The Journal of Rheumatology 2022;49:265–73
doi:10.3899/jrheum.210471
First Release January 15 2022

The Journal of Rheumatology

Spinal Radiographic Progression and Predictors of Progression in Patients With Radiographic Axial Spondyloarthritis Receiving Ixekizumab Over 2 Years

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ABSTRACT. ***Objective.*** To evaluate the long-term effect of ixekizumab (IXE) on radiographic changes in the spine in patients with radiographic axial spondyloarthritis (r-axSpA) by measuring change from baseline through 2 years in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), and to identify potential predictors of progression.

Methods. This study evaluates patients from COAST-V (ClinicalTrials.gov: NCT02696785, biologic disease-modifying antirheumatic drug–naïve) and COAST-W (NCT02696798, tumor necrosis factor inhibitor–experienced) who had mSASSS data at baseline in the originating studies and 108 weeks after baseline in the extension study COAST-Y (NCT03129100). We examined the proportion of patients who did not have spinal radiographic progression through 2 years (108 weeks) of treatment with IXE (80 mg every 2 or 4 weeks) and the change from baseline to year 2 in mSASSS. Potential predictors of spinal radiographic progression were also evaluated.

Results. Among patients with evaluable radiographs who were originally assigned to IXE (n = 230), mean (SD) change in mSASSS from baseline at year 2 was 0.3 (1.8). The proportion of nonprogressors over 2 years was 89.6% if defined as mSASSS change from baseline < 2 and 75.7% if defined as mSASSS change from baseline ≤ 0. Predictors of structural progression at year 2 (mSASSS change > 0) were age ≥ 40, baseline syndesmophytes, HLA-B27 positivity, and male sex. Week 52 inflammation in Spondyloarthritis Research Consortium of Canada spine was also a predictor of radiographic progression at year 2 in patients with magnetic resonance imaging data in COAST-V (n = 109).

Conclusion. The majority of patients with r-axSpA receiving IXE had no radiographic progression in the spine through 2 years of treatment. Predictors were generally consistent with previous studies.

Key Indexing Terms: ankylosing spondylitis, inflammation, interleukin-17, magnetic resonance imaging, radiography, spine

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease of the axial skeleton and includes radiographic axSpA (r-axSpA), also known as ankylosing spondylitis (AS), and nonradiographic axSpA (nr-axSpA). Patients with r-axSpA/AS have radiographically defined structural damage in the sacroiliac joint (SIJ). As the disease advances, progressive irreversible structural damage in the spine (ankylosis) may occur, resulting in functional deterioration.[1,2] Inflammation and excessive new bone

This study was funded by Eli Lilly and Company (Indianapolis, Indiana, USA).

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DvdH has received consulting fees and/or speaking fees and/or honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and UCB Pharma, and is the Director of Imaging Rheumatology BV. MØ has received consulting fees and/or speaking fees and/or honoraria from AbbVie, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Hospira, Janssen, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi, and UCB. JDR has received consulting fees and/or speaking fees and/or honoraria from Eli Lilly and UCB. XB has received consulting fees and/or speaking fees and/or honoraria from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Roche, and UCB. AK, DMS, XL, HC, and DHA are current employees of Eli Lilly and Company and own stock or stock options in Eli Lilly and Company. WPM has received consulting fees and/or speaking fees and/or honoraria from AbbVie, BMS, Boehringer Ingelheim, Galapagos, Gilead, Eli Lilly, Novartis, Pfizer, and UCB.

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Accepted for publication on November 19, 2021.

formation (syndesmophytes) drive the pathophysiology of the disease and the initial spine inflammation (osteitis) is followed by bone remodeling, which may also lead to syndesmophytes.[1] It is important to understand the potential effect that long-term therapy with biologics can have on the structural changes in the spine and if these effects can mitigate this aspect of the disease.

Nonsteroidal antiinflammatory drugs (NSAIDs), anti–tumor necrosis factor (TNF) agents, and interleukin (IL)-17 antagonists have been demonstrated to improve the signs and symptoms of AS. Comparison of anti-TNF agents with historical cohorts of biologic-naïve patients treated with NSAIDs has not shown a significant added benefit in reducing radiographic progression at 2 years.[3,4,5] A low radiographic progression rate through 2 years was reported for secukinumab (an IL-17A antagonist)[6] and for certolizumab pegol (CZP; an anti-TNF agent)[7,8] compared to previous studies.

Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets IL-17A[9] and has demonstrated efficacy and safety in phase III, randomized, placebo-controlled trials in axSpA,[10,11,12,13] including 2 studies in r-axSpA/AS (COAST-V and COAST-W).[10,11,12] Patients in COAST-V and COAST-W who completed 1 year were eligible to enroll in the long-term extension trial, COAST-Y. Here, we examine spinal radiographic progression at year 2 for patients with r-axSpA/AS treated with IXE continuously through 2 years. Patients with nr-axSpA were not considered for this analysis. Patients were either biologic disease-modifying antirheumatic drug (bDMARD)-naïve (COAST-V) or TNF inhibitor (TNFi)-experienced (COAST-W). We report mean change from baseline to year 2 in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and the proportion of nonprogressors at year 2 of treatment with IXE. We also evaluate potential predictors of spinal radiographic progression.

