Effectiveness of ixekizumab over 24 months in different clinical scenarios in psoriatic arthritis: results from the Gruppo Italiano Studio Early Arthritis multicentric prospective registry

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Abstract

Objective

We aimed to evaluate ixekizumab (IXE) effectiveness, drug survival and clinical response predictors in moderate-severe psoriatic arthritis (PsA) patients in different clinical scenarios.

Methods

This was a multicentre real-life observational study based on Gruppo Italiano Studio Early Arthritis (GISEA) registry of IXE treatment in PsA patients (January 2019-June 2023). Data were collected at baseline and every six months.

Results

223 PsA outpatients were included. Statistically significant improvement was observed after 6 (T6), 12 (T12) and 24 (T24) months of therapy for tender and swollen joint count (TJC and SJC), Visual Analogue Scale (VAS)-pain and Disease Activity in PSoriatic Arthritis (DAPSA) score. DAPSA remission was reached at T12 in 22% and at T24 in 18.5% of patients. At baseline, higher fibromyalgia and combination therapy with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in females with respect to males and higher Psoriasis Area Severity Index (PASI) in males than in females were observed. Therapeutic effectiveness showed in males higher DAPSA and VAS-pain reduction, higher percentage of males in DAPSA remission/low disease activity (LDA) at T6, and higher ΔPASI at T6 and T12 than in female patients. At multivariate analysis, male sex was predictive for treatment response at T6 [p=0.02, odds ratio (OR) 2.49 (95% confidence interval 1.11-5.54)], while it lost significance at T12.

Conclusion

IXE effectiveness was highlighted after 6 months at both joint and skin levels and lasted up to 24 months in different clinical scenarios, making IXE effective in the complexity of managing PsA in a real-life setting.

Key words

ixekizumab, psoriatic arthritis, registry, real-life, bDMARD, anti-IL17A

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis typically associated to psoriasis (PsO). PsA is characterised by both articular and periarticular involvement, making the disease and its management a challenge for rheumatologists (1). The pivotal role of interleukin-17A (IL-17A) in PsA pathogenesis is well-established, driving synovial and entheseal inflammation as well as bone damage, encompassing both resorption and formation (2,3). The monoclonal IgG4 antibody ixekizumab (IXE), a biological disease-modifying anti-rheumatic drug (bDMARD), exerts its therapeutic effect by inhibiting IL-17A (4, 5). IXE has demonstrated its efficacy in randomised clinical trials (RCTs) in PsA patients, both naïve and inadequate responders to prior biologic therapy (6-11). Nevertheless, the inherent biases in RCTs often limit the generalisability of findings, as they may exclude patients with various comorbidities and difficult-to-treat patients. Therefore, real-life data on the broad spectrum of PsA are required to evaluate IXE effectiveness and safety in clinical practice and to integrate all available levels of evidence. Since 2010, the nationwide Italian biologics' registry Gruppo Italiano Studio Early Arthritis (GISEA) has been collecting data regarding PsA patients initiating bDMARDs (12). This observational study aims to assess IXE effectiveness in different clinical settings, explore drug survival, identify predictors of clinical response and treatment discontinuation in moderate-to-severe PsA patients enrolled in the GISEA registry.

