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Original Research

Drug retention of TNF versus IL-23 inhibitors in psoriatic arthritis: a multicenter real-life cohort study

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Abstract

Background: Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by musculoskeletal and cutaneous involvement. While TNF inhibitors (TNFi) are commonly used as first-line biologic therapies, treatment failure is frequent. IL-23 inhibitors (IL23i) represent an alternative mechanism of action (MoA), but direct real-world comparisons between these drug classes remain limited.

Objectives: To compare the effectiveness of TNFi versus IL23i in real-life PsA patients.

Design: This multicenter retrospective observational study is part of the BIRRA (BIologics Retention Rate Assessment) project. Consecutive patients with PsA—classified according to the CASPAR criteria—were screened across 29 Italian rheumatology referral centers.

Methods: We analyzed 1418 therapeutic lines for PsA initiated between 2019 and 2024 across 29 Italian rheumatology centers. Treatment lines were categorized as TNFi or IL23i based on the drug's MoA. Demographic, clinical, and treatment-related data were collected. The primary outcome was treatment retention, evaluated by Kaplan–Meier survival analysis. A Cox proportional hazards model adjusted for a propensity score (PS) was used to account for confounding factors.

Results: Among 1418 prescriptions (1270 TNFi; 148 IL23i), IL23i lines were associated with older age, longer disease duration, higher baseline disease activity, and more prior biologic disease-modifying antirheumatic drugs exposure. Despite this, no significant difference in crude retention was observed. After PS adjustment, IL23i prescriptions showed significantly longer treatment retention than TNFi (hazard ratio 0.53; 95% confidence interval: 0.31–0.90; $p = 0.02$). Axial or mixed PsA phenotype and higher baseline Disease Activity in Psoriatic Arthritis score were associated with lower retention.

Conclusion: In this real-world cohort, IL23i prescriptions demonstrated comparable treatment persistence compared to TNFi, even in more challenging clinical scenarios. These findings support the inclusion of IL23i as a valid therapeutic option in PsA. Prospective studies are needed to confirm their positioning in treatment algorithms.

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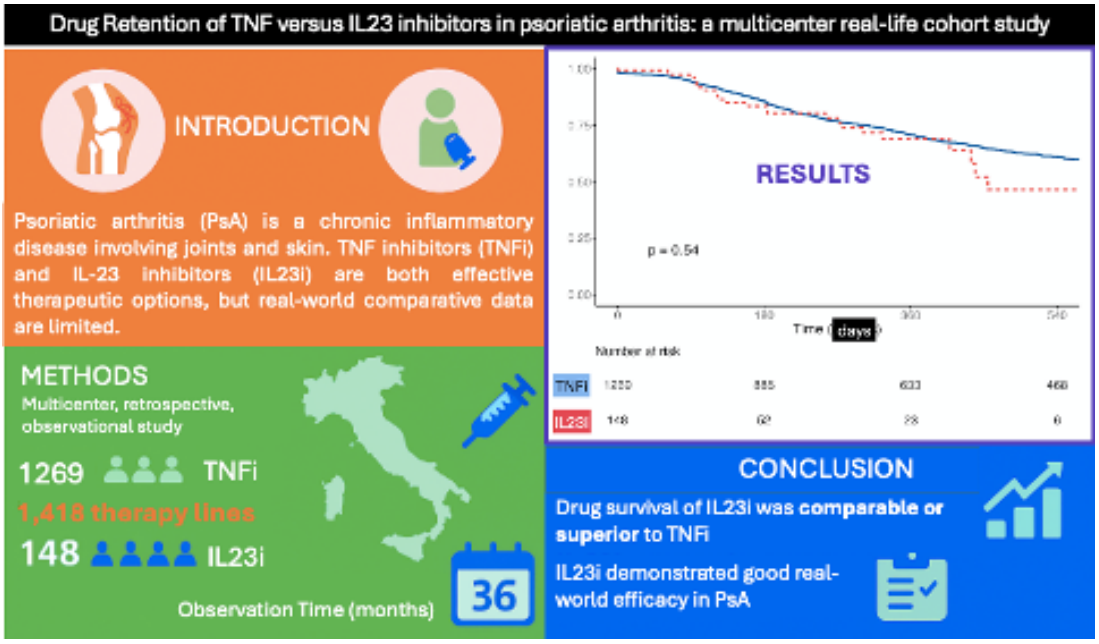
Infographic



