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The Sensitivity to Change of the ASAS Health Index in an Observational Real-Life Cohort Study

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ABSTRACT. ***Objective.*** The Assessment of Spondyloarthritis international Society Health Index (ASAS HI) measures global functioning and health in patients with axial spondyloarthritis (axSpA) covering domains of physical, emotional, and social functioning. The main aim of this study was to investigate the sensitivity to change of ASAS HI in comparison with established variables of disease activity, function, and mental health.

Methods. Patients with axSpA from the disease register RABBIT-SpA with follow-up time of at least 12 months and available ASAS HI questionnaires were included. Patients received questionnaires addressing disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Ankylosing Spondylitis Disease Activity Score [ASDAS]), physical function (Bath Ankylosing Spondylitis Functional Index [BASFI]), mental health (5-item World Health Organization Well-Being Index [WHO-5]), and global functioning (ASAS HI). Standardized response means (SRMs) were calculated to compare the sensitivity to change of different variables.

Results. Six hundred and sixty-seven patients were included, 552 treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and 115 with conventional synthetic DMARDs and/or nonsteroidal antiinflammatory drugs (control group). Between baseline and month 12, the mean ASAS HI declined from 6.9 to 5.1 in the bDMARD group and from 5.9 to 5.6 in the conventionally treated group. In the bDMARD group, the SRM of ASAS HI was 0.52, compared to 0.59 for BASFI, 0.65 for WHO-5, 0.73 for BASDAI, and 0.90 for ASDAS. The following ASAS HI domains were most frequently affected: pain (78% agreed), maintaining body position (75%), and energy/drive (73%). In the patients receiving bDMARDs, there was an improvement in all items. In the control group, the largest improvement was seen in pain.

Conclusion. As expected, ASDAS and BASDAI as disease activity scores showed high sensitivity to change, whereas changes in physical function (BASFI), mental health (WHO-5), and the broader concept of functioning and health (ASAS HI) were moderate.

Key Indexing Terms: ankylosing spondylitis, cohort study, outcome measure

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Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterized by pain, stiffness, fatigue, and impairments in physical functioning.[1] The treatment of axSpA has been revolutionized by the introduction of tumor necrosis factor (TNF) inhibitors and more recently complemented by interleukin (IL)-17 inhibitors and Janus kinase inhibitors.[2-4] Nevertheless, many patients still suffer from severe impairment in their daily activities.[5]

The Assessment of Spondyloarthritis international Society Health Index (ASAS HI) was developed as a spondyloarthritis (SpA)-specific instrument to measure the health status in patients with SpA.[6-8] The ASAS/World Health Organization (WHO) International Classification of Functioning, Disability, and Health core set for axSpA served as model and underlying construct to develop the ASAS HI.[9] The ASAS HI consists of 17 patient-reported items addressing the categories of pain, emotional function, sleep, sexual function, mobility, self-care, community life, and employment. Thus, the ASAS HI addresses disease-specific aspects of physical, emotional, and social functioning, which are summarized by the term of global functioning.

Psychometric properties of the ASAS HI have been studied

in an observational cohort and in some clinical trials. There are 2 randomized controlled studies on treatment of patients with radiographic (r-axSpA) and nonradiographic axSpA (nr-axSpA) with ixekizumab in which the ASAS HI was assessed as secondary outcome variable.[10,11] Approximately 50% of patients with r-axSpA and nr-axSpA receiving ixekizumab achieved an improvement of ≥ 3 in the ASAS HI score at weeks 16 and 52, respectively. The ASAS HI was chosen as the primary outcome variable in the first treat-to-target (T2T) strategy trial in axSpA, the Tight Control in Spondyloarthritis (TICOSPA) study.[12]

The main aim of this analysis was to investigate the sensitivity to change of the ASAS HI in comparison with established variables of disease activity, function, and mental health. We aimed to describe to what extent the improvements of global functioning and health measured by the ASAS HI are comparable with improvements in disease activity measured either by the Ankylosing Spondylitis Disease Activity Score (ASDAS) or by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), functional capacity measured by the Bath Ankylosing Spondylitis Functional Index (BASFI), and mental health measured by the 5-item WHO Well-Being Index (WHO-5) in patients with axSpA treated with routine care. Thus, we analyzed the effect size measure standardized response mean (SRM), which allows comparisons between similar outcomes measured with different instruments on a standardized scale. The higher the value of the SRM, the higher the ability of a specific outcome variable to show a clinically relevant change.

