Concise report

Improvement from ixekizumab treatment in patients with psoriatic arthritis who have had an inadequate response to one or two TNF inhibitors

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Abstract

Objective. To evaluate the efficacy of ixekizumab (IXE), a monoclonal antibody selectively targeting interleukin-17A, in patients with inadequate response to one or two TNF inhibitors (TNFi).

Methods. A phase 3 study (SPIRIT-P2; NCT02349295) randomized patients with PsA with inadequate response or intolerance to one or two TNF to receive 80-mg IXE every 2 weeks (n = 123) or every 4 weeks (n = 122) after a 160-mg starting dose or placebo (PBO; n = 118) through week 24. This post hoc analysis used data from inadequate responders to one or two TNF, measuring the percentage achieving: ≥50% improvement in ACR response criteria (ACR50) and 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI 100), ACR50, improvement in HAQ-Disability Index (HAQ-DI) ≥0.35, minimal disease activity (MDA), European League Against Rheumatism (EULAR) Good Response Criteria [improvement in Disease Activity Score 28 CRP (DAS28-CRP) > 1.2], and Disease Activity in PsA (DAPSA) ≤14.

Results. There were no significant differences in baseline characteristics between inadequate responders to one and two TNF. At week 24, significantly more patients irrespective of previous TNF experience receiving IXE than PBO achieved ACR50, HAQ-DI ≥0.35 improvement, MDA, EULAR good response, and DAPSA ≤14, and significantly more patients with inadequate response to one TNF receiving IXE than PBO achieved ACR50 and PASI 100. Improvement persisted in all measures through week 52.

Conclusion. IXE improved the signs and symptoms of PsA in a population of difficult-to-treat patients with inadequate response to one or two TNF.

Key words: psoriatic arthritis, tumour necrosis factor inhibitor, inadequate responders, interleukin-17A, ACR, HAQ-DI, DAPSA

Introduction

PsA is a chronic inflammatory disease that affects the joints, periarticular structures, skin and nails [1]. Treatment guidelines for PsA generally recommend TNF inhibitors (TNFi) as the first-line biologic disease-modifying antirheumatic drug (bDMARD) [2, 3]. Although TNFi are efficacious in treating the signs and symptoms of PsA, not all patients respond to TNFi, and over time, many lose response [4]. At one year, rates of drug survival for first-line TNFi have been reported at values ranging from 46% to 84%; two-year rates of survival for first-line TNFi have been reported at values ranging from 52% to 75% [5]. Patients who switch to a second TNFi have worse responses than those who do not switch, and drug survival for a second-line TNFi is lower than for first-line TNFi [5]. Treatments with different mechanisms of action may be an option for patients with PsA who have failed one or more TNFi.
Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets interleukin-17A, is approved for treating active PsA, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and moderate-to-severe plaque psoriasis [6]. IXE has shown efficacy in patients with PsA who are naive to bDMARD (SPIRIT-P1) and in those with an inadequate response or intolerance to TNFi (SPIRIT-P2) [7, 8]. In this post hoc subgroup analysis of SPIRIT-P2, we aimed to assess the efficacy of IXE in patients with inadequate response to one or two TNFi.

Methods

Study design

SPIRIT-P2 (NCT02349295; EudraCT 2011–002328-42) is a randomized, double-blind, placebo (PBO)-controlled phase 3 study in patients with active PsA and a previous inadequate response or intolerance to one or two TNFi. Detailed methodology has been published [8]. Briefly, patients were randomized 1:1:1 to subcutaneous administration of PBO or either 80-mg ixekizumab every 4 weeks (IXE Q4W) or 2 weeks (IXE Q2W) following a 160-mg starting dose at week 0. At week 16, inadequate responders [defined by blinded, predefined criteria of ≤20% improvement from baseline in both tender joint count (TJC) and swollen joint count (SJC)] were required to add or modify concomitant medications. At week 24, patients in the PBO group were re-randomized to IXE Q2W or IXE Q4W through the remainder of the study, and patients in the IXE group remained on their original dose. At week 32 and any subsequent visit, patients were discontinued if they did not achieve ≥20% improvement from baseline in both TJC and SJC. These post hoc data were derived from patients in the intent-to-treat (ITT) population with prior inadequate response to one or two TNFi; patients who were intolerant to TNFi were excluded from the analysis.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Bellberry Human Research Ethics Committee (Application #2015–01-049-AA). Patients provided written informed consent before the study-related procedures were performed.

