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U Kiltz [a,b,1,*], A Molto [c,d,1], C Lopez-Medina [e], M Dougados [c], D van der Heijde [f], A Boonen [g,h], F Van den Bosch [i], J Braun [j]

[a] Ruhr-Universität Bochum, Germany
[b] Rheumazentrum Ruhrgebiet, Herne, Germany
[c] Rheumatology Department, Cochin Hospital, Assistance Publique Hôpitaux de Paris, Paris, France
[d] ECAMO team, INSERM U-1153, Center for Research in Epidemiology and StatisticS (CRESS), Université Paris-Cité, Paris, France
[e] Rheumatology Department, Reina Sofia University Hospital, IMIBIC, University of Cordoba, Cordoba, Spain
[f] Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
[g] Dept. of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center+, Maastricht, the Netherlands
[h] Care and Public Health Research Institute (Caphri) Maastricht University, Maastricht, the Netherlands
[i] Department of Internal Medicine and Pediatrics, Ghent University and VIB Center for Inflammation Research, Ghent, Belgium
[j] Rheumatologisches Versorgungszentrum Steglitz, Berlin, Germany

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ABSTRACT

Objective: To test trial and longitudinal known group discrimination of thresholds of meaning for improvement and health states of the ASAS Health Index (ASAS HI) in patients with active axSpA treated in a randomized study.

Methods: Data from baseline and week 48 from the tight-controlled, treat-to-target trial TICOSPA study were used. The performance of different thresholds to assess change or health states of the ASAS HI were evaluated between arms and against changes in patients' relevant outcomes and various external responder criteria. Analyses were performed by comparing the mean values *t*-tests or proportion of responders of continuous and dichotomous external criteria respectively. Trial discrimination of the ASAS HI thresholds were assessed by odds ratios and Phi coefficient in a large number of potential ASAS HI thresholds. Differences in health states in relevant external outcomes between ASAS HI responders and non-responders was assessed by comparing the best performing improvement and state thresholds by using *t*-tests and chi-square, as appropriate. Missing data on outcomes was handled by non-responder imputation (NRI).

Results: All 160 patients had available ASAS HI data. Trial discrimination was larger for absolute ASAS HI change of $\geq$2.0, $\geq$2.5, and $\geq$3.0 points followed by ASAS HI 20 % improvement. Odds ratio ranged between 1.27 and 1.75 for absolute and between 1.0 and 1.64 for relative improvement outcomes. Longitudinal discrimination of ASAS HI improvement $\geq$30 % or $\geq$ 3.0 points had a larger reduction in patient global and disease activity and reached more often remission compared to patients with no significant improvement in global functioning. Patients who achieved ASAS HI $\leq$ 5.0 compared with patients who did not achieve such states were more likely to have ASAS partial remission, ASDAS inactive disease or ASDAS low activity at week 48.

Conclusions: The data-driven thresholds of the ASAS HI identified in a longitudinal observational setting perform well in the context of a randomized trial.

* Corresponding author at: Ruhr-Universität Bochum, Rheumazentrum Ruhrgebiet, Herne, Germany.
E-mail address: Uta.kiltz@elisabethgruppe.de (U. Kiltz).
[1] shared first authorship

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Background

Impact of the disease on functioning and health is selected as a mandatory domain in the Assessment of Spondyloarthritis international Society (ASAS) - Outcome Measures in Rheumatology (OMERACT) Core Domain Set for axial spondyloarthritis (axSpA). 0.[1, 2] The ASAS Health Index (ASAS HI) has been endorsed as the preferred measurement instrument to assess functioning and health in a clinical trial setting [1,2]. The construct 'functioning and health' includes health related impairments in physical, cognitive, mental and social activities [3]. It therefore reflects the impact of the disease on an individual's ability to live a normal fulfilling life.[3] The ASAS HI was developed several years ago as a SpA-specific patient-reported measurement instrument and addresses 17 aspects of functioning and health including pain, emotional functions, sleep and energy, sexual functions, mobility, self-care and community life [4-6]. The ASAS HI has been extensively validated and has shown to be feasible, truthful and discriminative according to the OMERACT Filter [4,7]. Discrimination included test-retest reliability, construct validity and known group discrimination and sensitivity to change, [4].

