Ixekizumab in radiographic axial spondyloarthritis with and without elevated C-reactive protein or positive magnetic resonance imaging

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Abstract

Objective. To evaluate response rates at week 16 with ixekizumab in patients with radiographic axial SpA (r-axSpA) and elevated or normal/low baseline inflammation measured by serum CRP or spinal MRI using data from two randomized, double-blind, placebo (PBO)-controlled phase III trials.

Methods. Biologic-naïve (COAST-V) or TNF inhibitor-experienced (COAST-W) adults with active r-axSpA received 80 mg ixekizumab every 2 weeks (IXEQ2W) or 4 weeks (IXEQ4W) or PBO or active reference [40 mg adalimumab every 2 weeks (ADA-Q2W)] in COAST-V. At week 16, patients receiving ixekizumab continued as assigned and patients receiving PBO or ADA were rerandomized 1:1 to IXEQ2W or IXEQ4W through week 52. Assessment of SpondyloArthritis international Society 40% (ASAS40) response rates were examined by baseline CRP (<5 mg/l) and Spondyloarthritis Research Consortium of Canada (SPARCC) MRI spine inflammation score (<2 or ≥2).

Results. In the COAST-V/W integrated dataset (N = 567), significantly more patients treated with ixekizumab achieved ASAS40 response at week 16 by CRP <5 mg/l (27% IXEQ4W, P < 0.05; 35% IXEQ2W, P < 0.01 vs 12% PBO), CRP >5 mg/l (39% IXEQ4W, P < 0.001; 43% IXEQ2W, P < 0.001 vs 17% PBO), SPARCC MRI spine score <2 (40% IXEQ4W P < 0.01, 52% IXEQ2W P < 0.001 vs 16% PBO), and SPARCC MRI spine score ≥2 (44% IXEQ4W P < 0.001, 47% IXEQ2W P < 0.001 vs 19% PBO). ASAS40 response was observed with CRP ≤5 mg/l and SPARCC MRI spine score <2 with IXEQ4W (29%) and was significant with IXEQ2W (48%; P < 0.05) vs PBO (13%).

Conclusion. Ixekizumab demonstrated efficacy in the treatment of AS/r-axSpA in patients with and without elevated CRP or evidence of spinal inflammation on MRI.

Trial registration. ClinicalTrials.gov (https://clinicaltrials.gov): NCT02696785, NCT02696798

Key words: AS, inflammation, CRP, MRI, randomized clinical trials, ixekizumab
Introduction

Axial SpA (axSpA) is a chronic inflammatory disease of the axial skeleton that includes patients with radiographic axSpA (r-axSpA), also referred to as AS, and patients with non-radiographic axSpA (nr-axSpA). The difference between the two is the presence (AS/r-axSpA) or absence (nr-axSpA) of definite sacroiliitis on plain X-rays [1–9]. Patients with axSpA present with chronic inflammatory back pain but may also have other clinical features, including peripheral inflammatory arthritis, enthesitis, dactylitis, uveitis, psoriasis or IBD [3–6].

Patients with r-axSpA who have persistently high disease activity (e.g. BASDAI ≥4) and inadequate response or intolerance to NSAIDs are often initiated on targeted biologic interventions [3]. TNF inhibitors and IL-17 antagonists are treatment options [3, 7–9], however, several factors are known to influence patient response to TNF inhibitors [3, 10]. Elevated serological CRP levels and evidence of inflammation on MRI of the SI joint are two objective measures of inflammation known to predict response to TNF inhibitors in patients with AS [11–15]. The roles of baseline CRP levels and inflammation on MRI of the spine or SI joint to predict response to ixekizumab, an IL-17A antagonist, have not been investigated. The question as to whether biologic DMARDs (bDMARDs) are effective in patients with active symptoms of r-axSpA, but without objective features of inflammation according to lab and imaging markers, has also not been previously assessed.

