The Minimum Clinically Important Improvement and Patient-acceptable Symptom State in the BASDAI and BASFI for Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To establish cutoffs for the minimum clinically important improvement (MCII) and the patient-acceptable symptom state (PASS) for the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) in patients with ankylosing spondylitis (AS).

Methods. Patients with AS who started nonsteroidal antiinflammatory drugs were included. After 4 weeks, the PASS and the MCII were defined using external anchor questions (for the PASS, patients considering their condition of AS over the prior 48 h as "acceptable" forever; and for the MCII, those reporting moderate or slightly important improvement). Consistency of the MCII and PASS were tested according to HLA-B27 status, presence/absence of SpA extraarticular manifestations, age, sex, disease duration, and baseline BASDAI/BASFI score. The 75th percentile of the cumulative distribution was used to determine the MCII and PASS.

Results. In total, 283 patients from a multinational cohort were included. Overall cutoffs for the PASS were 4.1 in the BASDAI and 3.8 in the BASFI. Cutoffs for the MCII were 0.7 and 0.4 for the BASDAI and BASFI, respectively. Subgroup analyses revealed that disease duration and baseline BASDAI/BASFI were significantly associated with the PASS and MCII. In a subanalysis limited to patients with active disease (baseline BASDAI ≥ 4), the MCII was 1.1 for the BASDAI and 0.6 for the BASFI.

Conclusion. The conceptual viability of the PASS for the BASDAI is questionable because levels approach those required for the start of biological therapy. Because the MCII is less variable than the PASS, we propose its exclusive use, with cutoffs of 1.1/0.6 for the BASDAI/BASFI in patients with active disease. Because these values are based on a subset of the study population, we recommend confirmation in larger studies focused on patients with baseline BASDAI ≥ 4. (J Rheumatol First Release June 15 2016; doi:10.3899/jrheum.151244)

Key Indexing Terms:
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To evaluate outcome measures in rheumatic diseases, several assessments are used, including inflammatory activity, structural damage, and patient-reported outcomes (PRO). At the group level, a significant mean change in a particular score [for example, mean change in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] may not necessarily be meaningful at the patient level because the effect of these mean changes on the patient condition is difficult to assess[1,2,3,4].

To improve generalizability in the interpretation of the study results, the concepts of the minimum clinically important improvement (MCII) and the patient-acceptable symptom state (PASS) were developed[2,4,5,6] as outcome measures that represent what is important to the patient. Their advantage is the capacity to report results through a dichotomous variable as the proportion of patients who achieve improvement exceeding the MCII or those who achieve a predetermined level defined as the PASS[2,5]. These levels are defined according to the patient's perception of what is significant. The MCII signifies an improvement of relevance, or the minimal meaningful change at an individual level. In contrast to the MCII, which is defined as a measure of change, the PASS is considered a state, defined as the highest level of symptoms that a patient considers acceptable[6].

Several cutoff values for the MCII and the PASS were recommended in the Rheumatological Evaluation of Facts Leading to Excellent Treatment (REFLECT) study performed by Tubach, *et al*. The reported values were intended for general use across 5 rheumatic diseases [rheumatoid arthritis (RA), ankylosing spondylitis (AS), osteoarthritis (OA) of the hand, OA of the knee and/or hip, and back pain] and were established for generic PRO of pain and disease activity on a 0–10 numerical rating scale (NRS)[4]. Their recommended values were 2 for the MCII and 4 for the PASS (0–10)[4] across the aforementioned diseases. The MCII and the PASS values for disease-specific PRO have already been established in OA[7] and will be beneficial for the remaining aforementioned.

For AS, the disease-specific questionnaires commonly used are the BASDAI, which is a comprehensive self-administered instrument used to monitor disease activity[8], and the Bath Ankylosing Spondylitis Functional Index (BASFI), which is used to evaluate functional impairment[9]. A value of at least 4 on the BASDAI is considered active disease, warrants consideration for biologic therapy initiation, and is frequently used for inclusion in clinical trials[10,11,12].

