







## ORIGINAL RESEARCH

# Comparative effectiveness and predictors of remission between adalimumab and ixekizumab in patients with psoriatic arthritis: findings from the 'AIRE' multicentre study

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**To cite:** Paci V, Zabotti A, Fontanarosa A, *et al.* Comparative effectiveness and predictors of remission between adalimumab and ixekizumab in patients with psoriatic arthritis: findings from the 'AIRE' multicentre study. *RMD Open* 2026;**12**:e006667. doi:10.1136/rmdopen-2025-006667

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/rmdopen-2025-006667>).

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Received 28 December 2025

Accepted 10 March 2026



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### ABSTRACT

**Background** Tumour necrosis factor  $\alpha$  (TNFi) and interleukin 17 (IL-17) inhibitors have demonstrated efficacy and safety in psoriatic arthritis (PsA) therapy through head-to-head randomised controlled trials, but evidence from real-world clinical practice (RWE) remains limited.

**Methods** Adalimumab vs Ixekizumab Real-world Effectiveness is a multicentre cohort study, aimed at comparing the effectiveness of these drugs in a 'real-world' PsA population. The primary outcome consisted of mixed-effects models comparing Disease Activity in Psoriatic Arthritis (DAPSA) and Psoriasis Areas and Severity Index (PASI) over 12 months in both treatment groups. Remission outcomes (DAPSA; Minimal Disease Activity (MDA)) were analysed using time-dependent Cox models adjusted for confounders.

**Results** A total of 437 patients (42% on adalimumab (ADA); 57% on ixekizumab (IXE)) were enrolled. At baseline, the ADA group mainly showed axial and nail involvement, while the IXE group was mostly biologic disease-modifying antirheumatic drug (bDMARD)-experienced and had higher C reactive protein levels and worse functional status. The DAPSA score improved in both groups, and between-treatment differences in DAPSA pathways over time were not significant. Probabilities of achieving DAPSA remission or MDA did not differ by drug at 12 months. PASI improved similarly in both groups, but IXE showed a greater early reduction from baseline at 3 months. DAPSA remission and MDA were primarily associated with male sex, absence of nail psoriasis, higher PASI, fewer prior bDMARDs and better functional status.

**Conclusions** This RWE study showed that ADA and IXE provide similar 12-month joint outcomes, while IXE showed a faster skin response. Baseline demographic and clinical features affect the chance of remission, highlighting the importance of personalised treat-to-target approaches in PsA.

### INTRODUCTION

Psoriatic arthritis (PsA) lies within the broader concept of psoriatic disease (PsD): a chronic, immune-mediated inflammatory disease affecting up to 30% of patients with psoriasis. It encompasses a heterogeneous spectrum of clinical domains, including peripheral arthritis, enthesitis, dactylitis, axial involvement, skin and nail disease.<sup>1</sup> Beyond musculoskeletal and dermatological manifestations, PsD is linked to heightened prevalence of cardiovascular, metabolic, neoplastic and psychiatric comorbidities, leading to substantial impairment in quality of life and functional status.<sup>2,3</sup>

Over the last two decades, the therapeutic landscape of PsA has undergone a relevant improvement with the introduction of biologic (b-) and targeted synthetic (ts-) disease-modifying antirheumatic drugs (DMARDs).<sup>4</sup> Tumour necrosis factor-alpha inhibitors (TNFi), such as adalimumab (ADA), have long represented a cornerstone of treatment, supported by robust evidence from randomised controlled trials (RCTs) and clinical practice.<sup>5-7</sup> More recently, bDMARDs targeting interleukin (IL)-17, including ixekizumab (IXE), secukinumab and, lastly, bimekizumab, have expanded therapeutic options, particularly for patients with inadequate response or intolerance to previous therapies, and for those with severe skin involvement.<sup>8-16</sup>

### WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ The randomised controlled trial SPIRIT-head-to-head (SPIRIT-H2H) showed that ixekizumab (IXE) is superior to adalimumab for the composite end point of simultaneous  $\geq 50\%$  response in the American College of Rheumatology scale score and 100% response in the Psoriasis Areas and Severity Index, with similar joint outcomes between the treatments.
- ⇒ Post hoc analyses confirmed faster and more profound skin responses with IXE regardless of psoriasis severity and greater effectiveness over adalimumab in peri-ungual disease.
- ⇒ Evidence from real-world settings comparing these two drugs remains limited to persistence analyses.

### WHAT THIS STUDY ADDS

- ⇒ The Adalimumab vs Ixekizumab Real-world Effectiveness study offers the first multicentre real-world comparison between adalimumab (ADA) and ixekizumab (IXE) for treating psoriatic arthritis (PsA), using validated composite outcomes and a dedicated statistical method to handle baseline confounding and longitudinal treatment trajectories.
- ⇒ Unlike randomised controlled trials and consistent with routine rheumatology practice, this study included a heterogeneous population, with bio-experienced patients, a high burden of comorbidities and lower baseline skin activity.
- ⇒ In this setting, ADA and IXE achieved similar joint outcomes and remission rates, but IXE led to quicker early improvements in skin scores and demonstrated higher effectiveness in patients who were biologic disease-modifying antirheumatic drug (bDMARD)-experienced and had worse Health Assessment Questionnaire scores.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Our study complements available head-to-head trial data by providing real-world evidence and valuable insights into the best management of PsA, emphasising a domain-driven approach as an essential treatment strategy in routine rheumatological practice and supporting the role of IXE as a valid treatment option in bDMARD-experienced patient populations.