Materials and methods

Patient selection and data collected

The study cohort, conducted using data from the web-based GISEA registry database, consisted of adult patients (≥18 years) affected by PsA fulfilling ClASsification criteria for Psoriatic ARthritis (CASPAR) (13) who initiated treatment with IXE 80 mg according to the standard of clinical care. The registry provided data of PsA patients with at least one visit in GISEA affiliated centres between January 2019 and June 2023. Demographic and clinical information, including age, sex, diagnosis, smoking habits, Body Mass Index (BMI), and disease duration were collected. Additionally, prior and ongoing treatments such as corticosteroids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), bDMARDs, comorbidities (ICD-9-CM), and extra-articular manifestations like PsO were recorded. At baseline and at 6 (±3), 12 (±3), and 24 (±3) months of follow-up, treatment efficacy was assessed by clinimetric indexes including physical examination with 68 tender (TJC) and 66 swollen joint count (SJC), erythrocyte sedimentation rate (ESR, mm/h), C-reactive protein (CRP, mg/dl), visual analogue scale (VAS) for pain, Patient Global assessment (PtGA), Physician Global assessment (PhGA), Disease Activity Index for Psoriatic Arthritis (DAPSA), Ankylosing Spondylitis Disease Activity Score (ASDAS, CRP-based), Health Assessment Questionnaire (HAQ), and Psoriasis Area Severity Index (PASI) score. IXE effectiveness and the state of remission or low disease activity (LDA) was assessed by DAPSA score (14, 15) Disease activity was monitored for up to 24 months for the entire population and up to 12 months when stratified by sex, BMI, lines of treatment and concomitant csDMARDs, due to a low number of patients in each subgroup at T24. Patients were categorised into remission, LDA, moderate disease activity, or high disease activity based on their DAPSA scores (≤4, >4 and ≤14, >14 and ≤28, or >28, respectively) (14). Reasons for treatment discontinuation were reported and classified as loss of effectiveness, lack of effectiveness, adverse event (AE), or others. Written informed consent was obtained from all patients prior to data collection.

The study adhered to the principles of the Declaration of Helsinki and received ethical approval from the Ethics Review Board of the Policlinico of Bari (protocol no. 598/2011).

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Continuous variables

Table I. Clinical characteristics of the entire population and of patients according to sex.

Clinical characteristics of the entire population	
Age; mean ± SD	55.5 ± 10.3
Females; n (%)	126 (56.5)
Males; n (%)	97 (43.5)
Smokers; n (%)	46/107 (43)
BMI	
normal weight; n (%)	36/120 (30)
overweight; n (%)	48/120 (40)
obese; n (%)	36/120 (30)
Disease duration (months); mean ± SD	124.2 ± 89.5
Psoriasis; n (%)	130/164 (79.3)
Axial involvement; n (%)	49/223 (21.9)
Fibromyalgia; n (%)	31/126 (24.6)
Comorbidities; median (IQR)	1 (0-2)
Concomitant glucocorticoids; n (%)	55 (24.7)
Prednisone equivalent dose; mean ± SD	7.2 ± 6
Concomitant csDMARDs; n (%)	96 (43)
IXE line of treatment	
first line; n (%)	54 (24.2)
second line; n (%)	60 (26.9)
third or more line; n (%)	109 (48.9)

Clinical characteristics of patients according to sex

	Females (126)	**Males** (97)	*p*-value
Age; mean ± SD	55.6 ± 9.7	55.3 ± 11.3	0.38
Smokers; n (%)	24/61 (39.4)	22/46 (47.8)	0.38
BMI normal weight; n (%)	24/68 (35.2)	12/52 (23.1)	0.26
BMI overweight; n (%)	22/68 (32.4)	26/52 (50)	0.05
BMI obese; n (%)	22/68 (32.4)	14/52 (26.9)	0.52
Disease duration (months); mean ± SD	121.4 ± 85.3	127.6 ± 94.8	0.34
Psoriasis; n (%)	69/89 (77.5)	61/75 (81.3)	0.54
Axial involvement; n (%)	16/82 (19.5)	19/68 (27.9)	0.22
Fibromyalgia; n (%)	27/70 (38.6)	4/56 (7.1)	<0.0001
Comorbidities; median (IQR)	1 (0-2)	1 (0-2)	1
Glucocorticoids taking; n (%)	27 (21.4)	28 (28.9)	0.20
Prednisone equivalent dose; mean ± SD	7.6 ± 6.2	7 ± 5.2	0.35
csDMARDs taking; n (%)	56 (44.4)	19 (19.6)	<0.0001
IXE first line; n (%)	24 (19.1)	30 (30.9)	0.04
IXE second line; n (%)	29 (23)	31 (32)	0.13
IXE third or more line; n (%)	73 (57.9)	36 (37.1)	0.002

SD: standard deviation; BMI: Body Mass Index; IQR: interquartile range; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; IXE: ixekizumab.

