Application and Modifications of Minimal Disease Activity Measures for Patients with Psoriatic Arthritis Treated with Adalimumab: Subanalyses of ADEPT

Philip J. Mease, Michele Heckaman, Sonja Kary, and Hartmut Kupper

ABSTRACT. ***Objective.*** This posthoc analysis evaluated the percentage of patients with psoriatic arthritis (PsA) who achieved minimal disease activity (MDA) and compared the results with a modified MDA substituting the physician global assessment (PGA) for the Psoriasis Activity and Severity Index (PASI) using data from the ADalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT; NCT00646386).

Methods. Patients with active PsA were randomized to receive adalimumab 40 mg or placebo every other week for 24 weeks. MDA was defined as achieving ≥ 5 of the following criteria: tender joint count ≤ 1; swollen joint count ≤ 1; PASI ≤ 1 or body surface area ≤ 3%; patient pain score ≤ 15 [1–100 mm visual analog scale (VAS)]; patient global assessment (PGA) of disease activity ≤ 20 (1–100 mm VAS); Health Assessment Questionnaire ≤ 0.5; and tender entheseal points ≤ 1 (only heels assessed). For modification of the MDA, PASI ≤ 1 was substituted with PGA "Clear" as MDA_{PGA1} and PGA "Clear" or "Almost clear" as MDA_{PGA2}.

Results. Sixty-seven patients were treated with adalimumab and 69 with placebo. At Week 24, MDA, MDA_{PGA1}, and MDA_{PGA2} were achieved by 39%, 37%, and 39%, respectively, of patients treated with adalimumab versus 7%, 5%, and 8% of patients on placebo ($p < 0.001$). Kappa coefficients indicated good agreement between PASI and PGA at Week 24.

Conclusion. ADEPT results indicated that significantly more patients treated with adalimumab achieved MDA by Week 24 compared with placebo. Modification of the MDA by replacing PASI ≤ 1 with PGA assessments did not alter the results, which may improve feasibility of practical use of the index. (J Rheumatol First Release March 15 2013; doi:10.3899/jrheum.120970)

Key Indexing Terms:
ADALIMUMAB PSORIATIC ARTHRITIS SEVERITY OF ILLNESS INDEX

Moderate to severe psoriatic arthritis (PsA) has traditionally been treated with disease-modifying antirheumatic drugs (DMARD), including methotrexate (MTX), sulfasalazine, and leflunomide1,2,3. Over the past decade, biologic agents, including the tumor necrosis factor (TNF) inhibitors infliximab, adalimumab, etanercept, and golimumab, have demonstrated effectiveness in the treatment of patients with PsA1,4,5,6,7. These biologic agents are recognized as having superior efficacy to that of conventional DMARD8.

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Adalimumab is a fully human anti-TNF monoclonal antibody approved for the treatment of patients with PsA. In the ADalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), patients with moderately to severely active PsA received adalimumab or placebo for 24 weeks. After 12 weeks of treatment, adalimumab significantly improved the American College of Rheumatology 20% (ACR20) responses, the modified total Sharp score, and the Psoriasis Area and Severity Index (PASI) compared with placebo[5]. Two-year results from ADEPT demonstrated that inhibition of radiographic progression and improvements in skin and joint disease were maintained in most patients during this extension period[9].

The availability of highly effective biologic therapies for the treatment of patients with PsA has made achievement of a minimal level of disease activity a realistic treatment target, and it is important to have metrics for responses to therapy to determine achievement of this state[10]. Treating to targets of remission or low disease activity has been recommended as the optimal way to manage patients with rheumatoid arthritis (RA)[11], but the metrics used to define remission in RA may not be appropriate for PsA[1,12]. Recently, Coates, *et al* created a composite measure for