RCTs have demonstrated the efficacy of both TNFi and IL-17 inhibitors across multiple PsA domains. Notably, the SPIRIT-H2H trial provided the first head-to-head RCT comparison of ADA and IXE in biologic-naïve patients, demonstrating the non-inferiority of IXE for achieving the  $\geq 50\%$  response in the American College of Rheumatology scale score (ACR50), and its superiority in achieving the 100% response in the Psoriasis Areas and Severity Index (PASI-100), as well as for the combined ACR50 plus PASI100 end point.<sup>17 18</sup>

While the stringent inclusion criteria and controlled conditions of RCTs enhance internal validity, they may limit the generalisability of findings to routine clinical practice, where patients often exhibit more complex phenotypes, higher comorbidity burdens and multiple prior biologic exposures. In this context, real-world evidence (RWE) is essential to complement RCT findings by assessing the effectiveness and safety of biologic agents in broader, more heterogeneous populations.<sup>19 20</sup>

The Adalimumab vs Ixekizumab Real-world Effectiveness (AIRE) study was designed to address this gap first by comparing the effectiveness of ADA and IXE in the management of PsA in a ‘real-world’ clinical setting over a 12-month period of follow-up; second by (1) identifying predictors of clinical remission, (2) evaluating joint and skin outcomes and (3) reporting adverse events (AEs).

## METHODS

### Study design and population

The AIRE study was designed as a multicentric, observational, longitudinal study and was conducted at seven third-level rheumatological Italian centres. The study was designed to include a 12-month follow-up.

From October 2019 to December 2023, consecutive adult patients with PsA were enrolled in the AIRE study after providing informed consent. The main inclusion criteria were the following: (a) the diagnosis of PsA, based on the rheumatologist evaluation of clinical, laboratory and imaging features, and considering the Classification criteria for Psoriatic Arthritis; (b) initiation of therapy with ADA or IXE following clinical indication; (c) availability of follow-up data allowing observation for up to 12 months after treatment initiation; (d) age  $> 18$  years.

Treatment allocation was not randomised and reflected routine clinical practice. The choice between ADA and IXE was made by the treating rheumatologist based on clinical judgement, previous treatment history, disease phenotype, comorbidities and in accordance with authorised therapeutic indications and reimbursement criteria in Italy. Each patient was assigned to a single study group. Accordingly, if a patient discontinued ADA and subsequently initiated IXE (or vice versa) during the study period, only data related to the first administered treatment were included in the analysis. Clinical data were recorded until completion of follow-up or until treatment discontinuation due to lack of effectiveness or AEs.

This observational cohort study was designed, conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

The study protocol was registered in the Italian Observational Studies Registry (‘Registro Studi Osservazionali’ - registration number: 1865) hosted by the Italian Drug Agency (‘Agenzia Italiana del Farmaco’).

### Study procedures

For all patients, we collected data on sex, age, smoking habits, disease and symptoms duration at the time of enrolment during the rheumatological visit. The patients’ comorbidities were collected at baseline and updated at every evaluation, including: (a) cardiovascular diseases, such as hypertension, ischaemic cardiomyopathy, heart failure, cardiac arrhythmias (any), valvular disease (any), stroke, venous thromboembolism, pericardial disease and other cardiomyopathies; (b) metabolic diseases, such as obesity, diabetes type I and II, dyslipidaemia and

osteoporosis; (c) chronic infections, such as hepatitis B and C virus, latent or active tuberculosis and HIV; (d) psychiatric conditions, such as anxiety and/or depressive disorders; (f) history of previous malignant neoplasms.

Previous and concurrent treatments for PsA were collected, including corticosteroids, conventional (cs-) and b/tsDMARDs.

Clinical data were obtained at baseline, and at 3, 6 and 12 months, including tender joint count 68 and swollen joint count 66, Visual Analogue Scale for pain, Patient and Physician Global Assessment. The Disease Activity in Psoriatic Arthritis (DAPSA) composite score, as well as the Psoriasis Area Severity Index (PASI), was evaluated in all patients at each time point. The Health Assessment Questionnaire (HAQ) patient-reported outcome was collected to assess the physical functioning. Finally, the Minimal Disease Activity (MDA) fulfilment was assessed at each time point.<sup>21</sup>

Laboratory data, including complete blood count, liver and kidney function tests and C reactive protein (CRP), were collected at the same time points.

Any AE occurring during the study period, and/or within 75 days after treatment discontinuation, was recorded and classified using the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.

## Outcomes

The primary outcome of the study was the comparison of disease activity between the two study groups, expressed as changes in DAPSA and PASI scores at three assessment points (3, 6 and 12 months).

The secondary outcomes were: (1) the predictors of clinical remission, which was defined as the achievement of DAPSA remission (ie, a DAPSA score  $\leq 4$ ) or MDA; (2) the proportion of patients who discontinued the study drug due to ineffectiveness or AEs; and (3) the proportion, type and severity of AEs recorded in the two treatment groups.

## Statistical analysis

Study data were collected and managed using the Research Electronic Data Capture (REDCap) electronic data capture tool hosted at the Italian coordinating centre 'Azienda Ospedaliero Universitaria delle Marche' ([www.project-redcap.org](http://www.project-redcap.org)). REDCap is a web-based software platform designed to support data capture for research studies.<sup>22</sup>

Clinical and demographic characteristics were summarised using median and IQR (first–third quartile) for quantitative variables with asymmetric distribution, and as absolute frequencies and percentages for categorical variables, and compared among patients divided according to drug treatment (ADA vs IXE). The  $\chi^2$  test or Fisher's exact test was used to compare two qualitative variables, and the Wilcoxon-Mann-Whitney U test was used for quantitative variables.

Remission probabilities, defined as a DAPSA score  $\leq 4$  and achievement of MDA, were analysed using a Cox

model, considering the dependent variable as time-dependent, adjusted for patients' clinical and demographic characteristics at baseline. Results were expressed as HR and 95% CI.

