Performance and Predictors of Minimal Disease Activity Response in Patients With Peripheral Spondyloarthritis Treated With Adalimumab

Laura C. Coates,1,2 Sonya Abraham,2 William Tillett,3 Philip J. Mease,4,5 Sofia Ramiro,5,6 Tianshuang Wu,6 Xin Wang,6 Aileen L. Pangan,6 and In-Ho Song6

Objective. To examine the concurrent validity and discrimination of criteria for modified minimal disease activity (MDA) in peripheral spondyloarthritis (SpA) following filter principles of Outcome Measures in Rheumatology (OMERACT) and to determine predictors of modified MDA response.

Methods. Four modified MDA versions were derived in the ABILITY-2 study using the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index or the Leeds Enthesitis Index (LEI) while excluding psoriasis. To assess concurrent validity, modified MDA versions were correlated with Peripheral Spondyloarthritis Response Criteria (PSpARC) remission, Ankylosing Spondylitis Disease Activity Score showing inactive disease (ASDAS ID), and physician global assessment of disease activity. Treatment discrimination was assessed between adalimumab and placebo at week 12. Multiple logistic regression was used to determine baseline predictors of long-term modified MDA responses and sustained modified MDA.

Results. The 4 modified MDA versions showed a stronger positive correlation with PSpARC remission ($r_	ext{tet} > 0.95$) versus ASDAS ID ($r_	ext{tet} > 0.75$) at week 12 and years 1–3 and were able to show discrimination ($P < 0.001$). Responsiveness was shown at week 12; significantly more patients receiving adalimumab versus placebo achieved all 4 versions of modified MDA. Approximately 40–60% of patients treated with adalimumab achieved modified MDA using the LEI or SPARCC enthesis index at years 1–3. Achieving modified MDA response after 12 weeks of adalimumab treatment was a robust positive predictor of attaining long-term modified MDA through 3 years (odds ratio [OR] 11.38–27.13 for modified MDA using the LEI; OR 17.98–37.85 for modified MDA using the SPARCC enthesis index).

Conclusion. All 4 versions of modified MDA showed concurrent validity and discriminated well between adalimumab and placebo treatment groups. Early modified MDA response is a more consistent predictor of long-term modified MDA achievement than baseline characteristics. The 5 of 6 versions of modified MDA could be an appropriate treatment target in patients with peripheral SpA.

INTRODUCTION

Peripheral spondyloarthritis (SpA) encompasses patients with predominantly peripheral symptoms such as peripheral arthritis, dactylitis, and/or enthesitis (1,2). To date, most studies in the field of peripheral SpA have focused on psoriatic arthritis (PsA). Relatively few outcome measures have been developed specifically for nonpsoriatic peripheral SpA. Due to a lack of...
SIGNIFICANCE & INNOVATIONS

- In patients with peripheral spondyloarthritis (SpA), using 4 modified minimal disease activity (MDA; excluding psoriasis) versions following aspects of the Outcome Measures in Rheumatology (OMERACT) filter criteria, the modified MDA version that used either of the psoriatic arthritis (PsA)-validated enthesal indices (Leeds Enthesitis Index and Spondyloarthritis Research Consortium of Canada enthesitis index) discriminated well between adalimumab and placebo treatment groups.
- Similar to MDA definitions used in PsA, the data presented here support the concurrent validity and discrimination of modified MDA using either of the enthesal indices, depending on physician preference.
- Early modified MDA response is a more consistent predictor of long-term modified MDA achievement than baseline characteristics, and identification of factors that predict long-term modified MDA response in peripheral SpA patients would help to facilitate treatment decisions.

Validated outcome measures in nonpsoriatic peripheral SpA, recent studies have used varying outcome measures such as improvement in the patient global assessment of disease activity (PtGA) used in the TIPES trial (>40% improvement in Peripheral Spondyloarthritis Response Criteria [PSpARC40]) developed as a novel primary end point in the ABILITY-2 trial, or clinical remission, defined as absence of peripheral arthritis, enthesitis, and dactylitis used in the golimumab CRESPA trial.

