POS0918

EVALUATION OF SPINAL RADIOGRAPHIC PROGRESSION IN PATIENTS WITH RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS RECEIVING IXEKIZUMAB THERAPY OVER 2 YEARS

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Background: It is important to understand the potential effect long-term therapy with biologics can have on structural changes in the spine among patients with active radiographic axial spondyloarthritis (r-axSpA, ankylosing spondylitis).

Objectives: We examined radiographic progression in the spine among patients with active r-axSpA treated with ixekizumab, an IL-17A antagonist, for 2 years, and potential predictors of spinal radiographic progression.

Methods: Patients with active r-axSpA, biologic-naïve (COAST-V, NCT02696785) or with prior experience with a maximum of 2 TNF inhibitors (COAST-W, NCT02696798), received 80mg ixekizumab every 2 or 4 weeks for 2 years (108 weeks, of which 56 weeks were the COAST-Y extension study, NCT03129100). Mean change from baseline of modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (average score from 2 selected readers, blinded for time order) for patients treated with ixekizumab for 2 years with data at both baseline and year 2 is presented (N=230; 54% of total randomized patients). Non-progression is presented for all patients and subgroups based on TNFi-experience. Predictors were identified in multivariate logistic regression models with stepwise selection criteria of p-value <0.1. All data are observed.

Results: At baseline, patients (N=230) were predominately male (82%) with an average age of 43 years, mean symptom duration of 16 years, 52% were TNFi-experienced, mean (SD) ASDAS score was 4.0 (0.7), most were HLA-B27 positive (87%) and 40% had syndesmophytes (identified by both selected readers at the same location). Baseline mSASSS (SD) was 11.0 (16.3) and change from baseline at year 2 of treatment was 0.3 (1.8) (Table 1). The proportion of non-progressors (mSASSS change from baseline <2) over 2 years was 89.6% (total IXE [all patients]), 90.9% (biologic-naïve) and 88.3% (TNFi-experienced), and, if defined as mSASSS change from baseline ≤0, 75.7% (total IXE [all patients]), 78.2% (biologic-naïve) and 73.3% (TNFi-experienced) (Table 1). Predictors of structural progression at year 2 (mSASSS change >0) were age, baseline syndesmophytes, HLA-B27 status and gender (Table 1). Week 52 inflammation in MRI SPARCC spine was also identified as a predictor for structural progression at year 2 in a separate model for patients from COAST-V where MRI measures were available at baseline and Week 52 (N=109).

Conclusion: The majority of patients treated with ixekizumab for 2 years did not show radiographic progression, and the overall mean progression was low. Similar levels of non-progression were observed in biologic-naïve patients and patients previously exposed to TNFis. Predictors were generally consistent with previous studies.

Table 1. Spinal radiographic changes for patients with active r-axSpA treated with ixekizumab for 2 years

Change in mSASSS at year 2	All patients ^a N=230	Biologic-naïve N=110	TNFi-experienced N=120
Baseline mSASSS, mean (SD)	11.0 (16.3)	10.1 (15.5)	11.7 (17.0)
Change at year 2, mean (SD)	0.3 (1.8)	0.3 (2.0)	0.4 (1.6)
Change in total mSASSS <2, n (%)	206 (89.6)	100 (90.9)	106 (88.3)
Change in total mSASSS ≤0, n (%)	174 (75.7)	86 (78.2)	88 (73.3)
Multivariable logistic regression model			
Prediction for change in total mSASSS >0, OR (95% CI), p-value			
All patients^{a,b}			
	N=228		
Age (≥40 years vs. <40 years)	2.97 (1.41, 6.28)	p=0.004 ^c	
Baseline syndesmophytes ^b (yes vs. no)	2.31 (1.18, 4.54)	p=0.015 ^c	
Baseline HLA-B27 (positive vs. negative)	3.78 (1.04, 13.75)	p=0.044 ^c	
Gender (male vs. female)	3.16 (1.01, 9.86)	p=0.047 ^c	
Baseline ASDAS state (>3.5 vs. [2.1, 3.5])	2.26 (0.96, 5.34)	p=0.063	

