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Clinimetric Validation of the Assessment of Spondyloarthritis International Society Health Index in Patients With Radiographic Axial Spondyloarthritis in Ixekizumab Trials

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ABSTRACT. ***Objective.*** To assess test-retest reliability, construct validity, known groups discrimination, and responsiveness of the Assessment of the SpondyloArthritis international Society Health Index (ASAS HI) to evaluate functioning, disability, and health in patients with radiographic axial spondyloarthritis (r-axSpA).

Methods. Data were generated from 2 randomized, placebo-controlled, active-controlled phase III ixekizumab studies (COAST-V, N = 341; COAST-W, N = 316). Assessments included the following: test-retest reliability (ie, intraclass correlation coefficients [ICCs] between ASAS HI scores at screening and baseline), construct validity (ie, Spearman correlation with standard r-axSpA outcome measures), known groups discrimination (ie, 1-way ANOVA comparing the ASAS HI with different disease activity categories, measured by the Ankylosing Spondylitis Disease Activity Score [ASDAS]), and responsiveness (ie, Spearman correlation between changes in the ASAS HI and changes in the Bath Ankylosing Spondylitis Functional Index [BASFI], the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], the ASDAS, and the Patient Global Assessment [PtGA] as well as ANOVA comparing changes in the ASAS HI with various responder categories).

Results. The ICC for test-retest reliability was 0.78 for COAST-V and 0.76 for COAST-W, indicating adequate agreement. Moderate-to-large correlations (r = 0.40-0.61) were observed between the ASAS HI and the BASDAI. Statistically significant differences (all $P < 0.001$) between mean ASAS HI scores were observed for subgroups based on ASDAS-defined disease activity categories at baseline and week 16. Moderate-to-large correlations existed between changes in the ASAS HI and the BASFI, BASDAI, ASDAS, and PtGA from baseline to week 16. The ASAS HI differentiated statistically ($P < 0.001$) between ASAS, BASDAI, and ASDAS response groups.

Conclusion. The ASAS HI demonstrated reliability, construct validity, known groups discrimination, and responsiveness in adults with r-axSpA in 2 clinical trials.

Key Indexing Terms: ankylosing spondylitis, reproducibility of results, spondyloarthropathy

Radiographic axial spondyloarthritis (r-axSpA), also known as ankylosing spondylitis (AS), is a chronic, inflammatory condition characterized by inflammation and structural damage in the axial skeleton, particularly in the sacroiliac joints and the spine. Patients with r-axSpA may also suffer from inflammation associated with pain in peripheral joints and entheses as well as from extramusculoskeletal manifestations, such as uveitis, psoriasis, and inflammatory bowel disease.[1] Typical symptoms of r-axSpA

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include chronic inflammatory back pain that results in reduced physical functioning in daily activities, participation in social roles, and satisfaction with life.[2-4]

The Assessment of SpondyloArthritis international Society Health Index (ASAS HI) is a patient-reported outcome measure that asks patients to indicate whether r-axSpA and its treatment affect a broad range of aspects of functioning, including social participation.[5] The term "Health Index" was preferred above the common term "health-related quality of life," as this term better indicates that these instruments assess impairments and limitations in aspects of health. The International Classification of Functioning, Disability, and Health core set for r-axSpA provided the underlying construct for the development of the ASAS HI.[6,7] The ASAS HI provides additional information for the subdomains of health in the Assessment of SpondyloArthritis international Society (ASAS)/Outcome Measures in Rheumatology (OMERACT) Core Outcome Sets for outcome assessments[8,9] and thresholds of meaning to better characterize the broader effects of treatment on patients.[5]

The psychometric properties of the ASAS HI were assessed in a convenience sample of patients and in cross-sectional international observational studies, and the results confirmed the ASAS HI as a valid, reliable, and responsive tool.[10] The ASAS HI, however, has not yet been validated within the context of a phase III clinical trial. The aim of the current analysis, therefore, was to assess the reliability, convergent and discriminant construct validity, known groups discrimination, and responsiveness of the ASAS HI in patients with active r-axSpA within 2 phase III clinical trials of ixekizumab (IXE): COAST-V and COAST-W.[11,12]

METHODS

Patient population. The phase III clinical trials included in these analyses for the ASAS HI validation were multicenter, randomized, double-blind, placebo-controlled, parallel-arm, 52-week studies designed to assess the efficacy and safety of IXE in patients with r-axSpA (COAST-V ClinicalTrials.gov Identifier: NCT02696785; COAST-W ClinicalTrials.gov Identifier: NCT02696798).[11,12] The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with local laws and regulations. All patients provided written informed consent. The study protocols and consent forms were approved by each site's institutional review board (IRB) or ethics committee. The main ethics committee was Schulman Associates IRB, Cincinnati, Ohio, USA (COAST-V IRB no. 201506061; COAST-W IRB no. 201506079). Full lists containing investigator and site names are provided in the primary manuscript supplements.[11,12]

IXE, a monoclonal antibody that targets interleukin 17A,[13] is currently approved for the treatment of active psoriatic arthritis, moderate-to-severe plaque psoriasis, active r-axSpA, and nonradiographic axSpA in multiple countries.