Two mixed-effects models for repeated measures were estimated, considering as dependent variables DAPSA and PASI scores. Clinical and demographic characteristics were included in the model as explanatory variables. A sequential contrast approach was applied to assess differences in the dependent variables at consecutive time points. The interaction term between treatments and time points was evaluated to assess whether score differences varied between the two treatment groups at different time points. To account for repeated measures, patient identifier was included in the models as a random effect. Subjects who discontinued treatment were considered up to the last observation point, including all patients in the analyses, both those who discontinued therapy and those who continued treatment for up to 1 year. All statistical analyses were performed using the R software (V.4.4.2) and a p value  $< 0.05$  was considered statistically significant. The figures were generated using the R software (V.4.4.2) and the GraphPad Prism software (V.9.5.1).

## RESULTS

### Baseline characteristics

A total of 437 patients were enrolled in the study, of whom 186 (42.6%) and 251 (57.4%) were treated with ADA and IXE, respectively.

Table 1 and online supplemental figure 1 show the comparisons of the clinical and demographic characteristics of the patients in the ADA and IXE groups at baseline. The patients in the ADA group had a significantly higher prevalence of axial involvement and a lower prevalence of peripheral arthritis than those in the IXE group ( $p=0.005$  and  $p=0.010$ , respectively). Additionally, nail psoriasis was significantly more represented in the ADA group than in the IXE group ( $p=0.044$ ).

Regarding disease activity, both groups showed comparable DAPSA scores, but patients in the ADA group showed a lower proportion of moderate-to-high PASI score and a lower median HAQ compared with IXE ( $p=0.002$  and  $p<0.001$ , respectively).

Finally, patients in the ADA group were more frequently bio-naïve and had received fewer previous bDMARD lines compared with those treated with IXE ( $p<0.001$  and  $p=0.002$ , respectively). Among bDMARD-experienced patients in the ADA group, prior treatment most commonly involved TNFi (36/63; 57.1%), followed by IL-17 inhibitors and IL-12/23 or IL-23 inhibitors (33.3% and 14.3%, respectively); no patients in this group had previously received Janus kinase inhibitors (JAKi). In the IXE group, most bDMARD-experienced patients had been previously treated with TNFi (190/224; 84.8%) followed by IL-17 inhibitors, IL-12/23 or

**Table 1** Clinical and demographic characteristics of patients at baseline according to treatment

Variables	ADA (n=186)	IXE (n=251)	P value
Sex, male, n (%)	55 (29.6)	81 (32.3)	0.618*
*Age, years, median (IQR)	57 (47–65)	60 (50–67)	0.230†
Active smoker, yes, n (%)	32 (17.2)	40 (15.9)	0.824*
Axial involvement, yes, n (%)	103 (54.8)	104 (41.1)	<b>0.005*</b>
Peripheral involvement, yes, n (%)	169 (90.9)	243 (96.8)	<b>0.010*</b>
Enthesitis, yes, n (%)	66 (35.1)	93 (37.1)	0.813*
Nail disease, yes, n (%)	78 (41.5)	78 (31.1)	<b>0.044*</b>
Uveitis, yes, n (%)	6 (3.2)	9 (3.6)	0.999*
Cardiovascular diseases, yes, n (%)	77 (41.0)	117 (46.2)	0.323*
Metabolic diseases, yes, n (%)	77 (41.4)	122 (48.6)	0.162*
Obesity, yes, n (%)	29 (15.4)	59 (23.5)	0.055*
Chronic infections, yes, n (%)	13 (7.0)	33 (13.1)	0.055*
Anxiety/Depression, yes, n (%)	11 (5.9)	30 (11.9)	0.057*
Fibromyalgia, yes, n (%)	14 (7.5)	39 (15.5)	<b>0.025*</b>
Baseline DAPSA	/	/	0.183*
Low (>4)	19 (10.1%)	34 (13.4%)	/
Moderate (>14)	122 (64.9%)	141 (55.7%)	/
High (>28)	47 (25.0%)	77 (30.4%)	/
Baseline PASI	/	/	<b>0.002*</b>
Zero	19 (10.2%)	34 (13.5%)	/
Mild (<5)	121 (65.1%)	141 (56.2%)	/
Moderate-to-high (≥5)	46 (24.7%)	75 (29.9%)	/
Baseline HAQ, median (IQR)	0.875 (0.5–1.0)	1.0 (0.75–1.375)	<b>&lt;0.001†</b>
Baseline CRP, high§, yes, n (%)	63 (33.9%)	140 (55.8%)	<b>&lt;0.001*</b>
Concomitant csDMARD	25 (13.3%)	63 (24.9%)	<b>0.004*</b>
Bio-naïve, yes, n (%)	123 (66.1%)	27 (10.8%)	<b>&lt;0.001*</b>
Number of previous bDMARDs	/	/	<b>&lt;0.001‡</b>
1	44 (23.7%)	95 (37.8%)	/
2	16 (8.6%)	57 (22.7%)	/
>2	3 (1.6%)	72 (28.7%)	/

P values expressed in bold when significant (<0.05).

IQR: first–third quartile.

\* $\chi^2$  test.

†Mann-Whitney U test.

‡Fisher's exact test.

§CRP >0.5 mg/dl.

ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; HAQ, Health Assessment Questionnaire; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index.

IL-23 inhibitors and JAKi (35.3%, 21.0% and 3.6%, respectively). Notably, ADA was a prior treatment in 150/224 (67.0%) bDMARD-experienced patients in the IXE group, and 85 (37.9%) patients in this group had been exposed to two or more TNFi.

### Treatment effectiveness

The mixed-effects model for the DAPSA score, reported in [table 2](#) and [figure 1](#), demonstrated a significant

reduction from baseline to 3 months (−6.12;  $p<0.001$ ), followed by an additional decrease over the subsequent 3 months (−3.51;  $p<0.001$ ), and a further significant reduction of almost two points up to the 12th month (−1.90;  $p=0.004$ ).