^aCombined ixekizumab group of Q2W and Q4W patients with baseline and year-2 mSASSS data^bIdentified by both selected readers at the same location (2 patients were not evaluable by both readers)^cp<0.05Abbreviations: ASDAS=Assessment of Disease Activity, CI=confidence interval, IXE=ixekizumab, mSASSS=modified Stoke Ankylosing Spondylitis Spinal Score, OR=odds ratio, Q2W=every 2 weeks, Q4W=every 4 weeks, SD=standard deviation, TNFi=tumor necrosis factor inhibitor

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POS0919

BIMEKIZUMAB SHOWS SUSTAINED LONG-TERM IMPROVEMENTS IN PATIENT-REPORTED OUTCOMES AND QUALITY OF LIFE IN ANKYLOSING SPONDYLITIS: 3-YEAR RESULTS FROM A PHASE 2B STUDY

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Background: Bimekizumab (BKZ), a monoclonal antibody that selectively inhibits interleukin (IL)-17A and IL-17F, has demonstrated clinical efficacy and safety in patients with ankylosing spondylitis (AS) treated over a period up to 96 weeks.^{1,2}

Objectives: To report 3-year interim patient-reported outcomes (PROs) in patients with active AS treated with BKZ in a phase 2b dose-ranging study (BE AGILE; NCT02963506) and its open-label extension (OLE; NCT03355573).

Methods: BE AGILE study design has been described previously.¹ Patients treated with BKZ 160 mg or 320 mg every 4 weeks (Q4W) at Week 48 in BE AGILE were eligible for OLE entry. All OLE patients received BKZ 160 mg Q4W. Outcome measures are reported for the OLE full analysis set (patients who entered the OLE and had ≥1 dose of BKZ and ≥1 valid efficacy variable measurement in the OLE), and include: BASDAI, BASDAI50 responder rate, BASFI, fatigue (BASDAI Q1), morning stiffness (mean of BASDAI Q5+6), total spinal pain (numeric rating scale [NRS]), SF-36 PCS and MCS, and ASQoL. Missing data were imputed using multiple imputation (MI; based on the missing at random assumption) for continuous variables and non-responder imputation (NRI) for dichotomous variables.

Results: 262/303 (86%) patients randomised at BE AGILE study baseline (BL) completed Week 48 on BKZ 160 mg or 320 mg, of whom 255/262 (97%) entered the OLE (full analysis set: 254). From baseline to Week 48 in BE AGILE, BKZ-treated patients showed clinically relevant improvements in disease activity (BASDAI, BASDAI50), physical function (BASFI), fatigue, morning stiffness, spinal pain, and quality of life (SF-36 PCS and MCS, ASQoL) (Figure 1). Group-level improvements in all reported continuous efficacy measures exceeded published minimally important difference (MID), minimum clinically important improvement (MCII), and/or minimum clinically important difference (MCID) thresholds (Figure 1).^{3,4} Efficacy in all reported outcome measures was maintained or continued to improve from Week 48 to Week 144 or 156 (Figure 1).

Conclusion: BKZ treatment was associated with sustained and consistent efficacy in patients with active AS over 3 years, including patient-reported disease activity, physical function, fatigue, morning stiffness, spinal pain, and quality of life.

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Figure. Patient-reported outcomes over 3 years of BKZ treatment

Full analysis set (N=254). Weeks 0 and 48 refer to the BEAGLE and OLE baseline, respectively. All patients received BKZ 160 mg during the OLE after completing BKZ 160 mg or 320 mg in BEAGLE. SF-36 PCS, MCS and ASQoL were recorded to Week 144. Arrows indicate improvement; positive change from baseline represents improvement in SF-36 PCS and MCS; negative change from baseline represents improvement for all other outcomes. MID/MCII/MCID thresholds: BASDAI total score MCII = 0.7; fatigue (BASDAI Q1) MCID = 1.1; morning stiffness (mean of BASDAI Q5+6) MCID = 1.7; BASFI MCII = 0.4; total spinal pain MCID = 1.6; SF-36 PCS score MID = 2; ASQoL total score MCID = -2.1. SF-36 MID values are appropriate for groups with baseline mean T-scores of 30–40; for higher T-score ranges, MID values tend to be higher. MCII are not applied for improvement from baseline mean SF-36 T-scores >47, which are considered at least as good as the standard US population, hence no improvement is expected. Since mean SF-36 MCS at baseline was 54.3, the MID was not applied here. ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50: BASDAI 50% improvement from baseline; BASFI: Bath Ankylosing Spondylitis Functional Index; BKZ: bimekizumab; MCII: minimum clinically important improvement; MCID: minimum clinically important difference; MI: multiple imputation; MID: minimally important difference; NRI: non-responder imputation; NRS: numeric rating scale; OLE: open-label extension; SF-36 MCS: 36-Item Short-Form Survey Mental Component Summary; SF-36 PCS: 36-Item Short-Form Survey Physical Component Summary.