COAST-V. In the COAST-V trial (N = 341), patients were 18 years of age or older and were naïve to biologic disease-modifying antirheumatic drugs (DMARDs).[12] Patients had an established r-axSpA diagnosis and fulfilled the ASAS classification criteria for r-axSpA. Inclusion criteria required a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 4 or greater, a total back pain score of 4 or greater, and an inadequate response or intolerance to nonsteroidal antiinflammatory drug (NSAID) therapy. Patients were randomly allocated to treatment with 80 mg IXE once every 2 weeks (IXE 80 mg Q2W; n = 83), 80 mg IXE once every 4 weeks (IXE 80 mg Q4W; n = 81), 40 mg adalimumab [ADA] once every 2 weeks (ADA 40 mg Q2W; n = 90), or placebo (n = 87). Patients could continue to take stable doses of NSAIDs, protocol-defined conventional synthetic DMARDs, oral glucocorticoids, and opioids.

COAST-W. COAST-W (N = 316) and COAST-V trials had similar eligibility criteria; however, patients in the COAST-W trial had prior treatment with 1 or 2 tumor necrosis factor inhibitors (TNFi) and had to have discontinued 1 or both TNFi because of intolerance or inadequate response.[11] Patients were randomly allocated to the IXE Q2W (n = 98), IXE Q4W (n = 114), or placebo (n = 104) group. Patients could continue to receive sulfasalazine, methotrexate, prednisone, or equivalent, and NSAIDs at stable doses.

ASAS HI overview. The ASAS HI contains 17 items that assess the spectrum of functioning, disability, and health in patients with axSpA (eg, pain, emotional function, sleep, sexual function, mobility, self-care, and community life [ie, social roles/life]).[5,7] Each item is given a score of 1 ("I agree") or 0 ("I do not agree"), except for items 7 ("I have lost interest in sex") and 8 ("I have difficulty operating the pedals in my car"), which also offer a "not applicable/I do not want to answer" response option. Total scores range from 0 (good health) to 17 (poor health). For those patients who chose "not applicable," the sum score is analyzed based on 16 or 15 items, respectively. The ASAS HI instrument can be found at https://www.asas-group.org/clinical-instruments/asas-health-index/, where a validated version is available for multiple languages. The ASAS HI health status thresholds were defined in a data-driven approach and were prespecified in the analysis plan.

Additional outcome measures. The following validated outcomes were collected in both trials:

- BASDAI: this questionnaire has 6 items measured with a 0- to 10-cm numeric rating scale (NRS). The total score on a 0 to 10 scale is computed, and higher values represent higher disease activity.[14]
- Patient Global Assessment (PtGA): this is a single-item visual analog scale (VAS) ranging from 0 to 10, where higher scores indicate very active spondylitis.[15]
- Ankylosing Spondylitis Disease Activity Score (ASDAS): this composite score of disease activity is based on 3 questions from the BASDAI (ie, questions on back pain, peripheral joints, and duration of morning stiffness), the PtGA, and C-reactive protein (mg/L).[16-18]
- Bath Ankylosing Spondylitis Functional Index (BASFI): this questionnaire measures 10 items on a 0 to 10 VAS, where higher scores indicate worse function.[19]
- Spinal pain and night pain questions: 2 questions are measured on an NRS ranging from 0 ("no pain") to 10 ("most severe pain") regarding overall pain and night pain, respectively.[15]
- 5-level EuroQol-5 Dimension questionnaire (EQ-5D-5L): this is a questionnaire that includes 5 aspects of health, each rated on a Likert scale ranging from 0 to 5. An algorithm is available to convert resulting profiles on a scale representing the societal preferences for health (ie, health utility). On this scale, 0 is a health state equivalent to death; negative values indicate that the health state is valued as worse than death. The United Kingdom algorithm was applied in this study.[20]
- Medical Outcomes Study 36-item Short Form Health Survey (SF-36) version 2: this instrument of general health status calculates physical component summary (PCS) and mental component summary (MCS) scores ranging from 0 to 100.[21]

Most of the outcome instruments were completed at prespecified study visits: screening, baseline, and weeks 1, 2, 4, 8, 12, and 16. However, the ASAS HI and the SF-36 were administered at screening, baseline, and weeks 4, 8, and 16, and the EQ-5D was administered at baseline and at week 16.

Statistical analyses. Analyses were performed on an intent-to-treat population, which included all randomized patients. A modified baseline observation carried forward (mBOCF) approach was implemented for missing data imputation for continuous endpoints and for nonresponder imputation for categorical endpoints. SAS statistical software (version 9.4; SAS Institute Inc.) was used to conduct all analyses.

Distribution of response. The distribution of response focused on the percentage of missing items and the distribution of the total ASAS HI score, specifically floor and ceiling effects.