Considering that the BASDAI and BASFI are most commonly used in AS, we aimed to establish values for the MCII and PASS for these instruments, and to test whether these values were stable across important patient characteristics, such as HLA-B27 status, presence/absence of spondyloarthritis extraarticular manifestations (SpA-EAM), age, sex, disease duration, and baseline BASDAI/BASFI scores.

MATERIALS AND METHODS

Study design and study population. The population was derived from the REFLECT study, which was a prospective multicenter, multinational, observational 4-week study with patients included from Australia, France, Italy, Lebanon, Morocco, Spain, and the Netherlands[13]. Patients signed informed consent before entering the study. To be considered for the REFLECT study, outpatients had to be > 18 years of age, experiencing pain from musculoskeletal disease (≥ 3 on a 0–10–point NRS), have a new nonsteroidal antiinflammatory drug (NSAID) prescribed for the next 4 weeks (either start or switch), and be able to understand the objectives of our study and complete questionnaires in the national language of their country[13]. The REFLECT study included patients with AS, RA, hand OA, hip and/or knee OA, or mechanical back pain. Our analysis was limited to the group of patients with AS, as classified by the modified New York criteria according to the local rheumatologist[13], and with back pain at baseline. Inclusion began at the start of a first NSAID or a switch from 1 NSAID to another, of which the treating rheumatologist determined the drug and dose.

Data collection. Data were collected at 2 visits (the baseline visit and the 4-week followup). At the baseline visit, data collected included demographics (age, sex, weight, and height), HLA-B27 status, and disease characteristics (disease onset and presence or history of SpA-EAM). At both visits, patients assessed their status through responses to generic and disease-specific PRO. These were measured using a 0-10–point NRS with 0 being the best score and 10 the worst. The disease-specific PRO used were the BASDAI[8] and BASFI[9]. Generic PRO were the patient's global assessment (PtGA) of disease activity and functional disability. PtGA was determined by asking the patients to consider their disease activity in the past 48 h. Functional disability asked patients to consider their difficulty in doing daily physical activities because of AS in the past 48 h. At the final visit, patients were asked to answer several external anchor questions. The anchor question for the MCII assessed the patient's perceived change from baseline on a 3-point Likert scale (improved, no change, or worse.) If patients reported improvement, they were asked how important this improvement was (very important, moderately important, slightly important, or not at all important). The anchor question for the PASS asked patients, "If you were to remain for the rest of your life as you were during the last 48 hours, would this be acceptable or unacceptable for you," with a dichotomous response of yes or no.

Outcome measures. The BASDAI and BASFI were the main outcomes. To determine the MCII and the PASS, we used an external anchoring method based on patient perspective, as previously described[5,6]. The calculation for the MCII was estimated by the absolute difference in the BASDAI or BASFI (final value – baseline value). For the BASDAI, patients were selected based on their response to the external anchor question regarding the general outcome measure for the PtGA of disease activity. For the BASFI, we

selected patients based on their response to the general outcome measure of functional disability. Patients included for the calculation of the MCII were those who indicated a slightly or moderately important improvement during our study to the external anchor question described above. For the PASS determination, patients were used who considered their state acceptable regarding the external anchor question previously described. Patients included for the BASDAI determination were those who considered their state acceptable regarding the general outcome measure for PtGA of disease activity. For the BASFI, patients were included who considered their state acceptable regarding the general outcome measure of functional disability.

