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ORIGINAL ARTICLE

Measurement properties of the minimal disease activity criteria for psoriatic arthritis

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ABSTRACT

Objective To comprehensively assess evidence on the measurement properties of the minimal disease activity (MDA) criteria, a composite measure of the state of disease activity in psoriatic arthritis (PsA).

Methods A targeted literature review was conducted to identify studies that informed the validity and/or ability of the MDA to detect change among patients known to have experienced a change in clinical status. The search was conducted using MEDLINE and Embase databases (published as of October 2017). Pertinent articles provided by investigators and identified from select conference proceedings were also evaluated.

Results A total of 20 publications met the inclusion criteria. The MDA criteria were consistently associated with other indicators of disease activity/severity. The ability of the MDA criteria to detect change was supported in randomised controlled trials (n=10), with a greater percentage of patients randomised to active treatments achieving MDA relative to patients in comparator arms. Long-term observational studies (n=2) provided additional support for the ability of the MDA to detect within-subject change in the real-world settings.

Conclusion Evidence supports the MDA as a valid measure of disease activity in PsA that can detect between-group and within-subject change. The MDA is a comprehensive measure and clinically meaningful endpoint to assess the impact of interventions on PsA disease activity.

Key messages

What is already known about this subject?
► Psoriatic arthritis (PsA) is an immune-mediated disease with heterogeneous manifestations. Currently, available measures do not capture all relevant aspects of the PsA disease activity, thus emphasising the need for a disease assessment tool that is targeted and comprehensive, which can assess multiple domains of the disease.

What does this study add?
► This is a targeted literature review of the available evidence that supports utility, validity and relevance of the minimal disease activity (MDA) as a measure of disease activity in PsA.

How might this impact on clinical practice?
► This targeted literature review provides supportive evidence for MDA criteria as a targeted, practical and easy to interpret measure that can be used in both clinical practice and randomised controlled trials to assess disease activity in PsA.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory musculoskeletal disease.[1] As an immune-mediated disease with heterogeneous manifestations, it typically presents with skin and musculoskeletal symptoms, including skin and nail psoriasis, peripheral arthritis, enthesitis, dactylitis and spondylitis.[2,3] PsA may result in permanent joint damage leading to reduced health-related quality of life (HRQoL) and physical function.[2–4] Associated comorbidities include cardiovascular disease,[1,3,5] metabolic syndrome,[3,5] obesity,[3,5,6] depression,[1,3,5] anxiety,[1,3,5] and may include conditions, such as inflammatory bowel disease[3,5] and uveitis.[5,7] Prevalence among the general population has been reported to range from 1 to 420 cases per 100 000 globally; and 250 cases per 100 000 in the USA.[8] Among patients with psoriasis, the prevalence varies from 6% to 41% depending on study methodology[3] and the annual incidence has been reported to be approximately 3% in patients followed prospectively.[9] Diagnosis and assessment of PsA is complex as a result of heterogeneity in disease presentation and the presentation of symptoms that evolve over the course of the disease.[10,11] Patients can experience periods of disease flares, minimal disease activity (MDA) and remission.[12]

The ultimate treatment goal for PsA is clinical remission or inactive disease.[13,14] Since, for many patients, complete remission may

Table 1 Relationship between MDA status and CRP

Author (year)	Study description	Sample size	MDA subgroup	CRP score, median (IQR); mean (SD)
Coates and Helliwell (2010)[22]	Post hoc analysis of two RCTs to validate the MDA criteria	157	MDA (n=63)	Median, 0.4 mg/dL (0.4–0.6)
			Non-MDA (n=94)	Median, 0.5 mg/dL (0.4–1.3)
			P value	0.019
Queiro et al (2017)[25]	Cross-sectional observational study	277	MDA (n=133)	Mean, 2.8 mg/L (3.9)
			Non-MDA (n=144)	Mean, 4.7 mg/L (8.2)
			P value	<0.05

CRP, C reactive protein; MDA, minimal disease activity; Non-MDA, patients not achieving MDA; RCT, randomised controlled trial.

