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ORIGINAL RESEARCH

Two-Year Treatment Persistence and Effectiveness of Ixekizumab in Psoriatic Arthritis in Italian Clinical Practice: Results from the ROUTE-IXE Study

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ABSTRACT

***Introduction*:** Randomised controlled trials have demonstrated the efficacy and safety of ixekizumab as a treatment for active psoriatic arthritis (PsA), and real-world evidence on long-term persistence and effectiveness is emerging. This study aimed to characterise ixekizumab use in the Italian routine clinical setting and provide insights into its persistence and effectiveness, complementing real-world evidence from single-country cohorts and multinational studies.

***Methods*:** This descriptive, multicentre, retrospective study was conducted in Italy in adult patients with PsA who received a first prescription of ixekizumab after January 2021 and had a minimum of three subsequent evaluations. The primary objective was to describe treatment persistence at week 104. Secondary objectives aimed to describe patients' demographic and clinical characteristics and evaluate treatment persistence and effectiveness at weeks 12, 24, 52 and 104.

***Results*:** A total of 204 patients, of whom 88 (43.1%) were male and 116 (56.9%) were female,

Michele Maria Luchetti Gentiloni and Rosario Foti contributed equally to the realisation of this study.

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were eligible for inclusion in the study. The mean (standard deviation) age was 55.8 (11.0) years. Comorbidities were present in 66.7% (n = 136) of patients, with the majority being cardiometabolic disorders. The median (interquartile range) disease duration was 5.3 (2.4–12.2) years. Peripheral joint involvement was the most common PsA manifestation (66.7%, n = 136), followed by mixed symptoms (28.4%, n = 58) and axial-only symptoms (4.9%, n = 10). Most patients (74.5%, n = 152) had prior exposure to biologic therapy; most also presented with high or moderate disease activity (84.6%, n = 132). Treatment persistence at week 104 was 78.6% (n = 158), and the Kaplan–Meier estimate was 0.800 (95% confidence interval 0.736–0.850). Disease activity progressively improved. At week 104, 45.3% (n = 72) of patients had low disease activity, and 25.2% (n = 40) were in remission; 34.1% (n = 31) achieved very low disease activity, and, among patients with axial involvement, 61.9% (n = 26) had inactive or mild disease.

***Conclusion*:** Ixekizumab showed high 2-year treatment persistence and effectiveness in the treatment of patients with PsA and complex disease profiles, supporting its value in informing treatment decisions and optimising patient outcomes.

Keywords: Ixekizumab; Long-term effectiveness; Psoriatic arthritis; Real-world evidence; Treatment persistence

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Key Summary Points

Why carry out this study?

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease leading to a significant impact on health-related quality of life, severely compromising physical and psychosocial functioning, work ability and productivity

Ixekizumab has demonstrated its efficacy and safety in treating patients with PsA in randomised controlled trials, while real-world evidence on long-term persistence and effectiveness is still emerging

The ROUTE-IXE (ROUtine usE of IXEkizumab for the treatment of psoriatic arthritis in Italy) study aimed to characterise ixekizumab use in Italian clinical practice and provide insights into its long-term persistence and effectiveness

What was learned from the study?

The ROUTE-IXE study showed a high rate of treatment persistence with ixekizumab in PsA: at 2 years following treatment initiation, 78.6% of patients remained on therapy, and the proportion with controlled disease increased over time, with nearly seven patients in ten achieving remission or low disease activity (DAPSA/cDAPSA) by the end of follow-up. These benefits were observed in patients with complex disease profiles: almost one-third had mixed peripheral and axial involvement, and two-thirds had at least one comorbidity

ROUTE-IXE findings align with and support previous real-world evidence on ixekizumab in PsA. The persistence and effectiveness of ixekizumab over 2 years supports the use of this biologic as a therapeutic option for disease control in the real-world management of PsA

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory disease that affects approximately 0.1–0.3% of the general population and up to 30% of patients with psoriasis [1–5].

PsA presents with heterogeneous clinical manifestations, including peripheral arthritis, axial involvement, dactylitis, enthesitis and skin and nail disease, that can severely impair physical and psychosocial functioning and diminish health-related quality of life (HRQoL) [1, 2, 6–10]. In addition to musculoskeletal and skin manifestations, patients with PsA have a higher prevalence of comorbidities than the general population [11–14]. Cardiometabolic disorders are highly prevalent: approximately one in three patients with PsA has hypertension, three in ten have metabolic syndrome and one in four is affected by obesity [12]. Moreover, mental health disorders, including anxiety and depression, have been commonly observed in patients with PsA, with approximately one in three patients experiencing at least mild anxiety, and one in five reporting symptoms of depression [13, 14]. This multimorbid nature of PsA, combined with the high burden of cardiometabolic and mental health conditions, and the coexistence of other inflammatory and non-inflammatory diseases (such as gout, osteoarthritis and fibromyalgia), is associated with poorer quality of life and functional limitations, and with increased risks of treatment discontinuation, posing significant challenges for disease management [12–14].