METHODS

Trial design. COAST-Y (ClinicalTrials.gov: NCT03129100) is a phase III, multicenter, long-term extension study including patients with axSpA who completed any of the 1-year registration studies in axSpA[10,11,13] and elected to continue into the 2-year COAST-Y extension study. Detailed trial designs for the originating studies have been previously reported.[10,11,12,13]

COAST-Y was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by the main ethics committee Schulman Associates institutional review board (IRB), Cincinnati, Ohio, USA (IRB # 201607390), and the study was approved by the research ethics boards at each of 127 total participating sites. The full lists of investigators and study sites are reported in the COAST-Y randomized withdrawal study supplement.[14] Study participants provided written informed consent prior to starting study procedures.

Trial participants. Patients with r-axSpA who were bDMARD-naïve or had prior inadequate response or intolerance to 1 or 2 TNFi received 80 mg IXE subcutaneously every 2 weeks (IXE Q2W) or every 4 weeks (IXE Q4W) for 108 weeks (52 weeks in the originating r-axSpA/AS studies and 56 weeks in the COAST-Y extension study). Inclusion and exclusion criteria have previously been reported for COAST-V[10,12] and COAST-W.[11,12] In both trials, patients had a diagnosis of r-axSpA and fulfilled Assessment of SpondyloArthritis international Society (ASAS) criteria (sacroiliitis on radiography by modified New York [mNY] criteria and ≥ 1 SpA feature) and had active disease (defined as Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 and spinal pain ≥ 4 on a numerical rating scale). All patients who fulfilled the ASAS criteria for r-axSpA also fulfilled the mNY criteria for AS.

Randomization and blinding. As previously described,[10,11,12] in COAST-V, patients were randomized 1:1:1:1 to IXE Q2W, IXE Q4W, placebo, or an active reference arm (40 mg adalimumab every 2 weeks).[10,12] In COAST-W, patients were randomized 1:1:1 to IXE Q2W, IXE Q4W, or placebo.[11,12] In both trials, patients assigned to IXE were further randomized (1:1) to a starting dose of 80 mg or 160 mg IXE at week 0. For the analysis presented in this manuscript, the population was limited to patients who were originally assigned to IXE Q2W or IXE Q4W in COAST-V or COAST-W and continued the same IXE dosing regimen for 2 years (a duration of 52 weeks in the originating studies with a subsequent duration of 56 weeks in the COAST-Y extension study for a total of 108 weeks). The COAST-Y study included a double-blind, placebo-controlled randomized withdrawal–retreatment period that started at week 24 in the COAST-Y study based on the achievement of remission (defined as Ankylosing Spondylitis Disease Activity Score [ASDAS] < 1.3 at weeks 16 and 20 or ASDAS < 1.3 at week 16 or week 20, and ASDAS < 2.1 at the other visit). Patients who did not achieve remission continued to receive uninterrupted IXE Q2W or IXE Q4W. Patients who achieved remission were rerandomized to continue IXE (IXE Q2W or IXE Q4W) or withdraw to placebo. The population of patients presented in this manuscript are those who continued IXE Q2W or IXE Q4W uninterrupted or were rerandomized to IXE Q2W or IXE Q4W treatment (patients rerandomized to placebo were not included).

Procedures. For patients initially enrolled in COAST-V or COAST-W, lateral view radiographs of cervical and lumbar spine were performed at baseline and 2 years after baseline (or at the early termination visit for patients who left the study prior to year 2). Radiographs were scored using the mSASSS scoring criteria (total score range: 0–72).[15] Spinal changes were scored for each vertebral corner and graded according to the following scheme: 0 = normal; 1 = erosion, sclerosis, or squaring; 2 = syndesmophyte; 3 = bridging syndesmophyte. A score of "NA" was assigned in cases where the location was nonevaluable due to poor radiographic depiction, poor quality of the exposure, or an interfering condition such as osteoarthritis. If > 3 scoring units in either cervical or lumbar segments were missing, then no imputation was applied and total score was considered missing. If ≤ 3 scoring units in both cervical and lumbar segments were missing, then missing scoring units were imputed such that mean change of each scoring unit after the imputation was the same as the mean of nonmissing scoring units, with the following exception: if the mean change of nonmissing scoring units was negative, then each missing scoring unit was imputed such that it had no change from the corresponding baseline value.

All radiographs were read by 2 central readers, each scoring independently while blinded to treatment group and to image timepoint. An adjudicator performed a third read, blinded to the results of the primary readers, for cases where a visit was read by 1 primary reader and set as unreadable by the other reader, or when changes from baseline visit to a follow-up visit differed between the 2 primary readers by a predefined margin (≥ 5 units in change of mSASSS from baseline to year 2). Statistical analyses used the mean score of the 2 primary readers or, if adjudicated, the mean score of the adjudicator and the primary reader who scored closest to the adjudicator. Baseline syndesmophytes and new syndesmophytes at year 2 were confirmed if they were identified by both selected readers at the same location. Interrater reliability was calculated using Shrout-Fleiss intraclass correlations.[16]

Assessments. Structural progression was assessed for the total IXE group as well as for each IXE group (IXE Q2W or IXE Q4W). Assessments of structural progression included change in mSASSS from baseline at year 2, cumulative probability of change in mSASSS from baseline at year 2, and the proportion of nonprogressors at year 2 defined as change in total mSASSS < 2 and ≤ 0, respectively. We evaluated patients who received IXE Q2W or IXE Q4W through 2 years (108 weeks) and had evaluable radiographs at

both baseline and year 2 collected within predefined windows (range −150 to 60 days from the first study drug injection at baseline and ± 150 days from the year 2 visit).