be difficult to attain, MDA, low or very low disease activity (VLDA) have been proposed as alternative goals. Given the multiple domains of PsA, a composite endpoint that captures all relevant aspects of the disease is critical to the overall interpretation of research study results and patient management. The PsA core domain set recommended by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)/Outcome Measures in Rheumatology (OMERACT) for randomised controlled trials (RCTs) and long-term observational studies includes musculoskeletal disease activity, skin disease activity, fatigue, pain, patient global assessment (PtGA), physical function, HRQoL and systemic inflammation (defined by acute phase reactants) as key domains that are important to both patients and physicians.[15] The most common PsA endpoint for Food and Drug Administration approval of treatments is the American College of Rheumatology (ACR) response criteria,[16] which were developed as an endpoint for rheumatoid arthritis RCTs. The ACR response criteria do not capture the distinct features of PsA, such as enthesitis, dactylitis, axial disease or skin manifestations, thus, additional instruments to assess these manifestations are included in RCTs, such as the Psoriasis Area Severity Index (PASI) and assessments for the presence of dactylitis and enthesopathy.[17–19] Several composite disease measures have been proposed, including Disease Activity in Psoriatic Arthritis (DAPSA; focuses solely on arthritis), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PASDAS), Psoriatic Arthritis Response Criteria (focuses solely on arthritis) and GRAPPA Composite Exercise Index.[20] These measures are all continuous and remission is generally defined as a score below a cut-off value.

Recognising the need for a tool to better capture heterogeneous disease activity among PsA patients that equates to a clinically meaningful indicator of disease status, Coates et al developed a PsA-specific, composite measure of disease state, the MDA criteria.[21 22] The MDA criteria were developed consistent with OMERACT recommendations. In contrast to continuous measures, the MDA serves as an indicator of the current state of PsA disease.[20] Patients achieve MDA if they meet five of seven criteria: tender joint count ≤1; swollen joint count ≤1; PASI ≤1 or body surface area (BSA) ≤3; patient pain Visual Analogue Scale (VAS) ≤15; PtGA ≤20; Health Assessment Questionnaire (HAQ) ≤0.5 and tender entheseal points≤1 (21). MDA response rates have been assessed in longitudinal observational studies (LOSs) and RCTs.[20] Individual components of the MDA criteria are well established. Of the seven individual components, five components are included in the ACR response criteria and the remaining two components (ie, PASI ≤1 or BSA ≤3 and tender entheseal points ≤1) have been used in RCTs to assess the efficacy of PsA treatments. The MDA is gaining acceptance as a meaningful composite index that can be used to monitor disease activity across all PsA clinical pathologies[23] and has been proposed as a comprehensive measure for treat-to-target (T2T) approach in PsA.[13] Recently, VLDA has become a clinically relevant benchmark for disease remission and has been defined as meeting seven of the seven MDA criteria.[23]

The objectives of this targeted literature review were to comprehensively assess evidence regarding the performance characteristics of the MDA criteria and their utility as a measure of disease activity in PsA. Specifically, this review focused on summarising evidence of the validity of the MDA criteria, and the ability of the MDA criteria to detect between-groups and within-patient differences. The focus of this review was on MDA but when available, VLDA was reported.

METHODS

Search methodology

A targeted literature review was conducted to identify the existing evidence for the measurement properties of the MDA. Publications were identified using MEDLINE with PubMed Interface and Embase databases and there were no language or time frame restrictions for the literature search. The search terms used from controlled vocabularies MeSH were: 'minimal disease activity, minimal disease activity index, minimal disease activity measure, psoriatic arthritis, psoriatic arthropathy, surveys and