Thresholds of meaning have been developed for the ASAS HI but until now the performance has been tested less thoroughly. ASAS HI thresholds differentiating between health states of overall functioning and health have been identified: the cut-off of 5.0 separates patients with a good from those with a moderate health state, and the cut-off 12.0 differentiates patients with a moderate from those with a poor health state [4]. The threshold improvement has been determined by an absolute improvement of the ASAS HI of ≥3.0 - which represents the smallest detectable change between two different time points [4]. However, the discriminant capacity of ASAS HI thresholds has been tested in cohort studies on both, a cross-sectional and a longitudinal level, where change was expected [8-12]. However, the performance of the proposed status and change thresholds have not been evaluated in interventional trials to date.

Different measures of change in patients' relevant outcomes were studied in the tight-controlled, treat-to-target (T2T) trial TICOSPA, a pragmatic, prospective, cluster-randomised, controlled, open, 1-year trial that compared the effect of a T2T in axSpA with those of usual care (UC) [13]. The primary endpoint of this study was the percentage of patients with a relative improvement ≥30 % on the ASAS HI, the threshold of which was arbitrarily selected. The value of 30 % was chosen based on expert opinion considering this a meaningful improvement in global functioning. In that study, 160 bio-naive axSpA patients with an ASDAS ≥ 2.1 received either visits every 4 weeks applying a prespecified T2T algorithm based on treatment intensification until the target (i.e. ASDAS <2.1) was achieved or visits every 12 weeks and standard treatment at the rheumatologist's discretion. Improvement of the ASAS-HI by ≥30 % was reached by 47.3 % of patients treated based on the T2T strategy versus 36.1 % in the usual care arm. However, it was questioned whether the choice of 30% improvement was an optimal threshold and whether other thresholds would have discriminated better between trial arms.

Objectives

Using data from the TICOSPA study, we aimed to test trial and longitudinal known group discrimination of the thresholds of meaning for improvement and health states of the ASAS HI in patients with active axSpA starting disease modifying anti-rheumatic treatment. The performance of various thresholds to assess improvement (absolute (ranging between ≥1 to ≥5 points)) and relative (ranging between ≥20 and ≥90%)) as well as achievement of ASAS HI health states (ASAS HI ≤5.0 (good health state) and ≤12.0 (poor health state)) were evaluated in trial arms and against changes in other instruments and various external responder criteria at baseline and week 48.

Methods

Trial design

The following section briefly summarize the methodology of the TICOSPA study which was described in detail in the original publication [13]. Eligible patients diagnosed with axSpA by their rheumatologist, fulfilled the ASAS classification criteria for axSpA, and had high disease activity (e.g. Axial Spondyloarthritis Disease Activity Score (ASDAS) ≥2.1) were cluster-randomized into two arms: T2T versus UC per center. In the T2T arm a prespecified T2T strategy based on current international recommendations for axSpA was applied. Thus, if the target of low disease activity (i.e. ASDAS <2.1) was not met, intensification of treatment was executed by the investigator in order to reach the planned target, whereas in the UC arm, all treatment decisions were left to the investigator's discretion. Visits took place every 4 weeks in the T2T arm and every 12 weeks in the UC arm. All patients were followed up for 48 weeks. The primary outcome of TICOSPA was the percentage of patients achieving an improvement of ≥ 30 % in ASAS HI at the 48-week visit.

Selection of thresholds ASAS HI

To assess performance of thresholds for improvement, relative improvement at week 48 of ASAS HI by 20, 25, 30, 35, 40, 50, 60, 70, 80 and 90 %, as well as an absolute improvement by ASAS HI ≥1.0, 2.0, 2.5, 3.0, 3.5, 4.0, and 5.0 points were considered. To assess performance of previously defined threshold of ASAS HI, an ASAS HI threshold of ≤5.0 (good health state) and ≤ 12.0 (poor health state) points were considered to identify patients achieving a meaningful health status at week 48 [4].