Current guidelines recommend that treatment selection be based on active disease domains while considering comorbidities, prior therapies and patient preferences, with the aim to achieve the lowest possible disease activity and prevent structural damage [15, 16].

The development of biologic (b) and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs) has significantly improved both short-term and long-term outcomes in PsA [1, 17]. Their use is recommended when conventional therapy fails, or for patients with clear enthesitis and relevant axial disease [15, 16]. Despite this, discontinuation or switching

of biologic agents is common in practice, and about half of patients have poor adherence to bDMARDs, resulting in suboptimal outcomes [14]. Since long-term treatment is required for sustained PsA control, corroborating evidence on persistence and effectiveness in real-world practice is essential [18]. Persistence represents a real-world indicator of efficacy and safety [19, 20] and is often used as a surrogate for treatment effectiveness [20, 21].

Ixekizumab, a high-affinity monoclonal antibody targeting interleukin (IL) 17A, was approved in Europe for the treatment of moderate-to-severe plaque psoriasis in 2016 [22, 23], for the treatment of active PsA in 2017 [24, 25] and for the treatment of active axial spondyloarthritis in 2020 [26]. Its efficacy in treating PsA was established in two pivotal trials in patients who were bDMARD-naïve or bDMARD-experienced [27–29]. In both studies, after 24 weeks of treatment, a significantly higher proportion of patients achieved the American College of Rheumatology (ACR) 20 response (≥ 20% improvement from baseline in a core set of disease measures) with ixekizumab than with placebo, and disease activity (assessed with the Disease Activity Score 28 with C-reactive protein [DAS28-CRP]) and functional disability (measured with the Health Assessment Questionnaire Disability Index [HAQ-DI] score) were significantly improved [27–29].

Additionally, in a head-to-head, open-label, blinded-assessor clinical trial, ixekizumab demonstrated superiority over adalimumab in achieving the primary composite endpoint, defined as ≥ 50% improvement from baseline in ACR response (ACR50) and 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI100) after 24 weeks of treatment [30]. Moreover, significantly more patients achieved minimal disease activity and very low disease activity at week 24 in the ixekizumab group compared with the adalimumab group [30]. Data on clinical effectiveness and treatment persistence are emerging from real-world studies on patients with PsA [8, 31–33]. However, data remain heterogeneous because these studies used different clinical indices to assess ixekizumab effectiveness, and treatment persistence varies across clinical settings and patient characteristics.

In this context, the ROUTE-IXE study (ROUtine usE of IXEkizumab for the treatment of psoriatic arthritis in Italy) aimed to characterise ixekizumab use in Italian routine clinical practice, evaluating its long-term persistence and effectiveness, describing treatment patterns and outlining the sociodemographic and clinical characteristics of adult patients with PsA, thereby expanding the real-world evidence available for the Italian population [34–37].

METHODS

Study Design and Study Population

The ROUTE-IXE study is a descriptive, multicentre, retrospective observational study conducted in 15 rheumatology centres in Italy, based on patient-level data and observations collected from medical records at each time point. Patients were eligible for enrolment if they fulfilled all of the following criteria: (1) aged ≥ 18 years; (2) had a confirmed diagnosis of PsA by a rheumatologist; (3) had received at least one dose of ixekizumab prescribed for PsA in a real-world clinical setting; (4) initiated ixekizumab treatment from January 2021 onward; (5) attended a minimum of three visits after the first prescription (index date) independently from treatment status; (6) had at least 2 years of follow-up data at the study site; and (7) provided signed informed consent and privacy form. Patients participating in other clinical trials during the study period were excluded from this study. The observational study period ran from the index date, defined as the first ixekizumab prescription (starting from 1 January 2021), to the date of inclusion in the study.

Ixekizumab was dispensed and administered in hospitals as a subcutaneous injection. The recommended dose was 160 mg at week 0, then 80 mg every 4 weeks. For patients with concomitant moderate-to-severe plaque psoriasis,

the dosing regimen followed that recommended for plaque psoriasis (160 mg at week 0, then 80 mg every 2 weeks until week 12, followed by 80 mg every 4 weeks), as per the summary of product characteristics (SmPC) [38]. As this was an observational, retrospective, and non-interventional study, it did not influence patients' treatment or prescribing practicalities.

Outcome Measures

The primary objective of the study was to describe treatment persistence with ixekizumab in patients with PsA in routine clinical practice in Italy. For this purpose, the retention rate, defined as the percentage of patients remaining on ixekizumab treatment at week 104 (± 6 weeks), was assessed for all patients with available data, and treatment persistence time was analysed using the Kaplan–Meier method.