This infographic summarizes the results of a multicenter observational study comparing the real-world effectiveness of TNF inhibitors (TNFi) and IL-23 inhibitors (IL23i) in Psoriatic Arthritis (PsA). Based on 1418 therapy lines from Italian rheumatology centers, the study found that IL23i demonstrated comparable or superior drug retention compared to TNFi, despite being used more frequently in treatment-refractory patients. These findings support IL23i as a valuable therapeutic option and highlight the potential benefit of switching the mechanism of action after TNFi failure.

Keywords: drug retention rate, IL23i, psoriatic arthritis, TNFi

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease affecting approximately 0.25% of the population. It is characterized by pain, joint swelling, stiffness, bone erosions, and new bone formation. Among psoriatic diseases, cutaneous involvement (e.g., psoriasis) frequently occurs, further impacting quality of life and increasing the healthcare burden.[1,2]

Clinical guidelines and treatment recommendations aim to support therapeutic decision-making in PsA, especially in light of its heterogeneous clinical presentation and the rapid expansion of available therapies. In the last 5 years, six new therapies have been approved for psoriatic disease, including four first-in-class agents.[3,4]

Musculoskeletal manifestations of psoriatic disease include peripheral arthritis, axial involvement, enthesitis, and dactylitis. These often coexist with skin and nail involvement, fatigue, sleep disturbances, reduced work productivity, and social impairment. Moreover, comorbidities such as uveitis, inflammatory bowel disease (IBD), metabolic syndrome, cardiovascular disease, and mood disorders further complicate management strategies.[2,5]

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The data underlying this article will be shared on reasonable request to the corresponding author

Several biologic disease-modifying antirheumatic drugs (bDMARDs) are currently approved for PsA, including TNF inhibitors (TNFi, adalimumab, etanercept, infliximab, golimumab, certolizumab pegol), IL inhibitors (ustekinumab, secukinumab, ixekizumab), and co-stimulation modulators (abatacept). Oral options include apremilast and JAK inhibitors (tofacitinib, upadacitinib). More recently, IL-23 inhibitors (IL23i)—guselkumab and risankizumab—have been introduced as additional therapeutic options.[3,4]

Although TNFi remain the most commonly prescribed first-line agents, increasing real-world experience with alternative mechanisms of action has prompted interest in comparative effectiveness studies. However, direct head-to-head comparisons between different bDMARD classes remain scarce. The 2018 SPIRIT-H2H trial comparing ixekizumab and adalimumab is one of the few examples providing direct evidence.[6]

In this context, network meta-analyses have emerged as valuable tools to integrate both direct and indirect evidence, offering broader insights into the relative efficacy and safety of available treatments.[7–11]

This study aims to contribute real-world comparative data on TNFi and IL23i use in PsA, addressing an area of growing clinical relevance as therapeutic strategies diversify.

The main aim of this multicenter study was to compare the effectiveness of TNFi versus IL23i in real-life PsA patients.

Methods

Study design and ethics approval

This retrospective observational study is part of the BIRRA (BIologics Retention Rate Assessment) project. The study protocol received approval from the Comitato Etico dell'Area Vasta Emilia Nord (protocol code 34,713; approval date: August 28, 2019) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participating patients. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[12]

Study population

Consecutive patients with PsA (classified according to the CASPAR criteria[13]) were screened across 29 Italian rheumatology referral centers. Eligible participants were required to meet the following criteria: age >17 years, current or previous treatment with TNFi and/or IL23i started between 2019 and 2024, and a primary indication for bDMARDs due to PsA.

Data collection

Demographic data, including age, sex, and HLA-B27 status, were collected alongside disease characteristics at baseline (e.g., PsA phenotype—peripheral, axial, or mixed—disease duration, and disease activity). Treatment-related variables included the line and duration of bDMARD therapy, reasons for discontinuation (if applicable), and concomitant use of csDMARDs or steroids at baseline. Disease activity was assessed using validated clinimetric tools, including the Disease Activity in Psoriatic Arthritis score (DAPSA),[14] the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[15] and the Ankylosing Spondylitis Disease Activity Score (ASDAS),[16] according to their original descriptions and validation studies.