Study population

Detailed eligibility criteria have been published [8]. Briefly, enrolled adult patients were male or female who met the Classification Criteria for PsA (CASPAR), had active PsA (defined as the presence of ≥3 TJC and ≥3 SJC) and active psoriatic skin lesion or a documented history of plaque psoriasis. Patients were previously treated with TNFi and had to have an inadequate response or intolerance to one or two TNFi.

Assessments

Efficacy outcome measurements for this post hoc analysis included percentage of patients who attained simultaneous ≥50% improvement in ACR response criteria (ACR50) and 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI 100), ACR50, improvement in HAQ-Disability Index (HAQ-DI) ≥0.35 (minimal clinically important difference), minimal disease activity (MDA), European League Against Rheumatism (EULAR) Good Response Criteria [an absolute of ≤3.2 and improvement in Disease Activity Score 28–CRP (DAS28-CRP) >1.2], and Disease Activity in PsA (DAPSA) ≤14.

Statistical methods

All analyses were performed on the ITT population (defined as all patients randomized at week 0) stratified by previous TNFi experience, except for the simultaneous ACR50 and PASI100 where a subset of patients with baseline BSA ≥3% was used. Patients who were intolerant to TNFi were excluded from the analysis. Treatment comparisons between IXE and PBO up to week 24 were conducted using Fisher’s exact test. Missing values were imputed by non-responder imputation. Inadequate responders at week 16 were analysed as non-responders at weeks 20 and 24. Descriptive statistics were reported up to week 52 for patients initially randomized to either dose of IXE.

Results

In SPIRIT-P2, about 90% (332) patients had discontinued prior TNFi therapy due to an inadequate response, with 204 and 128 patients having inadequate response to one and two TNFi, respectively; the remainder of patients (31) were intolerant to TNFi and excluded from this post hoc analysis. Among the patients included in this analysis, the baseline demographics and disease characteristics were not significantly different between those who had an inadequate response to one TNFi (one-TNFi-IR) and those with an inadequate response to two TNFi (two-TNFi-IR). There were fewer males in the PBO and IXE Q2W groups among those patients who failed two-TNFi compared with those who failed one TNFi. On average, the time since PsA diagnosis was one to two years longer in patients who failed two TNFi than patients who failed only one TNFi. Patients in the two-TNFi-IR group on average had higher joint count than those in the one-TNFi-IR group (TJC: 25.0 vs 22.2; SJC: 13.1 vs 11.9). Among the two-TNFi-IR, patients randomized to IXE Q2W had the highest TJC and SJC (~29 and 16, respectively). About 50% of the patients remained on concomitant background conventional synthetic DMARD therapy during the study, and most of those patients were receiving methotrexate. The most common prior TNFi across all study groups was adalimumab or etanercept. About 25% of two-TNFi-IR patients had also received infliximab. Golimumab and certolizumab were used less frequently across both subgroups (Table 1).
Ixekizumab for TNFi Inadequate Responders

**Table 1** Baseline demographics and disease characteristics, ITT population

| Inadequate responders to 1 TNFi | Inadequate responders to 2 TNFi |
|-------------------------------|-------------------------------|
| **PBO** (n = 68)               | **IXE Q4W** (n = 71)           | **IXE Q2W** (n = 65) |
| Age (years)                   | 51.6 (9.6)                    | 52.5 (14.1)          | 50.8 (11.8) |
| Male, n (%)                   | 36 (52.9)                     | 37 (52.1)            | 30 (46.2)  |
| Time since PsA diagnosis (years) | 9.6 (7.7)                    | 10.9 (10.3)          | 9.3 (7.5)  |
| TJC (68 joints)              | 21.3 (17.0)                   | 22.3 (14.1)          | 23.1 (16.9) |
| SJC (66 joints)              | 10.1 (7.4)                    | 13.0 (11.3)          | 12.5 (9.6)  |
| CRP (mg/l)                    | 9.8 (15.6)                    | 16.0 (26.4)          | 17.1 (30.3) |
| HAQ-DI                        | 1.1 (0.7)                     | 1.2 (0.6)            | 1.2 (0.7)  |
| DAS28-CRP                     | 4.9 (1.2)                     | 5.1 (1.1)            | 5.1 (1.1)  |
| DAPSA score                   | 45.5 (24.1)                   | 50.1 (22.4)          | 51.5 (26.9) |