The discriminatory capacity of different outcome measures was evaluated in patients with peripheral SpA from the TIPES and ABILITY-2 studies. Although most of the outcome measures used in studies of peripheral SpA distinguished between active treatment and placebo, not all of the relevant disease manifestations of peripheral SpA were fully captured. Therefore, it may be worthwhile to develop and validate alternative peripheral SpA-specific composite indices that better capture relevant disease aspects of peripheral SpA.

The minimal disease activity (MDA) measure was developed and validated in patients with PsA to define a specific disease activity state and has been validated in interventional clinical trials and observational studies and recommended as a treatment target in patients with PsA (7–12). However, the potential applicability of MDA to other forms of peripheral SpA has not yet been established. If the measure shows validity in defining a disease state in peripheral SpA, identification of factors that predict long-term modification of the MDA response in patients with peripheral SpA would help to facilitate decisions regarding treatment initiation and maintenance.

The purpose of this analysis was to examine the concurrent validity and discrimination of modified MDA criteria (excluding psoriasis) following aspects of the Outcome Measures in Rheumatology (OMERACT) filter (including truth and discrimination) and to identify predictors of long-term modified MDA response following treatment with adalimumab in patients with peripheral SpA included in the ABILITY-2 study.

PATIENTS AND METHODS

Patient population. Results from ABILITY-2 (ClinicalTrials.gov identifier: NCT01064856), a phase 3, randomized, double-blind, placebo-controlled study, were reported previously (4,14). Briefly, ABILITY-2 included adult patients (≥18 years) with peripheral SpA who fulfilled the Assessment of SpondyloArthritis international Society criteria for peripheral SpA, with symptom onset at least 3 months prior to study entry (1). To avoid overlap in patient populations, patients with a history of psoriasis or PsA or ankylosing spondylitis (AS) were excluded from the study. Patients were randomized 1:1 to receive adalimumab 40 mg or placebo every other week during the 12-week placebo-controlled period, followed by an open-label extension during which they received open-label adalimumab for up to 144 weeks. Patients underwent a total of 16 visits during the open-label period of the study (14). In this analysis, data from the ABILITY-2 study were used to examine the concurrent validity and discrimination of modified versions of MDA and to identify predictors of long-term modified MDA following adalimumab treatment.

Outcome measures. The original MDA measure for PsA is defined as achieving ≥5 of the following 7 criteria: tender joint count of 78 joints (TJC78) of ≤1; swollen joint count of 76 joints (SJC76) of ≤1; duration of morning stiffness ≤15 minutes; noBallack pain (PSA≥10); Patient’s Global Assessment of Disease Activity (PtGA) used in the TIPES trial (3), or clinical remission, defined as absence of peripheral arthritis, enthesitis, and dactylitis used in the golimumab CRESPA trial (5).

The minimal disease activity (MDA) was developed and validated in patients with PsA to define a specific disease activity state and has been validated in interventional clinical trials and observational studies and recommended as a treatment target in patients with PsA (7–12). However, the potential applicability of MDA to other forms of peripheral SpA has not yet been established. If the measure shows validity in defining a disease state in peripheral SpA, identification of factors that predict long-term modification of the MDA response in patients with peripheral SpA would help to facilitate decisions regarding treatment initiation and maintenance.

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(SJC76) of ≤1; Psoriasis Area and Severity Index (PASI) score of ≤1; patient assessment of pain score of ≤15 on a visual analog scale (VAS) (0–100 mm); PtGA score of ≤20 on a VAS (0–100 mm); Health Assessment Questionnaire disability index (HAQ DI) score of ≤0.5; and ≤1 tender enthesal points (assessed bilaterally at 2 sites) (7).