Statistical analysis. Analyses were conducted using all patients with data available for both visits. Patients with missing data in 1 of the outcomes (general outcome measures or external anchor) were excluded from our analyses concerning this outcome. Data for patients lost to followup were excluded from our analysis. The 75th percentile approach was used for our analysis. This approach has been validated as a comparable alternative to the receiver-operation characteristic curve, and is much easier to derive, hence the decision to forgo dual analyses[5,6,14]. For the PASS, cutoff points were established corresponding to the 75th percentile of the distribution of the BASDAI/BASFI scores at the final visit in patients who considered themselves at an acceptable state. For the MCII, cutoff points were established corresponding to the 75th percentile of the distribution of change in BASDAI/BASFI scores for those patients who experienced an important improvement by the respective anchoring question. Values for the MCII corresponded to the magnitude of change in the negative direction, with cutoffs for change reported as absolute values in the negative direction. Ninety-five percent CI were constructed for descriptives and for values of the PASS and MCII. Subsequently, a stratified analysis of the PASS and MCII was performed to compare subgroups of sex (male vs female), age (above and below the median value of 41.4 yrs of age), HLA-B27 status (positive vs negative), disease duration (above and below the median of 11 yrs), country, and between those patients with/without a presence or history of SpA-EAM as defined by uveitis and/or psoriasis and/or inflammatory bowel disease. We also performed a restricted analysis for the MCII and PASS exclusively on those patients with a baseline BASDAI ≥ 4 to represent patients with active disease (active disease group) who were likely to receive treatment with biological agents in clinical practice[12] and those whom the MCII and PASS would be of most use for clinical practice. Statistical analysis was performed using SPSS version 22.

RESULTS

Baseline patient characteristics. A total of 283 patients with AS were included. Of these, 76% were men with a mean (SD) age of 43 (14) years and a mean disease duration of 13 (10) years (Table 1). Of those patients whose HLA-B27 status were available (n = 233), 78% were HLA-B27–positive. Patients with presence/history of at least 1 SpA-EAM consisted of 36% of the population. Mean (SD) baseline BASDAI and BASFI values were 5.0 (1.7) and 4.6 (2.3), respectively.

The PASS in BASDAI. Among the 178 patients included for analysis of the PASS in the BASDAI, the BASDAI value that cut off 75% of the BASDAI frequency distribution was 4.1 (95% CI 3.8–4.4; Table 2). The PASS in the BASDAI was stable across age, sex, HLA-B27 status, and history of SpA-EAM (Table 2). A difference was found between groups when stratified for disease duration according to the median value (11 yrs), with a higher PASS for patients with longer disease duration, 4.4 (95% CI 4.1–4.7) versus 3.5 (95% CI 3.1–3.9). A more notable difference between groups was observed when patients were stratified according to median baseline BASDAI score (4.9). This revealed a PASS of 4.8 (4.4–5.2) for baseline BASDAI ≥ 4.9 and a PASS of 3.1 (2.8–3.4) for baseline BASDAI < 4.9.

Table 1. Baseline characteristics. Values are n (%) unless otherwise specified.

Characteristics	n = 283
Male	214 (76)
Age, yrs, mean (SD)	42.8 (13.5)
Disease duration, yrs, mean (SD)	13.2 (9.7)
HLA-B27+	181 (78)*
Current or history of SpA-EAM	96 (36)
Acute anterior uveitis	61 (23)
Inflammatory bowel disease	21 (8)
Psoriasis	28 (11)
BASDAI, 0–10, mean (SD)	5.0 (1.7)
BASFI, 0–10, mean (SD)	4.6 (2.3)

* Data available from 231 patients [18% HLA-B27–negative and 50 patients (18%) with unknown HLA-B27 status]. SpA-EAM: spondyloarthritis extraarticular manifestations; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index.

Comparison of the active disease group (baseline BASDAI ≥ 4, n = 115) with those with a baseline BASDAI < 4 (n = 62) yielded a PASS of 4.5 (4.2–4.8) and 2.9 (2.5–3.3), respectively. In the subanalysis limited to patients with active disease (Table 3), the PASS in the BASDAI was stable across characteristics except disease duration (above and below the median), again with higher values for patients in the group above median disease duration, 4.8 (95% CI 4.4–5.2) versus 4.0 (95% CI 3.4–4.6).