Reliability (test-retest). This analysis assessed whether the ASAS HI was reproducible over time in persons with stable high disease activity, who were defined as those with a difference of less than 1.1[22] in the BASDAI score between screening and baseline. An intraclass correlation coefficient (ICC) was calculated with stable patients (ie, those with a difference of less than 1.1 in the BASDAI score during the interval between screening and baseline assessment, which could be separated by 4 to 42 days). An ICC ≥ 0.7 indicated represent adequate agreement.[23]

Construct validity. Construct validity assessed whether relationships between measures conform to hypotheses based on logical relationships that should exist with other measures at baseline and at week 16. Prior to this analysis, we hypothesized the magnitude and direction of correlations; correlations were considered low if equal to or less than 0.30, moderate if greater than 0.30 and equal to or less than 0.50, high if greater than 0.50 and less than 0.80, and very high if equal to or greater than 0.80.[7] Spearman correlation coefficients were then calculated for the overall sample between the ASAS HI and the following clinical assessments: BASFI, BASDAI, spinal pain, EQ-5D-5L index, SF-36 MCS, SF-36 PCS, and PtGA. Cohen conventions were applied to evaluate absolute values of the correlation coefficients (large: > 0.5; moderate: 0.3 to ≤ 0.5, small: 0.1 to < 0.3; and insubstantial: < 0.1).[24]

Known groups discrimination. Known groups discrimination assessed whether the mean ASAS HI scores varied across subgroups defined by the ASDAS status scores, as well as by the BASDAI and the BASFI. A 1-way ANOVA with the Scheffe correction for post hoc pairwise comparisons was used to compare the mean differences of ASAS HI scores among ASDAS status groups at baseline and week 16. The subgroups were defined as follows: ASDAS less than 2.1 (low disease activity), ASDAS 2.1 to 3.5 (high disease activity), and ASDAS greater than 3.5 (very high disease activity). An overall *P* value from the ANOVA F test was reported to indicate whether the ASAS HI score was significantly different for at least 1 group comparison. *P* values were also reported for each group comparison. A 1-way ANOVA was used to compare the discriminant validity of the ASAS HI stratified by disease activity based on the BASDAI and the BASFI.

Responsiveness. Responsiveness, also referred to by OMERACT as clinical trial discrimination, measured the ability of the ASAS HI to detect change over time in a setting when change is expected. We evaluated the correlations of ASAS HI change scores from baseline to week 16 for the overall sample with change scores from baseline to week 16 for the BASDAI, BASFI, ASDAS, and PtGA using the mBOCF approach. In addition, a 1-way ANOVA compared the mean changes of the ASAS HI in the following subgroups:

1. Patients who did not achieve ASAS20 response vs those who achieved ASAS20 response but no ASAS40 response vs patients who achieved ASAS40 response.
2. Improvement of less than 50% vs 50% or greater of the BASDAI score from baseline (BASDAI50 nonresponder vs BASDAI50 responder, respectively).
3. Change in ASDAS: less than 1.1 (did not meet clinically important improvement [CII] criteria), 1.1 to less than 2.0 (met CII criteria, but not major improvement [MI] criteria), or 2.0 or greater (met ASDAS MI criteria).
4. Improvement in BASFI of less than 1.7 (median improvement) vs 1.7 or greater.
5. Improvement in PtGA of less than 2 (median improvement) vs 2 or greater.

In addition, the Cohen *d* effect size for the changes in the subgroups described above was calculated by dividing the mean change in the treatment group by the SD of the change in the placebo group. Effect sizes of 0.2 or greater, 0.5 or greater, and 0.8 or greater were considered small, moderate, and large, respectively.[24]

Threshold of meaning. To facilitate the interpretation of change in the ASAS HI, where the proportion of patients could reach good (ASAS HI ≤ 5.0), moderate (ASAS HI > 5.0 to < 12.0), or poor (ASAS HI ≥ 12.0) health,[7] we evaluated the proportion of patients reaching good health in the placebo vs treatment group at baseline and at week 16.

RESULTS

The patient characteristics in both the COAST-V and COAST-W trials have been presented previously.[11,12] A total of 341 patients were randomly assigned to treatment in COAST-V, and 331 (97.1%) of them completed 16 weeks of treatment. A total of 282 (89.2%) of the 316 patients randomly assigned to treatment in COAST-W completed 16 weeks of treatment. Baseline demographics and clinical characteristics for patients included in the current analysis are found in Table 1. Most patients were men (81.2% in COAST-V and 80.1% in COAST-W), and the mean ages were 41.7 and 46.1 years for COAST-V and COAST-W, respectively. Patients in COAST-W tended to report higher disease activity and more symptoms compared to patients in COAST-V.

Functioning and health were also impaired in our patient population, as measured by the ASAS HI. The mean ASAS HI scores were 8.1 (SD 3.6) in COAST-V and 9.7 (SD 3.6) in COAST-W, indicating that, on average, patients experienced moderate effects on health based on the ASAS HI scores.

Distribution of response. Numbers of missing items occurred between 2.3% and 10.1% across both trials. Floor effects (ie, the percentage of respondents who had the lowest possible total score) or ceiling effects (ie, the percentage of respondents who had the highest possible total score) of the ASAS HI in this analysis were acceptable: 0.3% and 1.2% at baseline and 3.5% and 0.6% at week 16 in COAST-V, and 0% and 3.2% at baseline and 2.2% and 1.6% at week 16 in COAST-W.