Secondary objectives were to describe treatment persistence with ixekizumab at weeks 12, 24 and 52; the patients' sociodemographic and clinical characteristics and treatment patterns; and ixekizumab effectiveness at weeks 12, 24, 52, and 104. Sociodemographic variables included age, sex, body mass index (BMI), and smoking status. BMI was calculated as weight (kg)/height squared (m^2), and was categorised as underweight (< 18.5 kg/m^2), normal weight (18.5 to < 25.0 kg/m^2), overweight (25.0 to < 30.0 kg/m^2) or obesity (≥ 30.0 kg/m^2). Clinical variables included disease duration; time from symptom onset; PsA clinical manifestations (peripheral, axial or mixed involvement); comorbidities; prior and concomitant treatments; and the following disease activity measures: Disease Activity in Psoriatic Arthritis (DAPSA)/clinical DAPSA (cDAPSA) score; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); minimal disease activity (MDA), very low disease activity (VLDA), as well as laboratory parameters (CRP and erythrocyte sedimentation rate (ESR), as available in medical records.

The effectiveness of ixekizumab was evaluated in all eligible patients and in those who were on ixekizumab at week 104, and was defined as:

- the percentage of patients who achieved low disease activity or remission during follow-up, assessed with the DAPSA tool, with DAPSA > 4 to ≤ 14 indicating low disease activity, ≤ 4 indicating remission [39] or, if unavailable, cDAPSA);
- the percentage of patients who achieved MDA and VLDA during follow-up [40];
- the percentage of patients who achieved inactive disease with BASDAI < 4 [41] or who achieved an improvement of ≥ 50% on BASDAI during follow-up.

When both scores were available, DAPSA was prioritised over cDAPSA, using its cutoff (>4 to ≤ 14). At each time point, patients were classified into only MDA or VLDA; consequently, MDA and VLDA are reported separately rather than as a combined cumulative rate.

Statistical Analysis

All statistical analyses were descriptive due to the study's nature. No hypothesis tests were performed. For qualitative variables, relative and absolute frequencies were calculated. For quantitative variables, measures of centrality and dispersion (mean, median, standard deviation [SD], 25th and 75th percentiles [P], minimum, and maximum) were calculated. Descriptive statistics were based on observed cases with available data; missing values were not imputed.

A target sample of 200 patients, with 170 patients expected to be evaluable for the primary objective, was considered appropriate for providing a precision estimate of the primary endpoint. In fact, we considered that 68.5% of the subjects would achieve persistence at 104 weeks, and assuming a sample size of 170 effective patients, the half-width of the two-sided 95% confidence interval (CI) for the expected indicator was estimated to be 7%.

Ethical Considerations

This study was conducted in accordance with the protocol and ethical principles that have

their origin in the Declaration of Helsinki of 1964 and its later amendments, and that are consistent with applicable ICH Good Clinical Practice (GCP) Guidelines, Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations of the country or countries where the study was conducted, as appropriate. The study protocol was approved by the competent Territorial Ethics Committee (Comitato Etico Territoriale Lazio Area 3), whose approval was valid for all participating centres (Protocol No. 0001800/24, dated 15 November 2024). Informed consent for participation in the study and for the use of personal data was obtained from all subjects before any study-related procedure was performed. As no identifying information is included in the manuscript, additional consent for publication was not required. The study was registered within the Italian register of observational studies (Registro Studi Osservazionali [RSO]; Study ID 3402). Study conduct, data monitoring, electronic Case Report Form (eCRF) set-up and statistical analyses were performed by IQVIA Solutions Italy srl (Milan, Italy) on behalf of Eli Lilly S.p.A (Florence, Italy).

RESULTS

From February to September 2025, a total of 211 patients were enrolled in the ROUTE-IXE study across 15 rheumatology centres in Italy, among whom 204 (96.7%) met the inclusion criteria and were deemed eligible (Fig. 1).

Patient Characteristics and Clinical Features

Patient characteristics at the index date are described in Table 1. Specifically, the cohort included 88 (43.1%) male patients and 116 (56.9%) female patients with PsA, with a mean (SD) age of 55.8 (11.0) years. The median (interquartile range [IQR]) disease duration was 5.3 (2.4–12.2) years, while the median (IQR) time from the onset of symptoms was 8.9 (4.2–16.2) years.

Overall, 66.7% (n = 136) of the patients had past or ongoing comorbidities, of which the most frequently reported were hypertension (17.2%, n = 35 patients), obesity (15.2%, n = 31), diabetes (8.8%, n = 18), rheumatic disease (6.9%, n = 14), peripheral vascular disease (6.4%, n = 13) and depression or anxiety (5.4%, n = 11).