Skin outcome measures (using the PASI or body surface area), however, were not included in ABILITY-2, as patients with psoriasis or PsA were excluded. Hence, the MDA criteria were modified for the nonpsoriatic, peripheral SpA population by removing the psoriasis skin component (i.e., the PASI score), and 2 modifications were tested defined as achieving at least 4 or 5 of the 6 modified MDA components mentioned above, but excluding the PASI score. A previous study showed that the Leeds Enthesitis Index (LEI) and the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index were able to better discriminate between adalimumab and placebo treatment responses compared with the Maastricht Ankylosing Spondylitis Enthesitis Score in patients with peripheral SpA (15), but it has not been investigated whether the SPARCC enthesitis index or the LEI instrument is better in peripheral SpA. Thus, enthesitis was assessed by either the LEI or SPARCC enthesitis index in this analysis. The different enthesitis measures are described in Supplementary Table 1, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002acr.24442/abstract. To summarize, at each time point, the following 4 versions of modified MDA were evaluated: modified MDA 4 of 6 (LEI) (achieving 4 of 6 modified MDA components, and use of the LEI); modified MDA 5 of 6 (LEI) (achieving 5 of 6 modified MDA components); modified MDA 4 of 6 (SPARCC) (use of the SPARCC enthesitis index); and modified MDA 5 of 6 (SPARCC).

Remission according to the Peripheral SpA Response Criteria (PSPARC) and remission according to the Ankylosing Spondylitis Disease Activity Score showing inactive disease (ASDAS ID; ASDAS score <1.3) were used as outcome measures (4,16). Disease remission based on the PSPARC was defined as achieving an SJC of ≤1 and ≥24 of following 5 criteria: PtGA score of ≤20; patient assessment of pain score of ≤20; TJC78 of ≤1; an enthesitis count (based on 29 enthesitis sites) of ≤1; and a dactylitis count of ≤1 (4).

**Statistical methods.** Given that there is no true gold standard for disease control in peripheral SpA, criterion validity could not be assessed. Instead, concurrent validity was assessed by correlation of the 4 versions of the modified MDA with related disease outcome measures. Correlation analyses were therefore performed using PSPARC remission and ASDAS ID by tetrachoric correlation (r_tet) applicable for binary outcomes (17); in addition, the correlation between the 4 versions of modified MDA and physician global assessment of disease activity (PhGA) was evaluated by point-biserial correlation (r_pb) applicable for 1 continuous and 1 binary outcome (18).

The discriminatory ability of all 4 versions of modified MDA, PSPARC remission, and ASDAS ID comparing adalimumab treatment versus placebo at week 12 was assessed using Pearson’s χ² test (higher score meaning better discrimination). To differentiate between the 4 candidate modified MDA measures and to examine their threshold of meaning, residual disease in different domains despite achieving these candidate targets was analyzed.

Patients who received at least 12 weeks of adalimumab treatment during the placebo-controlled period or open-label extension with data available after 12 weeks of adalimumab exposure and at years 1, 2, and 3 were included in this analysis (data are presented as observed). The number and proportion of patients achieving a modified MDA response over time was calculated.

Multiple logistic regression with stepwise variable selection was used to determine predictors of long-term, 5 of 6 modified MDA responses at year 1, year 2, and year 3, respectively, and sustained modified MDA response at any time point (defined as achieving modified MDA for at least 24 consecutive weeks (14). Two sets of candidates predicting variables were considered in the model selection: baseline patient demographic and disease characteristics alone, and also the same potential predictors along with modified MDA response after 12 weeks of adalimumab exposure (modified MDA12). Candidate baseline variables included in the analysis were age, sex, duration of peripheral SpA (in years), HLA–B27 status (positive versus negative), high-sensitivity C-reactive protein (hs-CRP) status (elevated versus normal), prior treatment with disease-modifying antirheumatic drugs (yes versus no), TJC78, SJC76, enthesitis count (0–29), dactylitis count (0–20), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, ASDAS, PhGA (0–100 mm VAS), and treatment groups (adalimumab versus placebo).

**RESULTS**

Patients enrolled in ABILITY-2 had generally comparable demographic and baseline disease characteristics except for mean age, which was higher in the adalimumab group, and the percentage of patients with a dactylitis count of >1, which was lower in the adalimumab group versus placebo (4). Patients with peripheral SpA receiving adalimumab achieved significantly greater clinical responses compared with placebo at week 12, and the efficacy was maintained over 3 years (4,14).