The PASS in BASFI. Among the 166 patients included for analysis of the PASS in the BASFI, the BASFI value that cut off 75% of the frequency distribution was 3.8 (3.5–4.1; Table 2). The PASS in the BASFI was stable across age, sex, HLA-B27 status, and presence/history of Spa-EAM (Table 2). The PASS in the BASFI was influenced by stratification for disease duration (higher PASS for longer disease duration), and more so by baseline scores above and below the median value of 4.6 in the BASFI, which revealed a PASS of 5.8 (5.2–6.4) versus 2.9 (2.7–3.1), respectively. Comparison of the active disease group (baseline BASDAI ≥ 4, n = 103) with those below the threshold (n = 62) yielded a PASS of 4.6 (4.2–5.0) versus 2.5 (2.1–2.9), respectively. In the subanalysis limited to patients with active disease (Table 3), the PASS in the BASFI was stable across characteristics except disease duration, with values of 5.4 (4.8–6.0) versus 3.7 (3.1–4.3) in patients above and below the median disease duration, respectively.

The MCII in BASDAI. Among the 114 patients included for analysis of the MCII in the BASDAI, the BASDAI value that cut off 75% of the frequency distribution was 0.7 (0.4–1.0; Table 2). The MCII in the BASDAI was stable across age, sex, and HLA-B27 status (Table 2). Minor differences were

Table 2. Values for MCII/PASS for BASDAI/BASFI with stratified analysis. Numbers of the strata will not always add up to the total number of patients owing to missing values in the variable according to which patients are stratified. Continuous variables were stratified by the median value in their respective outcome measure: median baseline BASDAI = 4.9, median baseline BASFI = 4.6.

Variables	BASDAI				BASFI			
	PASS		MCII		PASS		MCII	
	n	Value (95% CI)	n	Value (95% CI)	n	Value (95% CI)	n	Value (95% CI)
Overall cutoff values	178	4.1 (3.8–4.4)	114	0.7 (0.4–1.0)	166	3.8 (3.5–4.1)	96	0.4 (0.2–0.6)
Stratified analysis								
Women	40	4.2 (3.5–4.8)	27	0.5 (0.0–1.0)	34	3.5 (2.7–4.3)	25	0.5 (0.0–0.9)
Men	136	4.1 (3.8–4.4)	87	0.7 (0.4–1.0)	130	3.8 (3.5–4.1)	70	0.4 (0.1–0.7)
HLA-B27+	121	4.1 (3.8–4.4)	75	0.6 (0.3–0.9)	117	3.8 (3.4–4.2)	57	0.4 (0.1–0.7)
HLA-B27–	28	4.1 (3.5–4.7)	15	0.5 (0.0–1.3)	23	3.5 (3.4–4.2)	16	0.7 (0.0–1.4)
SpA-EAM history, yes	60	4.2 (3.8–4.5)	41	1.0 (0.6–1.4)	58	4.1 (3.6–4.6)	35	0.4 (0.0–0.8)
SpA-EAM history, no	107	4.1 (3.8–4.4)	67	0.5 (0.1–0.9)	98	3.6 (3.2–4.0)	53	0.5 (0.1–0.9)
Age ≤ 41.4 yrs	79	4.0 (3.6–4.4)	53	0.7 (0.3–1.1)	74	2.9 (2.5–3.3)	49	0.4 (0.0–0.8)
Age > 41.4 yrs	91	4.2 (3.8–4.6)	60	0.5 (0.1–0.9)	85	4.8 (4.3–5.3)	46	0.5 (0.2–0.8)
Disease duration ≤ 11 yrs	82	3.5 (3.1–3.9)	52	0.8 (0.4–1.2)	83	3.2 (2.8–3.6)	51	0.5 (0.2–0.8)
Disease duration > 11 yrs	89	4.4 (4.1–4.7)	56	0.5 (0.2–0.8)	78	4.5 (4.1–4.9)	39	0.4 (0.0–0.8)
Baseline score < median	101	3.1 (2.8–3.4)	50	0.5 (0.2–0.8)	102	2.9 (2.7–3.1)	46	0.3 (0.1–0.5)
Baseline score ≥ median	76	4.8 (4.4–5.2)	64	1.2 (0.8–1.6)	64	5.8 (5.2–6.4)	50	0.6 (0.2–1.0)
Patients with baseline BASDAI ≥ 4	115	4.5 (4.2–4.8)	88	1.1 (0.8–1.4)	103	4.6 (4.2–5.0)	73	0.6 (0.3–0.9)
Patients with baseline BASDAI < 4	62	2.9 (2.5–3.3)	26	1.2 (0.8–1.6)	62	2.5 (2.1–2.9)	23	1.0 (0.6–1.4)

MCII: minimum clinically important improvement; PASS: patient-acceptable symptom state; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; SpA-EAM: spondyloarthritis extraarticular manifestations.