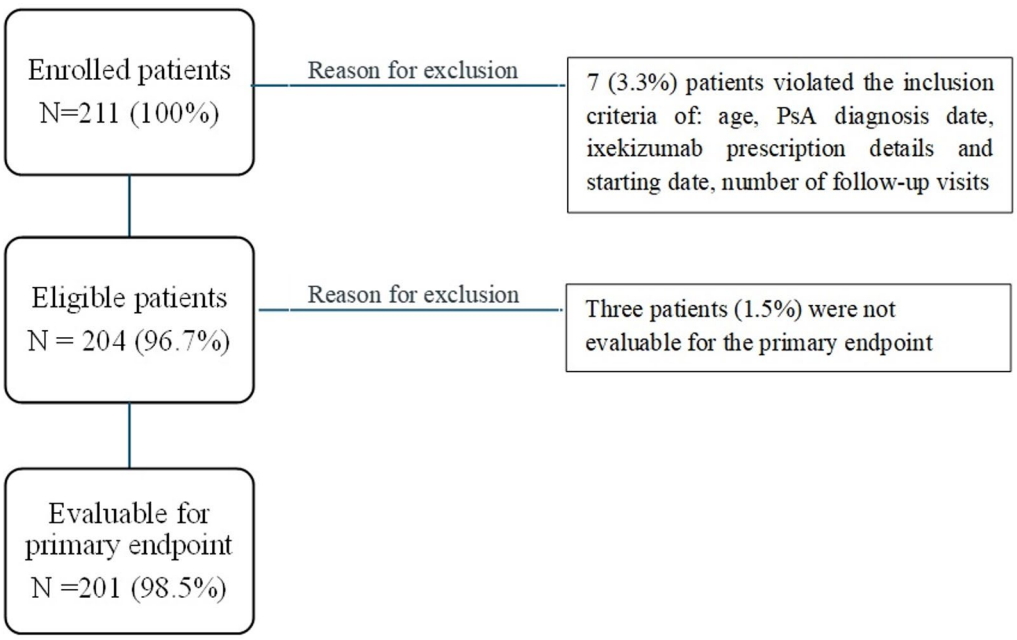


Fig. 1 Flow diagram of patients' disposition and analysis sets. PsA Psoriatic arthritis

Table 1 Patients' characteristics and psoriatic arthritis features at index date

	Eligible patients (*N* = 204)
Age at index date, mean (SD)	55.8 (11.0)
Male sex, *n* (%)	88 (43.1%)
Female sex, *n* (%)	116 (56.9%)
Time from PsA diagnosis (years), median (IQR)	5.3 (2.4–12.2)
Time from the onset of the first symptoms (years), median (IQR)	8.9 (4.2–16.2)
BMI category	***N*** **(%)**
Underweight (BMI < 18.5 kg/m^2)	2 (1.0%)
Normal weight (BMI ≥ 18.5 to < 25 kg/m^2)	56 (27.5%)
Overweight (BMI ≥ 25 to < 30 kg/m^2)	51 (25.0%)
Obesity (BMI ≥ 30 kg/m^2)	31 (15.2%)
Unknown	64
Smoking status	***N*** **(%)**
Current smokers	40 (19.6%)
Ex-smokers (> 6 months without smoking)	26 (12.7%)
Non-smoker	94 (46.1%)
Unknown	44
Past or ongoing comorbidities or medical conditions	***N*** **(%)**
Any medical condition and comorbidities	136 (66.7%)
Hypertension	35 (17.2%)
Obesity	31 (15.2%)
Diabetes	18 (8.8%)
Rheumatic disease	14 (6.9%)
Peripheral vascular disease	13 (6.4%)
Depression or anxiety	11 (5.4%)
Clinical features	***N*** **(%)**
Axial symptoms	10 (4.9%)
Peripheral symptoms	136 (66.7%)
Mixed symptoms	58 (28.4%)
Skin psoriasis (*n* available observations)[a,b]	161 (82.1%) [*n* = 196]
Nail psoriasis (*n* available observations)[a,b]	46 (23.5%) [*n* = 196]
Enthesitis (*n* available observations)[a,b]	61 (36.1%) [*n* = 169]

Table 1 continued

Clinical features	***N*** **(%)**
Dactylitis (*n* available observations)[a,b]	31 (17.3%) [*n* = 179]
Arthritis (*n* available observations)[a,b]	183 (92.0%) [*n* = 199]
Fatigue (*n* available observations)[a,b]	102 (62.6%) [*n* = 163]
Pain	189 (92.6%)
Disease activity (*n* available observations)[a]	**Mean (SD) [min–max]**
DAPSA/cDAPSA (*n* = 156)	22.9 (10.2) [0.0–57.0]
DAPSA (*n* = 144)[c]	23.1 (10.4) [0.0–57.0]
cDAPSA (*n* = 79)[c]	21.0 (10.2) [2.0–52.0]
BASDAI (*n* = 52)	5.2 (1.4) [1.0–7.8]
DAS28 (*n* = 75)	3.9 (1.2) [1.0–7.0]
Total joint count (*n* = 175)	8.0 (7.8) [0.0–41.0]
Number of TJC (*n* = 176)	5.7 (5.5) [0.0–25.0]
Number of SJC (*n* = 176)	2.3 (3.3) [0.0–18.0]
CRP concentration (mg/L) (*n* = 158)	6.5 (12.3)
ESR (mm/h) (*n* = 126)	20.8 (16.4)
Previous bDMARDs treatment	***N*** **(%)**
bDMARD-naïve	51 (25.0%)
bDMARD-experienced[d]	152 (74.5%)
UNK	1