minimal disease activity (MDA) in patients with PsA that encompasses all clinically important aspects of PsA: arthritis, psoriasis, enthesitis, pain, patient-assessed global disease activity, and physical function[13]. MDA is based on criteria determined at Outcome Measures in Rheumatology Clinical Trials conferences 7 and 8[14] and encompasses the concepts of clinical remission and low disease activity. This index was initially evaluated in an observational study in which patients received standard care for PsA according to their clinical need and were followed for up to 5 years[15]. In that observational cohort, 60% of patients with PsA (208/344) achieved MDA at 1 or more visits. Although an improved prognosis was demonstrated in patients who achieved MDA, whether the improvements were a reflection of the disease course or due to treatment regimens could not be determined with the study design. The MDA criteria were subsequently validated using data from the randomized, controlled IMPACT and IMPACT2 trials in which patients received infliximab for the treatment of PsA[16]. In those trials there were statistically significant differences (infliximab vs placebo treatment) in the percentage of patients who achieved MDA at Week 16 ($p < 0.0001$) and Week 24 ($p < 0.001$).

The first objective of the current study was to investigate the achievement of MDA in patients with moderate to severely active PsA who are treated with adalimumab versus placebo.

The PASI is one of the components in the MDA, but it is somewhat complicated to calculate, requiring multiple measurements on various areas of the body. While it has been used extensively in clinical trials, the PASI is not sensitive to change for small areas of involvement, and it is not often employed in clinical practice[17]. The physician global assessment of disease activity (PGA) is another measure for psoriasis that has been used extensively in clinical trials and it may be employed in a static form that measures the physician's impression of the disease at a point in time or in a dynamic form in which the global improvement from baseline is evaluated[17]. The PGA is highly correlated with the PASI, and results from 1 study showed that the correlation between PASI75 and a score of PGA "Clear" or "Almost clear" is $r^2 > 0.9$[18,19]. The simplicity of the PGA may make it more suitable for use in clinical practice and registries than the PASI[18]. The second objective of this study was to assess a modified MDA in which the PGA was substituted for the PASI in an analysis of the same clinical trial results.

MATERIALS AND METHODS

Study design. The design for ADEPT (NCT00646386) has been reported previously[5]. Briefly, in this double-blind study, patients with moderately to severely active PsA and a history of inadequate response to nonsteroidal antiinflammatory drugs (NSAID) were randomized to receive adalimumab 40 mg or placebo subcutaneously every other week for 24 weeks. The primary efficacy endpoints were ACR20 response at Week 12 and the change in the modified total Sharp score of structural damage in the hands and feet at Week 24. Secondary endpoints were measures of joint disease, disability, and quality of life in all patients, as well as the severity of skin disease in those patients with psoriasis involving at least 3% of body surface area (BSA)[5]. All research was conducted in compliance with the Declaration of Helsinki and the protocol was approved by each study site's institutional review board. Written informed consent was obtained from each patient.

Patients. ADEPT included adults aged ≥ 18 years with active PsA, defined as ≥ 3 tender joints and ≥ 3 swollen joints, and cutaneous lesions or history of psoriasis. Continuing systemic treatment with MTX (if taken for ≥ 3 months previously), NSAID, or glucocorticoids (maximum prednisone 10 mg equivalent) was allowed, but treatment with other DMARD within the past 4 weeks was prohibited. Patients who received ultraviolet A light phototherapy and topical treatment for psoriasis within 2 weeks previously were not allowed to enroll. Before randomization, patients were stratified according to continuing MTX use (yes or no) and extent of psoriasis (≥ 3% BSA and < 3% BSA). Per protocol, psoriasis evaluation after baseline was performed only for patients with BSA ≥ 3% at study entry, using both the PASI and the PGA.

Calculation of PASI and PGA. For the PASI, 4 anatomic sites (head, upper extremities, trunk, and lower extremities) were assessed for 3 morphologic signs (erythema, induration, and desquamation) on a 5-point scale (0 = none, 1 = slight, 2 = moderate, 3 = marked, and 4 = very marked)[20]. On the basis of the extent of lesions in a given body site, the area affected was assigned a numerical value (1, < 10%; 2, 10%–29%; 3, 30%–49%; 4, 50%–69%; 5, 70%–89%; and 6, 90%–100%). PASI was calculated using a formula that integrates the scores of morphologic signs and the extent of area affected by psoriatic lesions. The PGA was an assessment of psoriasis on a 7-point scale (1 = clear, 2 = almost clear, 3 = mild, 4 = mild to moderate, 5 = moderate, 6 = moderate to severe, and 7 = severe).