were presented as mean and standard deviation (SD) and were compared using the parametric unpaired t-test or the non-parametric Mann-Whitney U-test when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the Chi-squared test or Fisher's exact test when appropriate. The one-way ANOVA test for independent measures was used to compare the means of three or more independent samples simultaneously. The Kruskal-Wallis test was used for comparing non normally distributed variables for more than two groups. A p-value<0.05 was considered significant. The efficacy of IXE treatment was evaluated primarily through DAPSA assessment across the entire population, and secondarily by stratifying patients based on sex, BMI, IXE line of therapy, and concomitant use of csDMARDs, through factorial ANOVA analysis with Bonferroni correction. A binary logistic regression analysis was used to assess the adjusted risk of DAPSA remission + LDA with IXE treatment by the evaluation of the variables that emerged as statistically significant in the univariate analysis. An adjusted p-value<0.05 was considered significant. The Kaplan-Meier curve was used to explore the drug retention across the entire population and each subgroup of patients. All statistical analyses were performed using IBM SPSS Statistics v. 27 (IBM SPSS Software, Armonk, NY, USA).

Results

Patient characteristics

Among the 223 PsA outpatients enrolled, 126 were females (56.5%) and 97 were males (43.5%), with a mean (± SD) age of 55.5±10.3 years. About one quarter of patients received IXE as first biologic therapy (24.2%), about a quarter as second line (26.9%), and about the half as third or subsequent line (48.9%). Patients treated with IXE monotherapy were 57% of the total population. Clinical characteristics are summarised in Table I.

Therapeutic effectiveness

- Total population

The proportion of patients in DAPSA remission and LDA significantly increased from baseline (2.5 and 22.7%) to T6 (8.8% and 47.7%, p=0.03 and p<0.001), T12 (22% and 45.6%, p<0.0001 and p<0.001) and T24 (17.2% and 51.8%, p<0.001 and p<0.001) (Fig. 1A-B). Conversely, patients in DAPSA moderate disease activity and high disease activity (HDA) significantly reduced from baseline (57.7% and 17.1%) to T6 (36.3% and 6.2%, p<0.001 and p<0.001), T12 (26.5% and 5.9%, p<0.0001 and p<0.01) and T24 (27.6% and 3.4%, p<0.001 and p=0.02) (Fig. 1C-D). The mean TJC decreased from 6.5±6.2 at baseline to 3±3 (p<0.001) at T24, as well as the mean SJC (from 1.6±2.1 to 0.2±0.5, p=0.003). Significant improvements were observed also in VAS pain, VAS PtGA and VAS PhGA PASI score declined at T6 (3.1±4.4 *vs*. 0.6±2.2, p=0.02) and remained stable up to T24. The number of patients on concomitant glucocorticoids or csDMARDs and ESR and CRP values stayed constant during the follow-up (Table II).

- Patients divided according to sex

Females showed a higher prevalence of fibromyalgia (38.6% *vs*. 7.1%, p<0.0001), as well as a higher prevalence of concomitant csDMARDs treatment (44.4% *vs*. 19.6%, p<0.0001). At baseline, PASI score was higher in males than in females (4.7±5.6 *vs*. 1.9±3.1; p=0.01). Males were more frequently treated with IXE as first line therapy (30.9% *vs*. 19.1%, p=0.04) while in females IXE was more frequently used as

