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Minimal disease activity in Axial Spondyloarthritis: the need of the hour and a proposal for development

Atul Deodhar¹, Anand Kumthekar¹, and Maureen Dubreuil^{2,3}

¹Oregon Health & Science University, Portland, OR

²Boston University School of Medicine, Boston, MA

³VA Boston Healthcare System, Boston, MA

Abstract

Purpose of review—Axial Spondyloarthritis (axSpA) is a chronic inflammatory condition with articular and extra-articular manifestations. Remission, a state of absence of clinical and imaging signs of disease activity over time, is the goal of management. This review addresses the concept of minimal disease activity (MDA) in axSpA, which is less stringent than remission, and is closer to patient and provider acceptable low disease state.

Recent findings—Existing axSpA treatments improve physical function and quality of life, and lead to remission in a minority of patients. A consistent MDA state decreases disease progression in rheumatoid arthritis and psoriatic arthritis. We argue a need to develop MDA in axSpA for clinical practice and clinical trials; and propose methodology. Considering that MDA will be used in clinical practice, its elements must be easy to collect and cover both musculoskeletal and extra-articular domains. MDA will complement current disease activity measures in axSpA.

Summary—Defining an MDA target in axSpA would provide an outcome measure that is less stringent than remission, and will likely predict function and quality of life. We propose methods to develop MDA in axSpA and that further research be performed is required to determine if treating to an MDA target in axSpA.

Keywords

Minimal disease activity (MDA); Axial Spondyloarthritis (axSpA); Remission; Outcome Measure

Introduction and Background

Minimal disease activity, as defined by the Outcome Measure in Rheumatology Clinical Trials (OMERACT) 6 conference, encompasses both remission and low disease activity. MDA is a state that is deemed “a useful target of treatment by both patient and physician, given current treatments and knowledge”. MDA allows a small amount of residual disease activity, and is not a state of complete remission. MDA criteria have been developed for

Correspondence: Atul Deodhar, MD, Division of Arthritis and Rheumatic Diseases (OP09), Oregon Health & Science University, Portland, OR. 97239, deodhara@ohsu.edu.

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rheumatoid arthritis (RA) and for psoriatic arthritis (PsA).[1, 2] Development of MDA in RA and PsA have taken advantage of the OMERACT core sets. It has been shown that maintenance of an MDA state decreases the progression of joint damage.[3, 4] One study has also demonstrated that early achievement of MDA can be considered a predictor of treatment efficacy with TNF inhibitors (TNFi) in PsA.[5]

Disease activity in axSpA is correlated with both, radiographic and functional outcomes

In RA, greater disease activity, as measured by the DAS28, is correlated with both functional loss and radiographic damage.[4, 6] In AS, parallel relationships have been demonstrated between disease activity and both function and spinal radiographic changes. The OASIS study, which followed 184 AS patients for 12 years, found that for every unit increase in disease activity (Ankylosing Spondylitis Disease Activity Score; ASDAS), the radiographic damage as measured by modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), worsened by 0.72 units over 2 years. At study end, those with high disease activity had nearly twice the radiographic damage as those with inactive disease.[7] Similarly, the German cohort, GESPIC, demonstrated associations in a combined population of AS and nr-axSpA (n=178).[8] In GESPIC, the mSASSS increased by more than 2 units per unit increase in the time-averaged ASDAS. Disease activity was associated with syndesmophyte formation; no patients with low disease activity developed syndesmophytes, but 29% of those with very high disease activity had new syndesmophyte development or syndesmophytes progression.

Function in axSpA may reflect accrued damage over time, but evidence also shows that greater disease activity is associated with impaired function. Analysis of 2 year data from OASIS found that AS disease activity (BASDAI), was correlated with two patient-reported functional indices: BASFI (r=0.66) and the Dougados Functional Index (DFI; r=0.59), independent of structural changes.[9] Similarly, meta-analysis of clinical trials of TNF-inhibitors in AS demonstrated consistent improvements in disease activity and physical function, despite the fact that trials have not shown reductions in structural changes over periods up to 2 years.[10]

MDA Development in Other Forms of Arthritis

Rheumatoid Arthritis

The need for a definition of MDA in patients with RA was based on the conclusions from the TICORA study, which showed that intensive control of disease activity in RA reduced radiographic progression of disease, and improved physical function and quality of life.[11] It was therefore thought that achieving and maintaining a low disease activity or remission state was important in the long-term management of RA.

