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ORIGINAL RESEARCH

Exploring the Effects of Ixekizumab on Pain in Patients with Ankylosing Spondylitis Based on Objective Measures of Inflammation: Post Hoc Analysis from a Large Randomized Clinical Trial

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ABSTRACT

Introduction: The objective of this analysis is to evaluate the improvement in spinal pain with ixekizumab, placebo, and adalimumab based on objective measures of inflammation response in patients with ankylosing spondylitis (AS).

Methods: The COAST-V 52-week, double-blind, placebo-controlled, randomized phase III trial examined the efficacy of ixekizumab in patients with active AS; adalimumab was used as an active reference arm. Treatment effects on reduction in pain were assessed by objective measures of controlled and persisting inflammation (defined by magnetic resonance imaging [MRI], C-reactive protein [CRP], or MRI + CRP status). Pathway analysis was used to analyze treatment effect that was not attributable to reduction in inflammation biomarkers.

Results: In patients with AS, when inflammation was controlled as assessed by MRI, patients treated with ixekizumab experienced a reduction in spinal pain at night (SP-N, numeric rating scale, ixekizumab mean = − 3.9, $p < 0.001$, adalimumab mean = − 2.6, $p < 0.05$) compared to placebo (mean = − 1.6) at week 16. When inflammation was controlled as assessed by MRI + CRP, ixekizumab and adalimumab had numerically greater reductions at week 16 in SP-N versus placebo. All ixekizumab groups had further improvements at week 52. When inflammation was persisting as assessed by

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MRI + CRP, ixekizumab-treated patients had significant reduction in SP-N (mean = − 3.7, $p < 0.001$) versus placebo (mean = − 1.7), improvement with adalimumab did not reach significance (mean = − 2.6, $p = 0.06$). In the pathway analysis at week 16, ixekizumab had a greater effect on pain outcomes compared to adalimumab.

Conclusion: This post hoc analysis is supportive of the hypothesis that ixekizumab reduces pain in AS by additional mechanisms other than the reduction of measurable inflammation.

Trial Registration Number: NCT02696785.

Keywords: IL-17; Pain; Inflammation; Rheumatic disease; Spondylitis, ankylosing

Key Summary Points

Why carry out this study?

Pain in rheumatic disease is multifactorial in etiology, caused not only by inflammation-induced nociception but also central sensitization.

Therapies in rheumatic disease appear to have multiple mechanisms whereby they improve pain, by controlling inflammation but also, potentially, by improving centrally sensitized pain.

What was learned from this study?

This study supports the hypothesis proposing that IL-17 inhibition results in pain control via both inflammatory (indirect) and non-inflammatory (direct) mechanisms.

This research will support better understanding of the full spectrum of effect of IL-17 inhibition in ameliorating patient-centric disease manifestations.

This analysis provides insight into choice of clinical treatments for health care professionals and highlights the importance of pain assessment in future clinical trials.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that affects approximately 1% of adults [1]. AxSpA is characterized by back pain due to inflammation of the spine and sacroiliac joints, peripheral joint involvement, and extra-articular manifestations. Radiographic axSpA, also known as ankylosing spondyloarthritis (AS), is distinguished from non-radiographic axSpA (nr-axSpA) by radiographically defined structural damage of the sacroiliac joints [2]. Most patients with AS report at least moderate pain from the onset of the disease [3]. Chronic pain in patients with axSpA impacts their quality of life (QoL), leading to increased work disability and unemployment compared to the general population [4, 5]. Interestingly chronic pain in axSpA is considered one of the modifiable factors [6]. Maximizing long-term QoL by reducing pain, inflammation, and preventing progressive structural damage is the primary aim of treating patients with rheumatic diseases [7]. Pain in the early phases of axSpA is caused by inflammation. In the later stages of disease, pain is the result of both inflammation and damage. Despite effective new treatment options and emphasis on early intervention in the disease, which enables complete abolition of the inflammation and prevention of consequent damage, a substantial number of patients report persistent pain. There is also a lack of correlation between symptoms, objective findings on magnetic resonance imaging (MRI), and patients' responses to biologic treatment, as might be expected in the setting of emerging central sensitization [8].

Because of the poor association between pain and inflammation, other mechanisms need to be considered. Pain associated with inflammation or joint damage is classified as nociceptive pain. Other potential sources of pain associated with AS include neuropathic pain and nociplastic pain, which are defined by the International Association for the Study of Pain [9].

Neuropathic pain can be caused by lesions or dysfunctions affecting the somatosensory system and has been demonstrated to play a role in

back pain in more than 40% of patients with AS [10, 11]. The etiology of nociplastic pain is less well understood and includes fibromyalgia and widespread pain because of central sensitization [12, 13]. High central sensitization is reported in 29–60% of patients with AS [5].

The importance of differentiating between the different types of pain lies in the inclusion of pain as an outcome domain in the evaluation of disease activity. In those tools, pain is generally evaluated by a simple question and is rated on a visual analogue scale or a numeric rating scale (NRS). The phrasing of the questions does not include differentiating qualitative aspects of pain. This could induce an overestimation of the disease activity leading to inappropriate switching of disease-modifying antirheumatic drug (DMARD) treatments due to perceived inefficacy.

There is growing evidence that signaling through the interleukin (IL)-17 pathway is involved in the pathogenesis of axSpA [14]. As well, IL-17R/IL-17 signaling is an effective mediator of pain processing at several levels. Ixekizumab is a high-affinity monoclonal antibody that selectively targets IL-17A and is approved for the treatment of moderate-to-severe plaque psoriasis, active psoriatic arthritis, AS, and nr-axSpA [15–19].

The objective of this post hoc analysis was to evaluate improvement of spinal pain with ixekizumab, placebo, and adalimumab based on objective measures of inflammation response in patients with AS from the COAST-V randomized clinical trial.

METHODS

Trial Design

COAST-V (NCT02696785) was a phase III, multicenter, randomized, double-blind, active-controlled and placebo-controlled, 52-week trial [16, 20]. Briefly, participants had to be at least 18 years of age, have an established diagnosis of AS, and meet modified New York criteria (with central reading of radiographic sacroiliitis). Patients in COAST-V were biological DMARD-naïve.

COAST-V was carried out in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All investigation sites received approval from the appropriate authorized institutional review board or ethics committee. All patients provided written consent before the study-related procedures were carried out.

Randomization and Masking

The design of COAST-V has been described previously in detail [16, 20]. Briefly, after screening, patients were randomly assigned 1:1:1:1 to placebo, adalimumab 40 mg every 2 weeks (Q2W), ixekizumab 80 mg Q2W, or ixekizumab 80 mg every 4 weeks (Q4W) between June 20, 2016 and August 22, 2017. Patients assigned ixekizumab were randomly distributed 1:1 to a 160 mg or 80 mg starting dose. After week 16, patients entered a double-blind extended treatment period (weeks 16–52) when all remaining patients originally randomized to placebo or adalimumab were re-randomized 1:1 to ixekizumab 80 mg Q2W or Q4W.

Patient and Public Involvement

Patients were not involved in the design or conduct of the study, development of outcomes, or dissemination of study results.