External anchors

Several outcomes were available that could be used as external health outcomes to test longitudinal discrimination of the ASAS HI thresholds including: (i) change scores in ASAS40, BASDAI50 response, ASDAS improvement and mean changes in patient global, BASDAI, and) and (ii) external status scores (ASAS partial remission, ASDAS inactive disease or ASDAS low activity status) which were available at baseline and week 48 from the original trial.

Statistical analysis

All analyses were performed in the intent-to-treat (ITT) population. Missing data on outcomes was handled by non-responder imputation (NRI). Baseline demographic and disease characteristics were summarized using descriptive statistics. First, we analysed performance of all thresholds between treatment arms. Next, we analysed the performance of the previously defined thresholds of relative (ASAS HI ≥30 %) and absolute (ASAS HI ≥3 points) improvement between patients achieving or not achieving such a meaningful improvement (longitudinal known group discrimination) for a large number of external anchors. *Trial discrimination* of the extended list of ASAS HI thresholds were assessed by calculating the effect sizes (ES) as Phi Coefficient (calculated as $\varphi = \sqrt{(X^2 / n)}$, where: X^2 is the Chi-Square test statistic and n is the total number of observations. A value of Phi Coefficient of 0.1 is considered to be a small effect, 0.3 a medium effect, and 0.5 a large effect [14]. Odds ratios (OR) was analysed to facilitate interpretation of Phi Coefficient. Differences in health states in relevant external outcomes between ASAS HI responders and non-responders (longitudinal known group discrimination) was assessed by comparing the best performing improvement and state thresholds by using *t*-tests and chi-square, as appropriate.

Results

All 160 patients included in TICOSPA had complete data at baseline

and at week 48 and were analysed (82 were male (51.2 %), mean age 37.9 (11.0) years). The mean ASDAS at inclusion was 3.0 (0.7) and the mean ASAS HI 8.6 (3.7). At week 48, an improvement in ASAS HI of ≥ 30 % or ≥ 3.0 points was achieved by 56 (35 %) and 51 (31.9 %), respectively and an ASAS HI score ≤ 5.0 by 54 (33.7 %) patients.

Trial discrimination of ASAS HI

Table 1 refers to trial discrimination showing differences between intervention groups. The effect sizes in the treatment arms for all tested improvements and health states achieved in the ASAS HI are shown. OR ranged between 1.27 and 1.75 for absolute and between 1.0 and 1.64 for relative improvement outcomes. Overall, absolute improvement outcomes showed larger effect sizes than percentage changes outcome followed by status outcomes. The absolute ASAS HI improvement showed the highest effect size for ≥2.0, ≥2.5, and ≥3.0 followed by ASAS HI 20 % improvement but the differences were minor (Table 1). The differences in the performance of the various thresholds of meaning were relatively small.

Longitudinal known group discrimination

Patients with an improvement in ASAS HI of ≥ 30 % or ≥ 3.0 points had a larger reduction in mean patient global and disease activity scores and a higher chance to reach remission compared to patients not reaching this level of improvement in global functioning (Table 2). The Chi-square is higher for the ASAS HI of ≥ 30 % response measure for the BASDAI50, ASDAS CII and ASDAS MI. There are only marginal differences for the continuous change in patient global and BASDAI based on t-values. Patients who achieved ASAS HI ≤ 5.0 compared with patients who did not achieve such states were more likely to have ASAS partial remission, ASDAS inactive disease or ASDAS low activity at week 48 (Fig. 1).

Discussion

In this validation study using data from the TICOSPA trial, we show that different ASAS HI thresholds, including the relative improvement ≥30 % of the ASAS HI chosen in TICOSPA trial and the absolute ASAS HI change of ≥3.0 points defined in the ASAS HI international validation study, are able to discriminate between treatment arms and different patient groups. In this active comparator trial, absolute improvement scores of ASAS HI were generally superior to relative improvement scores.