Reliability (test-retest). Of the patients who met the criteria for stable health in the reliability analyses, the mean BASDAI values at baseline were 6.7 (SD 1.4) in COAST-V (n = 288) and 7.4 (SD 1.3) in COAST-W (n = 272). The ICCs for the ASAS HI were 0.78 for COAST-V and 0.76 for COAST-W. These results indicated adequate agreement between 2 ASAS HI assessments in patients with stable active disease.[22]

Construct validity. Study results demonstrated adequate construct validity, as hypothesized (Table 2). Moderate-to-large correlations were observed between the ASAS HI and the BASDAI at baseline (COAST-V: r = 0.43; COAST-W: r = 0.40) and week 16 (COAST-V: r = 0.63; COAST-W: r = 0.58). Likewise, moderate-to-large correlations were observed between the ASAS HI and the BASFI, SF-36 PCS, SF-36 MCS, spinal pain, and the EQ-5D-5L UK index at baseline and at week 16, which reflected the patient assessment of physical health, mental health, and health-related quality of life. Across both studies, the observed correlations were generally aligned with the preset expectations at week 16 (the hypothesis was met in 6 out of 7 [85.7%] associations) but not at baseline (the hypothesis was met in only 1 out of 7 [14.2%] associations).

Table 1. Baseline demographics and clinical characteristics for actively treated patients in COAST-V and COAST-W.

	COAST-V, N = 341	COAST-W, N = 316
Age, yrs	41.7 (11.7)	46.1 (12.4)
Sex, male, n (%)	276 (81.2)	253 (80.1)
Race, n (%)		
American Indian or Alaska Native	14 (4.1)	12 (3.8)
Asian	107 (31.5)	40 (12.7)
Black or African American	0 (0)	5 (1.6)
Native Hawaiian or other Pacific Islanders	0 (0)	0 (0)
White	213 (62.6)	254 (80.6)
Multiple	6 (1.8)	4 (1.3)
BMI[a]	26.5 (4.9)	28.7 (6.2)
Duration of symptoms since ankylosing spondylitis onset, yrs	16.0 (10.3)	18.4 (11.1)
Duration of disease since ankylosing spondylitis diagnosis, yrs	7.7 (8.4)	11.6 (9.1)
CRP, mg/L	13.5 (17.1)	17.8 (26.6)
CRP > 5.0 mg/L, n (%)	219 (64.4)	207 (65.5)
ASDAS	3.8 (0.8)	4.1 (0.8)
BASDAI	6.7 (1.4)	7.4 (1.3)
Patient Global Assessment, numeric rating scale 0-10	7.0 (1.6)	7.9 (1.7)
Spinal pain, numeric rating scale 0-10	7.2 (1.5)	8.2 (1.4)
Spinal pain at night, numeric rating scale 0-10	7.0 (1.6)	7.7 (1.7)
BASFI	6.2 (2.0)	7.3 (1.7)
EQ-5D-5L, UK algorithm	0.5 (0.2)	0.4 (0.2)
SF-36 physical component summary	33.4 (8.0)	28.6 (7.9)
SF-36 mental component summary	48.7 (12.1)	45.6 (12.5)
ASAS HI	8.1 (3.6)	9.7 (3.6)
ASAS HI, range	0.0-17.0	2.0-17.0

Data are in mean (SD) unless otherwise indicated. [a] BMI is calculated as weight in kilograms divided by height in meters squared. ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; EQ-5D-5L: 5-level EuroQol-5 Dimension questionnaire; SF-36: 36-item Short Form Health Survey.

Known groups discrimination. The ASAS HI mean scores increased between subgroups with different states of disease activity, as defined by ASDAS status groups, at baseline and at week 16 ($P < 0.001$ for all comparisons; Figures 1A and 1B). For patients with high disease activity ($2.1 \leq$ ASDAS ≤ 3.5), the mean ASAS HI scores ranged from 7.0 to 8.1 at baseline and 6.6 to 7.4 at week 16, which was significantly higher compared to patients with low disease activity (ASDAS < 2.1) at both timepoints. For patients with very high disease activity (ASDAS > 3.5), the mean ASAS HI scores ranged from 8.7 to 10.2 at baseline and from 8.2 to 10.2 at week 16, which were significantly higher than the values in patients with moderate or high disease at both timepoints. Known groups discrimination of assessment of the ASAS HI was also demonstrated by significant differences among BASDAI and BASFI groups at baseline and at week 16 in COAST-V and COAST-W (Supplementary Table S1, available with the online version of this article).

Responsiveness. Moderate-to-large correlations were observed between the ASAS HI and the BASFI, BASDAI, ASDAS, and PtGA scores for changes from baseline to week 16 for both COAST-V and COAST-W (Table 3).