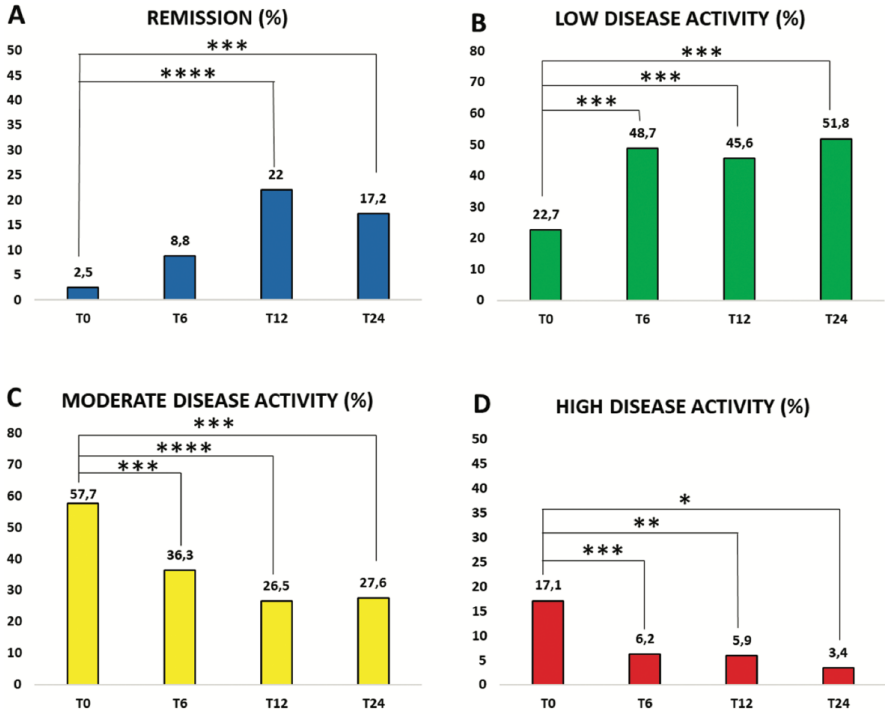

Fig. 1. DAPSA remission (**A**), low disease activity (**B**), moderate disease activity (**C**) and high disease activity (**D**) from T0 to T24 in the entire cohort.
*p<0.05; **p<0.01, ** p<0.001, ***p<0.0001. DAPSA: Disease Activity in PSoriatic Arthritis.

third line treatment (57.9% *vs*. 37.1%, p=0.002) (Table I). During the follow-up, the overall therapeutic effectiveness showed no statistically differences in clinical variables except for ΔPASI that reduced with higher rates in males (p=0.01) (Table II). The DAPSA score reduced similarly in both sexes (Fig. 2). However, males responded faster, as showed by a greater proportion of patients in DAPSA remission or LDA at T6 (70.2% *vs*. 48.4%, p=0.03) males responded faster, as showed by a greater proportion of patients in DAPSA remission or LDA at T6 (70.2% *vs*. 48.4%, p=0.03).

- Patients divided according to BMI

No significant differences were observed when patients were stratified according to their BMI in both clinical and clinimetric characteristics at T0 (Supplementary Table S1). In each group about the half of patients received IXE as a third or more biologic therapy. The DAPSA score reduced similarly in each group (Fig. 2, Suppl. Table S2) with the proportion of patients achieving DAPSA remission or LDA at T12 of 70% (normal weight), 77.3% (overweight) and 57.1% (obese), respectively.

- Patients divided according to lines of treatment

Patients treated with IXE as third or further line of treatment presented at baseline higher prevalence of female sex (66.9%), higher disease duration (139.8±75.2 months), and less prevalence of patients in DAPSA remission or LDA (17.5%) compared to the other groups of patients (Suppl. Table S1). During the follow-up, similar effectiveness was detected in all groups (Fig. 2, Suppl. Table S2), and the proportion of patients achieving DAPSA remission or LDA at T12 were 75% (IXE first line), 75% (IXE second line) and 61.1% (IXE third or further line).

- Patients divided according to concomitant csDMARDs

Patients receiving IXE monotherapy presented a higher disease duration (139.9.2±94.9 months *vs*. 101±75.9 months, p=0.01) and were less frequently treated with IXE as first line biologic (19.7% *vs*. 30.2%). The two groups of patients showed a similar sex distribution and concomitant PsO prevalence (Suppl. Table S1). No substantial differences in clinical effectiveness were observed according to this stratification and after 24 months percentages of patients in DAPSA remission or LDA were 63.3% and 61.5%, respectively (Fig. 2, Suppl. Table S2).

Predictive factors of IXE treatment response

After 6 months of treatment, the only variable associated with the outcome of DAPSA remission or LDA was male sex [p=0.02, OR 2.49 (95% CI 1.11–5.54)], which however lost its significance at T12 (p=0.27). No other variables such as combination therapy and IXE as first line of therapy have shown to be predictive factors of treatment response at either T6 or T12.

Drug survival

The median persistence in therapy was 17 months (16–19 months 95% CI), with 6-month, 12-month and 24-month IXE retention rates of 84.3%, 75.6% and 67.4%, respectively (Fig. 3A). No statistically significant differences in drug retention were observed when patients were stratified by sex (Fig. 3B, p=0.63), BMI (Fig. 3C, p=0.93), IXE line of treatment (Fig. 3D, p=0.53), concomitant csDMARDs (Fig. 3E, p=0.73), and axial involvement (Fig. 3F, p=0.40).

