Low disease activity state in rheumatoid arthritis: concepts and derivation of minimal disease activity

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ABSTRACT

With recent advances in therapy, the proportion of patients achieving a satisfactory state of minimal disease activity (MDA) is becoming a more important measure with which to compare different treatment strategies. MDA is between high disease activity and remission and anyone in remission will also be in MDA. This paper summarizes the process of coming to a definition of minimal disease activity in rheumatoid arthritis. Two equivalent preliminary definitions of minimal disease activity for use as secondary outcome measures in clinical trials in RA are proposed: a core-set definition based on the WHO/ILAR core set and a DAS-based definition based on the DAS28.

Introduction

The need for a definition of minimal disease activity (MDA) arose from the observation that achieving (and maintaining) a satisfactory state of disease activity is probably more important in the long term than improvement from a high level of disease activity documented in trials, and that remission (‘absence of disease activity’) is not a frequent occurrence in usual clinical practice. Any definition of MDA should be a compromise that best reflects the opinions of patients and physicians. The process required to develop such a consensus definition includes three basic steps: conceptual definition, operational definition, and prospective validation. First, from the conceptual perspective, the definition of MDA is anchored to the clinical experience of the physician and personal experience of the patient: for the physician it is linked to treatment decisions and to prognosis; for the patient it is linked to satisfaction and adaptation. One suggestion is to define MDA as a state deemed a useful target of treatment by both the physician and patient given current treatments and knowledge. What constitutes a useful target of therapy is likely a moving target, so any MDA definition would require regular review. Second, a data-driven consensus process is required to arrive at an operational definition. Two fundamental approaches can be taken: the judgmental approach that gauges the opinion of patients and physicians on a useful target using methods such as direct questioning, patient profiles, physician-submitted cases, and direct observation of clinical practice; or the statistical approach that considers the range of states obtained using the judgmental approach applied to existing data sets to recognise which best distinguishes a weak from a strong treatment. Third, to validate the definition prospectively, longitudinal data sets will be required to determine whether being in a state for a period of time leads to benefits in terms of functional disability and structural damage. This paper summarises the process of developing a definition of MDA in RA by reviewing:

1) The fundamental concepts and conceptual definition of MDA;
2) Methods and procedures for deriving an operational definition of MDA; and
3) Strategies for prospective validation of candidate definitions.

The paper will then summarise our experience in developing a definition of MDA for patients with RA.

Review of fundamental concepts and conceptual definition of MDA

Both the criteria of “important” (improvement) and “minimal” (disease activity state) are part of the mindset of the rheumatologist and the patient and are anchored to their experience with the disease. For the physician, they are linked to treatment decisions in a broad sense (i.e., not only drug treatment but
also other types of interventions) and to prognosis. For the patient, they are linked to satisfaction and adaptation until there is a real chance for cure. As such, any definition is a construct in that there is no absolute “truth” in it. Agreement on what constitutes the most useful definition is thus a task suited for consensus exercises.

One suggestion could be to define MDA as the state that is deemed a useful target of treatment by both physician and patient, given current treatment possibilities and limitations. A procedure for doing this might follow the example set by the Nijmegen and Groningen groups in the Netherlands when they started the process of defining the disease activity state (DAS) (1). They reasoned that any index of disease activity should reflect clinical practice, and they defined as “high” a level of activity demonstrated at a clinic visit for which the physician decided to initiate or change treatment and as “low” a level of activity at a visit for which the physician did not change treatment. The DAS index then resulted from a discriminant function analysis that optimally distinguished between these two states (1). In fact, one could argue that these definitions still hold, and we could simply use the patient-moments that were used to derive the DAS low disease state definitions. However, it is important to note that the usefulness of any definition agreed on is limited in time. The past decades have seen increased willingness of rheumatologists to treat earlier and more aggressively, reflecting a movement towards lower disease activity (and more improvement) as a treatment target. Thus, the DAS definitions are likely out of date, and any new definition should also be regularly updated as treatment options and knowledge about them evolve. This does not decrease the usefulness of the DAS index itself; it is a continuous measure of disease activity that can be used to set more ambitious treatment targets. The validity of the index will come into question only when new measures are introduced into the treatment decision process such as possible prognostic markers currently not in routine use.