Ixekizumab is a high-affinity monoclonal antibody that selectively targets IL-17A [16] and has demonstrated efficacy and safety in three phase III, randomized, placebo (PBO)-controlled trials in axSpA [31–20], two of which were in patients with active r-axSpA who were biologic naive (COAST-V) [17, 18] or previously treated with one or two TNF inhibitors (COAST-W) [18, 19]. These trials were the first in r-axSpA to have both CRP and MRI or two TNF inhibitors (COAST-W) [18, 19]. Both trials had a double-blind treatment period (weeks 0–16) in which patients in COAST-V [17] were randomized 1:1:1:1 for 80 mg ixekizumab every 2 weeks (IXEQ2W) or 80 mg ixekizumab every 4 weeks (IXEQ4W) (with a further 1:1 randomization to a 160 mg or 80 mg ixekizumab starting dose), PBO or an active reference arm (40 mg adalimumab every 2 weeks (ADAQ2W)). ADA was an active reference arm in COAST-V only and the study was not powered to test equivalence or non-inferiority of ixekizumab vs ADA. Patients in COAST-W [19] were randomized 1:1:1 to IXEQ2W or IXEQ4W (with further 1:1 randomization to a 160 mg or 80 mg ixekizumab starting dose) or PBO.

At week 16, patients in both trials began a dose double-blind extended treatment period up to week 52 [18]. Patients treated with ixekizumab continued their assigned treatment (IXEQ2W/IXEQ2W or IXEQ4W/IXEQ4W) and patients who received PBO were rerandomized 1:1 to IXEQ2W (PBO/IXEQ2W) or IXEQ4W (PBO/IXEQ4W) with a 160 mg ixekizumab starting dose. In COAST-V, patients who received the active reference treatment ADA were rerandomized 1:1 to 80 mg IXEQ2W (ADA/IXEQ2W) or IXEQ4W (ADA/IXEQ4W). Patients received their last dose of ADA at week 14 and, after a 6 week washout period, they received their first dose of ixekizumab at week 20.

Assessments

Patients were stratified at study entry by baseline CRP ≤5 or >5 mg/l. It was prespecified that efficacy analysis be carried out by stratifying the patients based on baseline CRP (≤5 and >5 mg/l) and Spondyloarthritis Research Consortium of Canada (SPARCC) MRI inflammation scores (≤2 or ≥2). Baseline spine MRI was read by central readers using the SPARCC MRI spine inflammation scoring method evaluating all 23 disco-vertebral

Patients and methods

Trial design and participants

Detailed trial designs and patient eligibility criteria for COAST-V (NCT02696785) and COAST-W (NCT02696798) have been reported [17–19]. Briefly, COAST-V and COAST-W were phase III, randomized, double-blind, PBO-controlled trials that enrolled biologic-naive or TNF inhibitor–experienced patients, respectively. In both trials, patients had active disease (BASDAI ≥4 and spinal pain ≥4 on a numeric rating scale) and an established diagnosis of r-axSpA and fulfilling ASAS criteria (sacrociliitis on radiograph by modified New York (mNY) criteria and one or more SpA feature) [21, 22]. All patients who fulfilled the ASAS criteria for r-axSpA also fulfilled the mNY criteria for AS. Both trials were conducted in accordance with the ethical principles of the Declaration of Helsinki. The COAST-V and COAST-W studies were approved by ethics review boards at each participating study site and all patients provided written informed consent prior to the initiation of study procedures. The main ethics committee was the Schulman Associates Institutional Review Board, Cincinnati, OH, USA (201506061 for COAST-V and 201506079 for COAST-W). The full lists of investigators and sites are provided in the primary manuscript supplements [17, 19].
units [23], with patients categorized by scores of <2 or \( \geq 2 \). Baseline SI joint inflammation on MRI was assessed only in COAST-V using the SPARCC MRI SI joint inflammation scoring method [24], with patients categorized by scores of <2 or \( \geq 2 \). MRI of the SI joint was not performed in the COAST-W trial.

Statistical analysis

Baseline CRP and MRI readings were analysed to determine their association with ASAS40 response rates at week 16 using two types of analyses. First, subgroups were defined according to CRP and MRI spinal inflammation cut-offs and analyses were performed using individual study data from COAST-V and COAST-W or integrated data from COAST-V and COAST-W (for PBO and ixekizumab-treated patients only). For individual study data at week 16, treatment group comparisons were made using Fisher’s exact test. For COAST-V/W integrated data at week 16, treatment group comparisons were made using a Cochran–Mantel–Haenszel test stratified by study. Missing data were imputed using non-responder imputation and patients were considered non-responders if they did not meet the clinical response criteria or had missing clinical response data at the analysis time point. There are no inferential statistics (P-values) at week 52. Summary statistics for subgroup analysis at week 52 are provided in Supplementary Tables S1–S3 (available at Rheumatology online).