**Correlation between modified MDA and other outcome measures for peripheral SpA.** To explore the relationship between modified MDA and outcome measures for peripheral SpA used in prior clinical trials, response rates were compared at week 12 and years 1–3. All 4 versions of modified MDA response showed a stronger positive correlation with PSPARC remission (r_tet > 0.95) compared with ASDAS ID.
(\( r_{\text{tot}} > 0.75 \)) at week 12 and years 1–3 (Table 1). There was a moderate negative correlation between the 4 versions of modified MDA response and PhGA \( (r_{\text{ab}} = 0.43–0.61) \) at week 12 and years 1–3. However, the 4 versions of modified MDA did not correlate with CRP levels (data not shown). Correlation with PtGA was not performed as PtGA is part of the MDA measure.

**Achievement of modified MDA over 3 years.** Among 163 patients (82 receiving adalimumab, 81 receiving placebo) who completed week 12 of the double-blind period of ABILITY-2, a significantly greater proportion of patients receiving adalimumab achieved modified MDA (regardless of the definition) compared with placebo \( (P < 0.001 \) for all comparisons) (Figure 1). At week 12, 40.2%, 28.0%, 35.4%, and 26.8% of patients treated with adalimumab achieved modified MDA based on LEI 4 of 6, LEI 5 of 6, SPARCC 4 of 6, and SPARCC 5 of 6, respectively, compared with 13.6%, 4.9%, 12.3%, and 4.9% of patients treated with placebo.

Among patients who achieved modified MDA at week 12, 48.5% (LEI 4 of 6; n = 16), 69.6% (LEI 5 of 6; n = 16), 48.3% (SPARCC 4 of 6; n = 14), and 63.6% (SPARCC 5 of 6; n = 14) of patients with adalimumab attained all 6 components of modified MDA compared with only 18.2% (n = 2), 50.0% (n = 2), and 50.0% (n = 2) of patients treated with placebo.

During the open-label extension, the proportion of patients who achieved modified MDA (as observed) were maintained over 3 years across all 4 versions (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24442/abstract). However, the rate of modified MDA achievement, including achievement of sustained modified MDA, was numerically higher at every time point among patients initially randomized to receive adalimumab compared with patients switching from placebo to adalimumab.

**Ability of modified MDA for detection of treatment effect.** All 4 versions of modified MDA had numerically higher Pearson’s \( \chi^2 \) values compared to PSpARC remission and the ASDAS ID. All 4 versions showed the ability to detect significant efficacy difference between adalimumab and placebo treatment groups (Table 2).

**Individual modified MDA components and criteria not met.** To establish the threshold of meaning of the measure, the individual modified MDA components that were not achieved in the patients treated with adalimumab achieving each version of modified MDA were assessed to better understand their contribution to the overall response. Among patients receiving adalimumab who fulfilled 4 of 6 modified MDA criteria (LEI or SPARCC) at week 12, the joint count criteria were most frequently not met (TJC: LEI 4 of 6 [27.3%]; SPARCC 4 of 6 [20.7%]; SJC: LEI 4 of 6 [30.3%]; SPARCC 4 of 6 [24.1%]) (Table 3). However, the 5 of 6 criteria (LEI or SPARCC) were more stringent, with approximately only 4% and 13% not meeting the TJC or SJC criterion, respectively. Approximately 5–10% of patients treated with adalimumab achieving modified MDA did not attain the HAQ DI criterion. For enthesitis, there was no big difference between the 4 of 6 or the 5 of 6 modified MDA versions; but using the LEI versions of modified MDA, patients treated with adalimumab all attained the enthesitis criterion compared with 9% and 10% of patients not meeting this criterion using the modified MDA versions and the SPARCC enthesitis index, respectively.