Table 3. MCII/PASS for BASDAI/BASFI restricted to patients with baseline BASDAI ≥ 4. Numbers of the strata will not always add up to the total number of patients owing to missing values in the variable according to which patients are stratified.

Variables	BASDAI				BASFI			
	PASS		MCII		PASS		MCII	
	n	Value (95% CI)	n	Value (95% CI)	n	Value (95% CI)	n	Value (95% CI)
Patients with baseline BASDAI ≥ 4, n = 177	115	4.5 (4.2–4.8)	88	1.1 (0.8–1.4)	103	4.6 (4.2–5.0)	73	0.6 (0.3–0.9)
Women	26	4.3 (3.5–5.1)	23	1.2 (0.6–1.8)	22	4.2 (3.2–5.2)	20	0.6 (0.0–1.2)
Men	88	4.6 (4.2–5.0)	65	1.0 (0.6–1.4)	80	4.6 (4.2–5.0)	52	0.5 (0.1–0.9)
HLA-B27+	75	4.6 (4.2–5.0)	54	1.0 (0.6–1.4)	69	4.7 (4.1–5.3)	40	0.5 (0.1–0.9)
HLA-B27–	17	4.5 (3.5–5.5)	22	1.1 (0.3–1.9)	14	3.6 (2.4–4.8)	12	1.0 (0.2–1.8)
Age ≤ 41.4 yrs	48	4.4 (4.0–4.8)	39	0.9 (0.5–1.3)	40	3.3 (2.7–3.9)	37	0.8 (0.4–1.2)
Age > 41.4 yrs	60	4.8 (4.4–5.2)	48	1.1 (0.7–1.5)	57	5.3 (4.7–5.9)	35	0.3 (0.0–0.7)
SpA-EAM history, yes	43	4.5 (3.9–5.1)	31	1.1 (0.7–1.5)	40	4.6 (4.0–5.2)	25	0.7 (0.3–1.1)
SpA-EAM history, no	66	4.7 (4.3–5.1)	52	0.8 (0.4–1.2)	58	4.8 (4.2–5.4)	42	0.5 (0.1–0.9)
Disease duration ≤ 11 yrs	50	4.0 (3.4–4.6)	39	1.2 (0.6–1.8)	50	3.7 (3.1–4.3)	38	0.7 (0.3–1.1)
Disease duration > 11 yrs	59	4.8 (4.4–5.2)	44	0.8 (0.4–1.2)	49	5.4 (4.8–6.0)	31	0.5 (0.1–0.9)

MCII: minimum clinically important improvement; PASS: patient-acceptable symptom state; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; SpA-EAM: spondyloarthritis extraarticular manifestations.

observed with stratification for disease duration (higher value for patients with shorter disease duration), with the largest effect on the MCII observed when stratified for baseline BASDAI score above and below the median yielding values of 1.2 (0.8–1.6) versus 0.5 (0.2–0.8), respectively. Comparison of the active disease group (baseline BASDAI ≥ 4, n = 88) with those below the threshold (n = 26) yielded similar results with a 1.1 (0.8–1.4) versus 1.2 (0.8–1.6), respectively. In the subanalysis limited to patients with active disease, the MCII was stable across patient characteristics (Table 3). Disease duration maintained a marginal influence on the MCII with higher values for patients with shorter disease duration.