Statistical Analysis

In this post hoc analysis, changes in spinal pain at night (SP-N), spinal pain (measured at each study visit using a NRS score, 11-point scale from 0 to 10, 0 = "no pain" and 10 = "most severe pain"), and the Medical Outcomes Study 36-item Short-Form Health Survey (SF)-36 bodily pain domain (summary scores, range 0–100, higher scores indicate better levels of function and/or health) were analyzed while controlling for inflammation status as assessed by MRI and C-reactive protein (CRP) levels. Observed data analyses are presented for each group stratified by treatment arm and compared to placebo. In the first analysis (Fig. 1a and b, Fig. 2a and b,

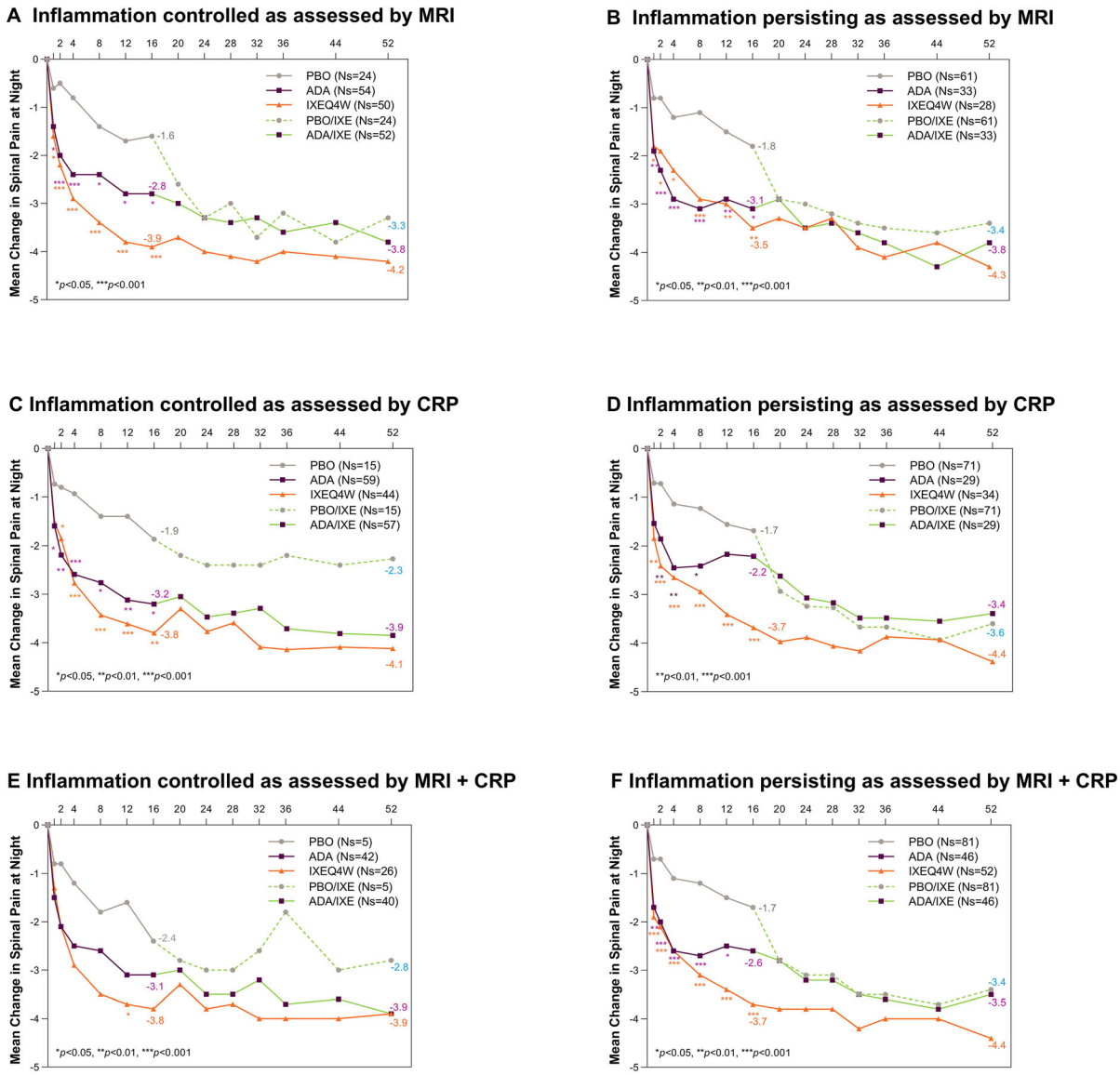

Fig. 1 Change in SP-N in patients with AS over 52 weeks. Change in spinal pain at night in patients with inflammation **a** controlled as assessed by MRI (SPARCC SI joint < 4 and MRI SPARCC Spine < 3 at week 16) or **b** persisting as measured by MRI (SPARCC SIJ ≥ 4 at week 16 or SPARCC Spine ≥ 3 at week 16). Change in spinal pain at night in patients with inflammation **c** controlled as assessed by CRP (CRP < 5 mg/L from week 4 to week 16) or **d** persisting as measured by CRP (CRP ≥ 5 mg/L at any visit between weeks 4 and 16). Change in SP-N in patients with inflammation **e** controlled as assessed by CRP (CRP < 5 mg/L from week 4 to week 16) and MRI (SPARCCJ < 4 and MRI SPARCC Spine < 3 at week 16) or **f** persisting as measured by CRP (CRP ≥ 5 mg/L at any visit between weeks 4 and 16) and MRI (SPARCC SIJ ≥ 4 at week 16 or SPARCC Spine ≥ 3 at week 16). $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$. *ADA* adalimumab, *AS* ankylosing spondylitis, *CRP* C-reactive protein, *IXE* ixekizumab, *MRI* magnetic resonance imaging, *Ns* number of participants, *PBO* placebo, *Q4W* every 4 weeks, *SI* sacroiliac, *SP-N* spinal pain at night, *SPARCC* Spondyloarthritis Research Consortium of Canada