METHODS

Data source. The German disease register RABBIT-SpA is a long-term observational cohort study that started in 2017.[13] Patients diagnosed by the treating rheumatologist either with axSpA or psoriatic arthritis who start a new treatment with a biologic disease-modifying antirheumatic drug (bDMARD), targeted synthetic DMARD, or conventional treatment (conventional synthetic [cs] DMARDs and/or nonsteroidal antiinflammatory drugs [NSAIDs]) are included. After enrollment, data are collected every 6 months covering physician- and patient-reported variables. The ASAS HI is assessed at the baseline visit and then annually.

Patients. Patients with axSpA with a follow-up time of at least 12 months and with available ASAS HI questionnaires at baseline and after 12 months were included in this analysis. We selected patients who remained on their treatment for at least 12 months after inclusion (completer analysis) and assigned them according to their treatment to the bDMARD or control group. Switch from the biooriginator to its biosimilar was not considered as treatment change and hence these patients were included and assigned to the bDMARD group. Patients in the control group were treated with csDMARDs and/or NSAIDs. Database closure was September 1, 2021. Prior to enrollment in RABBIT-SpA, all patients gave their informed consent. RABBIT-SpA received approval from the ethics committee of the Charité University Medicine, Berlin (#EA1/246/16).

Instruments. The ASAS HI contains 17 items with a dichotomous response option: "I agree" (1 point) and "I do not agree" (0 points). The sum score of the ASAS HI ranges between 0 (good functioning) and 17 (poor functioning). Global functioning is categorized based on thresholds as good (ASAS HI ≤ 5), moderate (ASAS HI > 5 and < 12), and poor (ASAS HI ≥ 12).[7] A change from baseline of ≥ 3 points (smallest detectable change [SDC]) in an individual patient is considered to be larger than measurement error and thus indicates "true change." In RABBIT-SpA, the validated German version of the ASAS HI is used.[8]

The following established instruments were used for comparison: ASDAS is a composite score of physician, patient, and laboratory variables and is used to assess disease activity.[14] BASDAI is a patient-reported score used to measure disease activity.[15] BASFI measures the impairment of physical function in axSpA.[16] The WHO-5 score is a depression screening tool consisting of 5 questions and is used as a patient-reported mental health instrument.

Statistical analysis. The parametric ANCOVA was used to compare BASDAI, ASDAS, BASFI, WHO-5, and ASAS HI changes from baseline to 1 year of observation for the bDMARD and the control group. Adjustment for possible differences was made for sex, HLA-B27 status, C-reactive protein (CRP) value at baseline, and bDMARDs before inclusion into the register as covariables. Changes over time are shown as adjusted mean scores (least squares mean) with 95% CI. To assess the sensitivity to change in ASAS HI from baseline to 12 months, the SRM was calculated as SRM = (ASAS HI mean baseline – ASAS HI mean 12 months)/ASAS HI SD of differences. In addition, SRM was evaluated for BASDAI, ASDAS, WHO-5, and BASFI.

A SRM < 0.40 was considered to represent a low effect, 0.40 to 0.79 a moderate effect, and ≥ 0.80 a large effect.[7] The SRMs were interpreted in these categories; further statistical analysis of the SRMs was not undertaken. In addition, for both groups, ASAS HI changes from baseline were calculated and proportions of patients who reached the SDC of ≥ 3.0.[7]

RESULTS

Description of the study sample. Of 988 patients with axSpA with a follow-up time of at least 12 months, 82 patients were excluded because of a missing baseline patient questionnaire and 54 patients because of missing treatment information during the 12-month follow-up period (Figure 1). Excluded patients did not differ significantly in baseline characteristics (sex, disease duration, HLA-B27, CRP) from included patients (data not shown). A further 185 patients were excluded from the analysis as a result of treatment switch within the first 12 months after enrollment (Figure 1).

The 667 remaining patients were included in the analysis, of whom 552 were treated with a bDMARD (bDMARD group) and 115 patients with csDMARDs and/or NSAIDs (control group) and did not change treatment during the 12-month follow-up period.