The responsiveness of the ASAS HI was supported by differentiating statistically ($P < 0.001$) between subgroups defined by ASAS20, ASAS40, BASDAI50, ASDAS status levels, and changes in the ASDAS, BASFI, and PtGA (Table 4). Cohen *d* effect sizes for the changes in the responder subgroups tended to be moderate (≥ 0.5) or large (≥ 0.8), indicating that ADA and IXE had a large effect on ASAS HI response.

Threshold of meaning. In COAST-V, 26.4% of placebo-treated patients, 25.6% of ADA 40 mg Q2W–treated patients, 33.3% of IXE 80 mg Q2W–treated patients, and 18.1% of IXE 80 mg Q4W–treated patients were in good health at baseline. At week 16, 39.5% of placebo-treated patients, 54.4% of ADA 40 mg Q2W–treated patients, 55.4% of IXE 80 mg Q2W–treated patients, and 58.0% of IXE 80 mg Q4W–treated patients were in good health. In COAST-W, 19.2% of placebo-treated patients, 13.2% of IXE 80 mg Q2W–treated patients, and 11.2% of IXE 80 mg Q4W–treated patients were in good health at baseline. Approximately 26.5% of patients in the placebo group were in good health at week 16; 23.7% and 35.1% of patients in the IXE treatment arms—IXE 80 mg Q2W and IXE 80 mg Q4W, respectively—were in good health at week 16.

Table 2. Correlation between ASAS HI and clinical endpoints at baseline and at week 16 for COAST-V and COAST-W.

	Baseline		Week 16	
	Spearman Correlation (95% CI)	Hypothesis/ Confirmation[a]	Spearman Correlation (95% CI)	Hypothesis/ Confirmation[a]
COAST-V, N = 341 at baseline; n = 340 at week 16				
BASDAI, n = 336 at baseline	0.43 (0.34 to 0.51)	High/no	0.63 (0.56 to 0.69)	High/yes
BASFI	0.46 (0.37 to 0.54)	High/no	0.61 (0.54 to 0.68)	High/yes
SF-36 PCS	−0.50 (−0.58 to −0.42)	High/no	−0.64 (−0.70 to −0.57)	High/yes
SF-36 MCS	−0.59 (−0.65 to −0.52)	Moderate/no	−0.57 (−0.64 to −0.49)	Moderate/no
Spinal pain	0.35 (0.25 to 0.44)	High/no	0.59 (0.52 to 0.65)	High/yes
PtGA	0.37 (0.27 to 0.46)	High/no	0.54 (0.46 to 0.61)	High/yes
EQ-5D UK index, n = 337 at week 16	−0.60 (−0.67 to −0.53)	High/yes	−0.62 (−0.68 to −0.55)	High/yes
COAST-W, N = 316 at baseline; n = 313 at week 16				
BASDAI, n = 313 at baseline	0.40 (0.30 to 0.48)	High/no	0.58 (0.50 to 0.65)	High/yes
BASFI	0.45 (0.35 to 0.53)	High/no	0.53 (0.45 to 0.61)	High/yes
SF-36 PCS	−0.41 (−0.50 to −0.31)	High/no	−0.64 (−0.70 to −0.57)	High/yes
SF-36 MCS	−0.64 (−0.70 to −0.57)	Moderate/no	−0.65 (−0.71 to −0.59)	Moderate/no
Spinal pain	0.39 (0.29 to 0.48)	High/no	0.54 (0.45 to 0.61)	High/yes
PtGA	0.31 (0.21 to 0.41)	High/no	0.47 (0.38 to 0.55)	High/no
EQ-5D-5L, UK algorithm, n = 307 at week 16	−0.64 (−0.70 to −0.57)	High/yes	−0.74 (−0.79 to −0.69)	High/yes

[a] Based on a priori hypotheses: correlations were considered moderate if > 0.30 and ≤ 0.50 and high if > 0.50 and < 0.80, according to Cohen.[24] ASAS HI: Assessment of SpondyloArthritis international Society Health Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; EQ-5D: EuroQol-5 Dimension questionnaire; MCS: mental component summary; PCS: physical component summary; PtGA: patient global assessment; SF-36: 36-item Short Form Health Survey.

DISCUSSION

This is the first study that we know of that reports clinical trial discrimination as a relevant part of ASAS HI validity. These analyses assessed the clinimetric properties of the ASAS HI in patients with active r-axSpA within 2 phase III clinical trials of IXE: COAST-V and COAST-W. These trials assessed different populations: 1 included patients with r-axSpA who were naïve to biologic DMARDs (COAST-V), and 1 included patients with r-axSpA who had experience with TNFi (ie, prior inadequate response or intolerance to TNFi; COAST W). Thus, clinimetric properties were evaluated for the 2 trials separately.

Floor and ceiling effects were limited and acceptable in our study. Test-retest reliability analyses indicated high levels of agreement among patients considered stable across 2 assessment periods and supported the reproducibility of the measure: ICCs for the ASAS HI were 0.78 for COAST-V and 0.76 for COAST-W. However, these values were lower than the ICCs of 0.87 and 0.98 reported previously among stable patients by Kiltz et al[7] and Di Carlo et al.[25] It is important to note that although patients were selected based on stable BASDAI scores at screening and baseline, patients were being treated with ADA or IXE because of high disease activity.