There were no significant differences in the changes over time of mean DAPSA scores between the ADA group and the IXE group ( $p=0.663$ ).

**Table 2** Factor associated with DAPSA score over time

Variables	b (95% CI)	P value
IXE vs ADA	0.40 (−1.41 to 2.22)	0.663
Time t3 vs t0	−6.12 (−7.31 to −4.94)	<b>&lt;0.001</b>
Time t6 vs t3	−3.51 (−4.71 to −2.30)	<b>&lt;0.001</b>
Time t12 vs t6	−1.90 (−3.18 to −0.62)	<b>0.004</b>
Drugs×Time t3 vs t0	0.39 (−1.18 to 1.95)	0.628
Drugs×Time t6 vs t3	0.01 (−1.58 to 1.61)	0.986
Drugs×Time t12 vs t6	1.10 (−0.60 to 2.79)	0.205
Discontinuation t3, yes vs no	2.65 (−0.31 to 5.60)	0.079
Discontinuation t6, yes vs no	5.76 (3.71 to 7.81)	<b>&lt;0.001</b>
Discontinuation t12, yes vs no	4.42 (2.21 to 6.62)	<b>&lt;0.001</b>
Males vs females	−1.97 (−3.52 to −0.41)	<b>0.013</b>
Obesity, yes vs no	1.49 (−0.29 to 3.28)	0.101
Axial involvement, yes vs no	1.20 (−0.23 to 2.64)	0.100
Nail disease, yes vs no	0.17 (−1.38 to 1.73)	0.826
PASI, mild vs zero	−0.92 (−2.53 to 0.68)	0.258
PASI, moderate-to-high vs zero	−3.47 (−6.06 to −0.88)	<b>0.009</b>
HAQ at baseline	5.80 (4.38 to 7.21)	<b>&lt;0.001</b>
Previous bDMARD, 1 vs no	3.06 (1.12 to 5.00)	<b>0.002</b>
Previous bDMARD, 2 vs no	2.93 (0.55 to 5.30)	<b>0.016</b>
Previous bDMARD, >2 vs no	1.01 (−1.5 to 3.52)	0.430

Results of linear mixed-effect model. The table presents  $\beta$  coefficients (b) with 95% CIs and p values. Negative  $\beta$  values indicate reductions in DAPSA score. ‘Time’ variables represent the change in mean DAPSA compared with the preceding time point (t0=baseline, t3=3 months, t6=6 months, t12=12 months). ‘Drugs×Time’ interaction terms assess whether DAPSA changes over time differed between ADA and IXE at each time point. ‘Discontinuation’ variables indicate the mean DAPSA difference in patients who discontinued treatment at 3, 6 or 12 months versus those who continued. P values are expressed in bold when significant (<0.05). ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; HAQ, Health Assessment Questionnaire; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index.

Patients with moderate-to-high PASI scores at baseline had significantly lower mean DAPSA scores over time than those without skin involvement (−3.47;  $p=0.009$ ). Additionally, for each unit increase in baseline HAQ score, the mean DAPSA score over time increased by 5.80 points ( $p<0.001$ ).

Finally, patients who had received one or two previous bDMARDs showed a higher mean DAPSA score over time

compared with bio-naïve patients, with differences of 3.06 ( $p=0.002$ ) and 2.93 ( $p=0.016$ ), respectively.

The mixed-effects model for the PASI score is reported in [table 3](#) and [figure 2](#). Patients treated with IXE showed a higher mean PASI score over time compared with ADA patients (+0.59;  $p=0.010$ ). Nevertheless, the improvement in PASI score between baseline and month 3 was on average 0.82 points greater in the IXE than in the ADA group ( $p=0.004$ ).

During the follow-up, male patients showed significantly higher mean PASI scores compared with females (mean difference: 0.61;  $p=0.002$ ). Similarly, patients with nail psoriasis had higher mean PASI scores over time than those without nail involvement (mean difference: 0.87;  $p<0.001$ ). Baseline DAPSA and HAQ scores, as well as the number of previous bDMARDs, did not significantly influence PASI outcomes.

Finally, online supplemental figures 2 and 3 show the longitudinal changes of several disease-related outcomes within each treatment group. These measures are reported for descriptive purposes without adjustment for baseline differences and should not be interpreted as comparative estimates between treatment groups.