**Background cDMARD therapy**

| Current use of cDMARD, n (%) | 32 (47.1) | 37 (52.1) | 37 (56.9) |
| Current use of MTX, n (%)    | 23 (33.8) | 28 (39.4) | 30 (46.2) |
| Prior failed TNFi, n (%)     | 23 (33.8) | 24 (33.8) | 29 (44.6) |

Data are mean (s.d.) unless stated otherwise. a1 TNFi Inadequate Responders, Nx: PBO = 67, IXE Q4W = 69, IXE Q2W = 65; 2 TNFi Inadequate Responders, Nx: PBO = 40, IXE Q4W = 41, IXE Q2W = 46. b1 TNFi Inadequate Responders, Nx: PBO = 67, IXE Q4W = 70, IXE Q2W = 64; 2 TNFi Inadequate Responders, Nx: PBO = 41, IXE Q4W = 41, IXE Q2W = 44. c1 TNFi Inadequate Responders, Nx: PBO = 67, IXE Q4W = 69, IXE Q2W = 64; 2 TNFi Inadequate Responders, Nx: PBO = 41, IXE Q4W = 41, IXE Q2W = 45. cDMARD: conventional disease-modifying antirheumatic drug; DAPSA: Disease Activity in Psoriatic Arthritis; DAS28-CRP: Disease Activity Score 28–CRP; HAQ-DI: HAQ-Disability Index; ITT: intent-to-treat; IXE Q2W: 80-mg ixekizumab every 2 weeks; IXE Q4W: 80-mg ixekizumab every 4 weeks; MDA: Minimal Disease Activity; PASI: Psoriatic Arthritis Severity Index.

At week 24, regardless of inadequate response to one or two TNFi, significantly more patients who received IXE than PBO achieved ACR50, HAQ-DI ≥0.35 improvement, MDA, EULAR good response, and DAPSA ≤14 (Fig. 1). Further, significantly more patients who received IXE than PBO who had inadequate response to one TNFi achieved ACR50 and PASI 100 simultaneously (Fig. 1A). Additionally, the responses achieved were comparable between the subgroups. In the approved dosing regimen for patients with active PsA (IXE Q4W), 15% and 17% of patients with an inadequate response to one or two TNFi, respectively, simultaneously achieved ACR50 and PASI 100 at week 24; 34% and 37% of patients with an inadequate response to one or two TNFi, respectively, achieved ACR50 at week 24. Almost 50% of patients in both subgroups had an improvement from baseline of ≥0.35 in HAQ-DI (45%) and achieved an EULAR good response (44%). There were numerical differences between the one-TNFi-IR and two-TNFi-IR populations with regard to MDA and DAPSA ≤14, but both subgroups had statistically greater differences compared with PBO at week 24 (MDA in one-TNFi-IR group: IXE Q4W vs PBO P < 0.001 and IXE Q2W vs PBO P < 0.01; two-TNFi-IR group: IXE Q4W vs PBO P < 0.05 and IXE Q2W vs PBO P < 0.001; and DAPSA in one-TNFi-IR group: IXE Q4W vs PBO P < 0.001 and IXE Q2W vs PBO P < 0.05; two-TNFi-IR group: IXE Q4W vs PBO P < 0.01 and IXE Q2W vs PBO P < 0.01).

At week 52 in the IXE Q4W treatment group, 25% of one-TNFi-IR patients and 22% of two-TNFi-IR patients simultaneously achieved ACR50 and PASI 100; 41% of one-TNFi-IR patients and 44% of two-TNFi-IR patients achieved ACR50. Numerically, more one-TNFi-IR patients than two-TNFi-IR patients achieved HAQ-DI ≥0.35 improvement as well as the more stringent outcomes of EULAR good response, DAPSA ≤14, and MDA. Overall, responses were consistent among both subgroups across the five outcomes analysed.