For construct validity, Kiltz et al[7] reported a high correlation between the ASAS HI and the PtGA, spinal pain at night, spinal pain, BASFI, ASDAS, BASDAI, EQ-5D, SF-36 MCS, and SF-36 PCS. Additionally, patients with greater disease activity had higher mean ASAS HI scores than those with lower disease activity. Likewise, Di Carlo et al[25] noted high correlations between the ASAS HI and the BASFI and strong correlations between the BASDAI and the EQ-5D. In COAST-V and COAST-W, except for the EQ-5D UK index, baseline hypotheses were not confirmed. At baseline, when patients had high disease activity, correlations were lower than expected. This might indicate that the ASAS HI is less sensitive to the detection of increasing disease activity or that overall health is influenced by unmeasured factors. At week 16, all hypotheses, except for those related to the SF-36 MCS (COAST-V and COAST-W) and the PtGA (COAST-W), were confirmed. The findings at week 16 are consistent with results reported previously by Kiltz et al[7] and Di Carlo et al.[25] Kiltz et al[7] and Di Carlo et al[25] assessed the clinimetric properties of the ASAS HI in stable patients; thus, similar results after 16 weeks of treatment in our study were anticipated.

For assessments of known groups discrimination, the mean ASAS HI of patients with high disease activity in our study was significantly higher, although numerically moderately higher, compared to that of patients with low disease activity. In addition, the mean ASAS HI for patients with very high disease activity was significantly higher than the values in patients with moderate or high disease activity.

For responsiveness, Kiltz et al[7] noted moderate-to-large effects with the ASAS HI after treatment with NSAIDs (standardized response mean [SRM] = −0.44), conventional synthetic DMARDs (SRM = −0.69), and TNFi (SRM = −0.85) in 1548 patients treated in clinical practice. It should be noted, however, that there was no comparator in the aforementioned study, and the current studies are large phase III studies that similarly observed moderate-to-large correlations with the ASAS HI after 16 weeks of treatment.

In general, the a priori hypotheses related to construct and known groups discrimination as well as the trial responsiveness hypothesis in our study were confirmed at week 16. These