Safety

Overall, IXE treatment was well tolerated for the entire duration of the follow up. At T6, 21 patients out of 134 (15.7%) suspended IXE therapy: 14 due to lack of efficacy/loss of effectiveness, 1 due to pregnancy, and 6 due to non-serious AE (4.5% of the total). At T12, 15 patients out of 77 (19.5%) suspended IXE therapy: 11 due to lack of efficacy/ loss of effectiveness, and 4 due to non-serious AE (5.2%). At T24, 4 patients out of 37 (10.8%) suspended IXE therapy: 3 due to lack of efficacy/ loss of effectiveness, and 1 due to non-serious AE (2.7%).

Discussion

This study describes the clinical characteristics of PsA patients initiating IXE treatment and its effectiveness in a real-life clinical setting. The 223 patients enrolled in the GISEA national registry were mainly females, overweight or obese, and had on average moder-

Table II. Therapeutic effectiveness in the entire cohort and in patients stratified according to sex.

Therapeutic effectiveness in the entire cohort

	T0 (223)	T6 (134)	T12 (77)	T24 (37)	*p*-value
DAPSA, mean ± SD	20.5 ± 11.6	13.5 ± 7.5	11.7 ± 7.7	11.4 ± 7.3	**<0.001**
ASDAS-CRP, mean ± SD	2.9 ± 2.8	2.6 ± 2.2	2.6 ± 2.5	3 ± 2.4	0.83
BASDAI, mean ± SD	5.5 ± 2.6	5 ± 2.3	5.5 ± 2.3	5.2 ± 2.3	0.79
PASI, mean ± SD	3.1 ± 4.4	0.6 ± 2.2	0.6 ± 2	0.6 ± 2.1	**0.02**
TJC, mean ± SD	6.5 ± 6.2	3.6 ± 3.9	3.1 ± 3.5	3 ± 3	**<0.001**
SJC, mean ± SD	1.6 ± 2.1	0.8 ± 1.5	0.5 ± 1.1	0.2 ± 0.5	**0.003**
CRP (mg/L), mean ± SD	6 ± 8.5	4.5 ± 4.9	4.1 ± 4.6	5.5 ± 5.7	0.18
ESR (mm/h), mean ± SD	20.2 ± 16.1	20.1 ± 16.3	18.7 ± 16.4	24.9 ± 20.1	0.57
VAS pain, mean ± SD	60 ± 23.5	45 ± 25.9	40.2 ± 27	37.9 ± 25.9	**<0.001**
VAS PtGA, mean ± SD	62.7 ± 22.4	46.7 ± 24.5	39.4 ± 25.3	39.5 ± 26.2	**<0.001**
VAS PhGA, mean ± SD	44.5 ± 25.6	29 ± 23	24 ± 21.2	25.2 ± 22.1	**<0.001**

Therapeutic effectiveness according to sex

	Female			**Male**			
	T0 (126)	T6 (78)	T12 (43)	T0 (97)	T6 (56)	T12 (34)	*p*-value
DAPSA, mean±SD	20.7 ± 11.6	15.1 ± 8.6	12.5 ± 7.3	20.3 ± 11.7	11.2 ± 7	10.6 ± 8.2	0.23
ΔDAPSA, mean ± SD	-	-3.4 ± 9.5	-6.7 ± 10.1	-	-6.6 ± 9.4	-6.4 ± 8.7	0.76
PASI, mean ± SD	1.9 ± 3.1	0.9 ± 2.3	0.9 ± 1.3	4.7 ± 5.6	0.8 ± 2.1	0.7 ± 2.1	0.37
ΔPASI, mean ± SD	-	-0.9 ± 3.6	-0.1 ± 2.9	-	-4 ± 6.2	-11.1 ± 6.6	**0.01**
TJC, mean ± SD	6.8 ± 6.5	3.8 ± 3.7	3 ± 2.6	6.2 ± 5.8	3.3 ± 4.3	3 ± 3.2	0.38
SJC, mean ± SD	1.2 ± 1.9	0.8 ± 1.6	0.6 ± 1.4	2.1 ± 2.4	0.8 ± 1.2	0.3 ± 0.3	0.64
VAS pain, mean ± SD	61.7 ± 22	49.5 ± 23.6	43.9 ± 23.9	57.8 ± 25.4	39.3 ± 27.8	33.6 ± 27.4	0.36

DAPSA: disease activity in psoriatic arthritis; SD: standard deviation; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; PASI: Psoriasis Area Severity Index; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; PtGA: patients global assessment; PhGA: physician global assessment; BMI: Body Mass Index; IXE: ixekizumab; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.