In patients treated with adalimumab achieving 4 of 6 modified MDA criteria (LEI or SPARCC), the mean TJC and SJC were at or above the modified MDA cutoff (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24442/abstract), while all other components were lower than the modified MDA cutoff. The 5 of 6 modified MDA criteria were more stringent, with the mean of each MDA component lower than the modified MDA cutoff. Among patients with peripheral SpA who did not achieve modified MDA at week 12, 83–88% of patients treated with adalimumab achieved 1 of 6 modified MDA criteria (LEI or SPARCC), while the rate was 66–79% in patients treated with placebo (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24442/abstract).

### Table 1. Correlation between modified minimal disease activity (MDA) and peripheral spondylitis outcome measures

| Modified MDA | Week 12 (DB) | Year 1 (OLE) | Year 2 (OLE) | Year 3 (OLE) |
|--------------|-------------|-------------|-------------|-------------|
| 4 of 6 LEI components | | | | |
| PSpARC remission† | 0.99† | 0.99 | 0.96 | 0.99 |
| ASDAS ID‡ | 0.82 | 0.79 | 0.89 | 0.86 |
| PhGA§ | -0.50 | -0.51 | -0.51 | -0.61 |
| 5 of 6 LEI components | | | | |
| PSpARC remission† | 0.98 | 0.98 | 0.97 | 0.99‡ |
| ASDAS ID‡ | 0.82 | 0.80 | 0.88 | 0.84 |
| PhGA§ | -0.44 | -0.47 | -0.54 | -0.55 |
| 4 of 6 SPARCC components | | | | |
| PSpARC remission† | 0.99 | 0.99 | 0.96 | 0.99 |
| ASDAS ID‡ | 0.76 | 0.76 | 0.89 | 0.85 |
| PhGA§ | -0.49 | -0.55 | -0.54 | -0.58 |
| 5 of 6 SPARCC components | | | | |
| PSpARC remission† | 0.97 | 0.98 | 0.97 | 0.99 |
| ASDAS ID‡ | 0.80 | 0.79 | 0.86 | 0.83 |
| PhGA§ | -0.43 | -0.46 | -0.50 | -0.54 |

* ASDAS ID = Ankylosing Spondylitis Disease Activity Score showing inactive disease; DB = double-blind period; LEI = Leeds Enthesitis Index; OLE = open-label extension; PhGA = physician global assessment of disease activity; PSpARC = Peripheral Spondyloarthritits Response Criteria; SPARCC = Spondyloarthritis Research Consortium of Canada enthesitis index.
† Tetrachoric correlation.
‡ Value >0.99.
§ Point-biserial correlation.
Predictors of long-term modified MDA response.

Multiple logistic regression analyses were performed for the more stringent 5 of 6 modified MDA definitions based on better face validity and identified modified MDA response after 12 weeks of adalimumab exposure (modified MDA12) as a strong and robust positive predictor of attaining both long-term modified MDA at years 1–3 and sustained modified MDA (P < 0.001 for the 5 of 6 modified MDA definitions, using either the LEI [odds ratio (OR) range 11.38–27.13] or the SPARCC enthesitis index [OR range 17.98–37.85] at years 1–3 and sustained over time) (Figure 2). In contrast, baseline BASDAI score was a consistent negative predictor of modified MDA achievement at years 1–3 and sustained over time, irrespective of the inclusion of the LEI (OR range 0.36–0.66) or the SPARCC enthesitis index (OR range 0.51–0.68) in the modified MDA definition (Figure 2).

Although prior DMARD use and baseline PhGA score were selected as positive predictors, and baseline enthesitis was selected as a negative predictor, these variables did not consistently predict achievement of modified MDA at every time point or sustained over time and were only weakly associated. The ASDAS showed positive association with achievement of modified MDA at year 3. An analysis excluding the ASDAS was performed, as the ASDAS and BASDAI score are highly correlated outcomes. The analysis showed that both modified MDA12 and BASDAl score were still significantly associated with modified MDA achievement at year 3 (see Supplementary Figure 2, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24442/abstract). In addition, hs-CRP level showed a positive association with achievement of modified MDA at year 3.