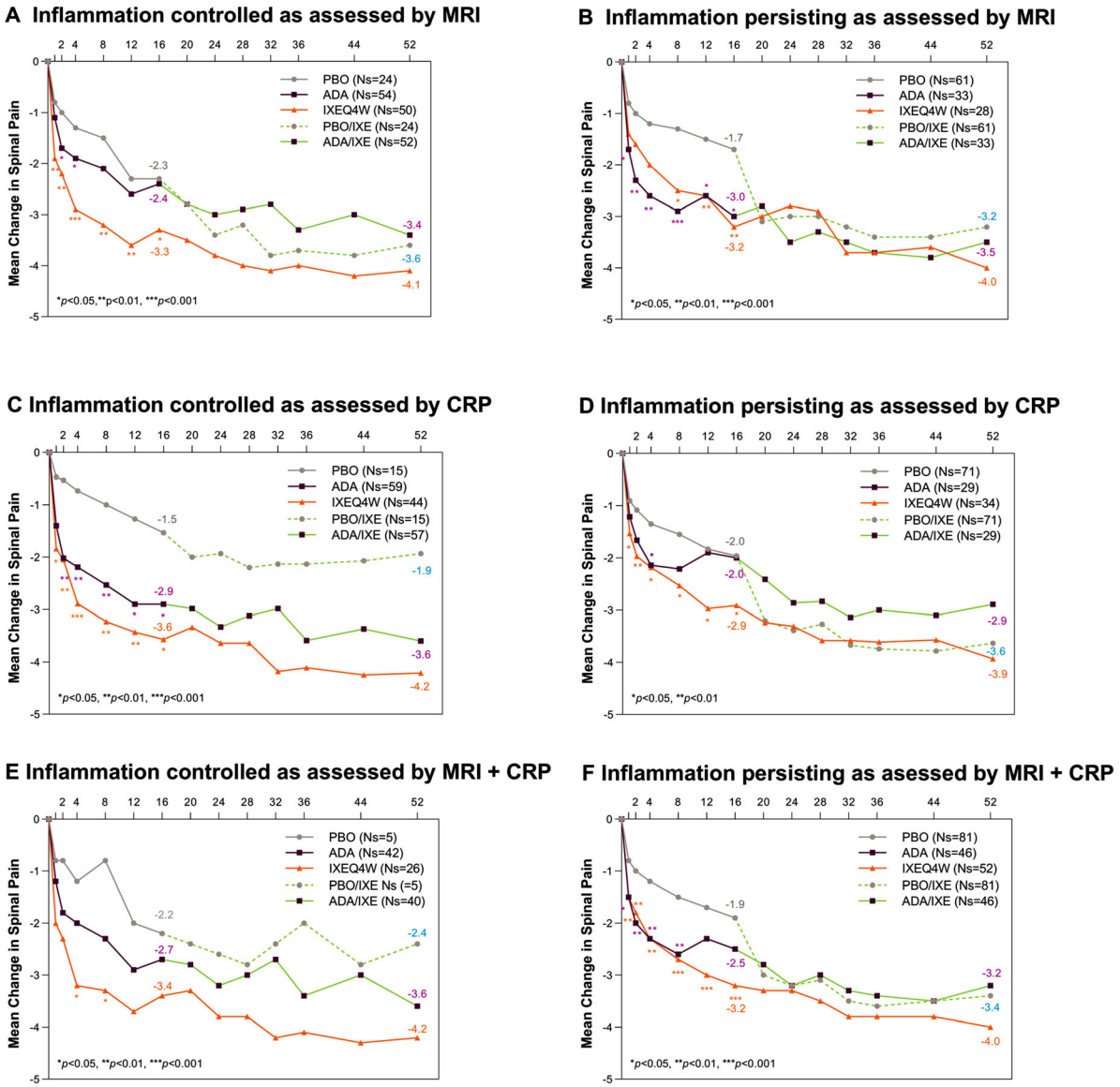

Fig. 2 Change in spinal pain in patients with AS over 52 weeks. Change in spinal pain in patients with inflammation **a** controlled as assessed by MRI (SPARCC SI joint < 4 and MRI SPARCC Spine < 3 at week 16) or **b** persisting as measured by MRI (SPARCC SIJ ≥ 4 at week 16 or SPARCC Spine ≥ 3 at week 16). Change in spinal pain in patients with inflammation **c** controlled as assessed by CRP (CRP < 5 mg/L from week 4 to week 16) or **d** persisting as measured by CRP (CRP ≥ 5 mg/L at any visit between weeks 4 and 16). Change in spinal pain in patients with inflammation **e** controlled as assessed by CRP (CRP < 5 mg/L from week 4 to week 16) and MRI (SPARCCJ < 4 and MRI SPARCC Spine < 3 at week 16) or **f** persisting as measured by CRP (CRP ≥ 5 mg/L at any visit between weeks 4 and 16) and MRI (SPARCC SIJ ≥ 4 at week 16 or SPARCC Spine ≥ 3 at week 16). $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$. *ADA* adalimumab, *AS* ankylosing spondylitis, *CRP* C-reactive protein, *IXE* ixekizumab, *MRI* magnetic resonance imaging, *Ns* number of participants, *PBO* placebo, *Q4W* every 4 weeks, *SI* sacroiliac, *SPARCC* Spondyloarthritis Research Consortium of Canada

and Fig. 3a and b), patients with AS were categorized into two subgroups defined as:

1. "Controlled" inflammation as assessed by MRI Spondyloarthritis Research Consortium of Canada (SPARCC [21]) sacroiliac joint (SIJ) < 4 at week 16 and MRI SPARCC Spine < 3 at week 16
2. "Persisting" inflammation as assessed by SPARCC SIJ ≥ 4 at week 16 or SPARCC Spine ≥ 3 at week 16

In a second analysis (Fig. 1c and d, Fig. 2c and d, and Fig. 3c and d) patients were categorized into two subgroups defined as:

1. "Controlled" inflammation as assessed by CRP < 5 mg/L weeks 4–16
2. "Persisting" inflammation as assessed by CRP ≥ 5 mg/L at any visit between weeks 4 and 16 respectively

In a third analysis (Fig. 1e and f, Fig. 2e and f, and Fig. 3e and f), patients were categorized into two subgroups defined as:

1. "Controlled" inflammation as assessed by CRP < 5 mg/L weeks 4–16, MRI SPARCC SIJ < 4 at week 16, and MRI SPARCC Spine < 3 at week 16
2. "Persisting" inflammation as assessed by CRP ≥ 5 mg/L at any point between weeks 4 and 16 or SPARCC SIJ ≥ 4 at week 16 or SPARCC Spine ≥ 3 at week 16

Pathway Analysis

A pathway analysis with multiple mediators was conducted on observed data to evaluate the relationship between levels of inflammation and pain relief in AS [22]. The effects of change in inflammatory factors (CRP, MRI SIJ, and MRI Spine) as multiple mediators on change in pain outcomes for each treatment over placebo during the 16-week period were evaluated. The approach uses structural equation modelling (SEM), a set of regression models that specifies the relation between treatment, mediators (inflammatory factors), and pain relief. The total treatment effect on pain relief over placebo that can be accounted for by changes in CRP, MRI SIJ, and MRI Spine in the mediation analysis is the "indirect" effect, while the total treatment effect that cannot be accounted for by the "indirect" effect is called the "direct" effect. Bar plots (Fig. 3) present total treatment effect (total height of the bars) on pain relief decomposed by direct and indirect effects, for ixekizumab and adalimumab. The greater proportion of indirect effect indicates that greater pain relief was due to the change in inflammatory factors instead of direct drug effect.

RESULTS

Baseline demographics and disease characteristics for COAST-V (N = 340) are summarized in Table S1. Briefly, most patients (N = 276, 81%) were male, the mean age was 41.7 ± 11.7 years, and 213 (63%) patients were of white race. A total of 781 patients were assessed for eligibility and 341 were randomly assigned to treatment. The trial profile up to week 16 is included in the supplement (Fig. S1).

In the first analysis when inflammation was controlled as assessed by MRI SPARCC SIJ < 4 at week 16 and MRI SPARCC Spine < 3 at week 16, both ixekizumab Q4W (mean = − 3.9 mm, $p < 0.001$) and adalimumab (mean = − 2.8 mm, $p = 0.02$) experienced significant reduction in SP-N at week 16 versus placebo (mean = − 1.6 mm, Fig. 1a, Table 1). In spinal pain, a significant difference was seen at week 16 between ixekizumab Q4W (mean = − 3.3 mm, $p = 0.041$) versus placebo (mean = − 2.3 mm); adalimumab (mean = − 2.4 mm) had a comparable reduction in spinal pain to placebo (Fig. 2a, Table 1). In the bodily pain domain, a significant difference was seen at week 16 between ixekizumab Q4W (mean = 22.5 mm, $p = 0.01$) versus placebo (mean = 11.9 mm); adalimumab (mean = 19.4 mm) had a greater, but non-significant, reduction in bodily pain compared to placebo (Fig. 3a, Table 1). Further improvements were experienced by patients in the adalimumab or placebo arm after they were re-randomized to ixekizumab at week 16 by week 52 in all three pain measures (Figs. 1a, 2a, and 3a, Table 1).