An important aspect of any desirable state is the time spent in that state. Regardless of the state definition, questions must be answered such as: Is the total length of time spent in that state the most important outcome? Is a minimum period necessary? What penalty is there for briefly leaving the state? However, answering these questions is complex and requires longitudinal studies that record disease activity repeatedly and in sufficient detail. Given the work to be done, the time component is an issue that may need to be addressed at a later stage.

The proposed conceptual definition of low disease activity is that state which is deemed a useful target of treatment by both physician and patient, given current treatment possibilities and limitations.

Methods and procedures for deriving an operational definition of MDA

As a start, the candidate measures considered in the operational definition include the current core set of disease activity measures (2) as well as the two existing response criteria (American College of Rheumatology [ACR] and DAS) (3, 4). This is limiting in the sense that other measures that might be useful for such a definition, such as fatigue or quality of life, are not considered. However, inclusion of other measures reflects back to discussions over the core set itself. When moving to an operational definition, the definition of low disease activity should probably be expressed in two ways, defined both in terms of the ACR core data set (3) and the DAS (4).

To go from the concept to something that is expressed as a quantity requires a data-driven consensus process. The chosen definition should pass the Outcomes Measures in Rheumatology (OMERACT) filter (truth, discrimination, feasibility) (5). As noted in the development of the RA core set (3), a judgmental and a statistical approach can be considered; often a combination is used.

Judgmental approach

In the judgmental approach, all parties (i.e., patients and physicians) are explicitly asked their opinion on what they would consider a useful target in daily practice. This should lead to a definition with high face validity and relevance in practice. Opinions could be elicited by direct questioning, by studying patient profiles, by asking physicians to submit cases, and by direct observation of clinical practice. The last method has perhaps the highest face validity, as Kirwan has shown that what rheumatologists say they do is not necessarily the same as what they really do (6). Probably more than one approach should be used to converge upon a single definition.

For an opinion-based approach involving a survey method and/or Delphi process, direct or indirect procedures can be used. Using a direct procedure, participants are presented with profiles describing actual levels of measures relating to each feature of disease activity. Different possible formats for profiles of core measures include: individual scenarios, that is, full scenarios for considering MDA; “stem” and “leaf” scenarios, that is, fix all core measures but one or two and request values on the other measure(s) for when the patient is in MDA; branching scenarios – that is, the specific response to one scenario will lead to different scenarios. Using an indirect approach, participants are presented with each disease activity feature one at a time.

Ideally, a process must be found to incorporate the trade-offs found in any decision in practice: such as, the increasing chance of serious toxicity when methotrexate (MTX) dose is increased, or the costs of high-dose anti-tumor necrosis factor-TNF, versus low dose. This could perhaps be done in a utility questionnaire setting, using a rating scale or standard gamble with selected scenarios.

The exercise would need to be limited to one or only a few drugs (such as: MTX at the highest tolerated dose up to 30 mg/wk; or MTX at 15 mg/wk increase or continue at present dose). Also, other co-factors, such as age and duration of RA, would have to be held constant. Although the state being defined should not be situation- or
treatment-specific, the example should be as simple and concrete as possible to elicit the most useful opinions. Again, what constitutes a “useful treatment target” is a reflection of current preferences and treatment options. It will be outdated when future therapy allows lower disease activity states with similar or lower toxicity.

**Statistical approach**

The second approach is an observation-based approach involving analysis of existing RA data and inferring low disease activity from a proxy variable, such as a clinician’s decision to reduce/not increase drug treatment. If the definition was primarily intended for use in clinical trials, we could follow the example of the ACR improvement process. That is, a range of state definitions could be applied in existing clinical trial data sets to determine which best distinguished active from placebo treatment or strong from weak treatment. Although trial duration has recently lengthened, trials usually have limited numbers of repeated measurements and are thus not very well suited to study a longitudinal component. Probably only the attainment of the state can be studied and not the length of time in which this state was enjoyed. On the whole, we feel that the statistical approach is less suited to arrive at a definition. Once a definition has been found, it could be tested in trial data sets. However, optimum discriminant validity in trials is not the stated goal for the definition. This is similar to the situation with the response criteria. The ACR50, ACR70, or the European League Against Rheumatism (EULAR) “good response” definitions are often less discriminative than their counterparts that require less treatment response (ACR20 and EULAR “moderate response”). Nevertheless, they have their own validity issues in describing higher levels of response. In other words, a definition of low disease activity that was found not to discriminate well between “weak” and “strong” antirheumatic treatment could point to a suboptimal definition or to the finding that “strong” antirheumatic treatment is not as strong as we would like.