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *bDMARDs* biologic disease-modifying antirheumatic drugs, *BMI* body mass index, *cDAPSA* Clinical Disease Activity in Psoriatic Arthritis, *cDMARDs* conventional disease-modifying antirheumatic drugs, *CRP* C-reactive protein, *DAPSA* Disease Activity in Psoriatic Arthritis, *DAS28* Disease Activity Score 28, *ESR* erythrocyte sedimentation rate, *PsA* psoriatic arthritis, *SD* standard deviation, *SJC* swollen joint count, *TJC* tender joint count, *tsDMARDs* targeted synthetic disease-modifying antirheumatic drugs

[a]For variables with missing data, the number of available observations is reported

[b]Percentages are computed from the number of available observations

[c]DAPSA and cDAPSA are not mutually exclusive, as some patients had both measurements available

[d]Including patients treated with at least one bDMARD

Peripheral symptoms were the most common manifestation of PsA, observed in 66.7% (*n* = 136) of patients. Mixed peripheral and axial patterns were seen in 28.4% of patients (*n* = 58), while axial symptoms alone occurred in 4.9% (*n* = 10). Skin psoriasis affected 82.1% of patients (*n* = 161), with a mean (SD) body surface area (BSA) of 3.9 (7.7). Nail psoriasis was present

in 23.5% (n = 46). Additionally, most patients presented with arthritis (92.0%, n = 183), while 36.1% (n = 61) had enthesitis and 17.3% (n = 31) had dactylitis. Pain was reported by 92.6% (n = 189) of the patients and fatigue by 62.6% (n = 102).

At index date, 84.6% (n = 132) of the cohort had moderate or high disease activity. PsA activity measured with the DAPSA score or, if unavailable, the cDAPSA score (data available for 156 patients), showed moderate disease activity in 57.7% (n = 90) of patients and high disease activity in 26.9% (n = 42). Three patients (1.9%) were in remission. The mean (SD) DAPSA/cDAPSA score was 22.9 (10.2).

Additionally, among the 98 patients with available data, 29.6% (n = 29) and 1.0% (n = 1) met MDA and VLDA criteria, respectively.

The BASDAI score was available for 52 of 68 patients with reported axial involvement. Active disease (BASDAI ≥ 4) occurred in 86.5% (n = 45) of patients, and inactive or mild disease occurred in 13.5% (n = 7). The mean (SD) BASDAI score was 5.2 (1.4).

Treatment Patterns

At the index date, 25.0% (n = 51) of the patients were bDMARD-naïve, while 74.5% (n = 152) were bDMARD-experienced, with the most frequently used prior bDMARDs being secukinumab (19.1%, n = 39), adalimumab (18.1%, n = 37), etanercept (14.2%, n = 29) and ustekinumab (5.4%, n = 11). Data on prior treatments were missing for one patient. All patients, whether bDMARD-naïve or bDMARD-experienced, received ixekizumab 160 mg as the initial dose (week 0), followed by the maintenance dose of 80 mg every 4 weeks, which was continued without modification through to the end of the observation period (week 104). Ixekizumab was used as monotherapy or in combination with conventional DMARDs (cDMARDs) (see Electronic Supplementary Material [ESM] Table S1 for details). Notably, at week 104, ixekizumab monotherapy was more frequent among bDMARD-naïve (60.8%) than bDMARD-experienced patients (44.1%).

Treatment Persistence

Among the 204 patients eligible for the analysis of treatment persistence, 201 were evaluable for the primary objective (Fig. 1). The percentage of patients remaining on ixekizumab treatment at week 104 (primary endpoint) was 78.6% (n = 158). At week 104, the treatment persistence probability, estimated by Kaplan–Meier analysis, was 0.800 (95% CI 0.736–0.850) (Fig. 2).

Regarding treatment persistence, the treatment persistence probability during the observational period (secondary endpoint) was 0.995 (95% CI 0.965–0.999) at week 12, 0.970 (95% CI 0.935–0.986) at week 24 and 0.910 (95% CI 0.862–0.943) at week 52 (Table 2).

Among the 201 patients evaluable for the primary objective, 43 permanently discontinued ixekizumab over the 2-year observation period. The most frequent reason for discontinuation was lack or loss of response (88.4%, n = 38), followed by other reasons (9.3%, n = 4) and patient's decision (2.3%, n = 1).