The MCII in BASFI. Among the 96 patients included for analysis of the MCII in the BASFI, the BASFI value that cut off 75% of the BASFI distribution of those subjects who met criteria for MCII was 0.4 (0.2–0.6; Table 2). The MCII in the BASFI was stable across age, sex, HLA-B27 status, presence/history of SpA-EAM, and disease duration (Table 2). The only variable influencing the MCII in the BASFI was baseline BASFI, yielding values of 0.6 (0.2–1.0) in the group of baseline BASFI ≥ 4.6 and 0.3 (0.1–0.5) in the group

baseline BASFI < 4.6. Comparing the active disease group (baseline BASDAI ≥ 4, n = 73) with those below the threshold (n = 23), the MCII was 0.6 (0.3–0.9) versus 1.0 (0.6–1.4).

In the subanalysis restricted to patients with active disease, the MCII for the BASFI was stable (Table 3).

Country effect. The numbers of patients who met the criteria for the PASS/MCII analysis were 72/40 in France, 14/20 in Morocco, 11/9 in Italy, 8/2 in the Netherlands, 48/29 in Spain, 21/19 in Lebanon, and 4/2 in Australia. These were insufficient numbers for an appropriate comparison across countries. Visual inspection of the raw data did not identify any substantial differences in the variables for the PASS or MCII in either the BASDAI or BASFI.

DISCUSSION

The MCII and PASS are used in clinical trials to better translate group-level results to the individual patient-level effects[1,3,4]. Although both measures describe the patient condition, each concept is unique and distinguishable from the other.

The PASS expresses a state of attainment for a patient, defined as "acceptable for life" or "acceptable for a given period of time." Values for the PASS vary by scale and across disease processes. For example, the PASS values in the BASDAI/BASFI recommended by Maksymowych, *et al*[15] are lower than ours, which reflects lower patient expectations in our population with regard to state attainment. Differences in time frame for defining the PASS between studies may explain the inconsistency, because they defined PASS as "satisfactory for the next few months," whereas we defined PASS as "acceptable state for the rest of your life." Another study evaluating the PASS within a Moroccan population[16] reported values for the PASS similar to ours; however, their description of PASS differed. They did not distinguish between global and functional impairment and did not delineate an associated time frame for the duration of the PASS. If the PASS is to become a universal concept for defining interventional success, a standard anchor question for meaningful comparison of results across groups should be established mainly regarding duration of an acceptable state. We believe that the definition of the PASS implies a state without change that can be extrapolated to mean for the rest of one's life.

Whereas the PASS defines a state, the MCII describes a degree of improvement rather than change, because the amount of change considered clinically important by patients is not the same in the case of worsening versus improvement[17,18,19]. In AS, the concept of the MCII was previously described by Pavy, *et al* as the minimum clinically important difference (MCID)[3]. This study examined the MCID in the BASDAI and BASFI and recommended values of 10 mm on a 100-mm visual analog scale for the MCID in the BASDAI and 7 mm for the MCID in the BASFI[3]. These are nearly identical to our results when transformed onto a 0–10 NRS. Unlike our study, Pavy, *et al* found no difference in the MCID according to baseline scores despite similarities in the baseline BASDAI/BASFI scores between studies. Etiology for this difference is unclear, but perhaps explained by a more homogeneous population with longer disease duration (mean duration of 20.7 yrs in their study compared with a median of 11 yrs in ours). For stability, our estimates for the PASS and MCII in both the BASDAI and BASFI were not affected by various patient characteristics (age, sex, HLA-B27 status, SpA-EAM). On the contrary, disease duration and baseline values in the BASDAI/BASFI influenced both the PASS and MCII values. Similar results were noted in a few studies evaluating the PASS and the MCII for patients with OA[5,6], in which both the PASS and MCII varied across tertiles of baseline scores, but were not affected by age, sex, and location. The aforementioned study differed from ours in that they did not find the disease duration to affect the PASS or MCII. We attribute this to factors such as shorter mean disease duration within the OA population of 3.4–4.8 years compared with our AS population of 13.2 years.