In addition, we explored the association of CRP and MRI with ASAS40 response at week 16 using a logistic regression model, with treatment and baseline values in the model for COAST-V and COAST-W separately. As prespecified in the statistical analysis plan, we fit a logistic regression model to include the individual effects of treatment (PBO, active reference ADA when applicable, IXEQ4W and IXEQ2W), baseline subgroup (CRP, MRI SI joint when applicable and MRI spine) and baseline subgroup by treatment interaction. The basis of using this model was to determine whether baseline inflammation was prognostic and/or predictive of ASAS40 response at week 16. The parameter estimates and the P-values (analysis of maximum likelihood estimates) are presented in Supplementary Table S4 (available at Rheumatology online).

Results

Patient characteristics

In COAST-V, 341 patients were randomized to PBO (n = 87), ADA (n = 90), IXEQ4W (n = 81) or IXEQ2W (n = 83). In COAST-W, 316 patients were randomized to PBO (n = 104), IXEQ4W (n = 114) or IXEQ2W (n = 98). Baseline demographics and clinical characteristics are listed in Table 1. As previously reported, baseline demographics and clinical characteristics were similar between treatment groups [17, 19]. The majority of patients had elevated CRP at baseline as measured by the cut-off of 5 mg/l (64% in COAST-V, 66% in COAST-W) or had an MRI spine SPARCC score \( \geq 2 \) (62% in COAST-V). Fewer patients in COAST-W (49%) had objective evidence of baseline spine inflammation as measured by a SPARCC MRI spine inflammation score \( \geq 2 \). Baseline spine MRI was available in 96% of patients in COAST-V and 51% in COAST-W; this was because COAST-W MRI was performed by protocol addendum only, where MRI was performed only on those patients who participated in the MRI addendum (n = 162). Baseline SI joint MRI was available in 96% of patients in COAST-V, of whom 62% had a SPARCC SI joint score <2 and 38% had SPARCC SI joint score \( \geq 2 \). MRI of the SI joint was not performed in the COAST-W trial. In COAST-V, for PBO patients, 87 were randomized at week 0 and 86 completed week 16; for patients on active reference ADA, 90 were randomized at week 0 and 88 completed week 16; for IXEQ4W, 81 patients were randomized at week 0 and 78 completed week 16; and for patients on IXEQ2W, 83 were randomized at week 0 and 79 completed week 16. In COAST-W, for PBO patients, 104 were randomized at week 0 and 93 completed week 16; for IXEQ4W, 114 patients were randomized at week 0 and 99 completed week 16; and for patients on IXEQ2W, 98 were randomized at week 0 and 90 completed week 16.

ASAS40 response by baseline CRP

In COAST-V, week 16 ASAS40 response rates in the normal (\( \leq 5 \text{mg/l} \)) baseline CRP group were 35% (95% CI 17, 52) for IXEQ4W, 43% (95% CI 25, 61) for IXEQ2W, 21% (95% CI 8, 34) for active reference ADA and 19% (95% CI 4, 34) for PBO, but were statistically significant with ixekizumab vs PBO in the elevated (\( > 5 \text{mg/l} \)) baseline CRP group: 56% (95% CI 42, 69; \( P < 0.001 \)) for IXEQ4W, 56% (95% CI 43, 70; \( P < 0.001 \)) for IXEQ2W, 46% (95% CI 33, 60; \( P < 0.01 \)) for active reference ADA and 18% (95% CI 8, 28) for PBO (Fig. 1A, B). In COAST-W, week 16 ASAS40 response rates (Fig. 1C, D) were similarly numerically higher with ixekizumab vs PBO in the normal baseline CRP group: 23% (95% CI 10, 35) for IXEQ4W, 27% (95% CI 10, 44) for IXEQ2W and 8% (95% CI 0, 16) for PBO, but ixekizumab (IXEQ2W) was statistically significant vs PBO in the elevated baseline CRP group: 27% (95% CI 17, 38) for IXEQ4W, 32% (95% CI 21, 43; \( P < 0.05 \)) for IXEQ2W and 15% (95% CI 7, 24) for PBO. In the COAST-V/W integrated dataset, all week 16 ASAS40 response rates were statistically significant for ixekizumab vs PBO, regardless of whether baseline CRP status was normal or elevated (Fig. 1E, F). Patients who were treated continuously with ixekizumab sustained an ASAS40 response up to week 52 in both CRP subgroups (Supplementary Table S1, available at Rheumatology online).