To evaluate potential predictors of spinal radiographic progression, an association analysis was performed for change in total mSASSS > 0 and ≥ 2, respectively. Magnetic resonance imaging (MRI) of the spine and SIJ was performed at baseline, week 16, and week 52 in COAST-V, and MRI of the spine was performed at baseline and week 16 in a subset of COAST-W patients who participated in the MRI addendum (approximately 50% of patients in the study). MRI was scored using the Spondyloarthritis Research Consortium of Canada (SPARCC) score.[17] Due to data availability, MRI variables were assessed only in the patients from COAST-V who had SPARCC spine and SIJ MRI at baseline and week 52 (n = 109), and in the patients from COAST-V and COAST-W who had SPARCC spine MRI at baseline and week 16 (n = 175).

Statistical analysis. Analysis for structural progression was performed for patients originally assigned to IXE who had both baseline and year 2 data. Descriptive statistics were provided for both continuous variables (ie, change from baseline) and categorical variables (ie, nonprogressor and new syndesmophyte) for the total IXE group and for each IXE group (IXE Q2W or IXE Q4W). Subgroup analysis was performed for mSASSS change from baseline and nonprogression (change in mSASSS ≤ 0 and < 2). Predictors of spinal radiographic progression were identified in logistic regression models in 2 steps. First, a univariate analysis was run with each of the variables of interest. Then, the multivariate analysis was performed using stepwise selection with $P < 0.1$ for entry and $P < 0.1$ for stay to select variables for the final prediction model with all selected variables included.

RESULTS

Patient characteristics. Baseline patient demographics and other characteristics are shown in Table 1 and were similar between dose groups. A total of 230 patients received IXE for 2 years (115 received IXE Q4W and 115 received IXE Q2W). At baseline, mean (SD) symptom duration was 15.9 (9.8) years, BASDAI score was 7.1 (1.3), ASDAS score was 4.0 (0.7), and serum C-reactive protein (CRP) level was 15.2 (21.2) mg/L. Patients were predominately male (81.7%), HLA-B27 positive (87.4%), and 51.3% had ever used tobacco. The mean baseline mSASSS score was 11.0 (16.3). Out of 228 patients who were evaluable by both readers, 91 (39.9%) had syndesmophytes at baseline. Mean (SD) baseline MRI spine SPARCC score was 12.6 (21.6).

mSASSS change from baseline and rates of nonprogression at year 2. Mean (SD) change in mSASSS from baseline at year 2 was 0.3 (1.8) for total IXE (n = 230), 0.4 (2.1) for IXE Q4W (n = 115),

Table 1. Baseline patient demographics and other characteristics.[a]

	IXE Q4W, N = 115	IXE Q2W, N = 115	Total IXE, N = 230
Age, yrs, mean (SD)	43.0 (12.4)	43.0 (10.5)	43.0 (11.5)
Male sex, n (%)	99 (86.1)	89 (77.4)	188 (81.7)
Duration of symptoms since AxSpA onset,			
yrs, mean (SD)	16.3 (10.4)	15.5 (9.0)	15.9 (9.8)
≥10 years, n (%)	74 (64.3)	80 (69.6)	154 (67.0)
Tobacco use, n (%)			
Ever	57 (49.6)	61 (53.0)	118 (51.3)
Never	58 (50.4)	54 (47.0)	112 (48.7)
bDMARD-naïve, n (%)	55 (47.8)	55 (47.8)	110 (47.8)
TNFi-experienced, n (%)	60 (52.2)	60 (52.2)	120 (52.2)
Baseline DMARD[b] use, n (%)	44 (38.3)	38 (33.0)	82 (35.7)
Baseline NSAID/COX-2 inhibitor use, n (%)	104 (90.4)	98 (85.2)	202 (87.8)
CRP, mg/L, mean (SD)	15.4 (23.3)	15.1 (18.8)	15.2 (21.2)
≤ 5 mg/L, n (%)	37 (32.2)	38 (33.0)	75 (32.6)
> 5 mg/L, n (%)	78 (67.8)	77 (67.0)	155 (67.4)
MRI spine SPARCC score, n	87	89	176
Mean (SD)	12.0 (18.3)	13.2 (24.5)	12.6 (21.6)
mSASSS score, mean (SD)	10.6 (15.4)	11.3 (17.2)	11.0 (16.3)
> 0, n (%)	76 (66.1)	73 (63.5)	149 (64.8)
0, n (%)	39 (33.9)	42 (36.5)	81 (35.2)
≥ 2, n (%)	64 (55.7)	63 (54.8)	127 (55.2)
Syndesmophyte present[c], n (%)	49 (42.6)	42 (36.8)	91 (39.7)
HLA-B27 positive, n (%)	101 (87.8)	100 (87.0)	201 (87.4)
ASDAS, mean (SD)	3.9 (0.7)	4.0 (0.8)	4.0 (0.7)
BASDAI, mean (SD)	7.1 (1.2)	7.2 (1.4)	7.1 (1.3)