### Predictors of remission

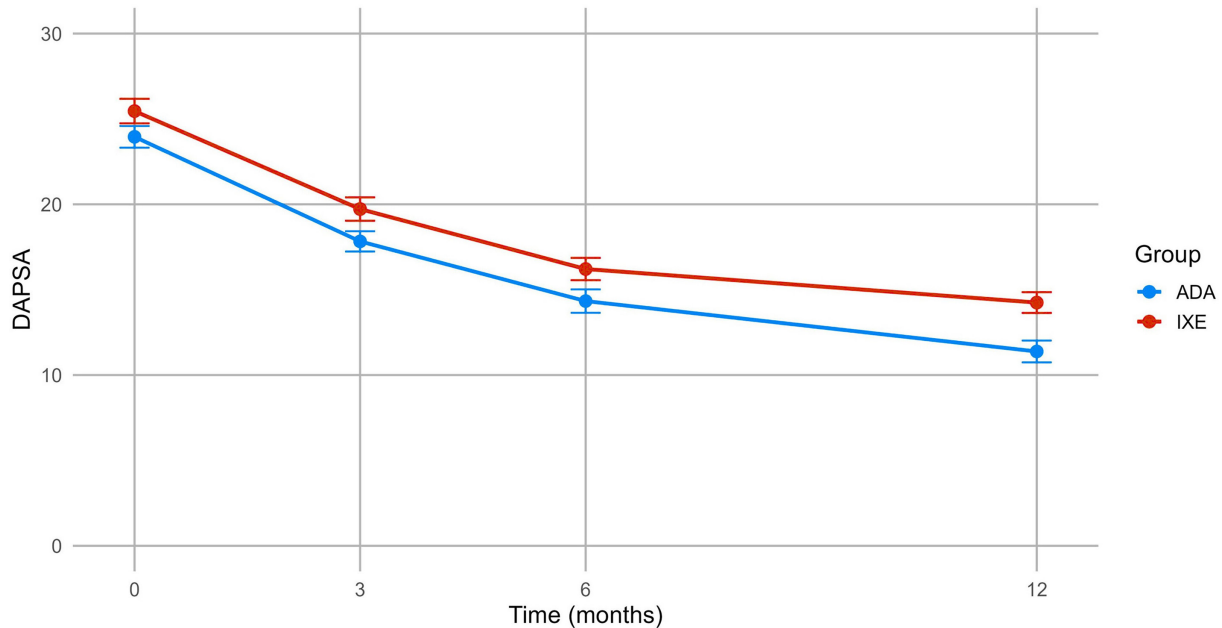
[Table 4](#) and online supplemental figure 4 report the clinical factors associated with disease remission, as assessed by the DAPSA score. No significant differences were found according to IXE or ADA treatments.

Male patients were approximately twice as likely to achieve DAPSA remission compared with females (HR 1.95, 95% CI 1.24 to 3.07,  $p=0.004$ ). A lower probability of reaching DAPSA remission was seen in patients with nail psoriasis (42%;  $p=0.041$ ) and in those with obesity (63%;  $p=0.014$ ). Similarly, patients who had previously received two or more bDMARDs had a decreased chance of DAPSA remission than those who were bDMARD-naïve, by 59% ( $p=0.035$ ) and 62% ( $p=0.040$ ), respectively.

Patients with a baseline moderate-to-high PASI score were six times more likely to get DAPSA remission ( $p<0.001$ ) than those without active skin involvement at baseline. Furthermore, the probability of achieving DAPSA remission decreased by 59% ( $p<0.001$ ) for each unit increase in baseline HAQ score.

[Table 5](#) and online supplemental figure 5 report the clinical factors associated with disease remission as assessed by the MDA. Once again, no differences were found related to IXE or ADA treatment, and males were more likely to reach MDA than females (60%,  $p=0.005$ ). Patients with nail psoriasis had a 43% ( $p=0.004$ ) lower likelihood of achieving MDA. Moreover, the higher the number of previous biologic treatments, the lower the probability of reaching MDA.

Patients with a moderate-to-high PASI score at baseline were three times more likely to attain MDA ( $p<0.001$ ) than those without active skin disease, whereas the probability decreased by 60% ( $p<0.001$ ) for each unit increase in baseline HAQ score.



**Figure 1** DAPSA mean values over time according to treatment. Values represent estimated marginal means and SEs derived from mixed-effects models for repeated measures. Both groups showed significant DAPSA improvement over time, with no significant treatment-by-time interaction between ADA and IXE. ADA, adalimumab; DAPSA, Disease Activity in Psoriatic Arthritis; IXE, ixekizumab.

### Drugs discontinuation and adverse events

A total of 140 (32.0%) patients discontinued treatment during the study period. Among them, 22 (5.0%), 65 (14.9%) and 53 (12.1%) patients discontinued the study drug at the 3-month, 6-month and 12-month visits, respectively. In the ADA group, 57 (30.6%) drug discontinuations were observed, 9 (4.8%) due to AEs and the remaining due to ineffectiveness. In the IXE group, 83 (33.1%) drug discontinuations were observed, 11 (4.4%) due to AEs and the remaining due to ineffectiveness. No significant differences in the probability of treatment discontinuation were observed between the two study groups (online supplemental table 1).

AEs reported during the study are summarised in online supplemental table 2. Overall, 52 AEs were reported, 28 in the ADA group and 24 in the IXE group, occurring in 43 patients (9.8% of the total cohort; 22 (11.8%) ADA, 21 (8.4%) IXE), and considered ‘possibly drug-related’ by the treating physicians.

The most frequently recorded AEs were classified as ‘infections and infestations’ (40.4%), followed by ‘skin and subcutaneous tissue disorders’ (11.5%), ‘blood and lymphatic system disorders’ (11.5%) and ‘general disorders and administration site conditions’ (11.5%). The overall AEs distribution was similar between the treatment groups, except for ‘blood and lymphatic system disorders’, which occurred exclusively in the ADA group.

Most AEs (43/52, 82.7%) were mild or moderate in severity (CTCAE V.5.0—grades 1 and 2). Severe AEs (CTCAE V.5.0—grade 3) were uncommon and occurred in six patients treated with ADA and three treated with IXE. In the ADA group, severe AEs included one case of septic arthritis, one of liver cirrhosis with portal

hypertension, two cases of intestinal subocclusion requiring hospitalisation and two cases of gastrointestinal cancer, which occurred during the study period and were therefore considered ‘possibly related’ to treatment. In the IXE group, severe AEs included one case of *Legionella pneumophila* pneumonia, one case of *Clostridium difficile* enterocolitis and one case of Crohn’s disease.

Herpes zoster reactivation was rare and happened equally in both groups (three cases each). Finally, one patient discontinued IXE due to pregnancy, which was classified as an AE for this reason.

No life-threatening AEs were reported during the study period.

### DISCUSSION

In this multicentre, real-world study, we have compared the clinical outcomes of ADA and IXE in a large cohort of patients with PsA, and, in the evolving therapeutic landscape of PsA, real-world comparative data between bDMARDs remain limited.