Table 1
Comparison of thresholds by treatment groups (trial discrimination).

	Non-responder imputation at w48		Effect size measures	
	T2T	UC	Phi Coefficient	OR
ASAS HI 20 % improvement	56.9 %	45.8 %	0.11 [0–1.0]	1.56
ASAS HI 25 % improvement	51.4 %	41.7 %	0.10 [0–1.0]	1.47
ASAS HI 30 % improvement	43.1 %	34.7 %	0.09 [0–1.0]	1.43
ASAS HI 35 % improvement	40.3 %	31.9 %	0.09 [0–1.0]	1.43
ASAS HI 40 % improvement	37.5 %	31.9 %	0.06 [0–1.0]	1.28
ASAS HI 50 % improvement	29.2 %	22.2 %	0.08 [0–1.0]	1.45
ASAS HI 60 % improvement	26.4 %	18.1 %	0.10 [0–1.0]	1.64
ASAS HI 70 % improvement	16.7 %	12.5 %	0.06 [0–1.0]	1.41
ASAS HI 80 % improvement	13.9 %	11.1 %	0.01 [0–1.0]	1.28
ASAS HI 90 % improvement	9.7 %	9.7 %	0.00 [0–1.0]	1.00
ASAS HI improvement ≥1.0	66.7 %	61.1 %	0.06 [0–1.0]	1.27
ASAS HI improvement ≥2.0	55.6 %	41.7 %	0.14 [0–1.0]	1.75
ASAS HI improvement of ≥2.5	44.4 %	31.9 %	0.13 [0–1.0]	1.69
ASAS HI improvement of ≥3.0	41.7 %	29.2 %	0.13 [0–1.0]	1.72
ASAS HI improvement of ≥ 3.5	29.2 %	22.2 %	0.08 [0–1.0]	1.45
ASAS HI improvement ≥4.0	29.2 %	22.2 %	0.08 [0–1.0]	1.56
ASAS HI improvement ≥5.0	16.7 %	12.5 %	0.06 [0–1.0]	1.47
ASASHI, end of study, ≤12.0	87.5 %	80.6 %	0.09 [0- 1.0]	1.43
ASASHI, end of study, ≤5.0	37.5 %	33.3 %	0.04 [0, 1.0]	1.43

ASAS=Assessment of Spondyloarthritis International Society; ASAS HI=ASAS Health Index; OR=Odds Ratio; T2T=Treat-to-target; UC=usual care; w48=week48.

Regarding discrimination between treatment arms, the previously proposed absolute improvement of ≥3.0 ASAS HI points demonstrated the highest effect size. However, other tested thresholds also performed well but the level of the Phi coefficient were relatively low for all thresholds indicting moderate capacity to differentiate. Nevertheless, as the ASAS HI ≥3.0 was the smallest detectable change for this outcome, this seems to be the most appropriate threshold to be used in future trials [4].

In addition, the thresholds for improvement that discriminated best between treatment arms (trial discrimination) also discriminated between mean changes of the proportion of patients who improve in other clinical relevant outcomes (longitudinal known group discrimination). Both thresholds (absolute improvement of ≥3.0 and relative improvement of ≥30 % of ASAS HI) were able to discriminate between treatment arms. However, the improvement of ≥30 % of ASAS HI performed better if you give most weight to the ASDAS improvement scores and BASDAI 50 % Furthermore, our data demonstrate that patients who achieved ASAS partial remission, ASDAS inactive disease or ASDAS low activity at week 48 were more likely to have an ASAS HI ≤ 5.0 compared with patients who did not achieve such a favourable state.

Our findings on thresholds of meaning of the ASAS HI are relevant since global functioning is an important domain included in the ASAS-OMERACT core set for reporting data in axSpA RCTs and longitudinal observational studies in axSpA [1,2]. ASAS HI and Short Form Health Survey (SF-36) were identified to assess global functioning in the instrument selection phase prior to the definition of the core set [2]. Both SF-36 and ASAS-HI showed comparable construct validity, but ASAS-HI performed better on test–retest reliability [2,4]. Based on the OMERACT algorithm the ASAS HI was provisionally endorsed because data were scarce to fulfil the domain “discrimination” of the OMERACT filter. The need for more research on clinical trial discrimination is provided with this study.