Baseline characteristics in bDMARD group compared to control group. Patients in the bDMARD group were slightly younger than the control group (mean age 44 yrs vs 47 yrs), the percentage of female patients was lower (40% vs 50%), and they had a longer duration of symptoms (12.9 yrs vs 7.7 yrs; Table 1). The percentage of patients with ≥ 3 comorbidities was higher in the bDMARD group (21% vs 8%). In the control group, 96% were bDMARD-naïve compared to 63% in the bDMARD group at inclusion into RABBIT-SpA.

Markers of disease status and physical function such as physician global assessment, BASFI, and number of affected joints were all higher in the bDMARD group compared to the control group.

Seventy-five percent of patients in the bDMARD group were treated with TNF inhibitors (adalimumab 30%, golimumab 21%, etanercept 12%, certolizumab 11%, infliximab 1%) and 25% of the patients with the IL-17 inhibitor secukinumab.

ASAS HI compared to disease activity, physical functioning,

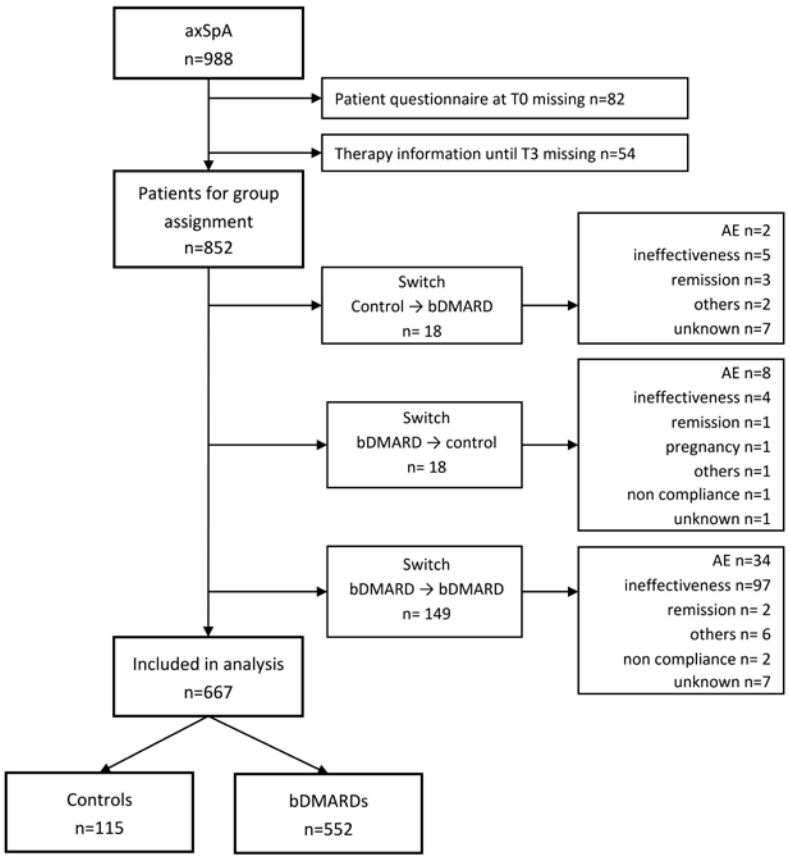

Figure 1. Flowchart of inclusion of patients. AE: adverse event; axSpA: axial spondyloarthritis; bDMARD: biologic disease-modifying antirheumatic drug; T0: baseline; T3: 12-month follow-up.

and mental health. In the bDMARD group, the mean (SD) ASAS HI declined between baseline and month 12 from 6.9 (3.5) to 5.1 (3.9) and in the conventional group from 5.9 (3.6) to 5.6 (3.9; Figure 2).

In the bDMARD group, the mean BASDAI, ASDAS, and BASFI decreased over the period of 12 months from 4.7 to 3.1, 2.9 to 1.8, and 3.9 to 2.8, respectively (Figure 2). The WHO-5 increased from 43.8 to 57.6. In the control group, the values decreased from 4.4 to 3.8 (BASDAI), 2.6 to 2.2 (ASDAS), and 3.2 to 3.0 (BASFI; Figure 2). The WHO-5 increased from 47.4 to 52.4.