Table 2. Discrimination between adalimumab and placebo treatment at week 12*

| Outcome measure | Adalimumab | Placebo | Pearson's $\chi^2$ | $P$ |
|-----------------|------------|---------|-------------------|-----|
| Modified MDA, 4 of 6 LEI components | 33/82 (40.2) | 11/81 (13.6) | 14.70 | <0.001 |
| Modified MDA, 5 of 6 LEI components | 23/82 (28.0) | 4/81 (4.9) | 15.75 | <0.001 |
| Modified MDA, 4 of 6 SPARCC components | 29/82 (35.4) | 10/81 (12.3) | 11.86 | <0.001 |
| Modified MDA, 5 of 6 SPARCC components | 22/82 (26.8) | 4/81 (4.9) | 14.57 | <0.001 |
| PSpARC remission | 33/81 (40.7) | 16/80 (20.0) | 8.18 | 0.004 |
| ASDAS ID | 27/80 (33.8) | 12/78 (15.4) | 7.17 | 0.007 |

* Values are the no./total no. (%) unless indicated otherwise. ASDAS ID = Ankylosing Spondylitis Disease Activity Score showing inactive disease; LEI = Leeds Enthesitis Index; MDA = minimal disease activity; PSpARC = Peripheral Spondyloarthritis Response Criteria; SPARCC = Spondyloarthritis Research Consortium of Canada enthesitis index.
3; elevated baseline hs-CRP was associated with increased likelihood of achieving modified MDA.

In the model examining the baseline variables alone (model without modified MDA12), age, enthesitis, and BASDAI scores were most commonly selected as negative predictors for achieving long-term response over 3 years and sustained modified MDA (Figure 3). Baseline PhGA, hs-CRP level, and male sex were selected as positive predictors, and dactylitis was selected as negative predictor; however, these predictors were not consistently selected for all time points or sustained modified MDA.

Table 3. Criteria not met in achievers of modified minimal disease activity (MDA) receiving adalimumab at week 12*

| Modified MDA       | TJ C78 ≤ 1 | SJ C76 ≤ 1 | Patient pain VAS score ≤ 15 | PtGA VAS score ≤ 20 | HAQ DI score ≤ 0.5 | Enthesitis index score ≤ 1 |
|--------------------|------------|------------|-----------------------------|---------------------|-------------------|---------------------------|
| 4 of 6 LEI components (n = 33) | 9 (27.3)   | 10 (30.3)  | 2 (6.1)                     | 3 (9.1)             | 3 (9.1)          | 0 (0.0)                   |
| 5 of 6 LEI components (n = 29) | 6 (20.7)   | 7 (24.1)   | 1 (3.4)                     | 2 (6.9)             | 3 (10.3)         | 3 (10.3)                  |
| 4 of 6 SPARCC components (n = 23) | 1 (4.3)    | 3 (13.0)   | 0 (0.0)                     | 1 (4.3)             | 2 (8.7)          | 0 (0.0)                   |
| 5 of 6 SPARCC components (n = 22) | 1 (4.5)    | 3 (13.6)   | 0 (0.0)                     | 1 (4.5)             | 1 (4.5)          | 2 (9.1)                   |

* Values are the number (%). HAQ DI = Health Assessment Questionnaire disability index (based on 20 questions); LEI = Leeds Enthesitis Index; PtGA = patient global assessment of disease activity; SJ C76 = swollen joint count of 76 joints; SPARCC = Spondyloarthritis Research Consortium of Canada enthesitis index; TJ C78 = tender joint count of 78 joints; VAS = visual analog scale.
† Patient pain = patient global assessment of pain.

The modified MDA response rates (probability of achieving modified MDA response) at years 1–3 and sustained over time in patients who achieved modified MDA after 12 weeks of adalimumab exposure compared with patients who did not achieve modified MDA12 are shown in Supplementary Table 4, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24442/abstract. The response rate was consistent with the model selection results, indicating that patients who achieved modified MDA after 12 weeks of adalimumab exposure were 80–90% more likely to achieve modified MDA response at years 1–3 and sustained over time.