Table 2 Relationship between MDA status and measures of structural damage

Author (year)	Study description	Definition joint damage progression	Analysis population/ subgroups	Time point	Subgroup	Measure
Cross-sectional studies						**Presence of hand erosions**
Queiro et al (2017)[25]	Cross-sectional observational study	Presence of hand erosions by radiographic evidence	—	—	MDA (n=133)	30.8%
					Non-MDA (n=144)	44.7%
					P value	<0.05
Longitudinal studies						**Percentage of patients with no progression of joint damage or mean (SD) of joint damage score**
Coates et al (2010)[26]	Prospective longitudinal observational study to establish the frequency and predictors of MDA	If any joint changed from being non-damaged to damaged	MDA at consecutive visits* ≥12 months (n=116)	Mean follow-up 34 months	MDA (n=116)	69
			Non-MDA (n=228)		Non-MDA (n=200)	51
					P value	<0.001†
Coates and Helliwell (2010)[22]	Post hoc analysis of two RCTs to validate the MDA criteria	Increase in modified SHS score of >0	Phase II RCT (n=63)	Week 50	MDA (n=26)	96
					Non-MDA (n=37)	67
					P value	0.012
				Week 100	MDA (n=12)	100
					Non-MDA (n=25)	58
					P value	0.03
			Phase III RCT (n=157)	Week 54	MDA (n=63)	78
					Non-MDA (n=94)	57
					P value	0.009
Geijer et al (2015)[27]	Prospective longitudinal observational study to evaluate the course of the disease and identify predictors of progression	Wassenberg score	—	256 week follow-up	MDA (males‡, n=10)	3.4 (3.99)
					Non-MDA (males, n=19)	10.94 (14.36)
					P value	0.042
Kavanaugh et al (2016)[28]	Post hoc analysis of RCT, placebo to explore relationship of MDA to radiographic progression	Increase in SHS score >0	In MDA ≥3 consecutive visits over the course of the 256 week study (n=116)	256 weeks	MDA (n=41)	35.3
					Non-MDA (n=75)	NR
					P value	0.054
			In MDA ≥4 consecutive visits over the course of the 256 week study (n=95)	256 weeks	MDA (n=34)	35.8
					Non-MDA (n=61)	23.2
					P value	0.056

*Patients evaluated every 6–12 months.
†P value represents comparison of mean change in joint damage over the study period in MDA versus non-MDA.
‡Mean scores not reported for females; however, it was noted that the statistical comparison of joint damage for MDA versus non-MDA was not significant.
MDA, minimal disease activity; Non-MDA, patients not achieving MDA; NR, not reported; RCT, randomised controlled trial; SHS, Sharp/van der Heijde Score.

questionnaires, questionnaires and rating scales, outcome assessment, minimal important change,' and combinations thereof. In addition, pertinent articles provided by the investigators were evaluated for selection, including abstracts from conference proceedings from the annual ACR meetings and EULAR meetings. The same selection criteria were applied to articles identified in literature databases and to conference abstracts.

Publications were identified in two separate literature searches. The first was conducted in February 2016; this search was updated in October 2017.

Study selection and data extraction

After an initial screen of title and abstract, potentially relevant full-text publications were retrieved for further review. Articles were included if they provided evidence regarding the development or measurement properties of the MDA. Publications were excluded if they met any of the following criteria: reported only the rationale for developing the MDA; examined the relationship between baseline variables associated with achievement of MDA but did not inform measurement properties; clinical effectiveness studies with no comparator group; and