For BASDAI, ASDAS, BASFI, WHO-5, and ASAS HI, changes from baseline between the 2 groups were compared (Table 2). Improvement in ASAS HI, taking the baseline status and covariates (see Methods) into account, was compared for the 2 groups using ANCOVA. ASAS HI at baseline (P = 0.001), CRP value at baseline (P = 0.02), and bDMARD treatment before inclusion to RABBIT-SpA (P = 0.0001) influenced ASAS HI change significantly and were used for adjusting, whereas HLA-B27 (P = 0.13) and sex (P = 0.17) did not.

The percentage of patients in good to very good health status (ASAS HI ≤ 5) increased in the bDMARD group from 34% at baseline to 56% at month 12, in contrast to the control group, which remained nearly unchanged with 49% at baseline and 51% at month 12.

The percentage of patients with an SDC ≥ 3 in the ASAS HI from baseline to follow-up at 12 months was 27% in the bDMARD group and 14% in the control group. This was a statistically significant difference between the groups (P = 0.01).

Sensitivity to change of ASAS HI. In order to analyze the sensitivity to change of the ASAS HI, we evaluated the SRM of ASAS HI separately for the 2 groups and in comparison with other instruments measuring disease activity, function, and mental health (Figure 3). The SRM of ASAS HI was higher in the bDMARD group than in the control group (0.52 vs 0.15, respectively). SRM for ASDAS (0.90), BASDAI (0.73), BASFI (0.59), and WHO-5 (0.65) also showed larger treatment effects in the bDMARD group than in the control group. SRMs for ASDAS, BASDAI, BASFI, and WHO-5 were 0.40, 0.29, 0.11, and 0.24, respectively, in the group of patients treated with conventional treatment.

ASAS HI single items. The 17 items of the ASAS HI are shown in the spider diagram in Figure 4. The following ASAS HI domains were most frequently affected: pain (78% of the patients agreed), maintaining body position (75%), and energy and drive (73%). In the patients treated with bDMARDs, there was an improvement in all items. In the control group, the largest improvement was seen in the pain item.

Table 1. Baseline characteristics of included patients.

	Control Group, n = 115	bDMARD Group, n = 552
Age, yrs	46.7 (13.1)	44.2 (12.8)
Female sex, n (%)	58 (50)	222 (40)
Symptom duration, yrs	7.7 (9.5)	12.9 (10.5)
Disease duration, yrs	4 (8)	7.6 (9.1)
HLA-B27, n (%)	65 (63)	413 (78)
CRP, mg/L	12.8 (20.1)	12.5 (17.3)
CRP positive ≥ 5 mg/L, n (%)	33 (51)	282 (57)
Enthesitis[a], n (%)	16 (14)	90 (16)
No. of sites with enthesitis (0-16)	3.3 (2.8)	2.7 (2.1)
Peripheral arthritis, n (%)	40 (35)	125 (23)
No. of joints with arthritis (0-44)	3.1 (1.7)	3.4 (4)
BMI, kg/m^2	27 (5.1)	26.9 (5.1)
BMI ≥ 30, n (%)	27 (24)	137 (25)
Comorbidities ≥ 3, n (%)	9 (8)	117 (21)
PGA (NRS 0-10)	4.2 (1.6)	5.7 (2)
BASDAI (0-10)	4.4 (1.9)	4.7 (2)
ASDAS	2.6 (1.1)	2.9 (1)
BASFI (0-10)	3.2 (2.2)	3.9 (2.4)
WHO-5 (0-100)	47.4 (22.1)	43.8 (20.2)
ASAS HI (0-17)	5.9 (3.6)	6.9 (3.5)
PtGA (NRS 0-10)	5.3 (2.3)	5.7 (2.3)

Values are mean (SD) unless otherwise indicated. [a] Enthesitis based on clinical judgement. 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; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; NRS: numerical rating scale; PGA: physician global assessment; PtGA: patient global assessment; WHO-5: 5-item World Health Organization Well-Being Index.