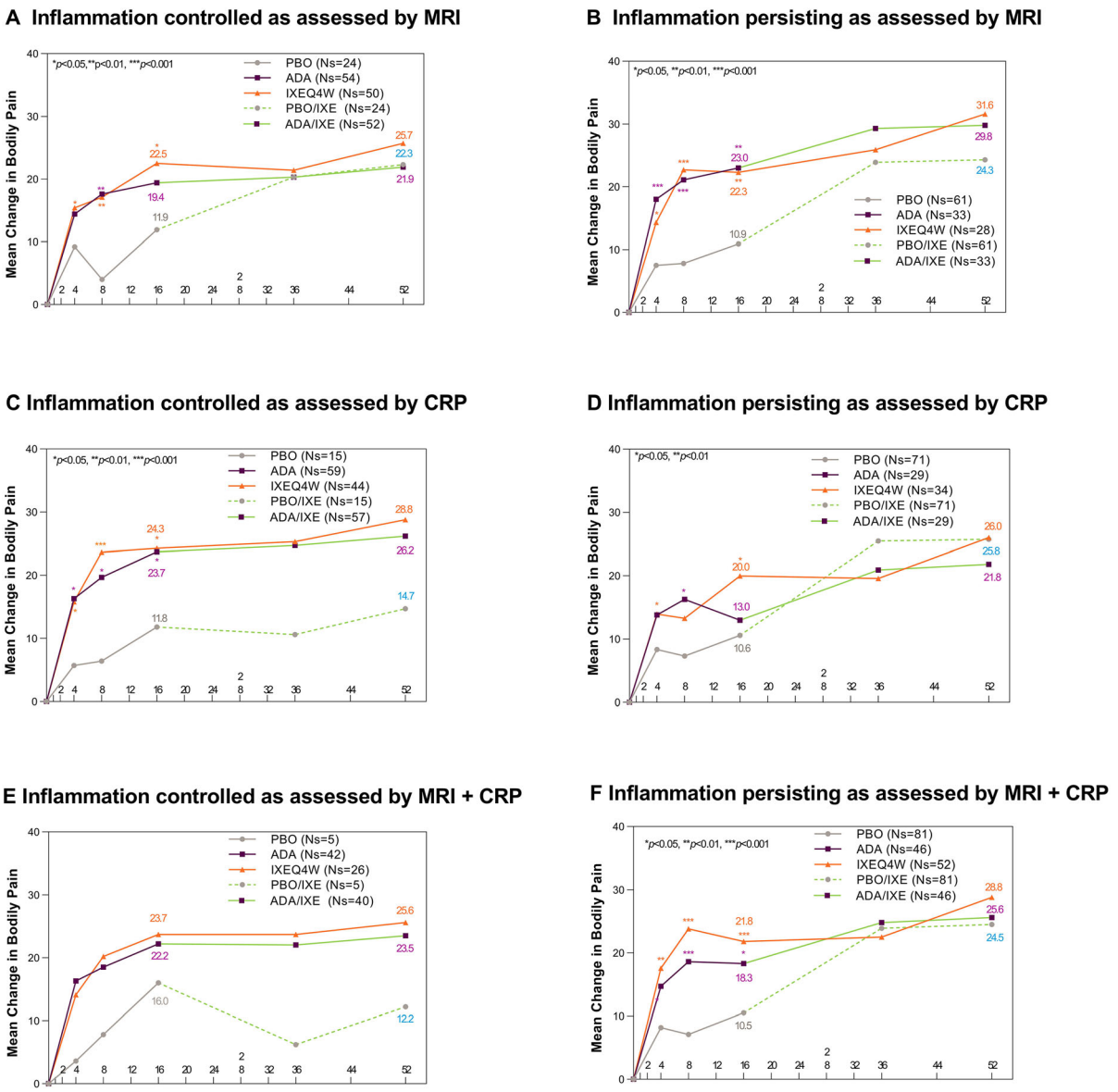

Fig. 3 Change in SF-36 bodily pain domain in patients with AS over 52 weeks. Change in SF-36 bodily pain domain in patients with inflammation **a** controlled as assessed by MRI (SPARCC SI joint < 4 and MRI SPARCC Spine < 3 at week 16) or **b** persisting as measured by MRI (SPARCC SIJ ≥ 4 at week 16 or SPARCC Spine ≥ 3 at week 16). Change in SF-36 bodily pain domain in patients with inflammation **c** controlled as assessed by CRP (CRP < 5 mg/L from week 4 to week 16) or **d** persisting as measured by CRP (CRP ≥ 5 mg/L at any visit between weeks 4 and 16). Change in SF-36 bodily pain domain in patients with inflammation **e** controlled as assessed by CRP (CRP < 5 mg/L from week 4 to week 16) and MRI (SPARCCJ < 4 and MRI SPARCC Spine < 3 at week 16) or **f** persisting as measured by CRP (CRP ≥ 5 mg/L at any visit between weeks 4 and 16) and MRI (SPARCC SIJ ≥ 4 at week 16 or SPARCC Spine ≥ 3 at week 16). $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$. *ADA* adalimumab, *AS* ankylosing spondylitis, *CRP* C-reactive protein, *IXE* ixekizumab, *MRI* magnetic resonance imaging, *Ns* number of participants, *PBO* placebo, *Q4W* every 4 weeks, *SF-36*, 36-item Short-Form Health Survey, *SI* sacroiliac, *SPARCC* Spondyloarthritis Research Consortium of Canada

Table 1 Change in SP, SP-N, and SF-36 by MRI, CRP, and MRI + CRP

	Controlled inflammation			Persisting inflammation		
	Change in SP by MRI (SPARCC SIJ < 4 and SPARCC spine < 3 at week 16)					
	PBO (Ns = 24)	IXEQ4W (Ns = 50)	ADA (Ns = 54)	PBO (Ns = 61)	IXEQ4W (Ns = 28)	ADA (Ns = 33)
Baseline (mean [SD])	7.3 (1.4)	7.1 (1.3)	6.6 (1.7)	7.4 (1.4)	7.5 (1.4)	7.5 (1.3)
Week 16	− 2.3 (1.6)	− 3.3 (2.8)*	− 2.4 (2.3)	− 1.7 (2.0)	− 3.2 (2.6)**	− 3.0 (2.5)*
	PBO/IXE (Ns = 24)	IXEQ4W (Ns = 50)	ADA/IXE (Ns = 52)	PBO/IXE (Ns = 61)	IXEQ4W (Ns = 28)	ADA/IXE (Ns = 33)
Week 52	− 3.6 (2.7)	− 4.1 (2.3)	− 3.4 (2.5)	− 3.2 (2.5)	− 4.0 (2.7)	− 3.5 (2.4)
	Change in SP by CRP (CRP < 5 mg/L at every week between weeks 4–16)					
	PBO (Ns = 15)	IXEQ4W (Ns = 44)	ADA (Ns = 59)	PBO (Ns = 71)	IXEQ4W (Ns = 34)	ADA (Ns = 29)
Baseline (mean [SD])	7 (1.5)	7.2 (1.3)	6.8 (1.7)	7.5 (1.4)	7.2 (1.3)	7.3 (1.2)
Week 16	− 1.5 (1.8)	− 3.6 (2.5)	− 2.9 (2.5)	− 2.0 (1.9)	− 2.9 (2.9)*	− 2.0 (2.1)
	PBO/IXE (Ns = 15)	IXEQ4W (Ns = 44)	ADA/IXE (Ns = 57)	PBO/IXE (Ns = 71)	IXEQ4W (Ns = 34)	ADA/IXE (Ns = 29)
Week 52	− 1.9 (2.2)	− 4.2 (2.6)	− 3.6 (2.5)	− 3.6 (2.5)	− 3.9 (2.3)	− 2.9 (2.2)
	Change in SP by MRI + CRP (SPARCC SIJ < 4 and SPARCC spine < 3 at week 16 + CRP < 5 mg/L at every week between weeks 4–16)					
	PBO (Ns = 5)	IXEQ4W (Ns = 26)	ADA (Ns = 42)	PBO (Ns = 81)	IXEQ4W (Ns = 52)	ADA (Ns = 46)
Baseline (mean [SD])	6.6 (1.1)	7.0 (1.2)	6.5 (1.6)	7.5 (1.4)	7.3 (1.4)	7.4 (1.3)
Week 16	− 2.2 (1.3)	− 3.4 (2.5)	− 2.7 (2.4)	− 1.9 (1.9)	− 3.2 (2.8)***	− 2.5 (2.5)
	PBO/IXE (Ns = 5)	IXEQ4W (Ns = 26)	ADA/IXE (Ns = 40)	PBO/IXE (Ns = 81)	IXEQ4W (Ns = 52)	ADA/IXE (Ns = 46)
Week 52	− 2.4 (2.3)	− 4.2 (2.6)	− 3.6 (2.5)	− 3.4 (2.6)	− 4.0 (2.4)	− 3.2 (2.4)
	Change in SP-N by MRI (SPARCC SIJ < 4 and SPARCC spine < 3 at week 16)					
	PBO (Ns = 24)	IXEQ4W (Ns = 50)	ADA (Ns = 54)	PBO (Ns = 61)	IXEQ4W (Ns = 28)	ADA (Ns = 33)
Baseline (mean [SD])	6.8 (2.0)	6.9 (1.3)	6.6 (1.9)	7.2 (1.6)	7.4 (1.5)	7.5 (1.4)
Week 16	− 1.6 (1.8)	− 3.9 (2.8)***	− 2.8 (2.6)*	− 1.8 (2.0)	− 3.5 (2.6)**	− 3.1 (2.7)*
	PBO/IXE (Ns = 24)	IXEQ4W (Ns = 50)	ADA/IXE (Ns = 52)	PBO/IXE (Ns = 61)	IXEQ4W (Ns = 28)	ADA/IXE (Ns = 33)
Week 52	− 3.3 (3.3)	− 4.2 (2.3)	− 3.8 (2.6)	− 3.4 (2.4)	− 4.3 (2.7)	− 3.8 (2.6)