Minimal disease activity. MDA requires achieving at least 5 of the following 7 criteria: tender joint count (TJC; 0–68) ≤ 1; swollen joint count (SJC; 0–66) ≤ 1; PASI ≤ 1 or BSA ≤ 3%; patient pain score on a visual analog scale (VAS; 0–100) ≤ 15; patient global assessment of disease activity (PaGA; VAS; 0–100) ≤ 20 mm; Health Assessment Questionnaire (HAQ; 0–3) ≤ 0.5; and tender entheseal points (0–13) ≤ 1[13]. In ADEPT, TJC and SJC were based on 78 and 76 joints, respectively, and enthesitis assessment was limited to the heels only. This limited score (range 0–4) was used for calculation of MDA. Alternatively, the enthesitis score was omitted and 5 out of 6 criteria of MDA were evaluated. The percentage of patients attaining MDA was evaluated at each study visit (Weeks 2, 4, 8, 12, 16, 20, and 24) and the individual components of MDA were evaluated at Week 24.

Modification of MDA by replacement of PASI by PGA. The criterion of PASI ≤ 1 was substituted with 2 alternative PGA criteria: the strict outcome of PGA = "Clear" (MDA_{PGA1}) and the less demanding outcome of PGA = "Clear" or "Almost clear" (MDA_{PGA2}). The percentage of patients attaining modified MDA was calculated only for Week 24.

Statistical analyses. Observed data from patients with active PsA (≥ 3% BSA) at baseline were included in this posthoc analysis. The percentages of adalimumab- and placebo-treated patients achieving the original composite MDA (with or without enthesitis) at Weeks 12 and 24 were compared using Fisher's exact test. Percentages of patients achieving each of the 2 modified MDA versions at Week 24 were compared using Fisher's exact test. Concordance of the PASI and PGA was compared by kappa coefficient from the combined adalimumab- and placebo-treated patient data.

RESULTS

Patients. Of the 313 patients enrolled in ADEPT, 67 patients treated with adalimumab and 69 with placebo had active psoriasis (BSA ≥ 3%) and SJC ≥ 3 at baseline. At Week 24, data were available for 62 patients in the adalimumab group

and 60 in the placebo group. Baseline disease characteristics for MDA criteria and PGA categories were similar between the adalimumab and placebo treatment groups (Table 1).

Attainment of MDA. The percentage of patients attaining MDA increased rapidly after starting adalimumab treatment (Figures 1A, 1B). The percentages of patients achieving a state of MDA at Weeks 12 and 24 were significantly greater in patients treated with adalimumab compared to patients treated with placebo ($p < 0.001$; Figure 1A). The percentage of patients attaining MDA calculated without the enthesitis score showed a similar pattern; the majority of these patients fulfilled the criterion for enthesitis at baseline (Figure 1B). At Week 24, 39%, 37%, and 39% of patients treated with adalimumab achieved MDA, MDA_{PGA1}, and MDA_{PGA2}, respectively, compared with 7%, 5%, and 8% of patients randomized to placebo ($p < 0.001$ for all comparisons between adalimumab and placebo groups; Figure 2). These results indicate that MDA calculated using PGA "Clear" (MDA_{PGA1}) or PGA "Clear" or "Almost clear" (MDA_{PGA2}) yielded results similar to those obtained using PASI ≤ 1.

Individual MDA criteria. The percentages of patients fulfilling individual components of the MDA criteria were similar between the treatment groups at baseline, but were greater in adalimumab-treated patients versus the placebo-treated patients at Week 24 (Table 2). The skin measures (PASI and PGA) showed the greatest difference in responsiveness between the treatment groups (Table 2).

Agreement between PASI and PGA outcome measures. Data for a total of 118 PASI and PGA assessments were available, irrespective of treatment. Kappa coefficients showed that PGA "Clear" or "Almost clear" (MDA_{PGA2}) agreed slightly better with PASI ≤ 1 than did PGA "Clear" (MDA_{PGA1}; Table 3). MDA_{PGA1} appeared more stringent than PASI ≤ 1. PASI ≤ 1 was achieved by 15 patients who were not categorized as "Clear" in the PGA. In contrast, PASI ≤ 1 was not achieved by 16 patients who were categorized as "Clear" or "Almost clear" in the PGA.