Effectiveness of Ixekizumab

During the observation period, the percentage of patients with favourable outcomes in disease activity increased over time and remained stable throughout the duration of the study (Table 3).

Specifically, DAPSA/cDAPSA low disease activity (>4 and ≤ 14) was achieved by 42.1% (n = 53) patients after 12 weeks of treatment and remained stable over time, reaching 45.3% (n = 72) at week 104. DAPSA/cDAPSA remission (≤4) was observed in 15.9% (n = 20) patients at week 12 and reached 25.2% (n = 40) at week 104. MDA and VLDA were assessed independently (see Discussion section).

MDA status was achieved by 25% (n = 19 of 76 evaluable patients) by week 12 and improved to 35.2% (n = 32) at week 104. A similar trend was observed for VLDA, with 23.7% (n = 18) achieving VLDA at week 12 and 34.1% (n = 31) at week 104. BASDAI scores showed inactive or mild axial disease (<4) in 48.8% (n = 20) of

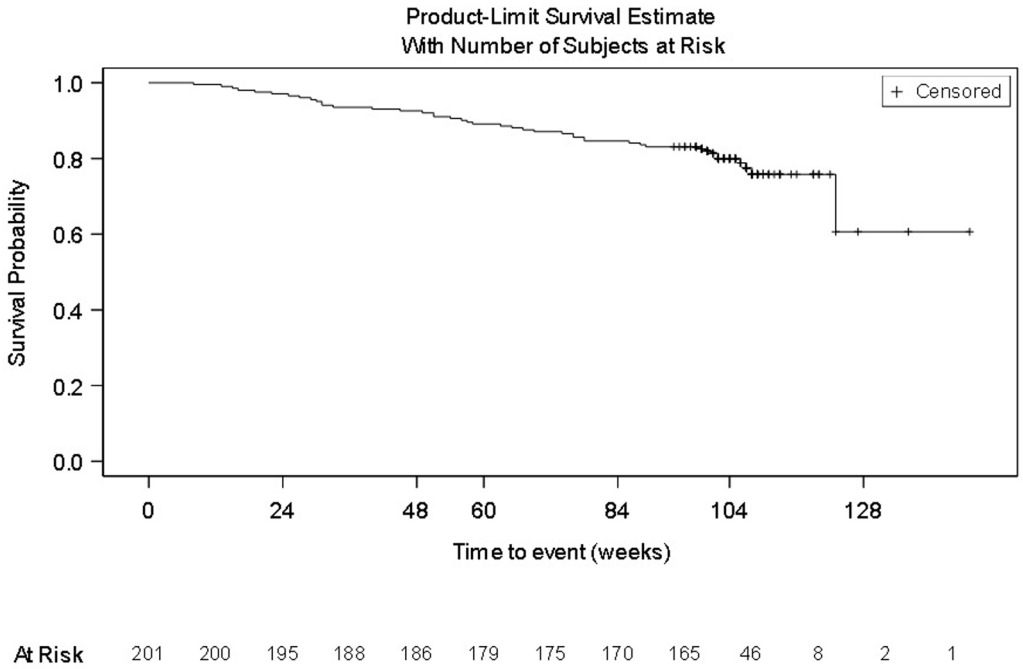


Fig. 2 Treatment persistence time from index date to week 104 (primary endpoint)

patients at week 12, rising to 61.9% (n = 26) at week 104. Additionally, at week 12, 12.8% (n = 5) of patients achieved ≥ 50% improvement in the BASDAI score, increasing to 26.3% (n = 10) at week 104.

Considering ixekizumab effectiveness among the 158 patients on treatment at week 104, the percentage of patients with favourable disease activity outcomes was consistent with that observed in the eligible population (see ESM Table S2 for details).

Table 2 Treatment persistence probability at each time point (secondary endpoint)

Assessment time point (weeks)	Treatment persistence probability (95% CI)
12	0.995 (0.965–0.999)
24	0.970 (0.935–0.986)
52	0.910 (0.862–0.943)
104	0.800 (0.736–0.850)

CI Confidence interval

DISCUSSION

The findings of the ROUTE-IXE study provide evidence on the use of ixekizumab in routine clinical practice for the treatment of PsA, showing high treatment persistence and clinical effectiveness. These findings are consistent with and extend previous real-world evidence from Italian and international settings. The results suggest high treatment persistence at 2 years and early improvement in disease activity among patients with PsA, including patients with mixed disease phenotypes and comorbidities.