Table 3 Relationship between MDA status and PRO measures

Author (year)	Study description	Sample size	Time point	Criterion variable	MDA subgroup	Score
Cross-sectional studies						**Mean (SD)**
Queiro et al (2017)[25]	Cross-sectional observational study	277	—	PsAID total score*	MDA	3.3 (3.1)
					Non-MDA	7.1 (5.2)
					P value	<0.001
Longitudinal studies						**Change from baseline**
Mease et al (2017a)[31]	Post hoc analysis of RCT to validate MDA criteria and HRQoL outcomes	135	Week 24	SF-36 PCS	MDA	13.3
					Non-MDA	3.5
					P value	<0.001
				SF-36 MCS	MDA	5.0
					Non-MDA	0.3
					P value	<0.01
				DLQI total	MDA	−5.8
					Non-MDA	−2.8
					P value	0.01
				FACIT Fatigue	MDA	8.6
					Non-MDA	1.3
					P value	0.001
Coates et al (2016)[30]	Post hoc analysis of RCT to validate MDA criteria and HRQoL outcomes	397	Week 24	SF-36 PCS	MDA	9.0
					Non-MDA	4.6
					P value	<0.001
				SF-36 MCS	MDA	6.9
					Non-MDA	4.1
					P value	<0.01
				DLQI	MDA	−9.9
					Non-MDA	−7.5
					P value	<0.01
				FACIT fatigue	MDA	9.0
					Non-MDA	4.9
					P value	<0.001
				PsA QoL	MDA	−5.2
					Non-MDA	−3.3
					P value	<0.001
			Week 52	SF-36 PCS	MDA	9.9
					Non-MDA	4.6
					P value	<0.001
				SF-36 MCS	MDA	6.8
					Non-MDA	4.4
					P value	<0.01
				DLQI	MDA	−10.7
					Non-MDA	−8.5
					P value	<0.01
				FACIT fatigue	MDA	9.5
					Non-MDA	5.4
					P value	<0.001
				PsA QoL	MDA	−5.7
					Non-MDA	−3.4
					P value	<0.001

*PsAID total score ranges from 0 (best health status) to 10 (worst health status).
DLQI, Dermatology Life Quality Index; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; MCS, Mental Component Score; MDA, minimal disease activity; Non-MDA, patients not achieving MDA; PCS, Physical Component Score; PROs, patient-reported outcomes; PsAID, Psoriatic Arthritis Impact of Disease; PsA QoL, psoriatic arthritis quality of life; RCT, randomised controlled trial; SF-36, Short Form 36 Health Survey.

Table 4 Kappa's agreement between MDA and alternate disease activity criteria

Author (year)	Study description	Sample size	Time point	Criterion	κ
Measures of disease activity					
Coates and Helliwell (2016)[32]	Prospective longitudinal observational study of GRACE dataset collected from 32 countries to explore the relationship between MDA and low disease activity cutoffs	503	Week 24	PASDAS	0.73
				CPDAI-4	0.75
				CPDAI-3	0.75
Rahman et al (2017)[33]	Prospective longitudinal observational study	223	12 months	DAS28 (<2.6)	0.65
				DAS28 deep remission (1.98)	0.60
				DAPSA remission (≤4)	0.65
Lubrano et al (2015)[34]	Prospective longitudinal observational study to compare PtGA with MDA and other outcome measures.	124	4 months	PtGA	0.73
			8 months	PtGA	0.72
			12 months	PtGA	0.73
Categorical measures					
Coates and Helliwell (2016)[32]	Described above	503	Week 24	MDA-joints*	0.86
				MDA-phys†	0.48

*BSA, and not the PASI, was the cut-off used for the skin domain.
†MDA as judged by the treating physician=do you think this patient is in an MDA state? (yes/no).
BSA, body surface area; CPDAI, Composite Psoriatic Disease Activity Index; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28, Disease Activity Score using 28 joints; GRACE, Group for Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Composite Disease Exercise; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PtGA, patient global assessment.

conference abstracts except those reporting results of phase III RCTs.

All studies were reviewed by an independent reviewer and the following data were extracted: author and year of publication; study characteristics, including study design and type (including but not limited to RCTs and post hoc analysis of RCTs; LOS and post hoc analyses of LOS; study years; sample size; study population characteristics; experimental treatment and findings related to the measurement properties of the MDA.

To evaluate the validity of the MDA, reported clinical endpoints were assessed and descriptive data and statistical comparisons were extracted for patients in MDA versus non-MDA for the following variables, where available:

1. C reactive protein (CRP)—patients in MDA were expected to have lower CRP levels, indicative of overall lower levels of inflammation.
2. Structural damage—patients in MDA were expected to have less evidence of joint damage by radiographs and/or clinical report.
3. Patient-reported outcomes (PROs)—patients in MDA were expected to report better HRQoL, physical and mental function, and lower levels of fatigue relative to patients not in MDA.