Table 1. Demographic and clinical results for patients included in the analysis.

Characteristic	Placebo, n = 69	Adalimumab, n = 67
Age, yrs	48 ± 12	50 ± 14
Male, n (%)	39 (57)	38 (57)
Minimal disease activity criteria, mean ± SD		
TJC (0–78)	28 ± 18	26 ± 19
SJC (0–76)	16 ± 12	17 ± 13
PASI (0–72)	8 ± 7	7 ± 6
HAQ (0–3)	1.10 ± 0.68	1.10 ± 0.64
Pain (0–100 mm)	49 ± 23	52 ± 21
PaGA (0–100 mm)	48 ± 23	48 ± 23
Enthesitis* (0–4)	1.0 ± 1.4	0.8 ± 1.3
Physician global assessment category, n (%)		
Clear	0	0
Almost clear	1 (1.5)	1 (1.5)
Mild	9 (13.2)	12 (17.9)
Mild to moderate	19 (27.9)	15 (22.4)
Moderate	25 (36.8)	17 (25.4)
Moderate to severe	11 (16.2)	19 (28.4)
Severe	3 (4.4)	3 (4.5)

* Plantar fascia and Achilles tendon insertion. HAQ: Health Assessment Questionnaire; PASI: Psoriasis Activity and Severity Index; PaGA: patient global assessment of disease activity; SJC: swollen joint count; TJC: tender joint count.

DISCUSSION

The MDA index developed by Coates, *et al*[13] provides a validated, thorough, and disease-specific metric of disease activity, but it has not been used to assess the effectiveness of adalimumab. The first objective of our analysis was to assess the percentage of patients with moderate to severe PsA (≥ 3 swollen and 3 tender joints) who achieved MDA after treatment with adalimumab compared with placebo. Treatment with adalimumab resulted in achievement of MDA in 37% to 39% (for the 3 different MDA calculations) of patients with active PsA after 24 weeks compared with 5% to 8% of patients who received placebo. Preliminary reports from 2 other studies indicate that treatment of patients with PsA with infliximab showed a similar degree of improvement[16]. These studies (IMPACT1 and IMPACT2) used the same definition of MDA to assess patients with active PsA (≥ 5 tender and swollen joints). In IMPACT1, 48% of patients (15/31) treated with infliximab achieved MDA compared with 3% (1/32) treated with placebo after 16 weeks of treatment[16]. In IMPACT2, 52% of patients (40/77) treated with infliximab achieved MDA compared with 21% (17/80) treated with placebo after 24 weeks of treatment[16].

The second objective of this study was to determine MDA results when the index was simplified by substituting the PGA for PASI. Results indicated that replacing PASI with PGA had almost no effect on the percentage of patients achieving MDA after 24 weeks of treatment with adalimumab compared with the unmodified MDA in patients with psoriasis affecting at least 3% of their BSA. Statistically, there was good agreement between the PGA and PASI assessments. This finding is consistent with results from studies indicating high correlations between the PGA and PASI[18].

PASI was one of the elements included in the original criteria for MDA. This measure is often employed in clinical trials of therapies for psoriasis and PsA, but it is not routinely used in clinical practice[17]. Criticisms of the PASI include decreased interrater agreement for high scores and poor sensitivity for treatment that decreases erythema, scaling, and infiltration of lesions when there is no modification of BSA affected[21]. PASI underestimates treatment-associated improvements compared with measures of patient's self-assessment[22]. Other limitations noted for the PASI are that lesion thickness is not carefully defined and