The proposed approach to develop the definition is judgmental, by eliciting opinions in several ways and merging these in a consensus process.

**Strategies for prospective validation of candidate definitions**

After one (or a few) candidate definitions have been proposed, the next step would be to evaluate (in longitudinal data sets) whether being in MDA for a certain period leads to benefits in terms of disability and damage compared to not being in this state. This will prospectively validate the definition. To be used as a prognostic instrument per se, it would have to be shown empirically that bisecting disease activity at the defined level and then studying state over time is better than measuring disease activity continuously and using an area under the curve (AUC) approach. However, the suggested process to come to a definition of MDA starts from the clinical perspective, because having such a definition is felt to be useful; it is not being developed because we think such a state will be the best prognostic indicator. Thus, although such a state should have predictive/prognostic validity for each defined outcome (e.g., disability, damage), better prognostic indicators may very well exist.

The proposed approach to validate the definition is using the definition as a secondary end point in randomised clinical trials and further validating it in other data sets and long-term outcome databases.

**Developing the definition of MDA for patients with RA**

Work on the definition of MDA for patients with RA has been going on for more than four years (7). The original name for this state was low disease activity state (LDAS), and the various OMERACT and ACR meetings, surveys, and presentations used the name LDAS. Over the course of time, it became apparent that the name LDAS gave the impression that this was referring to a state of low activity and excluded remission. The change of the name to MDA was, in part, to address this misconception.

**OMERACT 6 workshop**

The background work for the MDA began with the OMERACT 6 conference in 2002. The objective of the OMERACT 6 LDAS workshop was to meet the many challenges that exist in determining MDA by reviewing concepts and terminologies and deciding on a process for developing an operational definition (8-10). At OMERACT 6, the workshop had four breakout groups. One of these groups was comprised of patients who attended the conference. In this patient perspective group, patient concerns were critically reviewed and discussed with the goal of ensuring that any definition of MDA will take into consideration the patient perspective and ultimately be acceptable to patients. The final voting supported the development of a research agenda for measuring sleep and fatigue outcomes that were important to the patients so that these could be considered in the definition of MDA. The methods group was concerned with the methods and consensus process for developing an operational definition. A wide range of possible judgmental and statistical approaches were discussed, with the goal of developing a comprehensive methodologic strategy to be implemented for the development of an operational definition of MDA. The voting supported both an opinion-based approach (judgmental) and an observation-based approach (statistical). The candidate measures group reviewed the core measures used in indexes such as ACR20 and DAS, and added some measures (e.g., fatigue) and subtracted other measures as needed, with the goal of deriving a comprehensive and parsimonious list of candidate measures for use in a definition of MDA. The voting supported a comprehensive list of outcomes for assessing pain, function, inflammation, health-related quality of life, structure/damage and toxicity, and comorbidity for consideration in the definition of MDA. The definition formulation group focused on the levels and combinations of the measures considered, assuming measures used in the definition were given, with the goal of providing examples of definitions of MDA that have
A three-step process was followed to develop and gain consensus on the definition of MDA. First, at a MDA discussion group convened at the ACR meeting (October 2003), agreement was reached on candidate measures to consider in the initial definition of MDA, and options for opinion-based questions and design issues on surveying stakeholders on possible operational definitions of MDA were considered. Second, based on these discussions, a survey was designed and conducted among stakeholders between January and April 2004, to derive a limited set of possible definitions for MDA. Third, at the OMERACT 7 LDAS module, participants were presented with this limited set of candidate definitions to discuss and from which to choose an agreed definition.

**ACR meeting**

The objectives of the MDA session at the ACR meeting were to review the fundamental concepts associated with MDA; to obtain consensus on the candidate measures that should be considered in the definition of MDA; to consider options for an opinion-based survey using direct (profiles of measures) or indirect (individual measures) procedures for determining MDA; and to consider design issues on surveying stakeholders on possible operational definitions of MDA.

The meeting process consisted of a slide presentation summarising the work of the OMERACT 6 workshop and the tasks that had been accomplished since the workshop. A series of questions on key issues associated with the next steps in the development of MDA were posed during the presentation and discussed by the meeting participants. The goal was to help design the “survey of stakeholders,” which would be conducted in order to derive a limited set of possible definitions for MDA for consideration at the LDAS module of OMERACT 7.