To further evaluate the validity of the MDA, Kappa's agreement statistics were summarised between MDA and alternate measures of disease activity, where available. The kappa values associated with the level of agreement are as follows: none (κ=0–0.2); minimal (κ=0.21–0.39); weak (κ=0.40–0.59); moderate (κ=0.60–0.79); strong (κ=0.80–0.90) and almost perfect (κ>0.90).[24]

To determine the ability of the MDA to detect changes in clinical studies, descriptive data and statistical comparisons were extracted for treatment and comparator groups in RCTs and LOS. Study drugs with known efficacy were assessed for the percentage of patients taking the active treatment relative to the comparator arm in achieving MDA; a greater percentage receiving active treatment were expected to achieve MDA compared with those receiving placebo.

RESULTS
Search results and study characteristics
The combined literature reviews identified 20 relevant publications that provided information on the measurement properties of the MDA and these were selected for data extraction. One publication was a conference abstract presenting results of a phase III trial and the remainder of the publications were journal articles. Of these 20 publications, nine articles reported results from observational studies and the remaining reported results from RCTs. All publications that met eligibility criteria are summarised in online supplementary table S1.

Validity
MDA status and CRP
Two studies assessed the relationship between MDA and CRP, a marker of systemic inflammation (table 1).

Coates and Helliwell evaluated the ability of the MDA to differentiate among patients based on CRP and found an association between CRP levels and achievement of MDA.[22] In this analysis, CRP levels were significantly lower in patients who achieved MDA than in those who did not (p=0.019). Results of a cross-sectional observational study among Spanish PsA patients published by Queiro et al were consistent with the above findings.[25] Queiro et al reported that CRP scores were significantly lower in patients in MDA than in those who were not (p<0.05).

Table 5 Ability to detect change in RCTs

Author (year)	Study description	Sample size		Time point	Primary comparison	Percentage of patients achieving MDA
		Total	PsA only			
Coates and Helliwell (2010)[22]	Post hoc analysis of two RCTs to validate the MDA criteria	Phase 2=63	63	Week 16	Infliximab	48
					Placebo	3
					P value	<0.0001
		Phase 3=157	157	Week 24	Infliximab	52
					Placebo*	21
					P value	<0.001
Coates et al (2016)[30]	Post hoc analysis of phase III RCT	397	397	Week 16	Secukinumab 150 mg	23
					Secukinumab 300 mg	28
					Placebo	10
				Week 52	Secukinumab 150 mg	33
					Secukinumab 300 mg	35
Gladman et al (2017)[41]	Phase III RCT, placebo	394	394	Week 12	Tofacitinib 5 mg	22.9
					Tofacitinib 10 mg	21.2
					Placebo	14.5
					P value	NR
				Week 28	Tofacitinib 5 mg	23.7
					Tofacitinib 10 mg	23.5
					Placebo/tofacitinib 5 mg	18.2
					Placebo/tofacitinib 10 mg	29.2
					P value	NR
Kavanaugh et al (2016)[28]	Post hoc analysis of RCT, placebo to explore relationship of MDA to radiographic progression	395	395	Week 14	Golimumab	23.5
					Placebo	1
					P value	<0.0001
				Week 24	Golimumab	28.1
					Placebo	7.7
					P value	<0.0001
				Week 52	Golimumab	42.4
					Placebo	30.2
					P value	<0.0001
				≥5 consecutive time points	Golimumab	24.9
					Placebo	12.3
					P value	0.007
				≥6 consecutive time points	Golimumab	16.6
					Placebo	2.8
					P value	0.000
				≥7 consecutive time points	Golimumab	11.4
					Placebo	0
					P value	0.000
Mease et al (2017)[31]	Phase III RCT (week 24—active treatment end of study; weeks 48–144—open-label extension)	313	136	Week 24	Adalimumab	36.4
					Placebo	5.8
					P value	<0.001
				Week 48 (open-label extension)	Adalimumab	43.1
					Adalimumab naïve	32.2
				Week 96 (open-label extension)	Adalimumab	37.9
					Adalimumab naïve	27.1
				Week 144 (open-label extension)	Adalimumab	34.5
					Adalimumab naïve	22.0