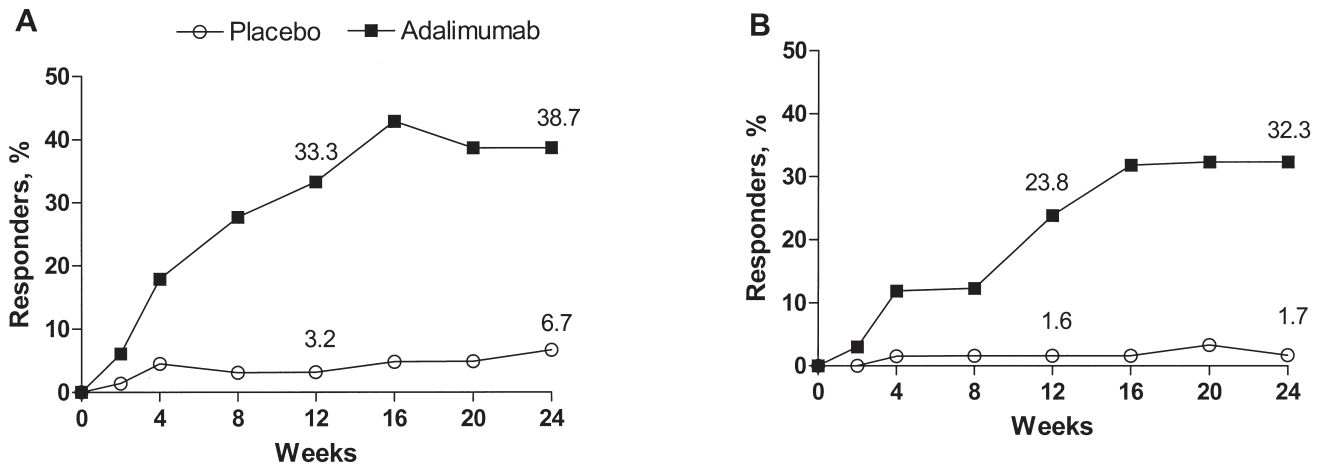

Figure 1. Percentage of patients achieving minimal disease activity (MDA): A. Five out of 7 criteria fulfilled. B. Five out of 6 criteria fulfilled. Data are observed values. For A, MDA is calculated using all 7 conditions with an enthesitis criterion of ≤ 1. Comparisons between adalimumab and placebo were significantly different from Week 4 ($p < 0.05$ at Week 4; $p < 0.001$ at Weeks 8 through 24). Note that a modified definition of MDA using enthesitis = 0 did not differ from this result (significant differences showed the same pattern). For B, MDA is calculated using 6 conditions (enthesitis is excluded). Comparisons between adalimumab and placebo were significantly different from Week 4 ($p < 0.05$ at Weeks 4 and 8; $p < 0.001$ at Weeks 12 through 24).

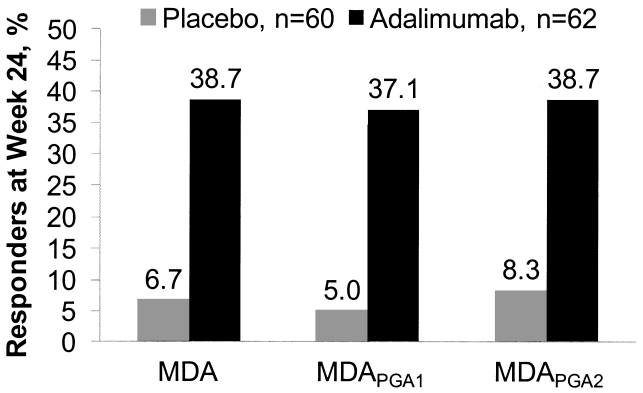

Figure 2. Percentage of patients achieving minimal disease activity (MDA), MDA$_{PGA1}$, and MDA$_{PGA2}$ at Week 24. MDA is calculated using all 7 conditions, with an enthesitis criterion of ≤ 1. For MDA$_{PGA1}$, PASI is replaced by PGA of "Clear." For MDA$_{PGA2}$, PASI is replaced by PGA of "Clear" or "Almost clear." PASI: Psoriasis Activity and Severity Index; PGA: physician global assessment. $P < 0.001$ for all treatment comparisons.

Table 2. Percentage of responders for individual criteria for minimal disease activity (MDA) at baseline* and Week 24**.