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POS0920

TARGETED SERUM PROTEOMIC ANALYSIS FOLLOWING UPADACITINIB TREATMENT IN ANKYLOSING SPONDYLITIS SHOWS ROBUST SUPPRESSION OF INNATE AND ADAPTIVE IMMUNE PATHWAYS WITH TISSUE REPAIR MODULATION

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Background: Upadacitinib (UPA), an oral JAK inhibitor selective for JAK1, demonstrated efficacy in patients with active ankylosing spondylitis (AS) with an inadequate response (IR) to nonsteroidal anti-inflammatory drugs (NSAID) therapy in the SELECT-AXIS 1¹ trial.

Objectives: To identify pathways modulated by UPA in AS patients with emphasis on those associated with response to treatment.

Methods: A subgroup of patients from the SELECT-AXIS 1 study, with available baseline and at least one follow up plasma sample during the placebo-controlled period, were selected for analysis (PBO, n= 65; UPA 15 mg QD, n=63). The levels of 92 inflammation related protein biomarkers (BioMs) were analyzed using the Olink® platform; change from baseline were expressed as Log₂ Fold Change; a repeated measure mixed linear model identified BioMs differentially modulated by UPA. Relationship between change in BioMs and change in clinical disease activity measures were derived using Pearson's correlation (ASDAS-CRP, BASDAI, and CRP) and Spearman's correlation (MRI Spine SPARCC). Pathway analysis was performed with Ingenuity® Pathway Analysis (Qiagen Inc.).

Results: Treatment with UPA 15 mg QD reduced the levels of BioMs associated with IFN, IL6, T Cells, M1 or "inflammatory" Macrophages, and Dendritic Cells (DC); and increased those of BioMs associated with tissue repair and hematopoiesis. The type of pathways, inferred *in silico* based on BM data, suggests that UPA exerts broad inhibitory activity directly on multiple JAK1-dependent upstream pathways (IL1, IL23, IL17, IL18, and TNFα), resulting in the inhibition of key functional pathways such as leukocyte activation and mobility, inflammatory response, and damage to connective tissue. Improvement in ASDAS-CRP, BASDAI, and MRI spine SPARCC correlated with increase in BioMs associated with tissue repair (FGF5, DNER [Delta/Notch Like EGF Repeat Containing]) and hematopoiesis (FLT3LG, and SCF/KITLG), while improvement in ASDAS-CRP and CRP correlated with decrease in CCL23, CSF1, IL-6, and MMP1; and reduction in only CRP correlated with decrease in IFN- and of TNFα-related BioMs (Data tables will be presented).

Conclusion: Treatment of NSAID-IR AS patients with UPA 15 mg QD resulted in the coordinated decrease in multiple BioMs associated with the innate and adaptive immune responses, and in the increase in BioMs generally associated with tissue repair and hematopoiesis. *In silico* pathway prediction indicates that treatment with UPA directly inhibits JAK1-dependent and indirectly JAK1-independent pathways, resulting in the down modulation of functional pathways related to inflammation and tissue damage which are known to be dysregulated in AS². Based on this observation and on the correlation of change in BioMs with change in clinical measures, we hypothesize that both increase in BioMs associated with tissue repair and hematopoiesis, and decrease in BioMs associated with inflammation may contribute to the clinical activity of UPA in AS patients.

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POS0921

EFFICACY AND SAFETY OF ACETEMETACIN IN THE TREATMENT OF 1215 ACTIVE ANKYLOSING SPONDYLITIS PATIENTS: DATA FROM A PROSPECTIVE COHORT MANAGED BY SMARTPHONE SPONDYLOARTHRITIS MANAGEMENT SYSTEM

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Background: Biological DMARDs have widely used in the treatment of AS in last two decades, but NSAIDs still serves as a cornerstone in the treatment.