Continued

Table 5 Continued

Author (year)	Study description	Sample size Total	PsA only	Time point	Primary comparison	Percentage of patients achieving MDA
Mease et al (2014)[42]	Post hoc analysis of RCT data to explore relationship with MDA	409	409	Week 24	Certolizumab pegol (200 mg and 400 mg)	33.3; 34.1
					Placebo	5.9
					P value	<0.001
Mease et al (2015)[43]	Post hoc analysis of RCT data to explore relationship with MDA	409	409	Week 48 (imputation)	Certolizumab pegol (combined patients randomised to active treatment at baseline)	38.8
				Week 96 (imputation)	Certolizumab pegol (combined patients randomised to active treatment at baseline)	41.0
Mease et al (2017)[19]	Post hoc analysis of RCT, placebo to investigate achievement of MDA	424	424	Week 24	Abatacept	11.7
					Placebo	8.1
					P value	0.205
				Week 52 (open-label extension)	Abatacept	17.4
					Placebo/abatacept	18.5
					P value	NR
Mease et al (2017)[44]	Phase III RCT to investigate achievement of MDA	422	422	Week 12	Tofacitinib (5 mg and 10 mg)	26.0; 26.0
					Adalimumab	25.0
					Placebo (pooled)	7.0
					P value	NR
				Week 52	Tofacitinib (5 mg and 10 mg)	37.0; 43.0
					Adalimumab	40.0
					Placebo/tofacitinib (5 mg and 10 mg)	31.0; 34.0
					P value	NR
Nash et al (2017)[45]	Post hoc analysis of RCT, placebo to investigate achievement of MDA	363	363	Week 24	Ixekizumab (2 weeks; 4 weeks)	24.0; 28.0
					Placebo	3
					P value	<0.0001

*Forty-seven patients in the placebo group entered the early escape arm at week 16 and received infliximab.
MDA, minimal disease activity; NR, not reported; PsA, psoriatic arthritis; RCT, randomised controlled trial.

MDA status and measures of structural damage

Queiro et al reported the relationship between MDA and presence of radiographic erosions in the hands and feet in a cross-sectional study (table 2).[25]

Patients in MDA were less likely to have evidence of hand erosions compared with those who were not (p<0.05); however, there were no significant differences among patients when evaluating presence of erosions in the feet.

Four longitudinal studies reported the progression of structural damage over time in patients achieving MDA and in those who did not (table 2).[22 26–28] Across these studies, patients in MDA had lower rates of structural damage progression; these differences were statistically significant in three of four studies. In a post hoc analysis of phase II and phase III RCTs, Coates and Helliwell reported that patients in MDA were less likely to exhibit structural damage progression.[22] In the phase II RCT, patients achieving MDA were significantly less

likely to have increases >0 in the modified Sharp/van der Heijde Scores (SHS) at week 50 (p=0.012) and week 100 (p=0.03) compared with patients not in MDA. In the phase III trial, patients in MDA at week 54 were also less likely to have evidence of structural damage progression (p=0.009). Kavanaugh et al conducted a post hoc analysis of a phase III RCT that reported the relationship between achievement of MDA over consecutive study visits (≥3 visits and ≥4 visits) and increases in SHS >0 over the 256-week treatment period.[28] Results for both subgroups (≥3 and ≥4) were in the anticipated direction; however, they were not statistically significant (p=0.054 and p=0.056, respectively). Coates et al assessed the rate of structural damage progression over a 5-year prospective LOS among patients in MDA and those who were not.[26] The average follow-up was 34 months and patients in MDA were significantly less likely to have structural damage progression (p<0.001). The rate of structural damage progression by the