Data on ASAS HI thresholds are also available based on observational trial data. Analysis of the German RABBIT registry showed that an improvement in ASAS HI of ≥ 3.0 at 12 months was present in 27 % of patients starting a bDMARD compared to 14 % of control patients [8]. Findings revealed that the standardized response mean of ASAS HI was higher in the bDMARD than in the control group (0.52 vs 0.15, respectively). Further, it was also shown that the percentage of patients reaching a good health state (ASAS HI ≤ 5.0) increased in the bDMARD group from 34 to 56 % at month 12. None of the observational studies tested the relative improvement score of ≥30 % of the ASAS HI.

The use of thresholds helps us to better understand the burden of disease on patients in routine clinical practice. Our data demonstrate that patients who achieved ASAS HI ≤ 5.0 compared with patients who did not achieve this low level were more likely to have absent to low disease activity. This is an accordance with published literature in which it has been unequivocally shown that patients achieving low disease activity were more likely to have lower scores of PRO and preserved physical function [15-17]. Data from the DESIR cohort showed a strong association between ASAS HI, disease activity and physical function were also confirmed by a clinical study from Germany [18,19].

Disease activity (e.g. ASAS40, BASDAI50 response, ASDAS scores) was chosen as the external health outcome to test longitudinal discrimination of the ASAS HI thresholds in the context of an intervention targeting disease activity, which means that we wanted to know if a change in disease activity is reflected in the ASAS HI.

This study has some strengths and limitations. The strength of our study is that the comparison of the thresholds is performed in a clinical trial with two active arms, the most challenging situation to show discrimination. Comparing thresholds in a placebo-controlled trial may show more clear differences. . Patient populations included in clinical

Table 2
Comparison of clinical outcomes and ASAS HI response at follow up (longitudinal known group discrimination).

	ASAS HI response ≥ 30 % improvement (NRI)			ASAS HI response ≥ 3 points improvement (NRI)		
	Achievement of ASAS HI response (n = 56)	No achievement of ASAS HI response (n = 104)	*Chi-square*	Achievement of ASAS HI response (n = 51)	No achievement of ASAS HI response (n = 109)	*Chi-square*
ASAS40 response at w48[#]	48.2 %	21.2 %	6.1	51.0 %	21.1 %	8.7
BASDAI50 at w48	71.4 %	28.8 %	25.1	68.6 %	32.1 %	17.4
ASDAS Major improvement (0 to 48 w)	23.2 %	6.7 %	7.6	23.5 %	7.3 %	6.9
ASDAS Clinically Important Improvement (0 to 48 w)	62.5 %	24.0 %	21.4	60.8 %	26.6 %	15.9
			T value			T value
Change in Patient Global (0 to 48 w)	−3.54 (2.77)	−1.81 (2.61)	3.7	−3.73 (2.85)	−1.80 (2.53)	4.0
Change in BASDAI (0 to 48 w)	−2.79 (2.09)	−1.42 (2.04)	3.9	−2.95 (2.17)	−1.40 (1.96)	4.2

ASAS40 =Assessment of Spondyloarthritis International Society 40 % improvement;ASDAS=Axial Spondyloarthritis Disease Activity Score;BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; NRI= non-responder imputation;SD=standard deviation;T2T=Treat-to-target; w48=week48.
#: dichotomous variables are presented as percentages and continuous variables are presented as mean (standard deviation).