Axial involvement was defined as investigator-reported axial disease, based on clinical judgment (presence of inflammatory back pain and/or imaging findings compatible with axial PsA when available). Formal ASAS classification criteria were not systematically applied across centers in routine practice.

Disease activity was assessed according to PsA phenotype: DAPSA for peripheral involvement and ASDAS and/or BASDAI for axial involvement. Reasons for discontinuation were categorized as lack of efficacy, loss of efficacy, adverse events, or death. Based on the mechanism of action (MoA), bDMARD prescriptions were stratified into two groups: TNFi and IL23i. Baseline was defined as the index date, that is, the start of the therapeutic line under observation. Disease duration was calculated from PsA diagnosis to index date. Baseline covariates refer to the clinical status at or immediately prior to line initiation.

Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQR), while categorical

variables were reported as percentages. Treatment retention, a proxy for effectiveness and tolerability, was estimated using the Kaplan–Meier method. Patients lost to follow-up or who discontinued bDMARDs for non-articular reasons (e.g., psoriasis, IBD, or uveitis) were censored in the survival analysis. Switching from an originator bDMARD to its biosimilar was not considered a discontinuation event.

Discontinuations driven by non-articular reasons (e.g., psoriasis-related treatment changes, IBD, or uveitis) were censored in the survival analysis, as the primary outcome was focused on musculoskeletal drug retention. This approach was chosen to isolate treatment durability in relation to articular disease control.

To account for potential confounding factors, a propensity score (PS; based on sex, PsA involvement, concomitant csDMARDs/steroids at baseline, year of prescription, age, disease activity, and disease duration) was incorporated into a Cox proportional hazards regression model, along with the treatment group (TNFi or IL23i).

Subgroup comparisons were performed using the Mann–Whitney *U* test for continuous variables and the Chi-squared test for categorical variables, as appropriate. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using Jamovi software (version 2.3; https://www.jamovi.org).

The PS for receiving an IL23i versus a TNFi was estimated using a multivariable logistic regression model including age, sex, disease duration, baseline disease activity, musculoskeletal pattern, concomitant csDMARDs and glucocorticoids, year of prescription, and treatment line (first line vs later lines), which was included a priori given its strong impact on drug retention.

The primary survival analysis was performed using a Cox proportional hazards model adjusted for the PS (as a continuous variable) and key clinical covariates, with cluster-robust standard errors using patient ID as the clustering unit to account for multiple therapeutic lines per patient.

As sensitivity analyses, we applied stabilized inverse probability weighting and PS-stratified Cox models (quintiles of the PS), which yielded consistent estimates in terms of direction and magnitude of effect.

The unit of analysis is the therapeutic line. Each line was classified by its MoA (TNFi or IL-23i). Patients who received multiple lines could contribute >1 observation, each with an independent risk period. "Survival time" (drug retention) was measured from the index date = start of that line to discontinuation (any cause) or censoring (last follow-up).

To account for within-patient correlation due to repeated lines, we used cluster-robust (sandwich) standard errors with the patient as the clustering unit.

Repeated measures

We computed cluster-robust standard errors (patient ID as cluster) to account for non-independence of multiple lines per individual.

Results

Baseline characteristics

A total of 1051 PsA patients from 29 Italian rheumatology centers were included in the study, accounting for 1418 prescriptions: 1269 TNFi and 148 IL23i (Table 1). Median age was slightly higher in the IL23i group compared to the TNFi group (57 (IQR 50–65) vs 55 (46–62) years; $p = 0.005$). Disease duration was significantly longer in the IL23i group (82 (31–117) vs 46 (12–109) months; $p < 0.001$).

The IL23i group exhibited higher disease activity at baseline, as measured by DAPSA (25.0 (19.1–31.0) vs 20.6 (13.0–27.1); $p < 0.001$), BASDAI (7.0 (5.1–8.2) vs 5.5 (4.0–6.9); $p < 0.001$), and ASDAS (3.7 (3.0–4.1) vs 3.1 (2.4–3.7); $p = 0.002$).

The distribution of PsA phenotypes also differed: the IL23i group had a higher prevalence of mixed involvement (28% vs 20%) and a lower prevalence of isolated axial disease (10% vs 17%; $p = 0.03$).