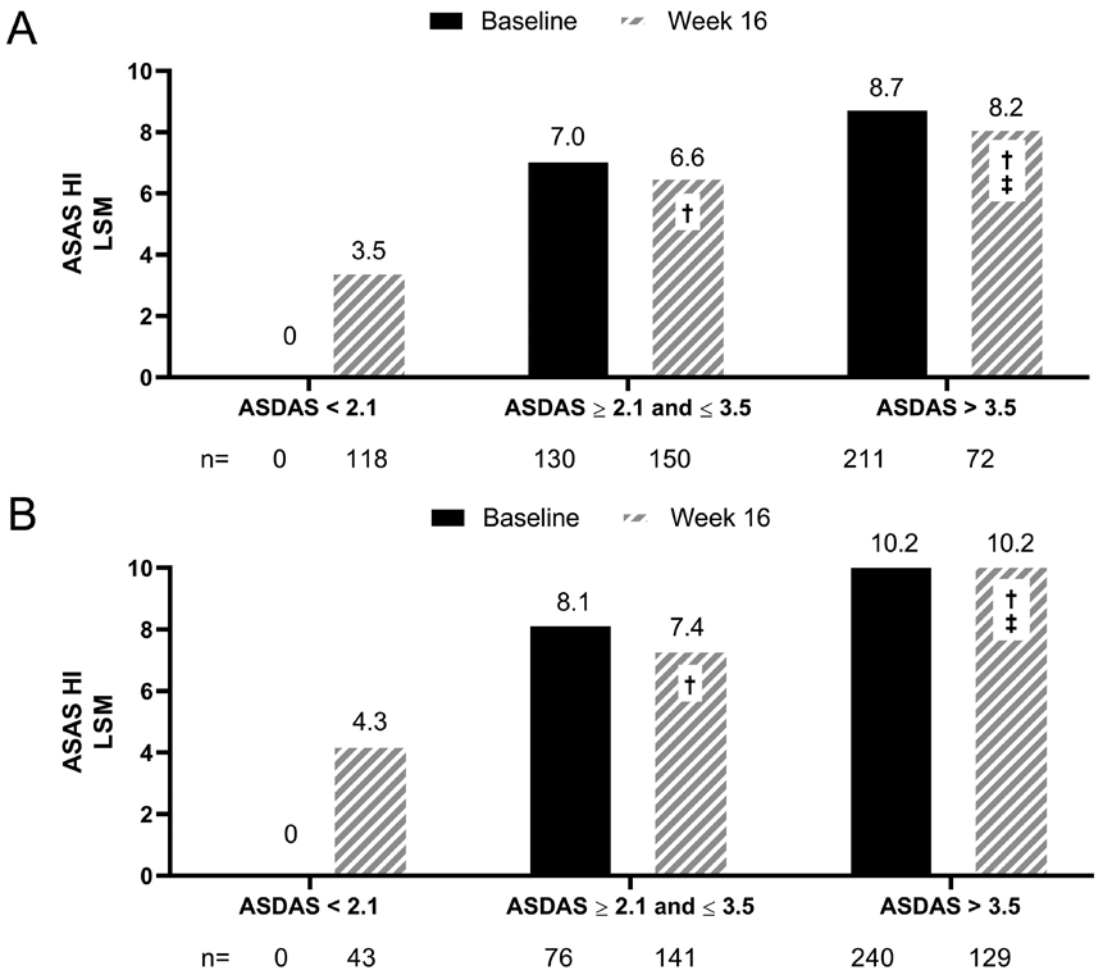

Figure 1. Discrimination of assessment among known groups of the ASAS HI (mBOCF) was demonstrated by significant differences among ASDAS categories at baseline and at week 16 in (A) COAST-V and (B) COAST-W studies. ASAS HI scores are listed at the top of each bar. * $P < 0.001$ vs ASDAS ≥ 2.1 and ≤ 3.5 at baseline. † $P < 0.001$ vs ASDAS < 2.1 at week 16. ‡ $P < 0.001$ vs ASDAS ≥ 2.1 and ≤ 3.5 at week 16. *P* values are based on 1-way ANOVA, with the ASAS HI score as the dependent variable and the ASDAS category as an independent variable. ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; LSM: least squares mean; mBOCF: modified baseline observation carried forward.

Table 3. Spearman correlation between changes from baseline at week 16 in the ASAS HI (mBOCF) with changes from baseline at week 16 in the BASDAI, BASFI, ASDAS, and PtGA (mBOCF) by treatment.

	Spearman Correlation (95% CI), Week 16 Overall
COAST-V, n = 340	
BASDAI	0.54 (0.46-0.61)
BASFI	0.49 (0.40-0.57)
ASDAS	0.51 (0.42-0.58)
PtGA	0.44 (0.35-0.52)
COAST-W, n = 313	
BASDAI	0.52 (0.44-0.60)
BASFI	0.45 (0.36-0.54)
ASDAS	0.51 (0.42-0.59)
PtGA	0.42 (0.32-0.51)

ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; mBOCF: modified baseline observation carried forward; PtGA: patient global assessment.

Table 4. ASAS HI change from baseline at week 16 among ASAS20/40, BASDAI50, ASDAS, BASFI, and PtGA response groups in good, moderate, or poor functioning by ASAS HI thresholds in COAST-V and COAST-W.

	ADA 40 mg Q2W			IXE 80 mg Q2W			IXE 80 mg Q4W		
	n	ASAS HI, mean change (SD)	Effect Size[a]	n	ASAS HI, mean change (SD)	Effect Size[a]	n	ASAS HI, mean change (SD)	Effect Size[a]
COAST-V									
ASAS response									
ASAS20 nonresponder	37	−1.0 (2.4)	0.1	26	−1.0 (2.2)	0.2	29	−0.7 (2.6)	0.3
ASAS20 responder but ASAS40 nonresponder	21	−2.0 (2.4)	−0.3	14	−1.9 (2.9)	−0.2	13	−1.0 (2.6)	0.1
ASAS40 responder	32	−4.2 (3.2)[b,c]	−1.0	43	−4.3 (3.1)[b,d]	−1.1	39	−3.8 (3.4)[b,d]	−0.9
BASDAI response									
BASDAI50 nonresponder	61	−1.6 (2.4)	−0.1	47	−1.6 (2.8)	−0.1	47	−1.0 (2.8)	0.1
BASDAI50 responder	29	−4.1 (3.4)[e]	−1.0	36	−4.5 (3.0)[e]	−1.2	34	−3.9 (3.3)[e]	−0.9
ASDAS improvement response									
< 1.1	41	−1.3 (2.6)	0.01	33	−0.9 (2.5)	0.2	31	−0.5 (2.6)	0.4
≥ 1.1 but < 2.0 (CII)	28	−2.2 (2.3)	−0.3	31	−3.1 (2.9)[f]	−0.7	26	−2.2 (2.8)[f]	−0.3
≥ 2.0 (MI)	21	−4.6 (3.5)[f,g]	−1.2	19	−5.8 (2.4)[f,g]	−1.8	24	−4.6 (3.4)[f,h]	−1.2
BASFI response									
Median improvement in BASFI < 1.7	44	−1.4 (2.6)	−0.02	36	−1.4 (2.9)	−0.01	35	−0.6 (2.6)	0.3
Median improvement in BASFI ≥ 1.7	46	−3.3 (3.1)[i]	−0.7	47	−4.0 (3.0)[i]	−0.9	46	−3.5 (3.3)[i]	−0.8
PtGA response									
Median improvement in PtGA < 2	34	−1.1 (2.2)	0.1	22	−0.8 (2.6)	0.2	28	−1.0 (2.8)	0.1
Median improvement in PtGA ≥ 2	56	−3.2 (3.2)[j]	−0.6	61	−3.6 (3.1)[j]	−0.8	53	−2.9 (3.4)[j]	−0.5
COAST–W									
ASAS response									
ASAS20 nonresponder	–	–	–	51	−0.4 (2.8)	0.1	59	−1.3 (2.7)	−0.2
ASAS20 responder but ASAS40 nonresponder	–	–	–	16	−0.5 (3.9)	0.1	26	−2.3 (3.1)[k]	−0.5
ASAS40 responder	–	–	–	30	−4.9 (3.9)[b,c]	−1.3	29	−3.2 (3.4)[b]	−0.8
BASDAI response									
BASDAI50 nonresponder	–	–	–	74	−0.9 (3.3)	−0.1	89	−1.4 (2.8)	−0.2
BASDAI50 responder	–	–	–	23	−4.8 (4.3)[e]	−1.2	25	−4.0 (3.2)[e]	−1.0
ASDAS improvement response									
< 1.1	–	–	–	49	−0.1 (3.1)	0.2	63	−1.1 (2.5)	−0.1
≥ 1.1 but < 2.0 (CII)	–	–	–	27	−2.1 (3.2)[f]	−0.4	33	−3.0 (2.9)[l]	−0.7
≥ 2.0 (MI)	–	–	–	21	−5.5 (3.9)[f,h]	−1.5	18	−3.4 (4.0)[l]	−0.8
BASFI response									
Median improvement in BASFI < 1.7	–	–	–	47	0.0 (2.5)	0.2	55	−1.3 (2.8)	−0.2
Median improvement in BASFI ≥ 1.7	–	–	–	50	−3.5 (4.2)[i]	−0.8	59	−2.7 (3.2)[m]	−0.6
PtGA response									
Median improvement in PtGA < 2	–	–	–	47	−0.6 (3.5)	0.04	52	−1.3 (3.0)	−0.2
Median improvement in PtGA ≥ 2	–	–	–	50	−3.0 (3.9)[j]	−0.7	62	−2.6 (3.1)[n]	−0.6