The MDA definition for RA was developed in a three-step process.[2] Firstly, an MDA discussion group was convened at the American College of Rheumatology (ACR) meeting in 2003. At this meeting agreement was reached on candidate measures to consider in the initial definition of MDA, and an opinion-based stakeholder survey on possible operational

definitions of MDA was developed. The second step in early 2004, was the stakeholder survey to derive a limited set of possible definitions for MDA. At the OMERACT 7 meeting, participants discussed this limited set of candidate definitions and chose an agreed definition. A database of 730 consecutive RA patients in 40 clinics around the US and Canada was used to obtain 60 subject profiles for inclusion in a subsequent questionnaire. The measures in the profile were from the RA core set as developed by OMERACT (i.e. pain, swollen joints, tender joints, HAQ, physician global, patient global and ESR). For each profile, respondents were asked “Is the patient described in the profile in MDA?” If 80% of respondents classified the profile as MDA, then the profile was considered to correspond to a patient in MDA. Thirty-eight respondents reviewed the profiles and there was 90%, 80%, and 70% agreement that 15, 17, and 22 profiles, respectively, were representative of MDA. In the end, the 80% consensus was selected as the threshold for the remainder of the project, and final MDA definitions were agreed upon, based on either DAS28 score of 2.85 or the core set definition. The core set MDA definition could be met if a patient had no tender or swollen joints and an ESR ≤ 10 , or if 5/7 of the following criteria were met:

- Pain ≤ 2 (VAS 0–10)
- Swollen joint count ≤ 1
- Tender joint count ≤ 1
- Health Assessment Questionnaire (HAQ) ≤ 0.5
- Physician global ≤ 1.5 (VAS 0–10)
- Patient global ≤ 2 (VAS 0–10)
- ESR ≤ 20 mm/h

Psoriatic Arthritis

One rationale for developing MDA criteria in PsA was the broad disease spectrum and complexity, which affects domains beyond the joints. The OMERACT 8 agreed upon a core set of measures for PsA in 2006 and these were used as an anchor to develop the MDA criteria.[1] A questionnaire was compiled consisting of 40 PsA patient profiles that included the following measures: tender joint count, swollen joint count, enthesitis count, psoriasis area and severity index (PASI), psoriasis body surface area (BSA), VAS pain, patient global disease activity, and HAQ. The questionnaire included the OMERACT definition of MDA and was sent electronically to rheumatologists and dermatologists identified through membership of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). The respondents were told “This patient comes to see you in the clinic. He/she has been on a stable dose of disease modifying anti-rheumatic drug (DMARD) therapy for over 6 months. Do you consider this patient to be in a ‘minimal disease activity’ state?” A 70% agreement was selected as a reasonable consensus, and profiles were classified as MDA if that threshold of agreement was reached between respondents. The final PsA MDA definition required 5/7 of the following criteria to be met:

- Tender joint count ≤ 1
- Swollen joint count ≤ 1

- PASI = 1 or BSA = 3
- Pain = 15 (VAS 0–100)
- Health Assessment Questionnaire (HAQ) = 0.5
- Patient global = 20 (VAS 0–100)
- Tender entheseal points = 1

Instruments for disease activity measurement in axSpA

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) are the most widely adopted disease activity instruments in axSpA.[12, 13] BASDAI can be simply calculated as a weighted average of 6 patient-reported questions regarding fatigue, spinal pain, pain originating in peripheral joints, enthesal pain, and morning stiffness. ASDAS includes 4 patient-reported questions, but additionally requires an ESR or CRP measurement and calculation of a complicated formula using a dedicated application or web-based calculator for most users (available on the ASAS website, <http://www.asas-group.org/mission-statement.php>). There is no validated definition for disease remission using BASDAI, although a threshold of 3 has been used in clinical trials for low disease activity.[14] In ASDAS, remission is defined as a score under 1.3, moderate disease activity 1.3–2.1, high disease activity 2.1–3.5 and very high disease activity >3.5.[15] ASAS also has developed treatment response criteria, 5/6 (domain) improvement criteria and partial remission criteria. Each of these instruments *additionally* includes an assessment of function (BASFI). The functional assessment, though critically important to patients, does not necessarily reflect current disease activity, as prior damage may have led to functional loss that may not be restored even with complete disease remission.[16, 17]

Limitations of existing disease activity measures

While thresholds for disease activity in axSpA have been established using rigorous methodology, and have been validated for the ASDAS, both the ASDAS and the BASDAI have important limitations, including their focus on only the musculoskeletal manifestations of axSpA. Given that axSpA commonly has extra-articular manifestations, such as uveitis, skin disease, nail disease, and inflammatory bowel disease, the lack of any assessment of these features in existing disease activity instruments is notable.

For example, a man with a 40-year history of AS and a fused spine may have low BASDAI and ASDAS scores indicating “remission” on treatment with a TNF-inhibitor, despite recurrent attacks of acute anterior uveitis leading to vision loss. Failure to account for extra-articular disease activity in axSpA may lead to inappropriately optimistic assessments using the existing axSpA disease activity instruments. The other drawback of the ASDAS is that, neither the ESR nor the CRP required to calculate the ASDAS is readily available at point-of-care, when the patient is being seen by the rheumatologist in the United States. To make a treatment decision based on the patient’s disease activity as measured by ASDAS is therefore not always possible. The BASDAI is solely patient driven, with no objective input

from the physician. The following proposed MDA measure in axSpA, which addresses extra-articular manifestations of axSpA and would be available at the point-of-care, will not replace any of the existing disease activity measures, but will complement them.