Concomitant csDMARD use was lower in the IL23i group (32% vs 46%; $p = 0.002$), whereas steroid use was higher (31% vs 22%; $p = 0.01$).

Table 1. Baseline characteristics of PsA patients in the two groups.

Variables	TNFi group	IL23i group	*p*-Value
N	1269	148	–
M:F	529:740	42:106	0.002
Age, median (IQR), years	55 (46–62)	57 (50–65)	0.005
PsA duration, median (IQR), months	46 (12–109)	82 (31–117)	<0.001
PsA involvement, *n* (%)			
Peripheral	797 (63%)	92 (62%)	0.03
Axial	215 (17%)	15 (10%)	
Both	258 (20%)	41 (28%)	
DAPSA, median (IQR)	20.6 (13.0–27.1)	25.0 (19.1–31.0)	<0.001
BASDAI,* median (IQR)	5.5 (4.0–6.9)	7.0 (5.1–8.2)	<0.001
ASDAS,** median (IQR)	3.1 (2.4–3.7)	3.7 (3.0–4.1)	0.002
Concomitant csDMARDs, *n* (%)	581 (46%)	48 (32%)	0.002
Concomitant steroid, *n* (%)	275 (22%)	46 (31%)	0.01
HLA B27, *n* (%)			
Yes	66 (5%)	3 (2%)	nss
No	353 (28%)	43 (21%)	
Unknown	851 (67%)	102 (77%)	
Line, *n* (%)	2 (1–3)	3 (2–5)	<0.001
bDMARD, *n* (%)			
Adalimumab	721 (33.5%)	–	–
Certolizumab	98 (15.3%)	–	
Etanercept	278 (30.6%)	–	
Golimumab	96 (13.4%)	–	
Infliximab	77 (6.9%)	–	
Guselkumab	–	107 (72,3.0%)	
Risankizumab	–	41 (27.7%)	

Data missing in 325 (*) and 203 (**) patients.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biologic Disease Modifying AntiRheumatic Drugs; csDMARD, conventional synthetic Disease Modifying AntiRheumatic Drugs; DAPSA, Disease Activity index for PSoriatic Arthritis; IL23i, IL-23 inhibitors; IQR, interquartile range; nss, not statistically significant; PsA, psoriatic arthritis; TNFi, TNF inhibitors.

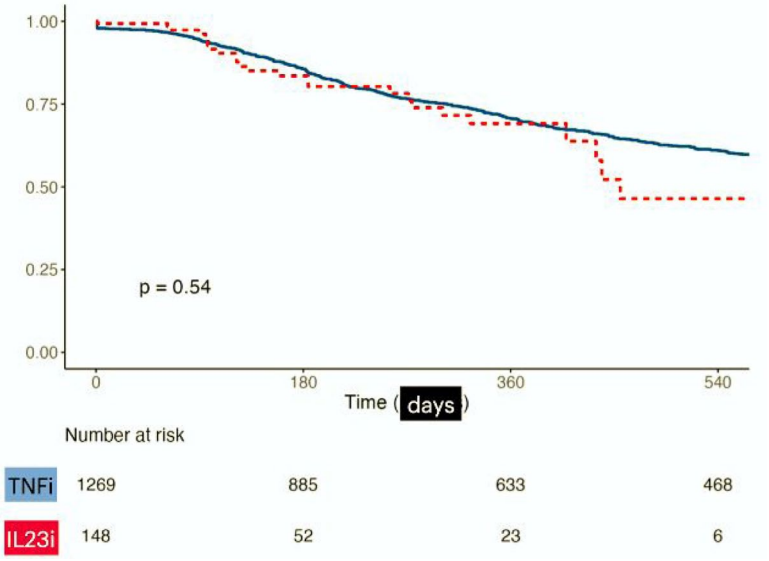

Figure 1. Kaplan–Meier survival curves of two groups at 6, 12, and 18 months: 85.6%, 70.7%, 61.0% for the TNFi group versus 83.5%, 69.1%, 46.4% for the IL23i group.
IL23i, IL-23 inhibitors; TNFi, TNF inhibitors.

Patients in the IL23i group had received a higher median number of previous bDMARD lines (3 (2–5) vs 2 (1–3); $p < 0.001$), indicating a more treatment-refractory population.