Table 1 continued

	Change in SP-N by CRP (CRP < 5 mg/L at every week between weeks 4–16)					
	PBO (Ns = 15)	IXEQ4W (Ns = 44)	ADA (Ns = 59)	PBO (Ns = 71)	IXEQ4W (Ns = 34)	ADA (Ns = 29)
Baseline (mean [SD])	7.2 (1.6)	6.9 (1.5)	6.8 (1.9)	7.0 (1.7)	7.4 (1.3)	7.2 (1.4)
Week 16	− 1.9 (1.8)	− 3.8 (2.5)**	− 3.2 (2.7)*	− 1.7 (2.0)	− 3.7 (2.9)***	− 2.2 (2.4)
	PBO/IXE (Ns = 15)	IXEQ4W (Ns = 44)	ADA/IXE (Ns = 57)	PBO/IXE (Ns = 71)	IXEQ4W (Ns = 34)	ADA/IXE (Ns = 29)
Week 52	− 2.3 (2.2)	− 4.1 (2.5)	− 3.9 (2.9)	− 3.6 (2.7)	− 3.4 (2.1)	− 4.4 (2.4)
	Change in SP-N by MRI + CRP (SPARCC SIJ < 4 and SPARCC spine < 3 at week 16 + CRP < 5 mg/L at every week between weeks 4–16)					
	PBO (Ns = 5)	IXEQ4W (Ns = 26)	ADA (Ns = 42)	PBO (Ns = 81)	IXEQ4W (Ns = 52)	ADA (Ns = 46)
Baseline (mean [SD])	6.8 (1.3)	6.7 (1.3)	6.5 (1.9)	7.1 (1.7)	7.3 (1.4)	7.3 (1.5)
Week 16	− 2.4 (1.5)	− 3.8 (2.6)	− 3.1 (2.7)	− 1.7 (2.0)	− 3.7 (2.8)***	− 2.6 (2.6)
	PBO/IXE (Ns = 5)	IXEQ4W (Ns = 26)	ADA/IXE (Ns = 40)	PBO/IXE (Ns = 81)	IXEQ4W (Ns = 52)	ADA/IXE (Ns = 46)
Week 52	− 2.8 (2.6)	− 3.9 (2.3)	− 3.9 (2.8)	− 3.4 (2.7)	− 3.5 (2.5)	− 4.4 (2.5)
	Change in SF-36 bodily pain domain by MRI (SPARCC SIJ < 4 and SPARCC spine < 3 at week 16)					
	PBO (Ns = 24)	IXEQ4W (Ns = 50)	ADA (Ns = 54)	PBO (Ns = 61)	IXEQ4W (Ns = 28)	ADA (Ns = 33)
Baseline (mean [SD])	37.0 (19.8)	40.0 (15.9)	38.6 (16.2)	34.0 (16.0)	35.4 (16.9)	35.8 (14.8)
Week 16	11.9 (17.3)	22.5 (21.9)*	19.4 (19.0)	10.9 (16.4)	22.3 (19.7)**	23.0 (21.8)**
	PBO/IXE (Ns = 24)	IXEQ4W (Ns = 50)	ADA/IXE (Ns = 52)	PBO/IXE (Ns = 61)	IXEQ4W (Ns = 28)	ADA/IXE (Ns = 33)
Week 52	22.3 (24.6)	25.7 (21.6)	21.9 (19.6)	24.3 (19.2)	31.6 (26.4)	29.8 (18.3)

Table 1 continued

	Change in SF-36 bodily pain domain by CRP (CRP < 5 mg/L at every week between weeks 4–16)					
	PBO (Ns = 15)	IXEQ4W (Ns = 44)	ADA (Ns = 59)	PBO (Ns = 71)	IXEQ4W (Ns = 34)	ADA (Ns = 29)
Baseline (mean [SD])	33.2 (12.3)	38.4 (17.6)	38.4 (14.7)	35.2 (17.9)	38.3 (14.6)	35.6 (17.4)
Week 16	11.8 (12.5)	24.3 (21.5)**	23.7 (20.5)**	10.6 (17.6)	20.0 (20.4)**	13.0 (19.6)
	PBO/IXE (Ns = 15)	IXEQ4W (Ns = 44)	ADA/IXE (Ns = 57)	PBO/IXE (Ns = 71)	IXEQ4W (Ns = 34)	ADA/IXE (Ns = 29)
Week 52	14.7 (15.7)	28.8 (24.5)	26.2 (21.9)	25.8 (21.3)	26.0 (21.6)	21.8 (14.5)
	Change in SF-36 bodily pain domain by MRI + CRP (SPARCC SIJ < 4 and SPARCC spine < 3 at week 16 + CRP < 5 mg/L at every week between weeks 4–16)					
	PBO (Ns = 5)	IXEQ4W (Ns = 26)	ADA (Ns = 42)	PBO (Ns = 81)	IXEQ4W (Ns = 52)	ADA (Ns = 46)
Baseline (mean [SD])	41.8 (14.2)	40.6 (16.7)	39.5 (14.4)	34.5 (17.2)	37.2 (16.1)	35.7 (16.6)
Week 16	16.0 (8.8)	23.7 (21.1)	22.2 (18.8)	10.5 (17.1)	21.8 (21.1)***	18.3 (22.4)*
	PBO/IXE (Ns = 5)	IXEQ4W (Ns = 26)	ADA/IXE (Ns = 40)	PBO/IXE (Ns = 81)	IXEQ4W (Ns = 52)	ADA/IXE (Ns = 46)
Week 52	12.2 (8.1)	25.6 (20.6)	23.5 (21.8)	24.5 (21.2)	28.8 (24.8)	25.6 (18.0)

Data presented as observed change (standard deviation) unless otherwise stated. Not controlled definitions: MRI = SPARCC SIJ $\geq$ 4 or SPARCC Spine $\geq$ 3 at week 16; CRP = CRP $\geq$ 5 mg/L at $\geq$ 1 visit between week 4–16; MRI + CRP = CRP $\geq$ 5 mg/L at $\geq$ 1 visit between week 4–16, or SPARCC SIJ $\geq$ 4 at week 16, or SPARCC spine $\geq$ 3 at week 16. Treatment comparison versus PBO up to week 16 was performed using ANCOVA model that included baseline pain outcome, treatment, inflammation status, and treatment-by-inflammation status. PBO/IXE and ADA/IXE = IXEQ4W

ADA adalimumab, *ANCOVA* analysis of covariance, *CRP* C-reactive protein, *IXE* ixekizumab, *MRI* magnetic resonance imaging, *Ns* < definition > , *PBO* placebo, *Q4W* every four weeks, *SD* standard deviation, *SF-36* Medical Outcomes Study 36-item Short-Form Health Survey, *SIJ* sacroiliac joint, *SP* spinal pain, *SP-N* spinal pain at night, *SPARCC* Spondyloarthritis Research Consortium of Canada

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

When inflammation was persisting as assessed by MRI SPARCC SIJ ≥ 4 at week 16 and MRI SPARCC Spine ≥ 3 at week 16, ixekizumab Q4W (mean = − 3.5 mm, $p < 0.01$) and adalimumab (mean = − 3.1, $p = 0.02$) experienced significant reduction in SP-N at week 16 (Fig. 1b, Table 1). In spinal pain, a significant difference was seen at week 16 between both ixekizumab Q4W (mean = − 3.2 mm, $p = 0.004$) and adalimumab (mean = − 3.0 mm, $p = 0.012$) versus placebo (mean = − 1.7 mm, Fig. 2b, Table 1). In the bodily pain domain, a significant difference was seen at week 16 between both ixekizumab Q4W (mean = 22.3 mm, $p = 0.005$) and adalimumab (mean = 23.0 mm, $p = 0.001$) versus placebo (mean = 10.9 mm, Fig. 3b, Table 1). Further improvements were experienced by patients in the adalimumab or placebo arm after they were re-randomized to ixekizumab at week 16 by week 52 in all three pain measures (Figs. 1b, 2b, and 3b, Table 1).