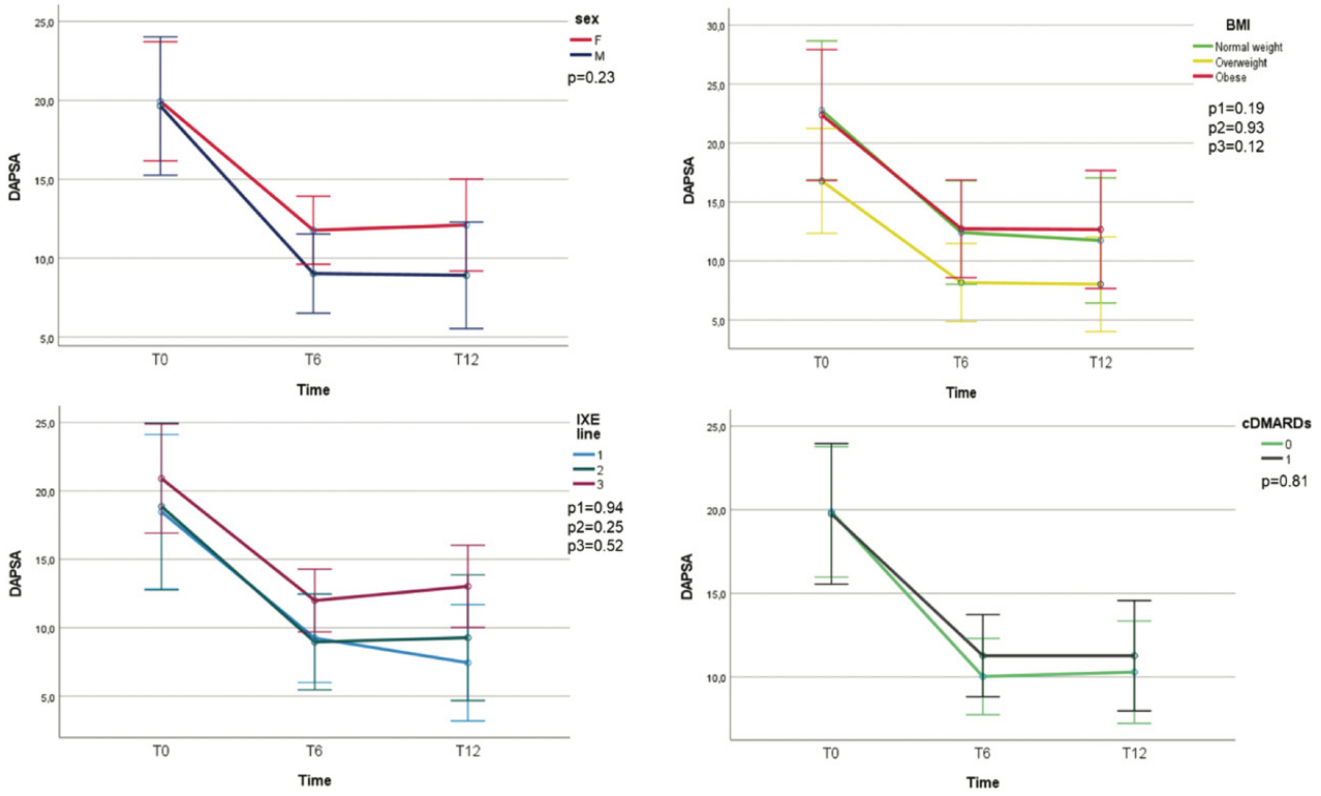

Fig. 2. DAPSA in patients stratified by sex (**A**), BMI (**B**), IXE line of treatment (**C**) and concomitant csDMARD therapy (**D**) from T0 to T12. BMI: Body Mass Index; IXE: ixekizumab; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.