While RCTs provide strong data on efficacy and safety, they often exclude patients with features common in everyday practice, such as multimorbidity, long-standing disease or exposure to multiple bDMARDs. As a result, the real-world effectiveness of a bDMARD may be impacted by these limitations, making observational comparative studies important to supplement RCT evidence and guide treatment decisions in more heterogeneous, pragmatic settings.

To our knowledge, this is one of the few (and the only one comparing ADA vs IXE) multicentre real-world studies to directly compare two bDMARDs with different

**Table 3** Factor associated with PASI values over time: results of mixed-effect model

Variables	b (95% CI)	P value
IXE vs ADA	0.59 (0.14 to 1.04)	<b>0.010</b>
Time t3 vs t0	-0.18 (-0.61 to 0.25)	0.413
Time t6 vs t3	-0.17 (-0.61 to 0.26)	0.435
Time t12 vs t6	0.01 (-0.46 to 0.47)	0.992
Drugs×Time t3 vs t0	-0.82 (-1.38 to -0.26)	<b>0.004</b>
Drugs×Time t6 vs t3	-0.07 (-0.65 to 0.51)	0.812
Drugs×Time t12 vs t6	-0.25 (-0.87 to 0.36)	0.420
Discontinuation t3, yes vs no	0.18 (-0.60 to 0.97)	0.647
Discontinuation t6, yes vs no	0.27 (-0.25 to 0.78)	0.313
Discontinuation t12, yes vs no	-0.11 (-0.65 to 0.44)	0.704
Males vs females	0.61 (0.23 to 1.00)	<b>0.002</b>
Obesity, yes vs no	0.24 (-0.20 to 0.68)	0.286
Axial involvement, yes vs no	-0.18 (-0.54 to 0.17)	0.310
Nail disease, yes vs no	0.87 (0.50 to 1.25)	<b>&lt;0.001</b>
DAPSA at baseline	-0.01 (-0.03 to 0.01)	0.196
HAQ at baseline	0.18 (-0.19 to 0.56)	0.344
Previous bDMARD, 1 vs no	0.14 (-0.34 to 0.63)	0.556
Previous bDMARD, 2 vs no	-0.21 (-0.80 to 0.38)	0.488
Previous bDMARD, >2 vs no	-0.17 (-0.80 to 0.45)	0.581

The table presents  $\beta$  coefficients (b) with 95% CIs and p values. Negative  $\beta$  values indicate reductions in PASI score. ‘Time’ variables represent the change in mean PASI compared with the preceding time point (t0=baseline, t3=3 months, t6=6 months, t12=12 months). ‘Drugs×Time’ interaction terms assess whether PASI changes over time differed between ADA and IXE at each time point. ‘Discontinuation’ variables indicate the mean PASI difference in patients who discontinued treatment at 3, 6 or 12 months versus those who continued. P values expressed in bold when significant (<0.05).

ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; HAQ, Health Assessment Questionnaire; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index.

mechanisms of action, with the outcome being disease activity assessed at successive time points, and, importantly, three key findings have emerged.

First, ADA and IXE achieved similar improvements in peripheral disease activity, with no significant difference in remission likelihood at 12 months as assessed by DAPSA and MDA. Consistently, mixed-effects modelling showed parallel DAPSA trajectories for both drugs: rapid improvement during the first 6 months followed by sustained low disease activity. Importantly, IXE was used in and proved to be effective in a larger group of

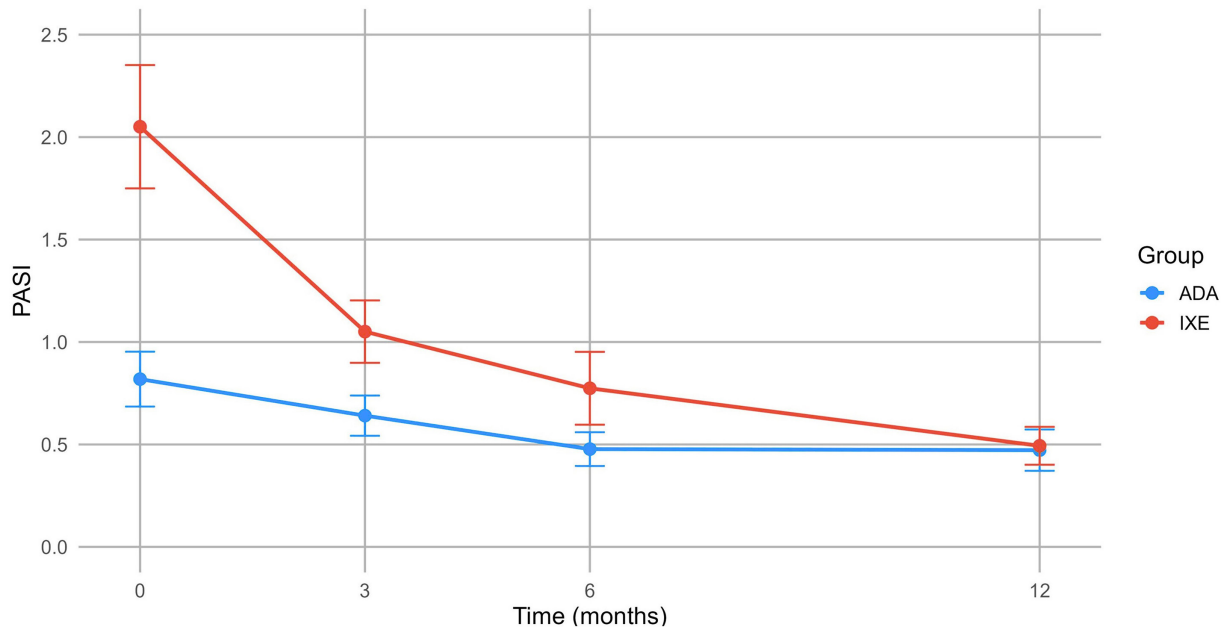
bDMARD-experienced patients. These findings should be interpreted within the context of a real-world observational setting, where patients contributed longitudinal data until treatment discontinuation.