[a] Patients were treated with IXE for 2 years (108 weeks). [b] Methotrexate, sulfasalazine, and hydroxychloroquine. [c] From both of the selected readers at the same location (total IXE, n = 229). ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; bDMARD: biologic disease-modifying antirheumatic drug; COX-2: cyclooxygenase-2; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; IXE: ixekizumab; IXE Q2W: 80 mg IXE every 2 weeks; IXE Q4W: 80 mg IXE every 4 weeks; MRI: magnetic resonance imaging; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; NSAID: nonsteroidal antiinflammatory drug; SPARCC: Spondyloarthritis Research Consortium of Canada; TNFi: tumor necrosis factor inhibitor.

and 0.2 (1.4) for IXE Q2W (n = 115; Table 2). The interrater reliability was 0.93 for total mSASSS at both baseline and year 2 and 0.33 for change from baseline at year 2. In the total IXE group, mean (SD) change in mSASSS from baseline at year 2 was numerically higher for patients ≥ 40 years vs < 40 years of age (0.4 [1.9] vs 0.2 [1.6]), for males vs females (0.4 [1.9] vs. –0.1 [0.7]), for patients with syndesmophytes at baseline vs those without syndesmophytes at baseline (0.6 [2.5] vs 0.2 [1.1]), for patients who were HLA-B27 positive vs negative (0.4 [1.9] vs 0.04 [0.5]), for patients with baseline ASDAS > 3.5 vs ASDAS

Table 2. mSASSS change from baseline at year 2 (observed).[a]

	IXE Q4W	IXE Q2W	Total IXE
Overall population	N = 115	N = 115	N = 230
Baseline mSASSS	10.6 (15.3)	11.3 (17.2)	11.0 (16.3)
Change at year 2	0.4 (2.1)	0.2 (1.4)	0.3 (1.8)
Median (IQR)	0.0 (0.2)	0.0 (0.0)	0.0 (0.0)
Age, ≥ 40 yrs	n = 70	n = 72	n = 142
Baseline mSASSS	12.8 (16.9)	13.2 (18.2)	13.0 (17.5)
Change at year 2	0.5 (2.1)	0.3 (1.7)	0.4 (1.9)
Age, < 40 yrs	n = 45	n = 43	n = 88
Baseline mSASSS	7.2 (11.9)	8.1 (15.2)	7.6 (13.6)
Change at year 2	0.3 (2.1)	0.1 (0.7)	0.2 (1.6)
Male sex	n = 99	n = 89	n = 188
Baseline mSASSS	11.8 (16.1)	13.1 (17.6)	12.4 (16.8)
Change at year 2	0.5 (2.2)	0.3 (1.6)	0.4 (1.9)
Female sex	n = 16	n = 26	n = 42
Baseline mSASSS	3.2 (5.5)	5.0 (14.3)	4.3 (11.7)
Change at year 2	–0.4 (0.9)	0.1 (0.4)	–0.1 (0.7)
Patients with syndesmophytes at baseline[b]	n = 49	n = 42	n = 91
Baseline mSASSS	21.3 (16.0)	28.0 (18.9)	24.4 (17.6)
Change at year 2	0.7 (2.7)	0.4 (2.1)	0.6 (2.5)
Patients without syndesmophytes at baseline[b]	n = 65	n = 72	n = 137
Baseline mSASSS	1.8 (4.1)	1.6 (3.1)	1.7 (3.6)
Change at year 2	0.2 (1.5)	0.1 (0.6)	0.2 (1.1)
HLA-B27 positive at baseline	n = 101	n = 100	n = 201
Baseline mSASSS	11.0 (15.8)	11.3 (16.7)	11.1 (16.2)
Change at year 2	0.5 (2.2)	0.3 (1.5)	0.4 (1.9)
HLA-B27 negative at baseline	n = 14	n = 15	n = 29
Baseline mSASSS	8.1 (11.9)	11.3 (20.9)	9.8 (16.9)
Change at year 2	0.1 (0.6)	–0.03 (0.5)	0.04 (0.5)
Baseline ASDAS (2.1–3.5)	n = 30	n = 28	n = 58
Baseline mSASSS	10.6 (18.6)	11.4 (17.5)	10.9 (17.9)
Change at year 2	–0.2 (1.2)	–0.04 (0.7)	–0.1 (1.0)
Baseline ASDAS (> 3.5)	n = 85	n = 87	n = 172
Baseline mSASSS	10.6 (14.1)	11.3 (17.3)	11.0 (15.8)
Change at year 2	0.6 (2.3)	0.3 (1.6)	0.5 (2.0)
Week 52 MRI in SPARCC spine ≥ 2	n = 21	n = 20	n = 41
Baseline mSASSS	14.8 (13.1)	14.7 (16.5)	14.7 (14.6)
Change at year 2	1.0 (3.8)	0.5 (1.3)	0.8 (2.8)
Week 52 MRI in SPARCC spine < 2	n = 34	n = 34	n = 68
Baseline mSASSS	6.8 (15.8)	8.0 (15.4)	7.4 (15.5)
Change at year 2	–0.1 (1.5)	0.04 (0.8)	–0.02 (1.2)
Week 16 MRI in SPARCC spine ≥ 2	n = 35	n = 40	n = 75
Baseline mSASSS	10.9 (11.5)	17.9 (20.7)	14.6 (17.3)
Change at year 2	0.7 (2.6)	0.1 (1.9)	0.4 (2.2)
Week 16 MRI in SPARCC spine < 2	n = 51	n = 49	n = 100
Baseline mSASSS	10.5 (18.9)	5.9 (11.3)	8.3 (15.7)
Change at year 2	0.1 (2.0)	0.2 (1.1)	0.2 (1.6)