MDA Criteria	Placebo, %	Adalimumab, %
Tender joint count ≤ 1		
Baseline	0	0
Week 24	10.0	38.7
Swollen joint count ≤ 1		
Baseline	0	0
Week 24	13.3	32.3
Patient global assessment of disease activity ≤ 20		
Baseline	14.7	17.9
Week 24	18.3	50.0
Pain ≤ 15		
Baseline	8.8	6.0
Week 24	11.7	48.4
Health Assessment Questionnaire ≤ 0.5		
Baseline	27.5	23.9
Week 24	35.0	51.6
Enthesitis ≤ 1***		
Baseline	68.1	75.4
Week 24	66.7	82.0
Psoriasis Activity and Severity Index ≤ 1		
Baseline	4.4	1.5
Week 24	3.4	59.7
Physician global assessment "Clear"		
Baseline	0	0
Week 24	0	33.9
Physician global assessment "Clear" or "Almost clear"		
Baseline	1.5	1.5
Week 24	12.1	72.6

* n = 69 for placebo; n = 67 for adalimumab. ** n = 60 for placebo; n = 62 for adalimumab. *** Enthesitis: plantar fascia and Achilles tendon insertion.

that it does not work well when the affected BSA is < 3% or the PASI score is < 2.5%[23]. The definition of disease severity based on PASI and percentage of BSA values is limited because these measures do not include information about the location of the disease, response to previous treatment, patient history, and patients' perceptions of their disease and quality of life[24]. Overall, these observations indicate that under certain conditions, the PASI has limitations that may result in underestimation of treatment effect.

The simplicity of the PGA may make it more suitable than the PASI for settings outside clinical trials, such as clinical registries, and for use in clinical practice settings[18]. The PGA is well accepted by practicing clinicians and has been reported to have good interrater reliability, and it does not appear to be influenced by the amount of rater experience[25]. The use of an MDA index that includes the

Table 3. Agreement between Psoriasis Activity and Severity Index (PASI) and physician global assessment (PGA) outcome measures at Week 24.

PASI ≤ 1	PGA "Clear"		Observed Agreement, %	Kappa	PGA "Clear" or "Almost Clear"		Observed Agreement, %	Kappa
	Yes	No			Yes	No		
Yes	20	15	87	0.65	34	1	86	0.69
No	0	83			16	67		

PGA, rather than the PASI, may facilitate practical assessment of disease activity in patients with PsA included in large registries. A BSA < 3% is an alternative criterion to PASI ≤ 1 in the MDA proposed by Coates, *et al*[13]. That study did not evaluate MDA using the BSA alternative.

In our study, the proportions of patients at Week 24 who qualified as responders for the arthritis- and skin-related components of the MDA were high in the adalimumab group compared with the placebo group. By comparison, the between-group difference for the enthesitis component was smaller. However, the percentage of patients achieving the enthesitis score ≤ 1 increased in the adalimumab group from baseline, whereas this percentage was relatively unchanged in the placebo group. These results indicate that adalimumab effectively improved enthesitis, in addition to arthritis and skin manifestations. Assessment tools for enthesitis in PsA are often originally developed for use in other spondyloarthropathies, such as ankylosing spondylitis. Other measures of enthesitis, such as the Leeds and Spondyloarthritis Research Consortium of Canada Enthesitis Indices, had not been published at the time the ADEPT trial was designed[26,27]. The original MDA is open to any enthesitis count up to a maximum of 13 entheseal points[13]. In that study, the enthesitis score used to calculate the MDA was assessed for the heel only and was limited to a score of 4. It is possible that some patients would have scored > 1 for other entheseal points. However, the scoring system for enthesitis used in this study falls within the design of the MDA criteria.

Results from this posthoc analysis of the ADEPT trial demonstrated that MDA can be achieved in 37% to 39% of patients with PsA treated with adalimumab. Further, substitution of the PGA for PASI in the composite measure used to assess MDA did not affect outcomes significantly, and thus it appears that PASI ≤ 1 can be used in an interchangeable manner with PGA of "Clear," or PGA of "Clear" or "Almost clear." This substitution can make the MDA index more feasible to apply in clinical practice and registry settings.

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