Second, skin outcomes diverged early between treatments. In fact, despite higher baseline PASI scores, the IXE group experienced a greater improvement in skin outcome during the first 3 months. Afterwards, PASI values gradually converged, reaching similar mean values between the two treatments at 1 year. Nail psoriasis was also associated with lower probabilities of remission. In this regard, the higher prevalence of nail involvement in the ADA group may appear counterintuitive, given the recognised efficacy of IL-17 inhibitors on nail psoriasis. However, in routine clinical practice, treatment choice is influenced by multiple factors beyond domain-specific efficacy, including prescribing habits, drug availability and reimbursement policies. Moreover, nail involvement was captured as a binary variable without severity assessment, which may partly explain the observed distribution and should be considered when interpreting these findings. Third, remission was also influenced by patient-specific factors independent of the treatment used. As expected and consistent with previous research, male sex, better functional status and prior exposure to a limited number of bDMARDs at baseline were linked to higher remission rates and lower disease activity over time.<sup>23 24</sup> Interestingly, moderate-to-high baseline PASI scores were associated with better outcomes, both in terms of increased likelihood of achieving MDA or DAPSA remission and lower average DAPSA values over time. Functional disability at baseline, assessed by the HAQ, also proved to be a strong negative prognostic factor.<sup>25</sup> In this regard, despite a higher baseline HAQ in the IXE group, longitudinal DAPSA trajectories and remission outcomes were comparable between treatments. This finding may be interpreted as reassuring evidence that IXE maintains articular effectiveness even in patients with worse baseline functional status. However, this observation was not a predefined study objective and warrants further investigation in dedicated analyses.

Finally, reported AEs were consistent with the known safety profiles of both drugs, and no unexpected safety signals emerged.

Comparative RCTs between IL-17 inhibitors and TNFi (ADA) in PsA are available for both IXE and secukinumab. The SPIRIT-H2H trial provided head-to-head evidence for IXE versus ADA in biologic-naïve PsA with concomitant psoriasis. At week 24, and sustained through week 52, IXE achieved superiority over ADA for the composite primary end point of simultaneous ACR50 and PASI100, and for PASI100 alone, while both performed similarly for the ACR50 outcome considered separately.<sup>17 18</sup>

Similar results were obtained in post hoc analyses restricted to patients with moderate-to-severe psoriasis,<sup>26</sup> and independently of psoriasis severity,<sup>27</sup> whereas IXE demonstrated greater efficacy over ADA regarding the ‘finger-unit’ involvement.<sup>28</sup> Similarly to the findings



**Figure 2** PASI mean values over time according to treatment. Values represent estimated marginal means and SEs derived from mixed-effects models for repeated measures. IXE showed a significantly greater early reduction in PASI at 3 months, while mean PASI levels converged between groups by month 12. ADA, adalimumab; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index.

above, the EXCEED trial comparing secukinumab with ADA in patients with biologic-naïve PsA confirmed superior skin efficacy of IL-17 blockade, without differences in peripheral joint outcomes.<sup>29</sup>

RWE directly comparing IL-17 inhibitors and TNFi remains limited, particularly with regard to comparative clinical effectiveness. Available observational studies have mainly focused on treatment persistence rather than on composite clinical outcomes, such as a recent

analysis comparing drug survival of TNFi versus IXE and secukinumab.<sup>30</sup>

The AIRE study complements the RCT evidence with RWE through accurate clinical characterisation and the use of validated composite outcomes. In this regard, an important aspect of this study concerns the use of composite outcomes traditionally employed as efficacy end points in RCTs, within a real-world effectiveness framework. While this approach improves standardisation, objectivity and comparability with RCT evidence, it

**Table 4** Probability of disease remission (DAPSA  $\leq 4$ )

Variables	HR (95% CI)	P value
IXE vs ADA	1.05 (0.60 to 1.85)	0.858
Males vs females	1.95 (1.24 to 3.07)	<b>0.004</b>
Obesity, yes vs no	0.37 (0.17 to 0.82)	<b>0.014</b>
Axial involvement, yes vs no	0.73 (0.45 to 1.19)	0.207
Nail disease, yes vs no	0.58 (0.34 to 0.98)	<b>0.041</b>
PASI, mild vs zero	1.04 (0.58 to 1.84)	0.902
PASI, moderate-to-high vs zero	6.02 (3.17 to 11.43)	<b>&lt;0.001</b>
HAQ at baseline	0.41 (0.24 to 0.69)	<b>&lt;0.001</b>
Previous bDMARD, 1 vs no	0.68 (0.38 to 1.21)	0.189
Previous bDMARD, 2 vs no	0.41 (0.18 to 0.94)	<b>0.035</b>
Previous bDMARD, >2 vs no	0.38 (0.15 to 0.96)	<b>0.040</b>

Results of Cox regression model. P values expressed in bold when significant (<0.05). ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; HAQ, Health Assessment Questionnaire; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index.