Figure 2. Factors associated with long-term and sustained modified minimal disease activity (mMDA) response predictors of long-term (years 1–3) and sustained mMDA responses at baseline and week 12 using a multiple logistic regression model, including mMDA response after 12 weeks of adalimumab treatment (mMDA12), for the 5 of 6 Leeds Enthesitis Index (LEI) components (A) and the 5 of 6 Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index components (B). Only variables selected by a stepwise selection model are shown (variables selected by the model are significant at P < 0.05). 95% CI = 95% confidence interval; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DMARDs = disease-modifying antirheumatic drugs; PhGA = physician global assessment of disease activity; SJ C76 = swollen joint count of 76 joints; SpA = spondyloarthritis.
DISCUSSION

The MDA measure has been established as a valid composite outcome measure and appropriate treatment target in patients with PsA (19,20). The present analyses evaluated the potential applicability and performance of a modification of the MDA following principles of the OMERACT filter in patients with nonpsoriatic peripheral SpA from the ABILITY-2 study and identified predictors of long-term modified MDA responses following treatment with adalimumab.

Given that there is no established gold standard in peripheral SpA, criterion validity could not be assessed. Therefore, we evaluated concurrent validity, which assesses how the modified MDA compares with other measures, to measure similar constructs (the PSpARC and the ASDAS). All 4 versions of modified MDA criteria showed strong positive correlations with PSpARC remission and ASDAS ID, disease-specific outcome measures in peripheral SpA, underlining the validity of applying modified MDA criteria to peripheral SpA. Among the response criteria evaluated, all 4 modified MDA versions, the PSpARC remission, and ASDAS ID overall discriminated well between adalimumab and placebo treatment groups, and the modified MDA version that used either of the PsA-validated enthesal indices (the LEI and the SPARCC enthesitis index) performed comparably.

Similar to definitions of MDA used in PsA, the data presented here support the concurrent validity and discrimination of modified MDA using either of the enthesal indices depending on physician preference. At week 12, nearly 35–40% of patients treated with adalimumab achieved 4 of 6 versions of modified MDA, while 27–28% achieved the more stringent 5 of 6 versions of modified MDA. The proportions of patients achieving modified MDA was maintained over 3 years across the different definitions of modified MDA, reaching up to 58–60% in patients initially randomized to adalimumab and continued therapy. Throughout the duration of the study (3 years), sustained modified MDA was achieved by 55% (4 of 6 versions) and 44% (5 of 6 versions) of patients initially treated with adalimumab. The rates of sustained modified MDA using the more stringent 5 of 6 versions of the LEI or the SPARCC enthesitis index are similar to the rates observed in previous studies (21,22). Also, at week 12, 17–20% of patients receiving adalimumab achieved 6 of 6 versions of modified MDA, which is in accordance with the rates of MDA using 7 of 7 criteria reported in patients with PsA (23,24).

In PsA, MDA requires achievement of 5 of 7 criteria. However, the MDA criteria were modified for the nonpsoriatic peripheral SpA population by removing the psoriasis skin component (i.e., the PASI score); with this modification, it was unclear if 4 of 6 or 5 of 6 would perform best in peripheral SpA. Concurrent validity and treatment discrimination were similar for both the 4 of 6 and the 5 of 6 versions, so residual disease was examined to compare these further. Among patients treated with adalimumab who achieved 4 of 6 versions of modified MDA at week 12, joint responses (TJC and SJC)
were most often the limiting factors in modified MDA attainment. In patients achieving 5 of 6 versions of modified MDA, SJC, followed by HAQ DI (LEI) or enthesitis (SPARCC), appeared to limit modified MDA achievement, but residual levels of disease were much lower. Interestingly, all patients treated with adalimumab achieving modified MDA based on the LEI met the enthesitis criterion, whereas 9–10% failed to meet the enthesitis criterion based on the SPARCC enthesitis index. This difference is likely attributed to more sites being assessed in the SPARCC enthesitis index compared with the LEI. More studies are needed to assess whether the LEI or SPARCC enthesitis index might be more appropriate to use in peripheral SpA.