[a] Data are mean (SD) for patients treated with IXE for 2 years (108 weeks) except where noted. [b] From both of the selected readers at the same location. ASDAS: Ankylosing Spondylitis Disease Activity Score; IXE: ixekizumab; IXE Q2W: 80 mg IXE every 2 weeks; IXE Q4W: 80 mg IXE every 4 weeks; MRI: magnetic resonance imaging; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; SPARCC: Spondyloarthritis Research Consortium of Canada.

2.1–3.5 (0.5 [2.0] vs –0.1 [1.0]), for patients with week 52 MRI in SPARCC spine ≥ 2 vs < 2 (0.8 [2.8] vs –0.02 [1.2]), and for patients with week 16 MRI in SPARCC spine ≥ 2 vs < 2 (0.4 [2.2] vs 0.2 [1.6]; Table 2; additional subgroup analyses are in Supplementary Figure 1 and Supplementary Tables 1–2, available with the online version of this article).

Among patients treated with IXE for 2 years (total IXE, n = 230), the proportion of nonprogressors was 89.6% if defined by mSASSS change from baseline < 2 and 75.7% if defined by mSASSS change from baseline ≤ 0 (Table 3, Figure 1). Using the same definitions (< 2 and ≤ 0, respectively), the proportion of nonprogressors for patients ≥ 40 years was 86.6% and 69.0%; for patients < 40 years was 94.3% and 86.4%; for males was 87.2% and 72.3%; for females was 100.0% and 90.5%; for patients with syndesmophytes at baseline was 80.2% and 62.6%; for patients without syndesmophytes at baseline was 96.4% and 84.7%; for patients who were HLA-B27 positive was 88.1% and 73.6%; for patients who were HLA-B27 negative was 100.0% and 89.7%; for patients with high baseline ASDAS (2.1–3.5) was 98.3% and 86.2%; for patients with very high baseline ASDAS (> 3.5) was 86.6% and 72.1%; for patients with week 52 MRI in SPARCC spine ≥ 2 was 82.9% and 63.4%; for patients with week 52 MRI in SPARCC spine < 2 was 95.6% and 86.8%; for patients with week 16 MRI in SPARCC spine ≥ 2 was 86.7% and 72.0%; and for patients with week 16 MRI in SPARCC spine < 2 was 94.0% and 84.0% (Table 3). Of 229 evaluable patients (91 with and 137 without syndesmophytes at baseline), 218 (95.2%) did not develop new syndesmophytes through 2 years treatment with IXE. No new syndesmophytes developed at year 2 for 90.1% of patients with syndesmophytes at baseline and 98.5% of patients without syndesmophytes at baseline (Table 3).

Predictors of structural progression at year 2. Twenty-six variables of interest were tested in the univariate model for patients treated with IXE for 2 years (total IXE, n = 230; Supplementary Table 3). A stepwise selection in a multivariate logistic regression model identified age, baseline syndesmophytes, HLA-B27 status, and sex as predictors of structural progression at year 2, defined as change in total mSASSS > 0 (Table 4), indicating that patients who were ≥ 40 years of age, male, with a presence of baseline syndesmophytes, and positive HLA-B27 were more likely to have structural progression. Very high baseline ASDAS disease severity (ASDAS > 3.5) tended to be related to structural progression, but when the above predictors were controlled, the effect did not reach statistical significance ($P = 0.06$). Predictors of structural progression at year 2 defined as change in total mSASSS ≥ 2 were baseline syndesmophytes, tobacco use, and baseline ASDAS disease severity (Table 4), indicating that patients who had ever used tobacco, had a presence of baseline syndesmophytes, and had very high disease activity (ASDAS > 3.5) were more likely to have structural progression.

Thirty variables of interest were tested in the univariate model for patients from COAST-V (bDMARD-naïve) where MRI measures were available at baseline and week 52 (n = 109; Supplementary Table 4, available with the online version of this article). Predictors of structural progression at year 2 (defined as change in total mSASSS > 0) were week 52 inflammation in SPARCC spine score ≥ 2 and week 52 ASDAS. Tobacco tended to be related to structural progression, but when the above predictors were controlled the effect did not reach statistical significance ($P = 0.07$). Week 52 inflammation in SPARCC spine score ≥ 2 was also identified as a predictor for structural progression at year 2, defined as change in total mSASSS ≥ 2 (Table 4).

Twenty-nine variables of interest were tested in the univariate model for patients from COAST-V (bDMARD-naïve) and COAST-W (TNFi-experienced) where MRI measures were available at baseline and week 16 (n = 175; Supplementary Table 5, available with the online version of this article). Predictors of structural progression at year 2 (defined as change in total mSASSS > 0) were age ≥ 40, baseline inflammation in SPARCC spine score ≥ 2, and baseline mSASSS. Baseline syndesmophytes was identified as a predictor for structural progression at year 2 (defined as change in total mSASSS ≥ 2), and baseline ASDAS disease severity tended to be related to structural progression; however, when baseline syndesmophytes was controlled, the effect did not reach statistical significance ($P = 0.08$; Table 4).