Baseline comparisons revealed several statistically significant differences between the two groups (Table 1). Patients prescribed IL23i tended to be older, with longer disease duration, higher disease activity, and a history of multiple prior bDMARD failures. While TNFi were more frequently prescribed for peripheral and axial PsA, IL23i were more commonly used in cases of mixed PsA involvement. Additionally, IL23i prescriptions were less frequently associated with concomitant csDMARD use compared to TNFi.

Treatment retention and survival analysis

Treatment effectiveness, assessed using Kaplan–Meier survival curves, did not show a significant difference between IL23i and TNFi groups (Figure 1). The retention rate data at 6, 12, and 18 months were 85.6%, 70.7%, 61.0% for the TNFi group versus 83.5%, 69.1%, 46.4% for the IL23i group, respectively. After adjusting for PS, IL23i demonstrated significantly longer treatment retention compared to TNFi (hazard ratio: 0.53, 95% confidence interval: 0.31–0.90, $p = 0.02$).

Discontinuation causes

Fewer than 600 prescriptions were discontinued, with 533 discontinuations in the TNFi group and 25 in the IL23i group. The primary reasons for discontinuation were similar between the two groups. Lack of efficacy accounted for 47.0% of TNFi discontinuations versus 40.7% for IL23i, while loss of efficacy was reported in 34.1% of TNFi and 40.7% of IL23i cases. Adverse events led to discontinuation in 18.9% of TNFi and 18.6% of IL23i prescriptions. Notably, the most severe adverse events—including infections (six cases), allergic reactions (three cases), and new-onset malignancies (two cases)—were exclusively observed in the TNFi group.

Additional methodological considerations

The study did not account for the specific TNFi used, the type of csDMARDs, or any dose modifications during follow-up. Also, no distinction between primary versus secondary failure was performed. These limitations typical of real-world, multicenter observational designs may partially limit the interpretability of certain predictors.

Discussion

This study was designed to compare real-world drug retention between TNFi and IL23i in PsA, accounting for treatment line and major clinical

confounders. We found that IL23i were associated with longer drug retention than TNFi after multivariable and PS-based adjustment. These results were consistent across different analytical approaches, supporting the robustness of the observation. Given that drug retention reflects a composite of effectiveness, safety, and tolerability in routine practice, our findings suggest that IL23i represent a durable therapeutic option in PsA. However, the observational design and the adopted censoring strategy require cautious interpretation and preclude any claim of class superiority.

Evaluating treatment retention and its predictors is a key strategy to assess the real-world effectiveness of biologic therapies in PsA. Treatment persistence is generally associated with stable disease control and reduced healthcare resource utilization.[17–19] In this context, understanding how different therapeutic classes perform in routine clinical practice is crucial to inform cost-effective and individualized treatment strategies.

While randomized head-to-head trials such as SPIRIT-H2H have provided valuable comparative data between TNFi and other drug classes (e.g., IL17i),[6] these studies often involve selected patient populations and standardized protocols that may not reflect the complexity of real-world scenarios. Moreover, they rarely explore treatment patterns beyond the first biologic line.

Our findings should be interpreted in the context of available head-to-head randomized controlled trials in PsA. SPIRIT-H2H and EXCEED represent key comparative studies between biologic classes, providing high-quality evidence on short-term clinical efficacy and domain-specific outcomes under controlled conditions. However, their primary endpoints were based on composite disease activity measures and response criteria, and their design differs substantially from real-world drug retention, which reflects a composite of effectiveness, safety, tolerability, patient preference, and treatment strategy in routine practice. Therefore, while these trials are essential to define comparative efficacy, they are not directly comparable with class-level drug survival analyses derived from observational cohorts.

In addition, the interpretation of treatment performance across different PsA phenotypes, particularly axial disease, remains challenging. In our cohort, axial involvement was defined on an investigator-reported basis, reflecting real-life clinical practice rather than standardized classification criteria. This approach may under-capture the heterogeneity and burden of axial disease and should be considered when interpreting potential differences in treatment retention between drug classes. Our findings add to the growing body of real-world evidence comparing different mechanisms of action in PsA. Although crude Kaplan–Meier survival curves did not show a significant difference between TNFi and IL23i prescriptions, adjustment for relevant confounders using a PS model revealed a significant longer retention for IL23i.