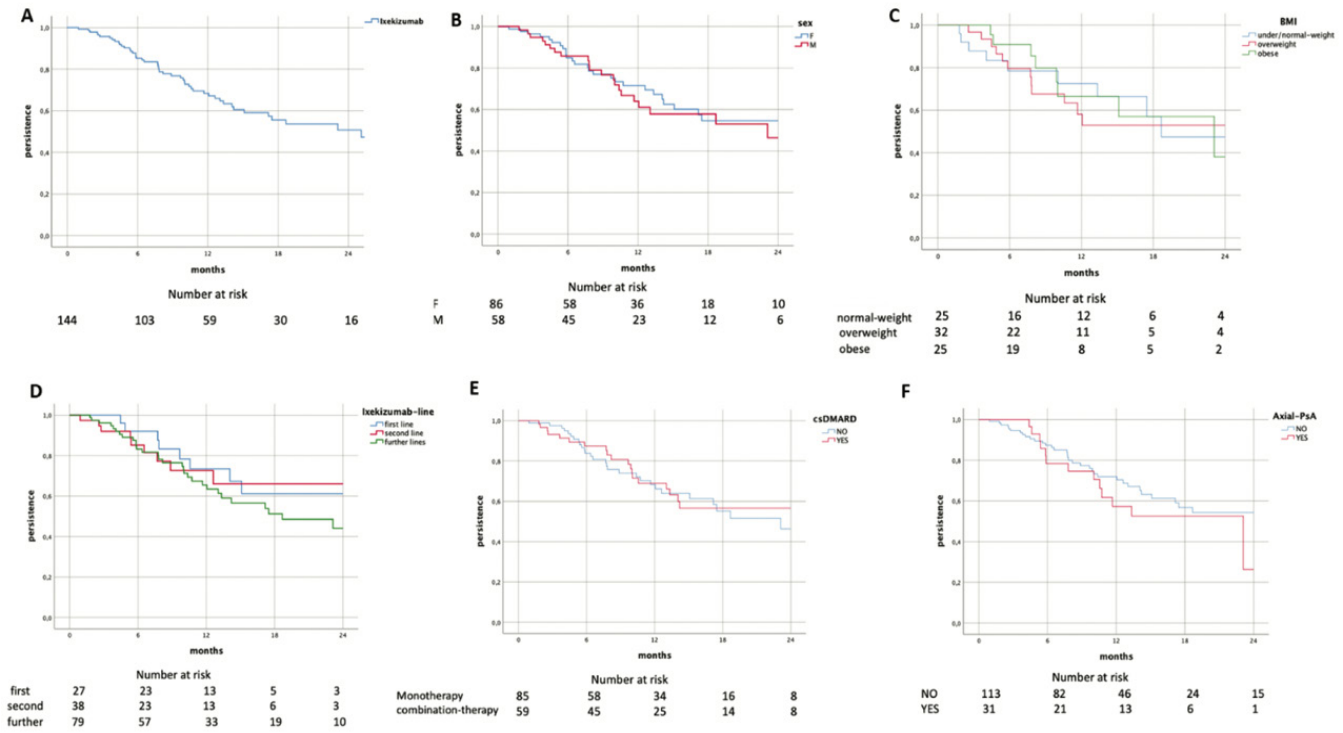

Fig. 3. Persistence on IXE treatment in the entire cohort (**A**), sex (**B**), BMI (**C**), IXE line of treatment (**D**), concomitant csDMARD therapy (**E**) and axial-PsA (**F**).
BMI: Body Mass Index; IXE: ixekizumab; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.

ate disease activity. As expected, given the preferred use of IL-17 inhibitors in patents with skin involvement (4), a high prevalence of PsO was observed in our cohort. The mean disease duration was approximately 10 years and around three-quarters of patients had already been treated with at least one bDMARD. This aligns with both Italian and international recommendations, advocating for biosimilars of anti-TNF-α as the initial biologic option (4, 16, 17). However, some patients with DAPSA remission or LDA at baseline started IXE therapy due to uncontrolled active skin disease despite conventional treatments. The effectiveness of IXE therapy was noted within 6 months, persisting up to 24 months, evident in both joint and skin domains. In this context, a progressive reduction of DAPSA score was observed, with a significant increase in the proportion of patients achieving remission or LDA over time, alongside a decline in the number of patients with moderate or high disease activity.

