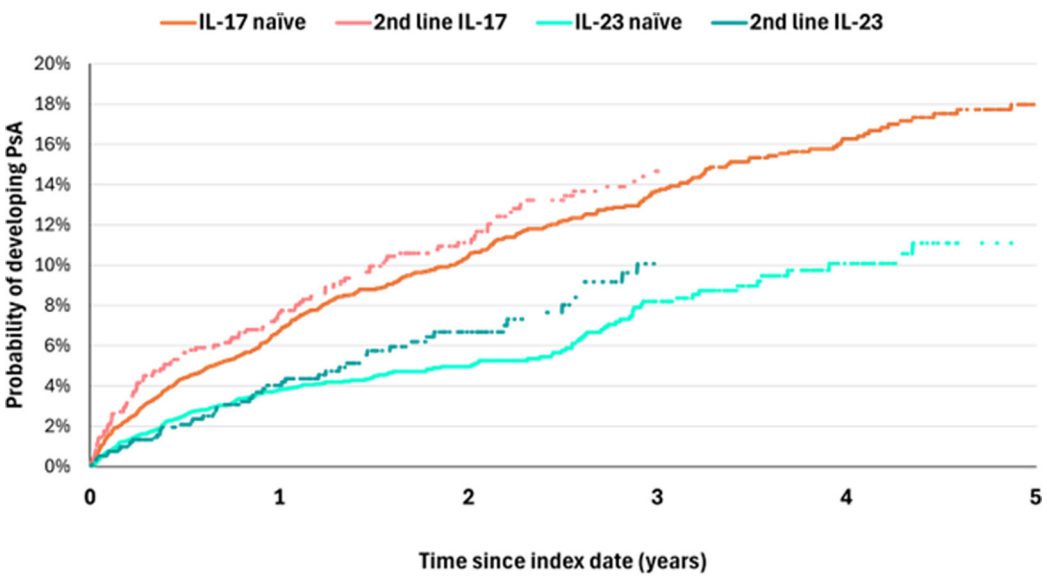
Cohort	Patients in cohort	Patients with outcome	Risk (%)	RR	AAR (cases avoided/1000 naïve patients)	NNT	RRR
IL-12/23 naïve	5480	350	6.4	0.66	33	30.3	34%
TNF naïve	5480	530	9.7	(0.58 - 0.75)			
IL-17 naïve	4910	460	9.4	0.88	12	83.3	12%
TNF naïve	4910	520	10.6	(0.78 - 1.00)			
IL-23 naïve	5640	240	4.3	0.40	64	15.9	60%
TNF naïve	5640	600	10.6	(0.35 - 0.46)			

Fig. 2. Time to psoriatic arthritis among patients with psoriasis without arthritis initiating some first-line biologic therapy. RR: relative risk; ARR: absolute risk reduction.



Cohort	Patients in cohort	Patients with outcome	Risk (%)	RR	AAR (cases avoided/1000 second line patients)	NNT	RRR
2nd line IL-12/23	2580	160	6.2	0.76	19	52.6	24%
TNF naïve	2580	210	8.1	(0.62 - 0.93)			
2nd line IL-17	1700	180	10.6	1.18	-12	-83.3	-18%
TNF naïve	1700	160	9.4	(0.91 - 1.41)			
2nd line IL-23	1010	60	5.9	0.60	40	25,0	40%
TNF naïve	1010	100	9.9	(0.44 - 0.82)			

Fig. 3. Time to psoriatic arthritis among patients with psoriasis without arthritis initiating treatment with IL12/23i, IL17i, or IL23i as second-line therapy vs those on TNFi as first-line therapy. RR: relative risk; ARR: absolute risk reduction.



Cohort	Patients in cohort	Patients with outcome	Risk (%)	RR	AAR (cases avoided/1000 naïve or second line patients)	NNT	RRR
IL-23 naïve	4730	200	4.2	0.45	51	19.6	55%
IL-17 naïve	4730	440	9.3	(0.38 - 0.53)			
2nd line IL-23	1010	60	5.9	0.55	50	20	45%
2nd line IL-17	1010	110	10.9	(0.41 - 0.74)			

Fig. 4. Time to psoriatic arthritis among patients with psoriasis without arthritis initiating treatment with IL17i and IL23i as both first- and second-line therapy. RR: relative risk; ARR: absolute risk reduction.

perhaps once activated, other pathways of immunity explain why IL17i or TNFi are more effective than IL12/23i and IL23i in established PsA with a high inflammatory burden, especially in axial forms.

This study has several limitations, primarily related to its observational and retrospective design, which limits the ability to establish causal relationships and necessitates cautious interpretation of the findings, as they are primarily hypothesis-generating. Potential inaccuracies in diagnostic coding and biases in the selection of biologic therapies may also be present within the dataset. In particular, protopathic bias – whereby treatment is initiated in patients with early or subclinical PsA before a formal diagnosis – is possible and may have led to an overestimation of the observed associations. Despite these limitations, the study has notable strengths. It represents one of the largest and longest investigations of patients with psoriasis treated with biologic agents, thereby providing valuable insights and contributing substantially to the existing body of evidence in this field.

Prospective studies are needed to determine whether treatment strategies for patients with psoriasis aimed at preventing PsA onset should differ from those used once PsA is established. In other words, should prevention and interception of PsA be managed in the same way?

Conflicts of interest

Raquel Rivera acted as a consultant and/or speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Abbvie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Incyte, Johnson & Johnson, Leo Pharma, Lilly, Novartis, Pfizer and UCB.

Carmen García-Donoso acted as a consultant and/or speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Abbvie, Almirall, Amgen, Bristol Myers Squibb, Johnson & Johnson, Leo Pharma, Lilly, Novartis and UCB.

Beatriz Joven collaborated as a consultant, speaker for Amgen, UCB, Abbvie, Johnson & Johnson, Novartis, Lilly and has participated as a researcher in Abbvie, Johnson & Johnson, Novartis, Lilly, Bristol Myers Squibb trials/studies.

Jose Luis Pablos collaborated as a consultant, speaker for Amgen, UCB, Abbvie, Johnson & Johnson, Novartis, Lilly and has participated as a researcher in Abbvie, Johnson & Johnson, Novartis, Lilly, Bristol Myers Squibb trials/studies.

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