In the second analysis when inflammation was controlled as assessed by CRP, ixekizumab Q4W (mean = − 3.8 mm, $p < 0.01$) and adalimumab (mean = − 3.2 mm, $p < 0.05$) achieved significantly greater reduction in SP-N at week 16 versus placebo (mean = − 1.9 mm, Fig. 1c, Table 1). In spinal pain, a significant difference was seen at week 16 between both ixekizumab Q4W (mean = − 3.6 mm, $p = 0.0038$) and adalimumab (mean = − 2.9 mm, $p = 0.0233$) versus placebo (mean = − 1.5 mm, Fig. 2c, Table 1). In bodily pain, a significant difference was seen at week 16 between both ixekizumab Q4W (mean = 24.3 mm, $p = 0.009$) and adalimumab (mean = 23.7 mm, $p = 0.009$) versus placebo (mean = 11.8 mm, Fig. 3c, Table 1). Further improvements were experienced by patients in the adalimumab or placebo arm after they were re-randomized to ixekizumab at week 16 by week 52 in all three pain measures (Figs. 1c, 2c, and 3c, Table 1).

When inflammation was persisting as assessed by CRP, ixekizumab Q4W (mean = − 3.7 mm, $p < 0.001$) achieved a significant reduction in SP-N versus placebo (mean = − 1.7 mm) at week 16; the observed improvement with adalimumab (mean = − 2.2 mm, $p = 0.4$) was not significant. Furthermore, patients re-randomized to ixekizumab from adalimumab or placebo at week 16 had further reductions in SP-N at week 52 (Fig. 1d, Table 1). In spinal pain, a significant difference was seen at week 16 between ixekizumab Q4W (mean = − 2.9 mm, $p = 0.018$) versus placebo (mean = − 2.0 mm); adalimumab (mean = − 2.0 mm) had a comparable reduction to placebo (Fig. 2d, Table 1). In the bodily pain domain, a significant difference was seen at week 16 between ixekizumab Q4W (mean = 20.0 mm, $p = 0.0063$) versus placebo (mean = 10.6 mm); adalimumab (mean = 13.0 mm) had a greater, but nonsignificant, improvement in bodily pain compared to placebo (Fig. 3d, Table 1). Further improvements were experienced by patients in the adalimumab or placebo arm after they were re-randomized to ixekizumab at week 16 by week 52 in all three pain measures (Figs. 1d, 2d, and 3d, Table 1).

In the third analysis, when inflammation was controlled as assessed by both MRI and CRP, ixekizumab Q4W (mean = − 3.8 mm) and adalimumab (mean = − 3.1 mm) demonstrated a numerically greater reduction versus placebo (mean = − 2.4 mm, Fig. 1e, Table 1) in SP-N at week 16, although neither drug had a significant reduction versus placebo. In the bodily pain domain, ixekizumab Q4W (mean = 23.7 mm) and adalimumab (mean = 22.2 mm) treated patients experienced a nonsignificant reduction versus placebo at week 16 (mean = 16 mm, Fig. 3e, Table 1). Further improvements were experienced by patients in the adalimumab or placebo arm after they were re-randomized to ixekizumab at week 16 by week 52 in all three pain measures, except for placebo when inflammation was controlled as assessed by MRI and CRP, there was decrease at week 52 (mean = 12.2 mm) compared to week 16 (mean = 16.0, Figs. 1e, 2e, and 3e, Table 1).

When inflammation was persisting as assessed by MRI and CRP simultaneously, ixekizumab Q4W (mean = − 3.7 mm, $p < 0.001$) achieved a significant reduction in SP-N versus placebo at week 16 (mean = − 1.7 mm); the observed improvement with adalimumab

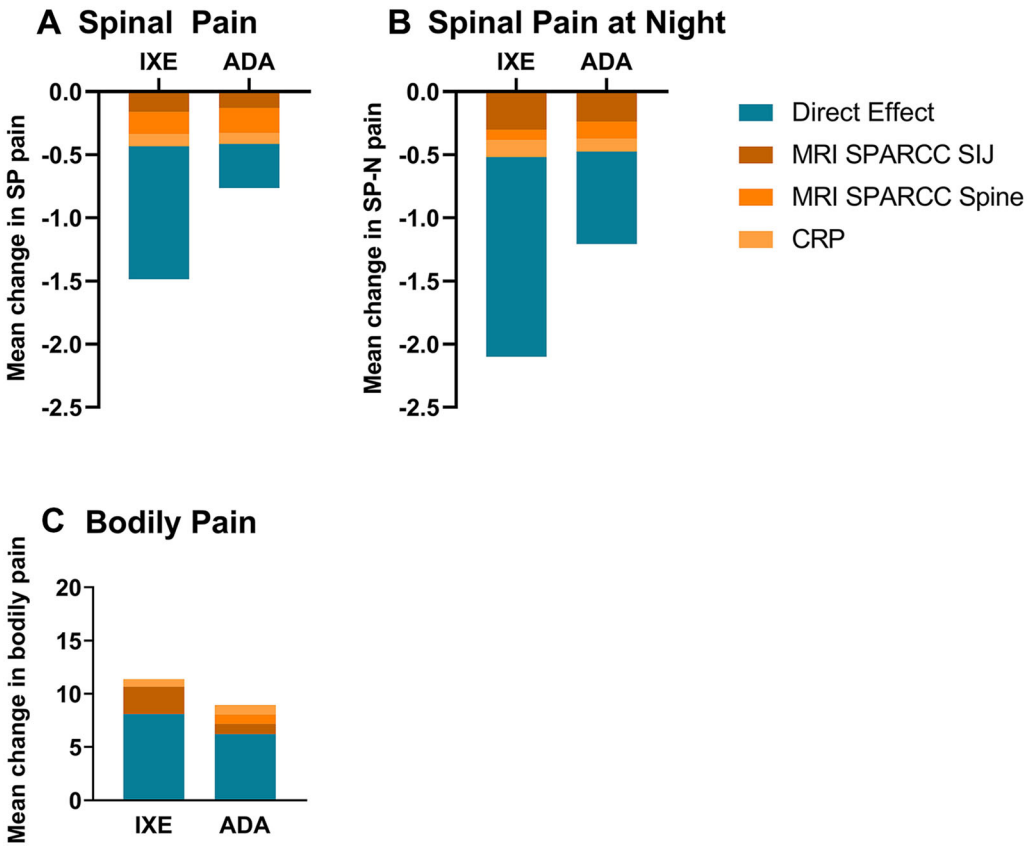

Fig. 4 Pathway analysis of treatment effect on spinal pain, SP-N, and bodily pain domain in ixekizumab ($N = 78$) and adalimumab ($N = 82$) treated patients versus placebo ($N = 79$) in the intent to treat population at week 16. Bar plots present total treatment effect on pain relief decomposed by direct and indirect effects, for ixekizumab and adalimumab. **a** Pathway analysis of treatment effect on spinal pain in ixekizumab and adalimumab-treated patients versus placebo in the ITT population at week 16. **b** Pathway analysis of treatment effect on SP-N in ixekizumab and adalimumab-treated patients versus placebo in the ITT population at week 16. **c** Pathway analysis of treatment effect on SF-36 bodily pain domain in ixekizumab and adalimumab-treated patients versus placebo in the ITT population at week 16. Figures show mean (standard error). *ADA* adalimumab, *CRP* C-reactive protein, *ITT* intent to treat, *IXE* ixekizumab, *MRI* magnetic resonance imaging, *SF-36* Medical Outcomes Study 36-item Short-Form Health Survey, *SIJ* sacroiliac joint, *SP-N* spinal pain at night, *SPARCC* Spondyloarthritis Research Consortium of Canada