In this real-world study, nearly two-thirds of patients had at least one comorbidity, predominantly cardiometabolic conditions, such as hypertension (17.2%), obesity (15.2%) and diabetes (8.8%). Patients with PsA may present associated comorbidities, with the most common including hypertension (34.2%), metabolic syndrome (28.8%), obesity (27.4%), hyperlipidaemia (24.2%), and any cardiovascular disease (19.4%) [12]. Cardiometabolic comorbidities, particularly obesity, are highly prevalent in patients with PsA and have been associated

Table 3 Disease activity outcomes in patients treated with ixekizumab

	Index date, *N* (%)	Week 12, *N* (%)	Week 24, *N* (%)	Week 52, *N* (%)	Week 104, *N* (%)
DAPSA/cDAPSA(*N*)	156	126	133	149	159
Remission	3 (1.9%)	20 (15.9%)	18 (13.5%)	37 (24.8%)	40 (25.2%)
Low disease activity	21 (13.5%)	53 (42.1%)	64 (48.1%)	62 (41.6%)	72 (45.3%)
MDA and VLDA (*N*)[a]	98	76	82	84	91
MDA	29 (29.6%)	19 (25.0%)	21 (25.6%)	20 (23.8%)	32 (35.2%)
VLDA	1 (1.0%)	18 (23.7%)	21 (25.6%)	31 (36.9%)	31 (34.1%)
BASDAI (*N*)	52	41	41	44	42
Inactive or mild disease (score < 4)	7 (13.5%)	20 (48.8%)	21 (51.2%)	28 (63.6%)	26 (61.9%)
BASDAI score (*N*)	–	39	37	36	38
BASDAI50 (Improvement of ≥ 50%)	–	5 (12.8%)	8 (21.6%)	8 (22.2%)	10 (26.3%)

Outcomes are reported for all eligible patients with available data at each time point (assigned treatment dataset), regardless of ongoing ixekizumab treatment

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *DAPSA* Disease Activity in Psoriatic Arthritis, c*DAPSA* Clinical Disease Activity in Psoriatic Arthritis, *MDA* minimal disease activity, *VLDA* very low disease activity

[a]At each time point, each patient was classified into only one response category

with increased clinical burden and a potential to influence treatment response [11, 12]. Moreover, research on the link between adiposity and psoriatic disease is increasing, with emerging evidence exploring both the impact of the pro-inflammatory state driven by obesity and the potential causal link between the two entities [42].

In previous Italian real-world studies of ixekizumab, a substantial proportion of patients presented with cardiometabolic comorbidities, with overall comorbidity rates reported in up to 57.5% of patients and obesity rates ranging from 24.6% to 33.8% across cohorts [34–37]. In this context, ixekizumab showed effectiveness in real-world clinical practice, including in heterogeneous populations representative of routine care. In the ROUTE-IXE study, almost one-third of patients had mixed peripheral and axial PsA involvement (28.4%, $n = 58$), and 4.9% ($n = 10$) had axial symptoms alone. Real-world effectiveness of ixekizumab has also been reported in bDMARD-experienced patients, including those with axial involvement [10]. These proportions mirror those observed in epidemiological studies, where the estimated prevalence of mixed axial and peripheral involvement is approximately 23–34% among patients with PsA, and axial involvement alone occurs in 2–5% [43, 44]. Additionally, a similar proportion of patients presenting with mixed or axial involvement was observed in four real-world studies in Italy [34–37], with axial/mixed involvement ranging from 21.9% [35] to 46.0% [36]. By contrast, in the two ixekizumab pivotal trials, only 1.9% and 2.2% of enrolled patients, respectively, presented with PsA with mixed or axial involvement [29], highlighting a difference between the clinical trial and real-world patient populations.

In addition, most patients enrolled in the ROUTE-IXE study (84.6%, $n = 132$) presented with high or moderate disease activity at the index date (as measured by DAPSA/cDAPSA score), while in other Italian real-world studies the proportion of patients with high or moderate

disease activity according to the DAPSA score was 74.8% [35] and 64.0% [36], respectively.

Despite the presence of comorbidities and mixed disease phenotypes in this PsA population, the persistence rate observed for treatment with ixekizumab at 2 years was high (78.6%, $n = 158$) further strengthening evidence already available in real-world practice.

Among available European real-world evidence, one Italian study of 132 patients treated with ixekizumab reported a 2-year persistence rate of 73.3%, which aligns with that observed in the ROUTE-IXE [34].

The 2-year treatment persistence reported in other Italian real-world studies of ixekizumab ranged from 49.0% [36] to 67.4% [35], with a gradual decline over time, consistent with patterns typically observed with biologic therapies in chronic conditions like PsA [3, 36]. Similar findings have emerged from other European observations of ixekizumab. In Spain, real-world cohorts showed 2-year persistence rates of 68.5% [45] and 57.0% [46], while a large Danish registry-based study including 478 patients reported a rate of 51.0% [32]. The GISEA study reported an improvement in DAPSA scores, with 51.8% of patients achieving low disease activity and 17.2% reaching remission after 2 years of ixekizumab treatment [35]. Similarly, Gentileschi et al. observed, after 2 years of ixekizumab treatment, remission in 46.7% of patients and low disease activity in 93.3% (according to DAPSA score), as well as VLDA in 16.0% of cases and an improvement in axial disease activity as measured by BASDAI [34].