The need for a Minimal Disease Activity measure in axSpA

Developing MDA criteria in axSpA would allow the assessment of important extra-articular manifestations that are associated with loss of function, as well as those affecting patients' quality of life. The goal of such an MDA assessment should be to incorporate disease features of importance to patients' function and radiographic progression, within an easy to calculate outcome measure. An important goal of establishing axSpA MDA would be its use in treatment trials as a measure that addresses the spectrum of axSpA disease and allows important comparisons of treatment effects across disease domains (e.g. eyes, skin, bowel). An MDA measurement that incorporates extra-articular manifestations may provide an additional basis for payors to cover treatments, which previously required evidence of spinal or peripheral arthritis activity, thereby improving patient access to effective treatments. Another equally important goal of the MDA criteria development would be application of MDA criteria in clinical care; such availability at the point-of-care may inform shared decision making between patients and clinicians. This MDA measure would have the potential to improve patient outcomes by allowing a treat-to-target strategy that ultimately prevents functional loss due to both articular and extra-articular manifestations.

Proposed method of development of MDA in axSpA

Development of MDA criteria in axSpA should involve both clinician and patient stakeholders, with methods similar to those used in the RA and PsA efforts (Figure 1).

As was done for RA and PsA, a list of candidate measures for the axSpA MDA could be derived from several sources including existing axSpA disease activity instruments, the ASAS/OMERACT core domains (Table 1), [18, 19] expert clinicians, and patient focus groups. An electronic stakeholder survey can subsequently reduce the set of candidate measures.

A sample of actual patient profiles (N~100) from existing axSpA cohorts representing the spectrum of axSpA disease will be required to evaluate if the patient is in an MDA state, or not in MDA using an electronic survey of expert clinicians from multiple disciplines (e.g. rheumatology, ophthalmology, dermatology and gastroenterology). The experts will need to define the maximum tolerated value for each measure that they would consider for the patient to remain in MDA methods for scoring MDA, including cut points for extreme values for each measure, and/or a maximum count of measures allowable for axSpA MDA. Discrete choice experiments will allow a data-driven final selection of the domains and categories for the axSpA MDA criteria set. Specific candidate formulas for MDA will then need to be tested with different cut points, their sensitivity/specificity and ROC curves plotted. The final preliminary MDA criteria will need to be established through expert consensus, and will require validation in a separate longitudinal axSpA cohort, as well as in prospective clinical trials in axial spondyloarthritis.

As noted above, an easy-to-calculate MDA assessment would be very valuable in daily clinical care, but another important goal of these MDA criteria would be for use as an endpoint in clinical research. Novel treatment modalities in axSpA are rapidly being developed; therefore any MDA criteria would need periodic reassessment, as would other outcome criteria.

Summary and conclusions

Axial spondyloarthritis is a multisystem disease with the potential to affect extra-articular sites, in which patients may experience significant functional impairment even when the musculoskeletal inflammatory process is quiescent. Establishment of Minimal Disease Activity criteria using a rigorous process that involves a multidisciplinary group of clinicians and patient stakeholders would be of great value. The development of axSpA MDA would primarily allow treatment comparisons across multiple disease domains in treatment trials, but will also be useful at the point-of-care to inform shared decision making between axSpA patients and clinicians.

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Key Points

A minimal disease activity (MDA) state encompasses both remission and low disease activity, and is described as “a useful target of treatment by both patient and physician, given current treatments and knowledge”. It has been previously established in both rheumatoid arthritis and psoriatic arthritis.

Disease activity in axial spondyloarthritis (axSpA) is associated with both functional and radiographic outcomes, thus MDA would be a valuable outcome measure in treatment studies of axSpA, and MDA assessment at the point-of-care would inform shared decision making.

Considering the multi-system involvement of axSpA, there is a need to establish MDA criteria that include assessments of extra-articular features for use in clinical practice as well as in clinical trials. Future ‘treat-to-target’ studies will establish if maintenance of MDA will improve long-term outcomes in patients with axSpA.

Figure 1.
Flow Diagram for axSpA Minimal Disease Activity Development Methodology

Table 1

ASAS/OMERACT Core Set domains for studies on Symptom-Modifying Anti-Rheumatic Drugs (SMARDs), Disease Controlling Anti-Rheumatic Treatments (DC-ART) and physical therapy

Domain	Instrument
Function	BASFI
Spine pain	VAS/NRS
Spinal mobility	Chest expansion, modified Schober and occiput to wall distance, lateral spinal flexion or BASMI
Patient global	VAS/NRS
Spine stiffness	Duration of morning stiffness in spine
Peripheral joints	Swollen joint count
Entheses	Validated enthesitis scores such as Berlin, MASES
Acute phase reactants	ESR and CRP
Spine radiographs	Lateral lumbar spine and lateral cervical spine
Fatigue	Fatigue question BASDAI

BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, DFI: Dougados Functional Index, VAS: Visual Analog Scale, NRS: Numeric rating Scale. Sources: [18, 19]