Table 6 Ability to detect change in prospective LOS

Author (year)	Study description	Sample size	Treatment	Time point	Percentage of patients achieving MDA
Rahman *et al* (2017)[33]	Biological treatment registry to examine MDA rate over time	233	Infliximab, golimumab, ustekinumab	Baseline	11.7
				Week 26	43.5*
				Week 52	44.8*
				P value	<0.001
Perrotta *et al* (2016)[36]	Prospective longitudinal study to examine MDA status with the indices of disease activity and to identify predictors for MDA	75	Adalimumab, etanercept, golimumab	Baseline	0
				4 months	22.6
				8 months	56.0
				12 months	61.3†

*P<0.001.
†Article reports the percentage of patients achieving MDA status at 12 months was significantly different from baseline but does not report p value.
LOS, longitudinal observational studies; MDA, minimal disease activity.

Wassenberg score over a 256-week follow-up period in a prospective LOS has been reported by Geijer *et al* for a cohort of PsA patients in Sweden and was found to be significantly lower among patients in MDA (p=0.042).[27]

MDA status and PROs

Three studies examined the relationship between MDA status and PROs and are summarised in table 3.

The relationship between MDA status and physical and psychological function measured by the PsA Impact of Disease Questionnaire (PsAID) was evaluated by Queiro and colleagues in an observational, cross-sectional study.[25] The PsAID measures the physical and psychological impact of disease on patients' lives.[29] Results indicated that patients in MDA reported significantly lower impacts of disease than patients who were not in MDA across all domains and total PsAID scores (p<0.001).[25] Eighty-eight (66.7%) MDA patients reported a PsAID score <4 compared with 34 (37.4%) non-MDA patients (p<0.0001).

Two studies reported the relationship between changes over time in PROs and MDA. In both, patients in MDA reported significantly more improvements across all PROs assessing HRQOL and fatigue: Short Form 36 Health Survey, Dermatology Life Quality Index (DLQI), Functional Assessment of Chronic Illness Therapy-Fatigue, and PsA quality of life.[30 31] Additional data from these studies are summarised in table 3.

AGREEMENT BETWEEN MDA AND ALTERNATIVE MEASURES OF DISEASE ACTIVITY

Several publications evaluated the relationship between MDA and other overall disease activity indicators (such as the PASDAS, CPDAI, Disease Activity Score (DAS), DAPSA and PtGA) by calculating Kappa's (κ) coefficients (table 4).

Coates and Helliwell reported moderate agreement (κ=0.73–0.75) with three alternative definitions of treatment responses: PASDAS, CPDAI-4 and CPDAI-3.[32] Agreement was also strong for MDA joints (κ=0.86) but weak for MDA-phys (κ=0.48). The relationship between MDA and disease activity reported by the patient (measured as a patient-reported overall indicator of disease activity) was also evaluated. The κ coefficient between MDA and patients' rating of whether they were in a minimal disease state was 0.30.

Rahman *et al* reported a moderate κ agreement between achievement of MDA and three additional disease activity measures, including DAS using 28 joints (DAS28, <2.6), DAS28 deep remission (DAS28 <1.98) and DAPSA remission (≤4).[33] Lubrano *et al* reported moderate agreement between MDA and a single item of the MDA, PtGA (κ=0.72–0.73).[34] As part of the same LOS, Lubrano *et al* then evaluated the sensitivity and specificity in differentiating patients rated by their physician as being in MDA (<10 mm on a 100 mm VAS) versus a higher disease state (≥10); sensitivity was 0.90 (0.74–0.98) and specificity 0.69 (0.57–0.79).[35]

Ability to detect change

Ten RCTs that provide evidence on the between-patient treatment effects of the MDA were identified (table 5) and indicated that those who received treatment with a targeted immunomodulator were significantly more likely to achieve MDA than those who received placebo.