This suggests that IL23i may be at least as effective as TNFi in routine care, even when used in more treatment-experienced and clinically complex cases. These findings are aligned with recent data from insurance registries and observational cohorts suggesting a benefit in switching to a different MoA after TNFi exposure.[7,20,21] However, earlier studies may have been biased toward TNFi due to historical availability and prescription patterns.[22,23]

Importantly, this study did not specifically analyze treatment sequences or second-line strategies, and thus conclusions about sequential therapy should be avoided. However, our results support the idea that IL23i prescriptions might exhibit a longer retention, regardless of treatment line, in comparison to TNFi.

Prior studies have yielded mixed results on retention across different bDMARDs. Some found no major differences,[24] while others reported drug-specific variations in persistence.[25–32] Takami et al.[28] suggested better outcomes with TNFi cycling, but their analysis did not account for disease phenotype or calendar year—both shown in our study to influence retention.

The Portuguese registry[31] and Nordic registries[32] also showed neutral or slightly favorable trends for MoA-switching strategies. However, the lack of granularity regarding prior biologic use and the grouping of heterogeneous therapies limit interpretability.

In our analysis, higher baseline disease activity and the presence of axial or mixed PsA were associated with reduced treatment persistence. This supports prior observations but remains a topic of debate in the literature.[12,25,27,30] Our study has

several limitations. Treatment discontinuations driven by non-articular disease domains (such as psoriasis, IBD, or uveitis) were censored in the survival analyses. Since the distribution of these extra-articular events may differ between drug classes, this strategy may have introduced informative censoring and potentially masked class-specific patterns of treatment discontinuation related to non-musculoskeletal disease activity. We did not account for variables such as BMI, smoking status, or prior response to specific TNFi agents. Reasons for initial TNFi discontinuation were not analyzed, although some evidence suggests that this does not strongly impact subsequent retention.[27] The classification of PsA phenotypes was based on clinical judgment, and axial disease was not defined according to ASAS criteria. Missing data precluded full inclusion of BASDAI and ASDAS in multivariate models. Moreover, potential confounders such as fibromyalgia or spinal osteoarthritis were not assessed.[31] The definition of axial involvement was based on investigator judgment and was not uniformly supported by standardized classification criteria (e.g., ASAS), which may have led to misclassification or underestimation of axial disease.

We acknowledge that data on specific disease domains (e.g., enthesitis, dactylitis, psoriasis severity, comorbidities) and detailed treatment-flow dynamics were not uniformly collected across centers, precluding a more granular analysis and visualization. This limitation reflects the real-world, practice-based nature of the cohort and will be addressed in future dedicated analyses as data maturity increases.

Finally, the observational design and absence of formal matching limit causal inference. Nonetheless, the use of a PS strengthens the internal validity of our findings.

From a clinical perspective, both TNFi and IL23i remain important options for PsA management. TNFi are well-established for joint involvement and have a broad evidence base. IL23i, particularly guselkumab, have demonstrated excellent efficacy in skin outcomes, a favorable safety profile, and increasing evidence for musculoskeletal benefit.[32–35]

Our findings contribute to a growing rationale for considering IL23i as a viable therapeutic alternative to TNFi in appropriate clinical contexts.

Further stratification by individual molecules or PsA clinical phenotypes (axial, peripheral, mixed) was not pursued, as it would have resulted in small and unbalanced subgroups, increasing the risk of unstable estimates and confounding by indication, and potentially compromising the robustness and interpretability of the results.

Conclusion

In this multicenter real-life cohort of therapeutic lines in PsA, IL23i showed longer drug retention than TNFi after adjustment for treatment line and clinically relevant confounders. Results were consistent across multiple PS approaches, though the observational design precludes causal inference or claims of class superiority. Limitations include non-articular censoring and unavailable primary versus secondary inefficacy classifications. These findings support IL23i as a durable option in routine practice while emphasizing the need for prospective, domain-integrated comparative studies.

Declarations

Ethics approval and consent to participate

The study protocol received approval from the Comitato Etico dell'Area Vasta Emilia Nord (protocol code 34713; approval date: August 28, 2019) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participating patients.

Consent for publication

Written informed consent was obtained from all participating patients.

Author contributions

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