DISCUSSION

The main aim of this study was to investigate the sensitivity to change of the ASAS HI in comparison with established variables of disease activity, function, and mental health in patients with axSpA treated in routine care. Moreover, we compared these results with BASDAI, ASDAS, BASFI, and WHO-5. The sensitivity to change of an outcome variable is an important value to measure and interpret treatment effects. As expected, in the bDMARD group, ASDAS and BASDAI as disease activity scores showed high sensitivity to change. Mental health (WHO-5), function (BASFI), and the broader concept of health (ASAS HI) showed lower sensitivity to change, however still representing a moderate change. As expected, in control patients, none of the variables showed a considerable sensitivity to change because of lower treatment effect.

The sensitivity to change measured by the SRM naturally depends on the treatment. It has been established to use thresholds for the interpretation of the sensitivity to change with an SRM < 0.40 representing a low effect, 0.40 to 0.79 a moderate effect, and ≥ 0.80 a large effect.[17] In the publication on measurement properties of the ASAS HI, the SRM of the ASAS HI was 0.44 for NSAIDs, 0.69 for csDMARDs, and 0.85 for TNF inhibitors.[7] In our analysis, the SRM of the ASAS HI was 0.54 in bDMARD-treated patients and 0.19 in the control group. In a metaanalysis on the efficacy of TNF inhibitors in patients with r-axSpA and nr-axSpA, the effect size for BASDAI and BASFI in the randomized clinical trials that were included were compared.[18] Although the effect size standardized mean difference that was used in the metaanalysis differs slightly from our effect size measure SRM, BASDAI also showed a higher effect size than BASFI, which is similar to our results.

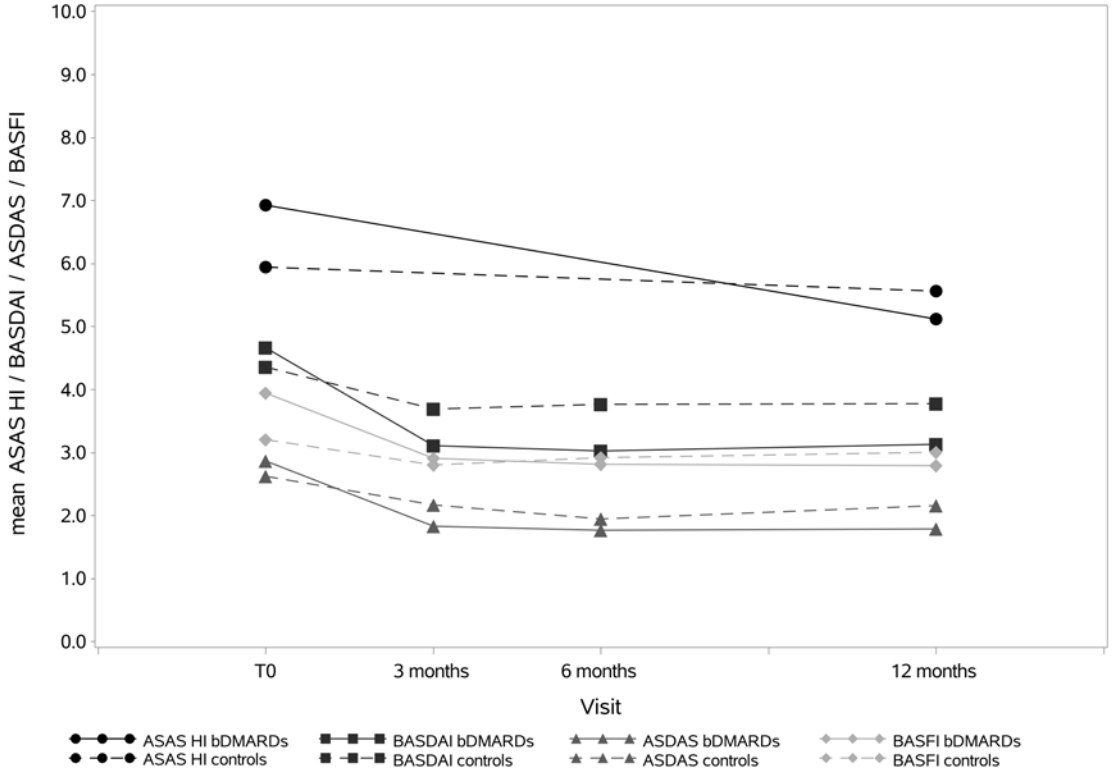

Figure 2. ASAS HI, BASDAI, ASDAS, and BASFI at T0 and after 12 months of follow-up. ASAS HI: Assessment of Spondyloarthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARD: biologic disease-modifying antirheumatic drug; T0: baseline.