A logistic regression model was used to assess whether baseline CRP, used as a continuous variable, was prognostic and/or predictive of ASAS40 response at week 16. In this analysis, baseline CRP tended to be positively associated (positive slope of the curve) with the probability of ASAS40 response in COAST-V (Fig. 1G) and COAST-W (Fig. 1H), irrespective of the
| Characteristics                              | COAST-V (biologic naïve) | COAST-W (TNFi experienced) |
|---------------------------------------------|--------------------------|---------------------------|
|                                             | PBO (n = 87)             | ADAa (n = 90)             | IXEQ4W (n = 81) | IXEQ2W (n = 83) | PBO (n = 104) | IXEQ4W (n = 114) | IXEQ2W (n = 98) |
| Age, years                                  | 42.7 (12.0)              | 41.8 (11.4)               | 41.0 (12.1)     | 41.3 (11.2)     | 46.6 (12.7)     | 47.4 (13.4)     | 44.2 (10.8)     |
| Male, n (%)                                 | 71 (82.6)                | 73 (81.1)                 | 68 (84.0)       | 64 (77.1)       | 87 (83.7)       | 91 (79.8)       | 75 (76.5)       |
| Weight, kg                                  | 79.9 (17.1)              | 78.2 (17.2)               | 77.6 (14.7)     | 76.6 (13.8)     | 84.3 (17.9)     | 85.5 (20.2)     | 79.3 (17.3)     |
| Duration of axSpA symptoms, years           | 16.6 (10.1)              | 15.6 (9.3)                | 15.8 (11.2)     | 15.8 (10.6)     | 19.9 (11.6)     | 18.8 (11.6)     | 16.5 (9.6)      |
| Time since axSpA diagnosis, years           | 6.8 (7.6)                | 7.5 (7.5)                 | 8.3 (9.6)       | 8.2 (9.0)       | 13.0 (10.5)     | 10.1 (7.8)      | 11.7 (8.8)      |
| Therapy, n (%)                              |                          |                           |                |                |                 |                |                |
| Current cDMARD use                          | 31 (36.0)                | 32 (35.6)                 | 33 (40.7)       | 29 (34.9)       | 33 (31.7)       | 29 (25.4)       | 24 (24.5)       |
| Current MTX use                             | 8 (9.3)                  | 6 (8.9)                   | 9 (11.1)        | 4 (4.8)         | 20 (19.2)       | 12 (10.5)       | 9 (9.2)         |
| IR to 1 TNFi                                | –                        | –                         | –               | –               | 64 (61.5)       | 75 (65.8)       | 66 (68.0)       |
| IR to 2 TNFi                                | –                        | –                         | –               | –               | 32 (30.8)       | 26 (22.8)       | 20 (20.6)       |
| Intolerance to TNFi                         | –                        | –                         | –               | –               | 8 (7.7)         | 13 (11.4)       | 11 (11.3)       |
| CRP, mg/L                                   | 16.0 (21.0)              | 12.5 (17.6)               | 12.2 (13.3)     | 13.4 (15.3)     | 16.0 (22.3)     | 20.2 (34.3)     | 16.9 (19.8)     |
| ≤5 mg/L, n (%)                              | 26 (30.2)                | 38 (42.2)                 | 29 (35.8)       | 28 (33.7)       | 39 (37.5)       | 44 (38.6)       | 26 (26.5)       |
| >5 mg/L, n (%)                              | 60 (69.8)                | 52 (57.8)                 | 52 (64.2)       | 55 (66.3)       | 65 (62.5)       | 70 (61.4)       | 72 (73.5)       |
| SPARCC MRI spine score                      | 15.8 (21.2)              | 20.0 (28.4)               | 14.5 (20.6)     | 16.6 (23.8)     | 6.4 (10.2)      | 8.3 (16.0)      | 11.1 (20.3)     |
| Patients, n                                 | 82                       | 85                        | 81              | 78              | 51              | 58              | 53              |
| <2, n (%)                                   | 32 (39.0)                | 31 (36.5)                 | 33 (40.7)       | 29 (37.2)       | 26 (51.0)       | 27 (46.6)       | 29 (54.7)       |
| ≥2, n (%)                                   | 50 (61.0)                | 54 (63.5)                 | 48 (59.3)       | 49 (62.8)       | 25 (49.0)       | 31 (53.4)       | 24 (45.3)       |
| SPARCC MRI SI joint score                   | 5.0 (9.6)                | 4.7 (11.2)                | 4.5 (9.1)       | 6.4 (10.9)      | –               | –               | –               |
| Patients, n                                 | 82                       | 85                        | 81              | 79              | –               | –               | –               |
| <2, n (%)                                   | 49 (59.8)                | 55 (64.7)                 | 54 (66.7)       | 45 (57.0)       | –               | –               | –               |
| ≥2, n (%)                                   | 33 (40.2)                | 30 (35.3)                 | 27 (33.3)       | 34 (43.0)       | –               | –               | –               |