Our findings are consistent with longitudinal observational studies in a real-word clinical setting (18, 19). In our cohort, males were treated more frequently with IXE as first biologic line, whereas more than half of female patients received IXE after at least two other bDMARDs. This discrepancy may be attributed to a higher prevalence, severity, and burden of skin involvement in males (20, 21), potentially prompting clinicians to opt for anti-IL-17A therapy over anti-TNF-α in male patients. Additionally, females were more likely to receive combination therapy with csDMARDs, potentially due to a higher number of previously failed biologic therapies, making combination therapy preferred for a refractory disease.

In our study, IXE proved to be equally effective in both sexes after 24 months of treatment, unlike a recent pooled data analysis on the phase 3 SPIRIT-P1 and SPIRIT-P2 RCTs highlighted higher DAPSA improvements in males (22). Although the long-term effectiveness is similar in both sexes, in our study males had a faster response than women on both articular and cutaneous domains. This result could be influenced by the fact that males tended to receive IXE as first line biologic treatment, as they presented high PASI at baseline. As expected, females had a statistically higher prevalence of concomitant fibromyalgia than males, which could confound the assessment of inflammatory disease activity (23). Despite this, in our cohort IXE therapy proved equally effective in both sexes over time, without significant differences in achieving DAPSA remission or LDA. Nevertheless, a study specifically designed on PsA patients and concomitant fibromyalgia would better clarify this aspect.

The effectiveness of IXE treatment was consistent across all patient subgroups based on BMI, without significant lower response in obese or overweight patients, unlike what generally happens with anti-TNF-α (24, 25). Analyses based on treatment lines revealed that greater previous biologic therapy failures were associated with higher disease activity, longer disease duration, and a higher proportion of female patients. During the follow up, patients treated with IXE as first line exhibited lower average DAPSA values and a greater proportion achieved DAPSA remission. However, first-line IXE therapy did not emerge as a predictive factor for treatment response in multivariable

analysis. Furthermore, the comparison between patients who received only IXE and patients who received combination therapy showed no significant differences in the primary outcome, indicating that concomitant csDMARDs did not influence IXE effectiveness, consistent with the SPIRIT-P1 and SPRIT-P2 studies (11). IXE showed a favourable drug survival rates in our cohort, with retention rates of 84.3% at 6 months, 75.6% at 12 months, and 67.4% at 24 months, slightly lower than those reported in a recent multicentric Spanish real-world observational study (26). Moreover, drug survival was independent from sex, BMI, IXE line of treatment, concomitant csDMARDs use and axial involvement.

Limitations of the present study include the lack of radiological joint assessment, a relatively small sample size at the 24-month follow-up and missing data. The multicentric nature of our study introduced variability in treatment and follow-up protocols, which were determined by the clinical judgment of rheumatologists at each participating center. To address potential issues of missing data and minimise the impact of this variability, we implemented a standardised approach for collecting demographic and clinical data. This data was systematically gathered at baseline and then again at 6 (±3), 12 (±3), and 24 (±3) months of follow-up. This structured method was carefully designed to ensure consistency in data collection across all centers, thereby enhancing the reliability of our findings despite the inherent challenges of a multicentric study design. The lack of information on enthesitis and dactylitis limited the evaluation of IXE efficacy in these domains and the assessment of disease activity using the Minimal Disease Activity (MDA) score. Similarly, the absence of data regarding the impact on patients' quality of life and functionality, such as the Health Assessment Questionnaire (HAQ), hindered the accurate construction of the American College of Rheumatology (ACR) responses. Of note, the results of this study, not being an RCT, require confirmation from further analyses. In conclusion, IXE demonstrated significant effectiveness within 6 months across joint and skin domains, persisting up to 24 months of treatment, irrespective of sex, BMI, prior bDMARDs, or combination therapy with csDMARDs.

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Competing interests

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