Table 2. Changes from baseline unadjusted and adjusted for baseline status after 1 year of observation in RABBIT-SpA.

	Mean Changes From Baseline				Adjusted Mean Changes			
	bDMARD		Controls		bDMARD		Controls	
	Mean (SEM)	95% CI	Mean (SEM)	95% CI	Mean (SEM)	95% CI	Mean (SEM)	95% CI
BASDAI	1.5 (0.09)	1.28-1.65	0.6 (0.21)	0.16-1.01	1.5 (0.09)	1.28-1.65	0.7 (0.31)	0.06-1.27
ASDAS	1.1 (0.06)	0.94-1.18	0.3 (0.2)	−0.12 to 0.71	1.1 (0.05)	0.98-1.18	0.5 (0.2)	0.08-0.87
BASFI	1.1 (0.09)	0.91-1.26	0.3 (0.2)	−0.07 to 0.73	1.1 (0.09)	0.92-1.28	0.4 (0.3)	−0.2 to 0.99
WHO-5	−13.7 (0.99)	−15.61 to −11.71	−5.7 (2.25)	−10.15 to −1.2	−13.5 (1.04)	−15.53 to −11.44	−6.9 (3.35)	−13.43 to −0.26
ASAS HI	1.7 (0.16)	1.39-2.03	0.3 (0.27)	−0.24 to 0.85	1.7 (0.17)	1.37-2.04	0.4 (0.55)	−0.66 to 1.48

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; bDMARD: biologic disease-modifying antirheumatic drug; SEM: standard error of the mean; WHO-5: 5-item World Health Organization Well-Being Index.

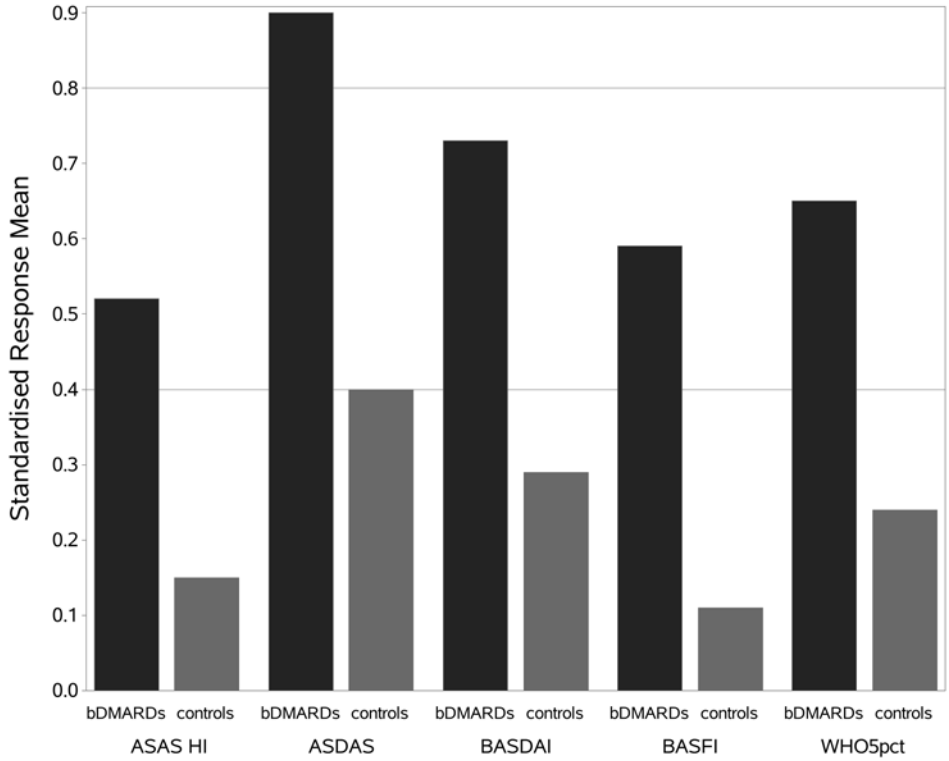

Figure 3. Standard response means of ASAS HI, ASDAS, BASDAI, BASFI, and WHO-5. ASAS HI: Assessment of Spondyloarthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARD: biologic disease-modifying antirheumatic drug; WHO-5pct: 5-item World Health Organization Well-Being Index percentage.