Although most modified MDA components were below the modified MDA cutoff in patients treated with adalimumab achieving 4 of 6 modified MDA criteria, the mean TJC and SJC were at or above the modified MDA cutoff. In contrast, the mean for all modified MDA components was below the modified MDA cutoff in patients treated with adalimumab achieving 5 of 6 versions. A measure of MDA or a treatment target should be associated with low levels of residual disease for face validity. The 5 of 6 modified MDA versions were more stringent than the 4 of 6 versions and more closely represent the concept of MDA with low values for most of the modified MDA components. Thus, to summarize: the 5 of 6 modified MDA criteria using either of the enthesal measures, rather than the 4 of 6 modified MDA criteria, could be an appropriate response measure in patients with peripheral SpA.

Multiple logistic regression analysis identified achievement of either of the 5 of 6 versions of modified MDA (modiﬁed MDA 5 of 6 [LEI] or modiﬁed MDA 5 of 6 [SPARCC]) after 12 weeks of adalimumab exposure as the strongest and most consistent predictors of long-term modified MDA, whether at 1, 2, or 3 years or sustained over time. That early clinical response is predictive of long-term response is in line with other studies in PsA, AS, or peripheral SpA (22,25,26). In PsA patients treated with certolizumab pegol, early clinical response at week 12 was identiﬁed as a positive predictor of MDA response at week 48 (27). Previously, achievement of early response at week 12 in patients with AS receiving adalimumab was found to be most predictive of long-term treatment response (28). Recently, in patients with peripheral SpA from ABILITY-2, ASDAS ID or PSpARC remission at week 12 were shown to predict subsequent long-term and sustained treatment response (14). All other variables including baseline BASDAI score were either only marginal predictors and/or did not reliably or consistently predict modiﬁed MDA response at every time point or sustained over time. In several studies evaluating predictors of MDA response in patients with PsA, baseline HAQ DI was most often reported as a negative predictor of long-term MDA (22,25,26).

Limitations of the current analysis include the limited sample size in each treatment arm and the lack of PASI score in the deﬁnition of MDA. However, ABILITY-2 had both a placebo-controlled period and long-term open-label extension, allowing the validation of modiﬁed MDA in a population of patients with peripheral SpA and identiﬁcation of predictors of long-term treatment response. As there is no gold standard in peripheral SpA, we used concurrent validity to assess the performance of modiﬁed MDA versions compared to other available outcome measures that have been used in the past in peripheral SpA. Correlation analyses were only performed with a limited number of other end points such as the PSpARC or ASDAS ID, as few outcome measures are established in this disease. This analysis did not aim to address all aspects of the OMERACT filter systematically, so further work is required using different methodology to address truth (content and face validity), feasibility, and reliability. However, it should be noted that the original MDA has been proven to be feasible, so the modiﬁcations by deﬁnition should also be feasible given that 1 domain was removed. The performance of the modiﬁed MDA could not be analyzed in subgroups of peripheral SpA patients with dactylitis, inﬂammatory bowel disease (IBD), or uveitis due to the limited sample size of these subgroups. While the modiﬁed MDA criteria could reasonably be applied to peripheral SpA patients with dactylitis, as they evaluate tender and swollen joints, further studies are needed for patients with IBD or uveitis.

In conclusion, modiﬁed MDA using 5 of 6 criteria in peripheral SpA appears to be a valid, discriminative measure to assess treatment differences in patients with peripheral SpA. Achievement of early modiﬁed MDA response following adalimumab treatment was the most robust and consistent predictor of long-term modiﬁed MDA response.

AUTHOR CONTRIBUTIONS
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Coates had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Mease, Pangan.

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Analysis and interpretation of data. Coates, Abraham, Tillett, Mease, Ramiro, Wu, Wang, Pangan, Song.

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