Long-term effectiveness was observed in the ROUTE-IXE study, with the proportion of patients with controlled PsA stabilising over the 2-year period: more than two-thirds of the patients achieved low disease activity (45.3%, $n = 72$) or remission (25.2%, $n = 40$), as assessed by DAPSA/cDAPSA scores, one-third achieved VLDA (34.1%, $n = 31$), MDA was achieved by 35.2% ($n = 32$) and, among patients with axial involvement, 61.9% ($n = 26$) presented inactive or mild axial disease (BASDAI score < 4).

The ROUTE-IXE study has a number of limitations due to its retrospective, real-world design. As the study was conducted across 15 Italian centres, the generalisability of the findings may be limited beyond the Italian real-world setting. Although the study included patients with a minimum of three visits over 2 years independently of treatment status, patients who discontinued ixekizumab and did not return to the site would not have met this eligibility requirement and would not have been included in the study, potentially leading to an overestimation of persistence. Nonetheless, the study still captured a substantial number of discontinuations as events, consistent with the 21.4% discontinuation rate observed by week 104. Moreover, the absence of a comparator arm may influence how persistence and effectiveness data should be interpreted. Furthermore, effectiveness outcomes were assessed based on observed cases with available data; the varying denominators across outcomes and time points may reflect differential data availability in routine clinical practice, potentially introducing availability bias in the interpretation of results.

In this study, MDA and VLDA status could either be calculated from the individual criteria or entered directly by the treating clinician as an overall clinical judgement. For this reason, at the time of data collection, patients were assigned to only one of the two categories, MDA or VLDA, rather than being classified cumulatively. Thus, MDA and VLDA have been reported separately rather than combined. The true proportion of patients achieving MDA may therefore be underestimated using this approach. Moreover, as adverse events were not actively collected per protocol in this study, safety data were not reported. Finally, information bias might have affected retrospective data collection; however, key clinical information relevant to the study objectives was expected to be available and appropriately documented in medical charts. Although missing data represent a potential limitation of retrospective studies, their extent was minimal in the present study, with only seven out of 211 enrolled patients excluded from the eligible population due to missing data. This was ensured through dedicated site monitoring and data cleaning activities conducted throughout the study.

CONCLUSIONS

This Italian multicentre retrospective study observed high treatment persistence and effectiveness in patients with PsA treated with ixekizumab over 2 years. Disease activity outcomes improved during follow-up, with an increasing proportion of patients achieving controlled disease throughout the study period. These findings, which are particularly relevant for patients with complex disease profiles, support ixekizumab as a valuable therapeutic option for the management of PsA in routine clinical practice.

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Data Availability. The datasets generated during and/or analysed during the current study are not publicly available as they contain proprietary data belonging to Eli Lilly and Company but are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Michele Maria Luchetti Gentiloni reports receiving research support for translational research (non-pharmacologic study) from AbbVie; and speaking and/or consulting fees from AbbVie, Amgen, Eli Lilly, Johnson & Johnson, Novartis and Pfizer. Rosario Foti reports consulting fees from AbbVie, Johnson & Johnson, Novartis, Eli Lilly, and GSK. Carlo Selmi reports fees as a paid instructor from AbbVie, AstraZeneca, Eli Lilly, Johnson & Johnson and Octapharma; speaker honoraria from AbbVie, Amgen, Alfa-Sigma, Biogen, Eli Lilly, Johnson & Johnson, Novartis, Octapharma, Pfizer, Recordati Rare Disease, SOBI and UCB; consulting fees from AbbVie, Amgen, Alfa-Sigma, Biogen, Eli Lilly, Johnson & Johnson, Novartis, Octapharma, Pfizer, Recordati Rare Disease, SOBI and UCB; and research grants from AbbVie, Amgen, Johnson & Johnson, Novartis and Pfizer. Francesco Cipollone declares no competing interests.

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Ethical Approval. This study was conducted in accordance with the protocol and ethical principles that have their origin in the Declaration of Helsinki of 1964 and its later amendments, and that are consistent with applicable ICH Good Clinical Practice (GCP) Guidelines, Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations of the country or countries where the study was conducted, as appropriate. The study protocol was approved by the competent Territorial Ethics Committee (Comitato Etico Territoriale Lazio Area 3), whose approval was valid for all participating centres (Protocol No. 0001800/24, dated 15 November 2024). Informed consent for participation in the study and for the use of personal data was obtained from all subjects before any study-related procedure was performed. As no identifying information is included in the manuscript, additional consent for publication was not required. The study was registered within the Italian register of observational studies (Registro Studi Osservazionali [RSO]; Study ID 3402). Study conduct, data monitoring, eCRF set-up and statistical analyses were performed by IQVIA Solutions Italy srl (Milan, Italy) on behalf of Eli Lilly S.p.A (Florence, Italy).

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