[a] Cohen *d* effect size is calculated as the difference in change in ASAS HI at week 16 from baseline between treatment and placebo divided by the pooled SD. Overall placebo patients across response groups are used. [b] $P < 0.001$ vs ASAS20 nonresponder. [c] $P < 0.001$ vs ASAS20 responder, but ASAS40 nonresponder. [d] $P < 0.05$ vs ASAS20 responder, but ASAS40 nonresponder. [e] $P < 0.001$ vs BASDAI50 nonresponder. [f] $P < 0.001$ vs ASDAS < 1.1. [g] $P < 0.001$ vs ASDAS ≥ 1.1 but < 2.0. [h] $P < 0.05$ vs ASDAS ≥ 1.1 but < 2.0. [i] $P < 0.001$ vs BASFI < 1.7. [j] $P < 0.001$ vs PtGA < 2. [k] $P < 0.05$ vs ASAS20 nonresponder. [l] $P < 0.05$ vs ASDAS < 1.1. [m] $P < 0.05$ vs BASFI < 1.7. [n] $P < 0.05$ vs PtGA < 2. ADA 40 mg Q2W: 40 mg adalimumab once every 2 weeks; ASAS: Assessment of SpondyloArthritis international Society; ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CII: clinically important improvement; IXE 80 mg Q2W: 80 mg ixekizumab once every 2 weeks; IXE 80 mg Q4W: 80 mg ixekizumab once every 4 weeks; MI: major improvement; PtGA: patient global assessment.

clinimetric properties of the ASAS HI support the use of the instrument in randomized controlled trials (RCTs) in addition to what has been demonstrated previously in clinical practice.[7,25,26] Health status has been recognized by patients, healthcare providers, and regulators as an important concept that should be measured in rheumatology RCTs, including those for r-axSpA, to assist patients in reporting how their disease and its treatment affect daily life. As emphasized by Kiltz et al,[27] the ASAS HI provides additional clinically useful information beyond core disease activity and response criteria traditionally used in such RCTs and, thus, allows a better characterization of the effects of treatment from the patient perspective by assessing the entire impact of the disease.

Recent developments regarding the integration of the ASAS HI into clinical trials have been made. Kiltz et al[28] demonstrated that contextual factors may influence ASAS HI results. An Environmental Contextual Factors Item Set was developed to complement the ASAS HI and understand the interaction between a health condition and contextual factors. Additionally, Molto et al[29] assessed the percentage of patients with axSpA who achieved a 30% or greater improvement in the ASAS HI score after 1 year of follow-up as a primary outcome in the Tight Control in Spondyloarthritis (TICOSPA) treat-to-target trial. The primary outcome was not met in the TICOSPA trial; however, additional studies are ongoing to determine the best differentiating ASAS HI cut-off for future studies.[29]

One limitation of this analysis was the lack of racial diversity, especially in COAST-W, as most patients were White. These findings, therefore, may not be generalizable to other groups.

The current analysis further demonstrated that the ASAS HI can discriminate between placebo and active treatment in a RCT to assess important patient-reported symptoms in adults with active r-axSpA.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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