**Table 5** Probability of disease remission (MDA)

Variables	HR (95% CI)	P value
IXE vs ADA	0.93 (0.62 to 1.41)	0.749
Males vs females	1.60 (1.15 to 2.21)	<b>0.005</b>
Obesity, yes vs no	0.64 (0.39 to 1.03)	0.066
Axial involvement, yes vs no	0.91 (0.66 to 1.27)	0.594
Nail disease, yes vs no	0.57 (0.39 to 0.83)	<b>0.004</b>
PASI, mild vs zero	0.85 (0.57 to 1.25)	0.404
PASI, moderate-to-high vs zero	3.34 (1.99 to 5.63)	<b>&lt;0.001</b>
HAQ at baseline	0.40 (0.28 to 0.57)	<b>&lt;0.001</b>
Previous bDMARD, 1 vs no	0.60 (0.39 to 0.91)	<b>0.016</b>
Previous bDMARD, 2 vs no	0.49 (0.28 to 0.87)	<b>0.016</b>
Previous bDMARD, >2 vs no	0.45 (0.24 to 0.85)	<b>0.013</b>

Results of Cox regression model. P values expressed in bold when significant (<0.05). ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index.

may not fully capture all dimensions of effectiveness that are relevant in routine clinical practice. Nevertheless, the use of validated treat-to-target outcomes reflects everyday rheumatology care and could represent a pragmatic trade-off between methodological rigour and real-world complexity.

While conceptually mirroring the RCT SPIRIT-H2H, the AIRE study differs in the composition of the patient cohort, including a significant proportion of biologic-experienced patients, and reflects the true spectrum of psoriasis activity in rheumatology practice, where many patients initiate or switch biologics with a low psoriasis burden. Unlike SPIRIT-H2H, which required at least a 3% body surface area affected by psoriasis, inclusion in AIRE did not necessitate active skin involvement, resulting in a mean baseline PASI of  $1.4 \pm 3.4$ , significantly lower than most RCTs on PsA. Under these conditions, floor effects are anticipated and attenuate measurable differences in skin outcomes, despite favouring IXE in the initial phase.

Regarding the observational setting, our study explicitly addressed confounding variables using mixed-effects longitudinal models for repeated measures and Cox proportional hazards models for remission. Nevertheless, as in all real-world observational studies, treatment selection may also be influenced by contextual factors such as centre-level prescribing policies, reimbursement constraints and concomitant csDMARD use. These elements represent potential sources of residual confounding and should be considered when interpreting the findings. Our findings endorse a domain-prioritised approach to PsA management in real-world care: when significant skin involvement exists, the choice of IXE leads to faster and likely more profound skin improvements with similar joint effectiveness to ADA; when skin disease is minimal, treatment outcomes may be comparable in real-world settings, and other factors such as comorbidity, previous biologic exposure, physician experience and, importantly, regulatory guidelines favouring the use of biosimilars can legitimately influence the treatment approach.<sup>31</sup>

Furthermore, the effectiveness of IXE in bDMARD-experienced patients with a higher disease burden at baseline than those treated with ADA may support consideration of its earlier use in the treatment sequence, where it could potentially lead to improved outcomes, although this interpretation remains speculative and warrants confirmation in future studies. The strengths of this study include its multicentre real-world design, comprehensive assessment using validated composite outcomes and an analytical approach to data that allows the assessment of disease activity over time in relation to treatments, taking into account individual clinical and demographic factors. Furthermore, our data address important gaps in the RCTs, such as drug efficacy for clinical remission and treatment response in patient populations not selected for the RCTs.

The limitations include the observational design, which introduces a risk of information bias, as well as the

potential for residual confounding factors that cannot be measured. In this regard, the extended enrolment period encompassed relevant contextual changes, including the COVID-19 pandemic and changes in biologic drug availability. These factors may represent unmeasurable confounders and should be considered when interpreting the study findings.

Additionally, the study focuses on articular and skin outcomes, with limited data on enthesitis, dactylitis, axial and nail domains. Furthermore, concomitant topical psoriasis treatments, which are challenging to account for in observational settings, may have lessened the apparent differences in skin outcomes. Finally, the study was conducted in tertiary referral centres in Italy, which may limit the applicability of the findings to other health-care settings or to community-based populations.

## CONCLUSIONS

In this real-world, multicentre study, ADA and IXE demonstrated comparable effectiveness in improving DAPSA scores and achieving remission-related outcomes over 12 months in patients with PsA. Additionally, IXE showed a faster improvement in the skin domain and, importantly, proved to be efficacious in a consistent group of bDMARD-experienced patients. Patient-specific factors, particularly male sex, better functional status and limited prior biologic exposure, emerged as key predictors of remission, emphasising the importance of personalised risk stratification to guide therapeutic decisions. The AIRE study extends evidence from RCTs to everyday rheumatological clinical practice, offering insights into the optimal management of PsA in real-life care.

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**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** VP reports speaking and/or consulting fees from AbbVie, Eli Lilly and Company and Johnson & Johnson. AZ reports speaking and/or consulting fees from AbbVie, Amgen, Eli Lilly and Company, Johnson & Johnson, Novartis and UCB. GM reports speaking and/or consulting fees from AbbVie, Johnson & Johnson, Novartis and Pfizer. MMLG reports research support from AbbVie, and speaking and/or consulting fees from AbbVie, Amgen, Eli Lilly and Company, Johnson & Johnson, Novartis and Pfizer. None of the other authors declared any potential conflicts of interest to disclose in relation to this work.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by the Marche Regional Ethics Committee (protocol no. 2024/208—Comitato Etico Territoriale delle Marche, Azienda Ospedaliero-Universitaria delle Marche, Ancona, Italy). This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. The individual participant data that underlie the results reported in this article, as well as the study protocol, will be made available on reasonable request to the corresponding author, after de-identification. Data will be shared with researchers who submit a methodologically sound proposal aimed at achieving the scientific objectives described in the approved request. Access will be granted beginning 3 months and up to 5 years after article publication. Requests for data sharing outside the European Union will be evaluated in accordance with the EU General Data Protection Regulation (Regulation (EU) 2016/679, GDPR) and applicable Italian privacy laws, to ensure appropriate safeguards for international data transfer.

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