(mean = − 2.6 mm, $p = 0.06$) was not significant (Fig. 1f, Table 1). Patients re-randomized to ixekizumab from adalimumab or placebo at week 16 had further reductions in SP-N at week 52 (Fig. 1f, Table 1). In spinal pain, a significant difference was seen at week 16 between ixekizumab Q4W (mean = − 3.2 mm, $p < 0.001$) versus placebo (mean = − 1.9); adalimumab (mean = − 2.5) had a greater but nonsignificant improvement compared to placebo (Fig. 2f, Table 1). In bodily pain, a significant difference was seen at week 16 between both ixekizumab Q4W (mean = 21.8 mm, $p < 0.001$) and adalimumab (mean = 18.3, $p = 0.015$) versus placebo (mean = 10.5, Fig. 3f, Table 1). Further improvements were experienced by patients in the adalimumab or placebo arm after they were re-randomized to ixekizumab at week 16 by week 52 in all three pain measures (Figs. 1f, 2f, and 3f, Table 1).

In the pathway analysis, while the total effect of ixekizumab on pain relief over placebo at week 16 was greater than that for adalimumab, treatment with ixekizumab versus placebo in patients with AS had a greater direct effect on spinal pain (ixekizumab = 70.8%, adalimumab = 45.7%), SP-N (ixekizumab = 75.4%, adalimumab = 60.7%), and bodily pain domain (ixekizumab = 71.7%, adalimumab = 69.4%) compared to adalimumab versus placebo at week 16 (Fig. 4). Pathway analysis enables a numerical comparison in the indirect effect between the two drugs, however no statistical comparison was conducted. Therefore, no statement regarding statistical significance can be made.

DISCUSSION

In a previous report from the COAST-V trial, improvements were seen in patients with AS treated with ixekizumab, an IL-17A monoclonal antibody, versus patients treated with placebo, with adalimumab as an active comparator, in spinal pain, and SP-N at week 16, further improvements with ixekizumab treatment were observed out to week 52 [23].

In the analysis presented here, ixekizumab significantly reduced SP-N in patients with AS irrespective of controlled or persisting levels of inflammation as assessed by CRP, MRI, or CRP + MRI (at several time points), and adalimumab appeared to reduce SP-N primarily when inflammation was also reduced. Patients treated with adalimumab or placebo and re-randomized to ixekizumab at week 16 experienced a further reduction in SP-N up to 52 weeks for controlled and non-controlled levels of inflammation. Pathway analyses of treatment effect on spinal and bodily pain revealed that both ixekizumab and adalimumab had direct effects on pain reduction, although ixekizumab may have had a greater reduction in pain due to a greater direct effect on pain compared to adalimumab in the pathway analysis.

Nociceptive sensory neurons express receptors for proinflammatory cytokines such as IL-17. Cytokine signaling induces changes in excitability, ion currents, and second messenger signaling of these nociceptors. The persistent activation/sensitization of nociceptive neurons at the site of inflammation (such as sacroiliac joints in AS) caused by the increased local expression of IL-17 and other cytokines magnifies the mechanical pain signal detected in the periphery [24].

Further along the pain signaling pathway, in the dorsal root ganglion (DRG), IL-17A/IL-17R signaling also impacts transmission, and contributes to the induction of neuropathic pain. IL-17R was found in most neurons in the DRG and in DRG neuronal cultures, and IL-17A has been shown to regulate inflammatory responses associated with neuropathic pain induced by nerve injury in neuropathic pain models [25, 26].

Centrally, pain is not perceived by a single area in the brain, rather the origin of pain results from functionally integrated neural networks [27] speculated to involve a wide range of somato-specific regions like the ventrolateral thalamus and the dorsal posterior insula [28], and limbic regions associated with affect and mood such as the amygdala, ventral striatum, and hippocampus [29].

Ixekizumab conveys its effects on the overt elements of inflammation in the periphery, which can have downstream effects on central process signaling. IL-17 is upregulated in the central nervous system (CNS) during inflammation, mainly through production by activated microglia and astrocytes, and promotes proinflammatory activity, increasing production of cytokines and chemokines, and disrupting the blood–brain barrier (BBB) [30, 31]. Further, the increased production of IL-17 at peripheral sites of inflammation pertinent to AS may influence the transmission of pain signals through the peripheral nervous system, eventually leading to CNS changes that reflect the sequelae of pain. The fact that IL-17 and IL-17R-expressing lymphocytes promote dysfunction of the BBB, increasing its permeability, may offer unique opportunities in curtailing the peripheral and CNS transmission of pain signals in such patients expressing higher IL-17 levels or activity [32]. Notably, an increase in IL-17 at peripheral tissues affected by AS (such as the

spine or appendicular skeleton) may result in several specific changes that transmit this pain signal more effectively. The transmission of the pain signal starting at the affected area occurs through specific pain fibers that impinge into the peripheral nervous system of the dorsal horn of the spinal cord. Central afferent neurons extend out of the dorsal horn and are influenced by the glial cells that surround the spinal cord. IL-17 can influence the signaling process through several mechanisms: (1) IL-17 directly enhances the central afferent neurons that transmit pain into pain centers within the CNS, (2) IL-17 reduces the inhibitory interneurons that modulate this afferent pain signal, and (3) IL-17 potentiates the descending pain signals from the nervous system to the target peripheral tissue [26, 30, 33]. Collectively, IL-17 modulates the perception of pain and related behavior in humans and animal models which may contribute to the observed direct benefit on pain amelioration observed after treatment with an IL-17A targeting antibody such as ixekizumab, in patients with AS. These effects are complementary yet distinct from the well-known proinflammatory actions of IL-17.

Like IL-17, tumor necrosis factor (TNF) also plays a role in both central and peripheral mediation of pain signaling [34]. Peripherally, TNF is produced at the site of inflammation and can enhance the pain signal to the DRG in the dorsal horn through initiation of an inflammatory cascade [35]. Centrally, TNF can cross the BBB from the periphery or be produced locally by inflamed neurons and microglia, and in turn promotes proinflammatory activity, propagating inflammation in the CNS [36, 37].

Since IL-17 and TNF have at least superficially similar effects on pain signaling, it is difficult to hypothesize why ixekizumab has a noticeably greater direct effect on pain signaling in the pathway analysis reported here compared to adalimumab. One potential explanation is that TNF acts as an inflammation master regulator, recruiting other inflammatory molecules, and cytokines and enhancing pain signaling using intermediaries. This could explain why adalimumab's pain-alleviating effects seem to be more associated with the measures used to estimate indirect effect in the pathway analysis (CRP, MRI SIJ, and MRI Spine) while IL-17 seems to act more directly on pain signaling, rather than through the activation and/or recruitment of other inflammatory molecules.

Limitations of this study include that the COAST-V study was conducted in a predominantly male population which may affect results, this study was a post hoc analysis that the clinical trials were not designed for, this study was not powered for a direct comparison with adalimumab, and that this study was not designed to provide mechanistic evidence to explain why ixekizumab has a direct beneficial effect on pain; both CRP and MRI may lack sensitivity for detection of inflammation. Further, CRP and MRI do not fully capture every aspect of inflammation and the absence of inflammatory signals in these measures does not mean a complete absence of inflammation in patients. As well, the pain measures used were qualitative patient-reported outcomes rather than quantitative objective measures which do not assess neuropathic or nociplastic pain. Concomitant medications may have affected patient responses. Most patients in this study ($\geq$ 90%) were using NSAIDs at baseline and we do not have data on concomitant opioid use. Fibromyalgia status of patients was not assessed in this study. Therefore, the results should be interpreted with these caveats in mind.