**Discussion**

In patients who had an inadequate response or were intolerant to one or two TNFis, treatment with IXE resulted in improvements in the signs and symptoms of PsA, and these improvements persisted over 52 weeks of treatment [8, 9]. Previously, we showed that IXE provides comparable efficacy between patients who have an inadequate response to one TNFi and those with two TNFis as measured by ACR20 [8]. In this report, we...
further investigated the effect of IXE among a subgroup of patients who had an inadequate response to one and two TNFi including more relevant clinical endpoints such as the simultaneous achievement of ACR50 and PASI 100, ACR50, HAQ-DI ≥0.35, EULAR good response, MDA, and DAPSA ≤14. Good Response Criteria defined as >1.2 improvement and ≤3.2 present DAS28-CRP.

*P < 0.05, †P < 0.01, ‡P < 0.001 vs PBO, Fisher’s exact test. ACR50: at least 50% improvement in ACR response criteria; ITT: intent-to-treat; IXE Q2W: 80-mg ixekizumab every 2 weeks; DAS28-CRP: Disease Activity score (28 diarthrodial joint count) based on CRP; HAQ-DI: HAQDisability Index; IXE Q4W: 80-mg ixekizumab every 4 weeks; MDA: minimal disease activity; Ns: number of patients in each subgroup; PASI 100: 100% improvement from baseline in the Psoriasis Area and Severity Index; PBO: placebo; TNFi: TNF inhibitor.

Although the 2018 ACR/National Psoriasis Foundation treatment guidelines for PsA encourage the use of a second TNFi if a patient has active disease despite receiving a TNFi, there is little evidence on the benefit of cycling TNFi in PsA [3]. These data are increasingly important because other mode-of-action therapies are now available. Several studies show that patients discontinue TNFi primarily due to lack of efficacy and have lower response rates and reduced drug survival with subsequent TNFi. One such study, from the DANBIO registry, suggested responses after one and particularly two previous TNFi therapies were poor. Their results showed that following 3–6 months of treatment, the proportion of patients on their first, second and third treatment courses who achieved ACR50 was 33%, 13% and 6%, respectively. In this analysis, about 50% of the patients switched
to a second and third biologic due to lack of effect: 57% of 548 switchers and 62% of 189 switchers, respectively [5]. The longitudinal observational NOR-DMARD study found that 1-year drug survival of a second TNFi was significantly less than that in patients staying on their first TNFi (56% vs 83%, respectively). This study also identified a trend towards poorer responses with the second TNFi compared with the first TNFi, with ACR50 at 3 months being achieved by 23% of 63 switchers to a second TNFi compared with 40% of 259 non-switchers \((P = 0.05)\) [10]. Similarly, the US-based CORRONA PsA/Spondyloarthritis Registry identified lack of efficacy as the most common reason for discontinuation in both TNFi-naive (90%) and TNFi-experienced (73%) patients, with shorter time to discontinuation for TNFi-switch patients compared with those on their first TNFi (20 months vs 27 months; \(P = 0.03\)) [11]. Data from the British Society for Rheumatology Biologics Register and DANBIO Registry corroborate decreased drug survival time in patients on their second TNFi [5, 12].

Patients with PsA who have had an inadequate response to TNFi present specific challenges to clinicians and have not been studied extensively (particularly two TNFi) in dedicated clinical studies. This post hoc analysis of SPIRIT-P2 suggests that IXE is also an effective treatment option if a patient with PsA has had an inadequate response to one or two TNFi.

**Conclusion**

This post hoc analysis suggests that IXE improved the signs and symptoms of PsA in a population of difficult-to-treat patients who had had inadequate response to one or two TNFi. IXE Q2W and Q4W demonstrated improvement at week 24, which persisted among patients continuously dosed with IXE through week 52 on all the six outcomes analysed. Therefore, IXE may provide clinicians with an effective treatment option for patients with PsA who have failed one or two TNFi.

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**Data availability statement**

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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