Although ASAS HI is a rather new outcome variable, it is becoming an important tool in axSpA research. For example, ASAS HI was chosen as primary outcome variable in the first T2T strategy trial in axSpA, the TICOSPA study.[12] The main outcome was defined as percentage of patients reaching ≥ 30% improvement in ASAS HI. The T2T strategy was numerically superior but not statistically significantly superior to usual care (47.3% vs 36.1%). Further, most secondary efficacy outcomes were in favor for T2T. The authors and others discussed the results and that the trial might have been underpowered. The outcome parameter ASAS-HI has also been questioned in this discussion.[19-21] Our data add to this debate in showing a smaller sensitivity to change for ASAS HI in comparison to ASDAS and BASDAI.

As expected in an observational cohort, patients treated with conventional therapies showed less severe disease compared to patients assigned to bDMARDs at inclusion into the register. After 1 year of treatment, the disease activity, functioning, and health status were similar in both groups, reflecting adequate treatment for both groups.

We showed that global functioning measured by ASAS HI improved in patients with bDMARDs, whereas it remained

Figure 4. Single-item analysis of ASAS HI at baseline (black lines) and after 12 months (gray lines) shown as spider diagram. Solid lines show the results for bDMARD group, dotted lines for the control group. ASAS HI: Assessment of Spondyloarthritis international Society Health Index; bDMARD: biologic disease-modifying antirheumatic drug.

stable in control patients. In addition, the percentage of patients with a good to very good health status increased in the bDMARD group, in contrast to the control group, which remained unchanged. The patients treated with bDMARDs showed greater improvement in ASDAS, BASDAI, BASFI, and ASAS HI compared to the patients in the conventional treatment group. Consistently, the percentage of patients with an SDC ≥ 3 was larger in the bDMARD group compared to the control group. As this is a completer analysis, these results cannot be interpreted in terms of effectiveness of the treatment groups.

In addition to our global evaluation of the ASAS HI, we analyzed the 17 single items of the ASAS HI score separately. The pattern of affirmed items is similar to a previous analysis of the performance of the ASAS HI in a cross-sectional single center analysis from Spain.[22] We compared the treatment groups and the change in the ASAS HI results between baseline and 12 months of follow-up. The treatment groups show large differences in the response pattern. Although the sum score declines in both groups, in the control group this change was mainly driven by an improvement in pain. However, in the bDMARD group, numerical improvements were seen in all 17 items. In the control group, most patients were treated with NSAIDs only. As is generally known, NSAIDs have a good analgesic capacity but their effect on other aspects that impair the health status of patients with axSpA such as mobility or emotional functions is minimal or nonexistent.

This is an analysis of an independent cohort analyzing the new ASAS HI questionnaire in a real-world setting. ASAS HI can easily be implemented in routine care; the results of the questionnaire can help the treating rheumatologist in understanding the health functioning of their patients with axSpA.

A limitation of this study is that the cohort, especially in the conventional group, is rather small. Nevertheless, this cohort is independent from the previously published studies analyzing ASAS HI. The comparison of the 2 treatment groups (bDMARDs vs conventional treatment) shows differences in baseline characteristics. These differences are typical for observational cohort studies and reflect confounding by indication. They were taken into account in the statistical analysis. Unfortunately, the radiographic status of the patients could not be included in the model because of the high portion (46%) of missing values in this variable. We focused on SRMs for different outcomes in patients staying on 1 treatment (either bDMARDs or conventional treatment) for a period of 12 months. This completer analysis approach hampers direct comparisons of the treatment groups. However, it allows analyzing the sensitivity to change of the outcome variables of interest.

We conclude that the ASAS HI is a useful tool for routine clinical care of patients with axSpA. In patients newly started on a bDMARD, improvement was seen in all 17 ASAS HI domains, whereas in conventionally treated patients this was only the case for the pain item. Since the ASAS HI covers broad concepts of physical and mental health, it is not surprising that its sensitivity to change is lower than that of measures of disease activity. However, changes in important domains of global health and burden of illness can be shown by this instrument and are of interest to the treating rheumatologist.

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