DISCUSSION

One of the long-term treatment goals in patients with r-axSpA is the prevention of structural progression. In general, results of the present analysis with IXE are consistent with 2-year radiographic progression studies with secukinumab (both IL-17 antagonists).[6] The majority of patients did not have spinal radiographic progression after 2 years of treatment with IXE. In the current study, where patients had long symptom duration (mean of 16 yrs), the mean (SD) change in mSASSS through 2 years of IXE treatment was 0.3 (1.8) in total IXE, with a range of –0.1 to 0.6 in patients with predictors of structural progression (defined as change in total mSASSS > 0) identified in this analysis (age ≥ 40 yrs, presence of syndesmophytes, HLA-B27 positivity, and male sex). Baseline inflammation in SPARCC spine was a predictor of structural progression (defined as change in total mSASSS > 0) in the COAST-V and COAST-W group of patients who had MRI measures at baseline and week 16. Week 52 inflammation in SPARCC spine was also a predictor of structural progression by both cutoffs (change in total mSASSS > 0 and ≥ 2) in the COAST-V population who had MRI measures at baseline and week 52.

Previous studies with TNFi reported an mSASSS progression rate of 0.8–0.9 over 2 years, which was similar to the mSASSS changes observed in matched historical control cohorts,[3,4,5] but it is difficult to compare as these studies are older and there are differences in populations. Over time, the patient populations may have changed, resulting in overall lower progression rates. In a more contemporary trial with CZP (an anti-TNF agent),[8] mean change in mSASSS was 0.31 (from week 96 to week 204) and 0.98 (from baseline to week 204). In our study, change in mSASSS through 2 years for IXE was most similar to studies of secukinumab through 2 years.[6]

The predictors that we identified were generally consistent with what has previously been observed, with the exceptions of the MRI observations and that CRP was not identified

Table 3. mSASSS nonprogression and new syndesmophytes at year 2 (observed).*

	IXE Q4W	IXE Q2W	Total IXE
Nonprogression at year 2			
Overall population	N = 115	N = 115	N = 230
Change in total mSASSS < 2	102 (88.7)	104 (90.4)	206 (89.6)
Change in total mSASSS ≤ 0	86 (74.8)	88 (76.5)	174 (75.7)
Age, ≥ 40 yrs	n = 70	n = 72	n = 142
Change in total mSASSS < 2	60 (85.7)	63 (87.5)	123 (86.6)
Change in total mSASSS ≤ 0	49 (70.0)	49 (68.1)	98 (69.0)
Age, < 40 yrs	n = 45	n = 43	n = 88
Change in total mSASSS < 2	42 (93.3)	41 (95.3)	83 (94.3)
Change in total mSASSS ≤ 0	37 (82.2)	39 (90.7)	76 (86.4)
Male sex	n = 99	n = 89	n = 188
Change in total mSASSS < 2	86 (86.9)	78 (87.6)	164 (87.2)
Change in total mSASSS ≤ 0	71 (71.7)	65 (73.0)	136 (72.3)
Female sex	n = 16	n = 26	n = 42
Change in total mSASSS < 2	16 (100.0)	26 (100.0)	42 (100.0)
Change in total mSASSS ≤ 0	15 (93.8)	23 (88.5)	38 (90.5)
Patients with syndesmophytes at baseline[a]	n = 49	n = 42	n = 91
Change in total mSASSS < 2	39 (79.6)	34 (81.0)	73 (80.2)
Change in total mSASSS ≤ 0	30 (61.2)	27 (64.3)	57 (62.6)
Patients without syndesmophytes at baseline[a]	n = 65	n = 72	n = 137
Change in total mSASSS < 2	62 (95.4)	70 (97.2)	132 (96.4)
Change in total mSASSS ≤ 0	55 (84.6)	61 (84.7)	116 (84.7)
HLA-B27 positive at baseline	n = 101	n = 100	n = 201
Change in total mSASSS < 2	88 (87.1)	89 (89.0)	177 (88.1)
Change in total mSASSS ≤ 0	74 (73.3)	74 (74.0)	148 (73.6)
HLA-B27 negative at baseline	n = 14	n = 15	n = 29
Change in total mSASSS < 2	14 (100.0)	15 (100.0)	29 (100.0)
Change in total mSASSS ≤ 0	12 (85.7)	14 (93.3)	26 (89.7)
Baseline ASDAS (2.1–3.5)	n = 30	n = 28	n = 58
Change in total mSASSS < 2	29 (96.7)	28 (100.0)	57 (98.3)
Change in total mSASSS ≤ 0	26 (86.7)	24 (85.7)	50 (86.2)
Baseline ASDAS > 3.5	n = 85	n = 87	n = 172
Change in total mSASSS < 2	73 (85.9)	76 (87.4)	149 (86.6)
Change in total mSASSS ≤ 0	60 (70.6)	64 (73.6)	124 (72.1)
Week 52 MRI in SPARCC spine ≥ 2	n = 21	n = 20	n = 41
Change in total mSASSS < 2	18 (85.7)	16 (80.0)	34 (82.9)
Change in total mSASSS ≤ 0	13 (61.9)	13 (65.0)	26 (63.4)
Week 52 MRI in SPARCC spine < 2	n = 34	n = 34	n = 68
Change in total mSASSS < 2	33 (97.1)	32 (94.1)	65 (95.6)
Change in total mSASSS ≤ 0	31 (91.2)	28 (82.4)	59 (86.8)
Week 16 MRI in SPARCC spine ≥ 2	n = 35	n = 40	n = 75
Change in total mSASSS < 2	29 (82.9)	36 (90.0)	65 (86.7)
Change in total mSASSS ≤ 0	24 (68.6)	30 (75.0)	54 (72.0)
Week 16 MRI in SPARCC spine < 2	n = 51	n = 49	n = 100
Change in total mSASSS < 2	49 (96.1)	45 (91.8)	94 (94.0)
Change in total mSASSS ≤ 0	44 (86.3)	40 (81.6)	84 (84.0)
Patients who normalized CRP at year 2 (≤ 5 mg/L)	n = 83	n = 87	n = 170
Change in total mSASSS < 2	73 (88.0)	77 (88.5)	150 (88.2)
Change in total mSASSS ≤ 0	61 (73.5)	67 (77.0)	128 (75.3)
Patients who did not normalize CRP at year 2 (> 5 mg/L)	n = 32	n = 28	n = 60
Change in total mSASSS < 2	29 (90.6)	27 (96.4)	56 (93.3)
Change in total mSASSS ≤ 0	25 (78.1)	21 (75.0)	46 (76.7)
No new syndesmophyte at year 2[a]			
Overall population	N = 115	N = 114	N = 229
	107 (93.0)	111 (97.4)	218 (95.2)
Patients with syndesmophytes at baseline	n = 49	n = 42	n = 91
	43 (87.8)	39 (92.9)	82 (90.1)
Patients without syndesmophytes at baseline	n = 65	n = 72	n = 137
	63 (96.9)	72 (100.0)	135 (98.5)