Data are mean (s.d.) unless stated otherwise. aADA represents an active reference arm in COAST-V only; the study was not powered to test equivalence or non-inferiority of IXE vs ADA. cDMARD: conventional DMARD; IR: inadequate response; IXE: ixekizumab.
Fig. 1 ASAS40 response by baseline CRP and relationship based on a logistic regression model

|        | CRP ≤5 mg/L (COAST-V) | CRP >5 mg/L (COAST-V) |
|--------|------------------------|------------------------|
|        |                        |                        |
|        | A                      | B                      |
|        | CRP ≤5 mg/L (COAST-W)  | CRP >5 mg/L (COAST-W)  |
|        | C                      | D                      |
|        | CRP ≤5 mg/L (COAST-V/W)| CRP >5 mg/L (COAST-V/W)|
|        | E                      | F                      |

ASAS40 response at week 16 by baseline CRP ≤5 or >5 mg/L (A–F) and the relationship between ASAS40 response at week 16 and baseline CRP levels based on a logistic regression model for (G) COAST-V and (H) COAST-W. The analysis was performed on the full range of baseline values. Baseline values of 0–50 are shown. n: number of patients with ASAS40 response; Ns: number of patients in the subgroup; Nx: number of patients with non-missing values; ADA: active reference, adalimumab; ASAS40: 40% improvement in disease activity by ASAS criteria; IXE: ixekizumab; PBO: placebo. *P < 0.05, †P < 0.01, ‡P < 0.001 vs placebo.
In COAST-V, all week 16 ASAS40 response rates were statistically significant for ixekizumab vs PBO irrespective of whether the baseline SPARCC MRI spine score was <2 [46% (95% CI 29, 62; P < 0.05) for IXEQ2W, 52% (95% CI 34, 70; P < 0.01) for IXEQ2W, 26% (95% CI 10, 41) for active reference ADA and 19% (95% CI 5, 32) for PBO] or whether the SPARCC MRI SI joint score was <2 [50% (95% CI 36, 64; P < 0.001) for IXEQ4W, 53% (95% CI 39, 67; P < 0.001) for IXEQ2W, 39% (95% CI 26, 52; P < 0.05) for active reference ADA and 16% (95% CI 6, 26) for PBO] (Fig. 2A, B). In COAST-V, similarly significant results were observed whether the SPARCC MRI SI joint score was <2 [41% (95% CI 28, 54; P < 0.01) for IXEQ4W, 49% (95% CI 34, 64; P < 0.001) for IXEQ2W, 24% (95% CI 12, 35) for active reference ADA and 14% (95% CI 5, 24) for PBO] or the SPARCC MRI SI joint score was ≥2 [63% (95% CI 45, 81; P < 0.01) for IXEQ4W, 56% (95% CI 39, 73; P < 0.01) for IXEQ2W, 53% (95% CI 36, 71; P < 0.05) for active reference ADA and 21% (95% CI 7, 35) for PBO (Fig. 2C, D). In COAST-W (Fig. 2E, F), week 16 ASAS40 response rates were numerically higher with ixekizumab vs PBO in the elevated baseline MRI spine inflammation group [SPARCC score ≥2; 36% (95% CI 19, 52) for IXEQ4W, 33% (95% CI 15, 52) for IXEQ2W and 24% (95% CI 7, 41) for PBO], but ixekizumab (IXEQ2W) was statistically significant vs PBO in the normal/low baseline SPARCC MRI spine inflammation group (score <2; 33% (95% CI 16, 51) for IXEQ4W, 52% (95% CI 34, 70; P < 0.01) for IXEQ2W and 12% (95% CI 0, 24) for PBO). In the COAST-V/W integrated dataset, all week 16 ASAS40 response rates were statistically significant for ixekizumab vs PBO, regardless of whether the baseline SPARCC MRI spine score was <2 or ≥2 (Fig. 2G, H). Patients who were treated continuously with ixekizumab sustained ASAS40 response up to week 52 in both SPARCC MRI spine inflammation subgroups (Supplementary Table S2, available at Rheumatology online) and in both MRI SI joint SPARCC subgroups in COAST-V (Supplementary Table S3, available at Rheumatology online).