Two prospective LOS provide evidence on the within-patient treatment effects (table 6). In these studies, over 1 year of treatment with a disease-modifying antirheumatic drug resulted in an increasing proportion of patients achieving MDA.[33 36]

Very low disease activity

One study reported both MDA and VLDA from a post hoc analysis of a 24-week RCT that compared adalimumab to placebo. Mease *et al* reported that of 66 patients receiving adalimumab, 24 (36.4%) achieved MDA and 10 (15.4%)

VLDA. In contrast, of 69 patients in the placebo group, only four (5.7%) and zero (0%), respectively, achieved MDA and VLDA.[31]

DISCUSSION

This targeted literature review assessed the current evidence of the performance characteristics of the MDA criteria and their utility as a measure of disease activity in PsA. The validity and relevance of the MDA as a measure of disease activity was strongly supported based on the strength and consistent association between MDA status and each of these domains.

Across studies, MDA responses were in the anticipated direction of other disease indicators, such as CRP, structural damage progression, patient-reported HRQoL, pain and fatigue and global assessments of disease activity. The consistency reported in the literature provides strong evidence that MDA is a valid indicator of disease activity in PsA.

MDA is frequently reported in RCTs that examine the efficacy of treatments for PsA. Across all RCTs included in this literature review, a greater proportion of patients assigned active treatment achieved MDA versus placebo/control groups. A growing body of evidence also supports the ability of the MDA criteria to detect within-patient changes over time, providing further support for its use in LOS and RCTs.

Recent T2T recommendations have highlighted the aspiration for remission or VLDA, but for many patients, low disease activity or MDA may be an appropriate treatment target.[13] The MDA criteria have been recommended by both the T2T international task force[13] and the GRAPPA/OMERACT group to assess treatment target goals.[37] While MDA does not measure disease activity, it is a feasible target of treatment assessing multiple domains of the disease. The MDA criteria can be used in all patients with PsA regardless of their disease pattern, whereas other measures do not reflect disease activity across all subgroups of PsA. It gives a target that is appropriate for both polyarticular and oligoarticular patients. In some other measures (eg, ACR response and DAPSA) of disease activity the focus is primarily on articular inflammation,[13] which may not reflect the full range of disease activity in some PsA patients. PASDAS is another disease activity measure that covers multiple domains, but it does not include skin and is complex to use in clinical practice at present.

Measures like MDA that generally focuses on multiple domains of the disease can evade inclusion of patients having an active domain, which may otherwise be categorised as cohort with remission or low disease activity. van Mens et al reported that prevalence of skin disease was higher in patients with PsA who had DAPSA remission compared with other measures. Given that DAPSA is an unidimensional measure, it particularly focuses only on peripheral joint disease. Hence, it does not address important manifestations of PsA, where MDA, a multidimensional measure, addresses all of them.[38] In a recently published study, Coates et al concluded that in comparison with DAPSA, definitions of VLDA and MDA are more stringent in evaluating PsA.[39]

The MDA criteria offer a targeted and easy to interpret disease assessment, and have been incorporated into both clinical practice and trial settings.[38] MDA is based on commonly performed clinical examinations, with some additional, easy to administer PROs (ie, PtGA, pain VAS and HAQ) and skin evaluations (ie, PASI or BSA), and determining MDA requires minimal training and time for the required assessments. PRO measures are increasingly being incorporated into clinical practice settings, which will further enable assessment of MDA.[40]

There are several limitations to this targeted literature review that warrant consideration when interpreting the results presented in this manuscript. This review sought to qualitatively characterise information on the measurement properties of the MDA. Although a thorough search strategy was employed to capture all pertinent publications, the potential exists that not all relevant publications were identified. Further investigation into this is needed to evaluate stability of the score among patients with stable disease activity. Furthermore, each of the studies included in this review used different methodological approaches to study design (cross-sectional vs longitudinal), population analysed, study duration and endpoints evaluated, thereby limiting the ability to collectively summarise findings.

This literature review provides a detailed evaluation of the measurement properties of the MDA and shows strong evidence for the validity of the MDA as a measure of PsA disease activity and its sensitivity to detect changes with treatment. Substantial data support its use as a practical, comprehensive and clinically meaningful endpoint for clinicians to assess the impact of specific treatment interventions on PsA disease activity.

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