* Data are N (%) or n (%) for patients treated with IXE for 2 years (108 weeks). [a] From both of the selected readers at the same location (total IXE: 1 patient had no syndesmophytes at year 2). ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; IXE: ixekizumab; IXE Q2W: 80 mg IXE every 2 weeks; IXE Q4W: 80 mg IXE every 4 weeks; MRI: magnetic resonance imaging; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score.

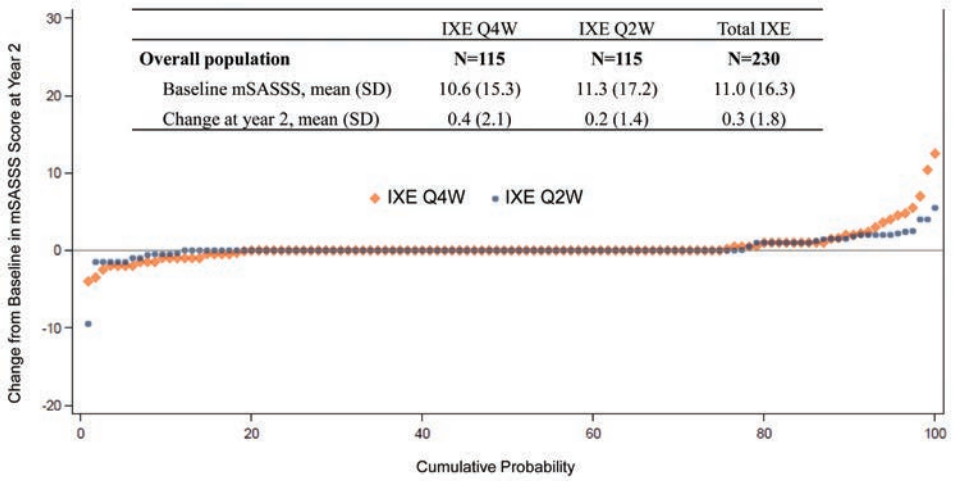

Figure 1. Cumulative probability plot for change from baseline in mSASSS at year 2 (observed). Patients were treated with IXE for 2 years (108 weeks). IXE: ixekizumab; IXE Q2W: 80 mg IXE every 2 weeks; IXE Q4W: 80 mg IXE every 4 weeks; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score.

Table 4. Predictors of structural progression at year 2 (multivariate final model).[a]