A logistic regression model was used to assess whether the baseline SPARCC MRI spine score (available in COAST-V and COAST-W) or baseline SPARCC MRI SI joint score (available in COAST-V only), entered as continuous variables, were prognostic and/or predictive of ASAS40 response at week 16. In this analysis, the baseline SPARCC MRI spine score and baseline SPARCC MRI SI joint score tended to be positively associated (positive slope of the curve) with the probability of ASAS40 response in COAST-V (Fig. 3A, B), irrespective of treatment assigned, with the exception of PBO for the baseline SPARCC MRI spine score (Fig. 3A, negative slope of the curve). In COAST-W (Fig. 3C), the opposite trend was observed. Regardless of these trends, the main effects for all MRI measures were not significant (Table S4), indicating that the level of inflammation measured by MRI at baseline was not significant in predicting ASAS40 response at week 16. The COAST-W logistic regression analysis had fewer patients per group vs the same analysis in COAST-V because in COAST-W, MRI was performed by protocol addendum only (Table 1).

**Discussion**

In this post hoc analysis, we demonstrated that ixekizumab shows efficacy (ASAS40 response) in the treatment of r-axSpA at week 16, even in the absence of an elevated serum CRP or evidence of spinal inflammation on MRI. In the integrated COAST-V/W dataset, where the number of patients per subgroup was the largest, significantly more patients achieved ASAS40 response with ixekizumab compared with PBO irrespective of baseline CRP status or baseline MRI spine inflammation status. In the individual studies, the treatment effect with ixekizumab was more pronounced in patients with elevated CRP >5 mg/l, but in the COAST-V trial, where the vast majority of patients (96%) had MRI available, significantly more patients achieved ASAS40 response with ixekizumab vs PBO, irrespective of positivity for baseline MRI spine or SI joint inflammation. Thus the data notably suggest that patients without objective inflammation (as measured by CRP and MRI) demonstrated ASAS40 responses with ixekizumab compared with PBO. These findings are important for clinical practice, as not all healthcare providers have prompt access to MRIs when patients are being seen [25] and may encounter access issues when MRI is not a covered service by health insurance providers [3]. In addition, many patients with AS present with normal or low CRP levels. This report suggests that even in the absence of elevated CRP or the presence of inflammation on spinal MRI, ixekizumab is an effective therapeutic option for these patients.
Fig. 2 ASAS40 response by baseline MRI inflammation

**A** MRI Spine SPARCC <2 (COAST-V)

- PBO (N = 32)
- ADA (N = 31)
- IXE Q4W (N = 33)
- IXE Q2W (N = 29)

| Week 16 | ASAS40 Response (%) |
|---------|---------------------|
| 19/32   | 0                  |
| 26/31   | 20                 |
| 46/33   | 40                 |
| 52/29   | 60                 |

**B** MRI Spine SPARCC ≥2 (COAST-V)

- PBO (N = 50)
- ADA (N = 54)
- IXE Q4W (N = 48)
- IXE Q2W (N = 49)

| Week 16 | ASAS40 Response (%) |
|---------|---------------------|
| 16/50   | 0                  |
| 39/54   | 20                 |
| 50/48   | 40                 |
| 53/49   | 60                 |

**C** MRI SIJ SPARCC <2 (COAST-V)

- PBO (N = 49)
- ADA (N = 55)
- IXE Q4W (N = 54)
- IXE Q2W (N = 45)

| Week 16 | ASAS40 Response (%) |
|---------|---------------------|
| 14/74   | 0                  |
| 24/55   | 20                 |
| 41/54   | 40                 |
| 45/45   | 60                 |