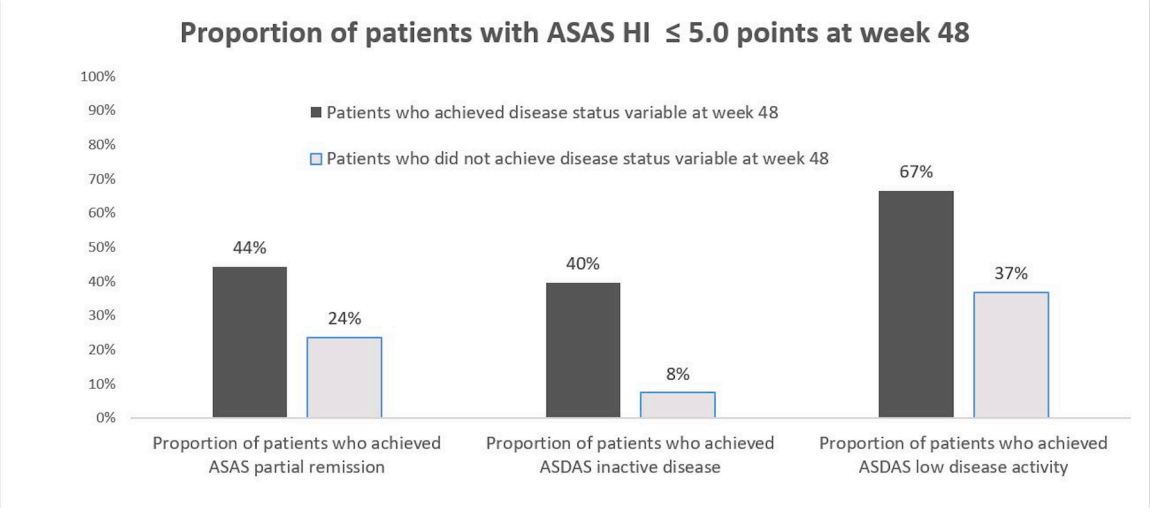

Fig. 1. Proportion of patients achieving a status of good global functioning at week 48.
The columns, grouped in three domains (ASAS partial remission, ASDAS inactive disease, ASDAS low disease activity, represent the proportion of patients who achieved or did not achieve a status of good global functioning at week 48.

trials are enriched with patients with high disease activity and therefore expected change and status scores will be different from that in other study settings. However, data on the psychometric properties of the ASAS HI investigated in other clinical trials showed similar trends in change and status scores of the ASAS HI [20-22].

Conclusion

The data-driven thresholds of the ASAS HI identified in a longitudinal observational setting perform well in the context of a randomized trial. A similar evaluation is needed in a placebo-controlled trial to be able to further validate the best outcome for the ASAS HI in a trial.

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Author contribution

All authors contributed to the design of the study and interpretation of the results.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: UK has received grant and research support and consultancy fees from AbbVie, Amgen, Biocad, Biogen, Chugai, Eli Lilly, Grünenthal, Janssen, MSD, Novartis, Pfizer, Roche, and UCB. UK is the chair of the quality of care Committee at EULAR. AM has received consulting fees from Abbvie, Lilly, BMS, Biogen, Celltrion, Pfizer, UCB, Janssen, Novartis and research grant from Biogen. AM is a Chair of the Epidemiology subcommittee from the EULAR Research Committee, DvdH has received consulting fees AbbVie, Argenx, BMS, Galapagos, Glaxo-Smith-Kline, Janssen, Lilly, Novartis, Pfizer, Takeda, UCB Pharma. Associate editor Annals Rheumatic Diseases, editorial board member Journal of Rheumatology and RMD Open, Advisor Assessment Axial Spondyloarthritis international Society and director of Imaging Rheumatology bv, CLM has received consulting/speaker fees AbbVie, UCB, Novartis, Lilly, Janssen and MSD. Research grants AbbVie, Lilly, UCB and Novartis, MD has received consulting fees from Pfizer, Abbvie, Novartis and UCB and research grants from Pfizer, Abbvie and UCB. Member of a DSMB of Galapagos. AB has received consulting fees AbbVie, Galapagos, Novartis, Pfizer, and UCB Pharma. Research grants AbbVie, Lilly. FvdB has received consulting fees AbbVie, Amgen, Fresenius, Galapagos, Janssen,

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Data availability

No data are available for this subanalysis

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