Although the stability of the PASS and MCII has been discussed in the literature[1,4,15], no such study has clearly evaluated the benefit of one over the other with apparent disagreement regarding which measure is more stable across patient characteristics[6]. Our study does evaluate these differences, with notable generalizability in the setting of our multicenter/multinational study population. We find that although both the PASS and MCII vary by baseline disease activity and disease duration, when restricting analysis to the active disease group, the MCII becomes stable. Theoretically, because failure to attain an acceptable state does not exclude a meaningful response for improvement, the MCII is potentially more realistic for measuring treatment efficacy. In attaching value to the beneficial effects of intervention, perhaps patients are first looking to improve, with hopes to eventually achieve an acceptable symptom state.

Our results demonstrate that the MCII is less variable than the PASS across patient groups and important baseline characteristics such as baseline BASDAI and BASFI, rendering it superior for use in clinical practice and as a more reliable tool to measure interventional success from a patient perspective. We recommend the value derived within the active disease group in anticipation that this tool will be used most frequently in patients recommended for biologic therapy (here defined as baseline BASDAI ≥ 4) and for application in clinical trials. We recommend an MCII of 1.1 for the BASDAI and 0.6 for the BASFI as minimum thresholds to separate those patients who achieve therapeutic success versus those who do not. Although the MCII proves to be more stable, it is still largely affected by baseline values of the outcome measure, and is best limited to the group of patients experiencing active disease and limited in its use to those patients whose baseline BASDAI is ≥ 4. Worth

mentioning, however, is that the standard cutoff point for establishing biologic start is near identical to the PASS in the BASDAI, perhaps suggesting that this value is too low and may warrant reconsideration.

Potential limitations of our study include low enrollment in several countries, which did not allow us to evaluate and report differences in the MCII and PASS by location[4]. We were also limited in our ability to assess the effect of educational level, prior therapies, or psychological state as potential confounders on cutoffs because we did not collect these data. Because our patients received NSAID, it was unclear whether the MCII and PASS varied depending on type of intervention. In a clinical trial of patients receiving adalimumab[20], thresholds for the PASS in the BASDAI and BASFI clearly varied in the treatment versus the placebo group. Future studies should evaluate the MCII by intervention (including those treated with biologics) to validate use regardless of intervention. Validity of the PASS and MCII values may also be subject to "response shift," for which we did not adjust. This occurs when a patient's perceived change is subject to a phenomenon in which perception of their disease state changes during a comparison of 2 longitudinal assessments, which could certainly affect perception of what is considered acceptable[21].

We considered potential criticism of our choice of the BASDAI over the various disease activity indices available for AS. Although a similar concept of improvement exists in the Ankylosing Spondylitis Disease Activity Score (ASDAS) as the minimum clinically relevant cutoff[22], the additional benefit of the MCII in the BASDAI and BASFI is derived from its uniqueness to the patient experience. Theoretically, because this concept was established to reflect the patient's perception of disease activity, use of a purely subjective disease activity score not influenced by objective measures (unlike the ASDAS) appears to be more in line with the intended purpose of these concepts.

Whereas values from the REFLECT study recommend only generic values for the MCII and PASS across rheumatic diseases, we focus specifically on the population of patients with AS with recommended values in disease-specific outcome measures for a more straightforward implementation in practice. To our knowledge, our study is the first to co-examine the MCII and PASS specifically in the BASDAI and BASFI while comparing their stability across various patient characteristics. Unlike previous studies in AS, which have reported values for either the PASS or MCII[1,3,15,16], we examined both the MCII and PASS within the same study population, which permitted the comparison of the robustness of one measure over another. This same approach was executed by Bellamy, *et al* in determining the PASS/MCII levels in OA with acknowledgment that further research should evaluate the overall stability of these measures[7].

Establishing validated outcome measures that enable clinicians and researchers alike to categorize improvement from a patient perspective is congruent with an evolving healthcare model, which emphasizes patient-centered outcomes to define therapeutic success[23]. Particularly in a disease such as AS, in which a patient's experience does not always correlate with objective measures such as the erythrocyte sedimentation rate, C-reactive protein, and imaging[3], the concept of defining thresholds in patient-centered outcome measures is instrumental in assessing the efficacy of therapeutic interventions. Since our cutoff values are based on a subset of the study population (BASDAI = 88, BASFI = 73), we propose that these cutoffs should be confirmed in larger studies focusing specifically on patients with baseline BASDAI ≥ 4.