**D** MRI SIJ SPARCC ≥2 (COAST-V)

- PBO (N = 33)
- ADA (N = 30)
- IXE Q4W (N = 27)
- IXE Q2W (N = 34)

| Week 16 | ASAS40 Response (%) |
|---------|---------------------|
| 21/73   | 0                  |
| 53/33   | 20                 |
| 63/27   | 40                 |
| 56/19   | 60                 |

**E** MRI Spine SPARCC <2 (COAST-W)

- PBO (N = 26)
- IXE Q4W (N = 27)
- IXE Q2W (N = 29)

| Week 16 | ASAS40 Response (%) |
|---------|---------------------|
| 12/23   | 0                  |
| 33/27   | 20                 |
| 52/29   | 40                 |

**F** MRI Spine SPARCC ≥2 (COAST-W)

- PBO (N = 25)
- IXE Q4W (N = 31)
- IXE Q2W (N = 24)

| Week 16 | ASAS40 Response (%) |
|---------|---------------------|
| 24/65   | 0                  |
| 36/31   | 20                 |
| 33/24   | 40                 |

**G** MRI Spine SPARCC <2 (COAST-V/W)

- PBO (N = 58)
- IXE Q4W (N = 60)
- IXE Q2W (N = 68)

| Week 16 | ASAS40 Response (%) |
|---------|---------------------|
| 16/95   | 0                  |
| 40/24   | 20                 |
| 52/30   | 40                 |

**H** MRI Spine SPARCC ≥2 (COAST-V/W)

- PBO (N = 75)
- IXE Q4W (N = 75)
- IXE Q2W (N = 73)

| Week 16 | ASAS40 Response (%) |
|---------|---------------------|
| 19/14   | 0                  |
| 44/35   | 20                 |
| 47/34   | 40                 |

ASAS40 response at week 16 by baseline SPARCC MRI spine score <2 or ≥2 (A, B, E–H) and baseline SPARCC MRI SI joint score <2 or ≥2 (C, D). n: number of patients with ASAS40 response; Ns: number of patients in the subgroup. *P < 0.05, †P < 0.01, ‡P < 0.001 vs placebo.
When subgroups of patients were defined by predetermined cut-offs in prespecified efficacy analysis (measured as baseline CRP ≤5 or >5 mg/l or baseline SPARCC MRI scores <2 or ≥2), treatment comparisons vs PBO were significant for ixekizumab with and without elevated inflammation, as described above. Treatment comparison vs PBO for the active reference, ADA, which was included only in COAST-V, was also significant in the presence of elevated inflammation. However, in subsequent prognostic/prediction analysis using logistic regression, there was no significant association with the level of baseline inflammation as measured by CRP or MRI to predict ASAS40 response at week 16 in any of the treatment groups.

Several limitations should be considered. The impact of ixekizumab in patients without evidence of spinal inflammation on MRI could reflect inflammation in the SI joint and/or the posterolateral parts of the spine (e.g. facet joints, costotransverse joints), which are not evaluated in the SPARCC spine scoring system. In other

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Fig. 3 Relationship between ASAS40 response and baseline MRI inflammation based on a logistic regression model

**A** COAST-V

![Graph A](image)

**B** COAST-V

![Graph B](image)

**C** COAST-W

![Graph C](image)

Relationship between ASAS40 response at week 16 and baseline SPARCC MRI spine score in (A) COAST-V and (C) COAST-W and (B) the relationship between ASAS40 response at week 16 and baseline SPARCC MRI SI joint score in COAST-V based on a logistic regression model. The analysis was performed on the full range of baseline values. Baseline values of 0–50 are shown. Nx: number of patients with non-missing values.
words, it is possible that the MRI-negative patients in the present study did in fact have inflammation at locations that were not investigated. It is possible that these observations also reflect the limited sensitivity of the short tau inversion recovery MRI sequence for inflammation, as has been observed in analyses of tissue biopsies from the SI joint, where MRI demonstrated sensitivity of only 38% when compared with histopathological inflammation evident on biopsy [26]. The study was limited by small numbers of patients in several groups, particularly those with normal/low baseline CRP ≤5 mg/l and those who had both normal/low baseline CRP ≤5 mg/l and low spine inflammation on MRI (SPARCC score <2). MRI of the spine was only available for half of the patients in COAST-W (TNF inhibitor–experienced patients), as MRI was performed by protocol addendum. While CRP was a stratification factor, MRI was not and thus CRP data are stronger than the MRI data. Overall, conclusions are limited, as these are post hoc analyses in small sample sizes.