CONCLUSIONS

The analysis presented here is supportive of the hypothesis that ixekizumab reduces pain in AS by mechanisms that cannot be attributed only to the reduction in inflammation, and that ixekizumab and adalimumab may differ in their pain-relieving mechanisms suggesting ixekizumab has a greater direct effect on pain relief.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. Kurt de Vlam has received grant/research support from Celgene and Galapagos; consultancy fees from Celgene, Eli Lilly, Galapagos, Novartis, and UCB; and speaker fees from Celgene, Eli Lilly, Galapagos, Novartis, and UCB. Walter P. Maksymowych is Chief Medical Officer of CARE Arthritis Limited, has acted as a paid consultant/participated in advisory boards for AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer, and UCB; received research and/or educational grants from AbbVie, Novartis, Pfizer, and UCB; and received speaker fees from AbbVie, Janssen, Novartis, Pfizer, and UCB. Proton Rahman has received consulting fees from Abbott, AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, and Pfizer, and has also received research grants from Janssen and Novartis. Philip Mease declares research grants, consultation fees, and/or speaker honoraria from AbbVie, Amgen, Bristol Myers, Boehringer Ingelheim, Galapagos, Gilead, GlaxoSmithKline, Inmagene, Janssen, Lilly, Merck, Novartis, Pfizer, SUN Pharma, and UCB. Philip G. Conagah reports speakers' bureaus for AbbVie, Eli Lilly, Novartis, and consultancies with AbbVie, Eli Lilly, Genascense, GSK, Galapagos, Grunenthal, Janssen, Levicept, Merck, Moebius, Novartis, Stryker, Takeda, and TrialSpark. Gaia Gallo, Venkatesh Krishnan, Conor J. McVeigh, Jeffrey Lisse, Danting Zhu, and Rebecca J. Bolce are all employees and shareholders of Eli Lilly and Company.

Ethical Approval. COAST-V was carried out in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All investigation sites received approval from the appropriate authorized institutional review board or ethics committee. All patients provided written consent before the study-related procedures were carried out. The master ethics committee was Schulman Associates IRB, Cincinnati, OH, USA.

REFERENCES

1. Strand V, Rao SA, Shillington AC, Cifaldi MA, McGuire M, Ruderman EM. Prevalence of axial spondyloarthritis in United States rheumatology practices: assessment of SpondyloArthritis International Society criteria versus rheumatology expert clinical diagnosis. Arthritis Care Res (Hoboken). 2013;65(8):1299–306.

2. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet. 2017;390(10089):73–84.

3. Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of ankylosing spondylitis patient advocacy groups. Curr Opin Rheumatol. 2000;12(4):239–47.

4. Bodur H, Ataman S, Rezvani A, et al. Quality of life and related variables in patients with ankylosing spondylitis. Qual Life Res. 2011;20(4):543–9.

5. Kieskamp SC, Paap D, Carbo MJG, et al. Central sensitization has major impact on quality of life in patients with axial spondyloarthritis. Semin Arthritis Rheum. 2022;52:151933.

6. Dean LE, Macfarlane GJ, Jones GT. Five potentially modifiable factors predict poor quality of life in ankylosing spondylitis: results from the Scotland Registry for Ankylosing Spondylitis. J Rheumatol. 2018;45(1):62–9.

7. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76(6):978–91.

8. Braun J, Baraliakos X, Hermann KG, et al. Effect of certolizumab pegol over 96 weeks of treatment on inflammation of the spine and sacroiliac joints, as measured by MRI, and the association between clinical and MRI outcomes in patients with axial spondyloarthritis. RMD Open. 2017;3(1):e000430.

9. Raja SN, Carr DB, Cohen M, et al. The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976–82.

10. Kim TW, Son SM, Lee JS. Neuropathic pain in ankylosing spondylitis: a meta-analysis. Z Rheumatol. 2020;79(1):95–102.

11. Wu Q, Inman RD, Davis KD. Neuropathic pain in ankylosing spondylitis: a psychophysics and brain imaging study. Arthritis Rheum. 2013;65(6):1494–503.

12. Azevedo VF, EoS P, Felippe LR, Moreira RA. Occurrence of fibromyalgia in patients with ankylosing spondylitis. Rev Bras Reumatol. 2010;50(6):646–50.

13. Aloush V, Ablin JN, Reitblat T, Caspi D, Elkayam O. Fibromyalgia in women with ankylosing spondylitis. Rheumatol Int. 2007;27(9):865–8.

14. Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. Arthritis Rheum. 2009;60(6):1647–56.

15. Mease PJ, Smolen JS, Behrens F, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomized, open-label, blinded-assessor trial. Ann Rheum Dis. 2020;79(1):123–31.

16. van der Heijde D, Cheng-Chung Wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomized, double-blind, active-controlled and placebo-controlled trial. Lancet. 2018;392(10163):2441–51.

17. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomized trials. Lancet. 2015;386(9993):541–51.

18. Deodhar A, van der Heijde D, Gensler LS, et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomized, placebo-controlled trial. Lancet. 2020;395(10217):53–64.

19. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomized, double-blind, placebo-controlled

period of the SPIRIT-P2 phase 3 trial. Lancet. 2017;389(10086):2317–27.

20. Dougados M, Wei JC, Landewé R, et al. Efficacy and safety of ixekizumab through 52 weeks in two phase 3, randomized, controlled clinical trials in patients with active radiographic axial spondyloarthritis (COAST-V and COAST-W). Ann Rheum Dis. 2020;79(2):176–85.

21. Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis research consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. Arthritis Rheum. 2005;53(4):502–9.

22. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008;40(3):879–91.

23. Deodhar AA, Mease PJ, Rahman P, et al. Ixekizumab improves spinal pain, function, fatigue, stiffness, and sleep in radiographic axial spondyloarthritis: COAST-V/W 52-week results. BMC Rheumatol. 2021;5(1):35.

24. Schaible HG. Nociceptive neurons detect cytokines in arthritis. Arthritis Res Ther. 2014;16(5):470.

25. Noma N, Khan J, Chen IF, et al. Interleukin-17 levels in rat models of nerve damage and neuropathic pain. Neurosci Lett. 2011;493(3):86–91.

26. Luo H, Liu HZ, Zhang WW, et al. Interleukin-17 regulates neuron-glial communications, synaptic transmission, and neuropathic pain after chemotherapy. Cell Rep. 2019;29(8):2384–97.e5.

27. Kuner R, Kuner T. Cellular circuits in the brain and their modulation in acute and chronic pain. Physiol Rev. 2021;101(1):213–58.

28. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med. 2013;368(15):1388–97.

29. Baliki MN, Apkarian AV. Nociception, pain, negative moods, and behavior selection. Neuron. 2015;87(3):474–91.

30. Sun C, Zhang J, Chen L, et al. IL-17 contributed to the neuropathic pain following peripheral nerve injury by promoting astrocyte proliferation and secretion of proinflammatory cytokines. Mol Med Rep. 2017;15(1):89–96.

31. Waisman A, Hauptmann J, Regen T. The role of IL-17 in CNS diseases. Acta Neuropathol. 2015;129(5):625–37.

32. Kebir H, Kreymborg K, Ifergan I, et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. Nat Med. 2007;13(10):1173–5.

33. Jiang X, Zhou R, Zhang Y, Zhu T, Li Q, Zhang W. Interleukin-17 as a potential therapeutic target for chronic pain. Front Immunol. 2022;13:999407.

34. Leung L, Cahill CM. TNF-alpha and neuropathic pain–a review. J Neuroinflammation. 2010;7:27.

35. Lee AS, Ellman MB, Yan D, et al. A current review of molecular mechanisms regarding osteoarthritis and pain. Gene. 2013;527(2):440–7.

36. Banks WA, Kastin AJ, Broadwell RD. Passage of cytokines across the blood-brain barrier. Neuroimmunomodulation. 1995;2(4):241–8.

37. Mukandala G, Tynan R, Lanigan S, O'Connor JJ. The effects of hypoxia and inflammation on synaptic signaling in the CNS. Brain Sci. 2016;6(1):6.