	Categorical or Continuous Variables	OR (95% CI)	*P*
Total IXE population, non-MRI measures (N = 228[b])			
Change in total mSASSS > 0			
Age	≥ 40 yrs vs < 40 yrs	2.97 (1.41–6.28)	0.004
Baseline syndesmophytes[b]	Yes vs no	2.31 (1.18–4.54)	0.02
Baseline HLA-B27	Positive vs negative	3.78 (1.04–13.75)	0.04
Sex	Male vs female	3.16 (1.01–9.86)	0.047
Baseline ASDAS state	> 3.5 vs (2.1–3.5)	2.26 (0.96–5.34)	0.06
Change in total mSASSS ≥ 2			
Baseline syndesmophytes[b]	Yes vs no	6.05 (2.11–17.30)	< 0.001
Tobacco	Ever vs never	2.89 (1.05–7.95)	0.04
Baseline ASDAS state	> 3.5 vs (2.1–3.5)	8.24 (1.05–64.51)	0.04
COAST-V, non-MRI and MRI measures[c] (N=109)			
Change in total mSASSS > 0			
Week 52 inflammation in SPARCC spine	≥ 2 vs < 2	2.91 (1.08–7.83)	0.03
Week 52 ASDAS	Continuous	1.97 (1.05–3.69)	0.04
Tobacco	Ever vs never	2.51 (0.92–6.90)	0.07
Change in total mSASSS ≥ 2			
Week 52 inflammation in SPARCC spine	≥ 2 vs < 2	4.46 (1.08–18.35)	0.04
COAST-V and COAST-W, non-MRI and MRI measures[d]			
Change in total mSASSS > 0 (N = 172)			
Age	≥ 40 yrs vs < 40 yrs	2.85 (1.21–6.70)	0.02
Baseline inflammation in SPARCC spine	≥ 2 vs < 2	2.56 (1.08–6.05)	0.03
Baseline mSASSS	Continuous	1.02 (1.00–1.04)	0.04
Change in total mSASSS ≥ 2 (N = 174)			
Baseline syndesmophytes[b]	Yes vs no	3.77 (1.23–11.52)	0.02
Baseline ASDAS state	> 3.5 vs (2.1–3.5)	6.20 (0.79–48.86)	0.08

[a] Patients were treated with IXE for 2 years (108 weeks). [b] From both of the selected readers at the same location (total IXE: 2 patients were not evaluable by both readers). [c] Patients who had SPARCC spine and SIJ MRI at baseline and week 52. [d] Patients who had SPARCC spine MRI at baseline and week 16. ASDAS: Ankylosing Spondylitis Disease Activity Score; IXE: ixekizumab; MRI: magnetic resonance imaging; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; SIJ: sacroiliac joint; SPARCC: Spondyloarthritis Research Consortium of Canada.

as a predictor of progression in this analysis. Other features were previously identified as predictors of radiographic spinal progression (ie, male sex, syndesmophytes, and smoking).[18] Ignoring the MRI measures (due to limitation of availability and small sample size), baseline syndesmophytes were predictors of structural progression by both cutoffs (change in total mSASSS > 0 and ≥ 2). Tobacco use was not a predictor for structural progression by total mSASSS > 0 but was a predictor for change in total mSASSS ≥ 2; however, it is difficult to interpret tobacco use in the prediction analysis because of the way the smoking status was collected in this study, where more information (eg, pack-year, duration) could be useful. Symptom duration and baseline mSASSS were significantly related to structural progression in the univariate model, but they were not identified as predictors in the final multivariate model when syndesmophytes (another sign of structural damage) were also included. In the final multivariate model, baseline syndesmophytes had a stronger association with structural progression. CRP was not significant in the univariate model for the cutoffs of 5 mg/L and 10 mg/L, which differed from previous publications where elevated CRP predicted future radiographic progression.[18,19] Further analysis also showed that CRP normalization at year 2 was not significantly related to radiographic progression from a logistic regression analysis with treatment and CRP normalization in the model. No difference was observed in the prediction analysis between IXE doses, which is consistent with the findings of the primary studies.[10,11,12] There may also be a window of opportunity for structural modification, after which disease could advance to be more complex where bone formation pathways are already activated and not amenable to intervention with currently approved therapies.[20]

Several limitations should be considered. Longer-term data beyond 2 years would be beneficial given the slow nature of structural progression in r-axSpA, but the challenge of longer-term follow-up is that progressive patient dropout may lead to more missing data, thereby complicating data interpretation. Patients who had imaging data outside of the prespecified windows were not included. While there were no differences in their baseline characteristics, patients who continued in the study were generally getting more benefit from treatment than those who discontinued. Although small numeric differences were observed between the IXE Q2W and IXE Q4W treatment groups, the study was not powered to look at those differences. There may be some unmeasured confounders that are unknown, but this study was not designed to address this question. Since very few patients had structural progression in the IXE-treated group and sample sizes by prior TNFi experience were relatively small, the study did not have enough power to detect a significant interaction of treatment group by prior TNFi experience. The analysis lacked a comparator cohort and, for ethical reasons, a placebo control to 2 years. While blinded to treatment groups, readers were aware that all patients received IXE, thus potentially leading to a reader bias in which readers may have scored change more conservatively.

In conclusion, the majority of patients treated with IXE for 2 years did not show radiographic progression, and the overall mean progression was low. We identified age ≥ 40 years, baseline syndesmophytes, HLA-B27 positivity, and male sex as potential predictors of progression at year 2. We also identified baseline spine inflammation as a predictor of progression at year 2 in patients with MRI data in the COAST-V and COAST-W studies and week 52 inflammation in SPARCC spine as a predictor of progression at year 2 in patients with MRI data in the COAST-V study.

ACKNOWLEDGMENT

We thank Emily Seem, MS (an employee of Eli Lilly and Company), for statistical data analysis, and Jiandong Ke, MS (an employee of Brightech International), for delivery of statistical analysis tables, listings, and figures (support for this assistance was funded by Eli Lilly and Company). Medical writing support was provided by Melody Pupols, PhD (an employee of Syneos Health), and support for this assistance was funded by Eli Lilly and Company. We also thank the investigators of COAST-V, COAST-W, and COAST-Y for their contributions and the patients who participated in these studies.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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