Our study demonstrates that both the PASS and MCII values vary significantly by disease duration and baseline disease activity, although the MCII varies to a lesser extent. We find that values for the PASS in our multinational population approach the cutoff established for biologic intervention initiation, which substantiates its use as superfluous. As a result of the MCII's superior stability in evaluating treatment efficacy in patients with active disease, we recommend exclusive use of the MCII, with associated cutoffs of 1.1 in the MCII for the BASDAI and 0.6 for the BASFI.

REFERENCES

1. Dougados M, Luo MP, Maksymowych WP, Chmiel JJ, Chen N, Wong RL, et al; ATLAS STUDY GROUP. Evaluation of the patient acceptable symptom state as an outcome measure in patients with ankylosing spondylitis: data from a randomized controlled trial. Arthritis Rheum 2008;59:553-60.
2. Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean? Ann Rheum Dis 2007;66 Suppl 3:iii40-1.
3. Pavy S, Brophy S, Calin A. Establishment of the minimum clinically important difference for the bath ankylosing spondylitis indices: a prospective study. J Rheumatol 2005;32:80-5.
4. Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: results from a prospective multinational study. Arthritis Care Res 2012; 64:1699-707.
5. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005;64:29-33.
6. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;64:34-7.
7. Bellamy N, Hochberg M, Tubach F, Martin-Mola E, Awada H, Bombardier C, et al. Development of multinational definitions of minimal clinically important improvement and patient acceptable symptomatic state in osteoarthritis. Arthritis Care Res 2015; 67:972-80.
8. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.

9. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
10. Braun J, Davis J, Dougados M, Sieper J, van der Linden S, van der Heijde D; ASAS Working Group. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. Ann Rheum Dis 2006; 65:316-20.
11. Braun J, Pham T, Sieper J, Davis J, van der Linden S, Dougados M, et al; ASAS Working Group. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 2003; 62:817-24.
12. Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC Jr, Dijkmans B, et al; 'ASsessment in AS' international working group; European League Against Rheumatism. ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2006;65:442-52.
13. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
14. Tubach F, Dougados M, Falissard B, Baron G, Logeart I, Ravaud P. Feeling good rather than feeling better matters more to patients. Arthritis Rheum 2006;55:526-30.
15. Maksymowych WP, Richardson R, Mallon C, van der Heijde D, Boonen A. Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis. Arthritis Rheum 2007;57:133-9.
16. Wariaghli G, Allali F, Idrissi Z, Berrada K, Hmamouchi I, Abouqal R, et al. Evaluation and stability of the Patient Acceptable Symptom State (PASS) over time in patients with ankylosing spondylitis. Clin Exp Rheumatol 2012;30:106-9.
17. Cella D, Hahn EA, Dineen K. Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. Qual Life Res 2002;11:207-21.
18. Guyatt GH, Jaeschke RJ. Reassessing quality-of-life instruments in the evaluation of new drugs. Pharmacoeconomics 1997;12:621-6.
19. Schwartz AL, Meek PM, Nail LM, Fargo J, Lundquist M, Donofrio M, et al. Measurement of fatigue. Determining minimally important clinical differences. J Clin Epidemiol 2002;55:239-44.
20. Maksymowych WP, Gooch K, Dougados M, Wong RL, Chen N, Kupper H, et al. Thresholds of patient-reported outcomes that define the patient acceptable symptom state in ankylosing spondylitis vary over time and by treatment and patient characteristics. Arthritis Care Res 2010;62:826-34.
21. McPhail S, Haines T. Response shift, recall bias and their effect on measuring change in health-related quality of life amongst older hospital patients. Health Qual Life Outcomes 2010;8:65.
22. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al; Assessment of SpondyloArthritis international Society. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47-53.
23. Snyder CF, Jensen RE, Segal JB, Wu AW. Patient-reported outcomes (PROs): putting the patient perspective in patient-centered outcomes research. Med Care 2013;51 Suppl 3:S73-9.