The beneficial impact of IL-17-targeted therapy on patient symptoms may reflect the capacity of this cytokine to sensitize joint nociceptors to mechanical stimuli and contribute to arthritic pain [27]. A recent study has implicated IL-17 in influencing pain behaviours in mice with antigen-induced arthritis, an animal model with abundant IL-17 expression [27, 28]. An antibody against IL-17 improved the guarding score and reduced secondary mechanical hyperalgesia at the ipsilateral paw [27]. Consequently, IL-17 could have the potential to act both as a cytokine involved in the pain neuropathic pathway as well as an enhancer of the inflammatory response. This hypothesis would also be compatible with our observation that MRI inflammation scores were less associated with ASAS40 response in TNF inhibitor–experienced than TNF-naïve patients and may also be why MRI inflammation has been previously shown to correlate with clinical outcomes in early disease [29].

In conclusion, ixekizumab is effective in improving the signs and symptoms of AS in patients with inflammation and even in the absence of elevated CRP levels or MRI spine inflammation at baseline. The conclusions of this post hoc analysis are based on low patient numbers and findings should be confirmed in larger samples. Additional studies are also needed to better understand the potential role of IL-17 in pain reduction in axSpA.

Acknowledgements

The authors would like to thank Fangyi Zhao for statistical analyses. Medical writing support was provided by Melody Pupols of Syneos Health, funded by Eli Lilly. We thank the investigators of COAST-V and COAST-W for their contributions and the patients who participated in these studies. Portions of this work were presented as an abstract/poster at the Annual European Congress of Rheumatology hosted by the EULAR (June 2019) and the American College of Rheumatology Annual Meeting (November 2019). Eli Lilly contributed to the study design, data collection, data analysis, data interpretation, preparation of the manuscript and the decision to submit the paper for publication. W.P.M., R.B., V.J.G., D.M.S. and A.D. contributed to study conception and design. W.P.M., V.J.G., A.D. and K.T. contributed to data acquisition. W.P.M., R.B., G.G., E.S., V.J.G., D.M.S., M.O., X.B. and L.S.G. contributed to analysis and interpretation of data. All authors had full access to all the data in the study, provided critical revisions and approved the final version of the manuscript.
**Funding:** This work was supported by Eli Lilly (Indianapolis, IN, USA).

**Disclosure statement:** W.P.M. is Chief Medical Officer of CARE Arthritis and has received research and/or educational grants from AbbVie, Novartis, and Pfizer and consulting fees from AbbVie, Boehringer, Celgene, Galapagos, Gilead, Janssen, Eli Lilly, Novartis, Pfizer and UCB. R.B., G.G., E.S., V.J.G. and D.M.S. are employees of Eli Lilly and own stock or stock options. M.O. has received consulting fees, speaking fees and/or honoraria from AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Hospira, Janssen, Merck, Novartis, Novo Nordisk, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB. K.T. has no disclosures to report. X.B. has received consulting fees, speaking fees and/or honoraria from AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Hospira, Janssen, Merck, Novartis, Novo Nordisk, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB. A.D. has received consulting fees, speaking fees and/or honoraria from AbbVie, Bristol-Myers Squibb, Celgene, Chugai, Galapagos, Hexal, Janssen, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Sandoz and UCB. A.D. has received consulting fees, speaking fees and/or honoraria from AbbVie, Bristol-Myers Squibb, Celgene, Chugai, Galapagos, GlaxoSmithKline, Eli Lilly, Janssen, Novartis, Pfizer and UCB. L.S.G. has received consulting fees, speaking fees and/or honoraria from AbbVie, Eli Lilly, Galapagos, GlaxoSmithKline, Gilead, Novartis, Pfizer and UCB.

**Data availability statement**

Eli Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available for request 6 months after the indication studied has been approved in the USA and European Union 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 availability agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report and blank or annotated case report forms will be provided in a secure data availability environment. For details on submitting a request, see the instructions provided at www.vivli.org.

**Supplementary data**

Supplementary data are available at *Rheumatology* online.

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