Specific decisions regarding the definition of MDA were made at the ACR meeting. In particular, although the list from OMERACT 6 was more comprehensive, it was determined that for the initial definition of MDA only the core measures would be included. If other measures were included, then this would force a redefinition of disease activity, a process that could take several years. Also, some measures (e.g., health-related quality of life) were thought to be different dimensions of burden of disease that were relevant to treatment but only loosely bound to the concept of disease activity. In summary, more data and consensus building were needed for other measures to be included. Also, it was decided that until patient-specific outcomes (such as sleep and fatigue) could be properly measured, the candidate variables should be limited to the core measures. This agenda is currently being executed by the study group **Patient Perspective in Outcome Assessment** (11, 12).

The different approaches for deriving an operational definition were discussed. It was believed that the opinion-based approach involving a survey method and/or Delphi process would be more timely and feasible than an observation-based approach involving analysis of existing data and inferring MDA from a proxy variable, such as a clinician’s decision to reduce/not increase drug treatment. Further, it was determined that a direct procedure (i.e., have respondents assess descriptions of patients using profiles that provide results of all the core set measures) was better than an indirect procedure (i.e., polling for desired levels for each core set measure separately). The sampling frame and sampling methodology for the survey were discussed. Although different sampling methodologies for surveying groups were considered (including simple random sampling, stratified random sampling), it was believed that a nonrandom sampling targeted at key opinion leaders and the OMERACT participants would be the initial approach. Names of key decision makers and groups that should be surveyed were suggested, and others were forwarded to the module organisers by the meeting participants. Concern on the length and format of the survey questionnaire was expressed, but it was noted that a wide range of profiles would be needed.

**Survey of stakeholders**

It was determined that attendees of that meeting, previous chairs and co-chairs of the OMERACT Minimal Clinically Important Difference (MCID)/LDAS modules and workshops, key research and opinion leaders, and others that these individuals identified, would be surveyed. Further, for the opinion-based questions, the general stem-and-leaf format of the profiles was determined. Over the next 2 months, the lists of those to be surveyed were assembled and the questionnaire was designed and tested. In addition, the questionnaire was posted on the OMERACT 7 conference web site, and participants were invited to complete the questionnaire. The survey questionnaire consisted of 60 profiles. The profiles used measures taken from the core set (4) to describe patients with various states of disease activity. The examples were of real RA patients, selected from the Rheumatoid Arthritis Evaluation Survey (RAES) database (13). This database contains the results of a cross-sectional survey of disease activity in 730 consecutive RA patients attending 40 clinics in the United States and Canada. The data presented for each patient was unaltered from that recorded in the database. The profiles were selected to encompass the full range of disease activity present in the data set and enriched with profiles that showed physician global assessments between 1 and 3 (range 0-10). The stakeholders surveyed were instructed to consider...
the same setting for each profile, that is, to consider that the profile corresponded to a RA patient started on MTX that had been increased to the dose usually used by the stakeholder. The profile described the disease activity after at least 6 months of therapy at that dose. The core measures provided in the profile were as follows (“better” is indicated by a lower score):

<table>
<thead>
<tr>
<th>Measure (range)</th>
<th>Result</th>
<th>% of Max</th>
<th>Highest result tolerated (all else equal)</th>
<th>LDAS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>pain (0-10)</td>
<td>2</td>
<td>20</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>swollen joints (0-28)</td>
<td>0</td>
<td>0</td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>tender joints (0-28)</td>
<td>0</td>
<td>0</td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>0.3</td>
<td>10</td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>physician global (0-10)</td>
<td>1</td>
<td>10</td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>patient global (0-10)</td>
<td>3</td>
<td>30</td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>ESR (0-120)</td>
<td>4</td>
<td>3</td>
<td></td>
<td>no</td>
</tr>
</tbody>
</table>

* The term LDAS has now been replaced by MDA.

For each profile, the question to be answered was, “Is the patient described in the profile in MDA using the definition agreed on at OMERACT 6 and reinforced at the ACR meeting?”; that is, that state which is deemed a useful target of treatment by both physician and patient, given current treatment possibilities and limitations.

A typical profile is given in Fig. 1. For “scoring” the profiles, a two-step process was suggested, and the instructions provided to those surveyed were as follows: 1) For each profile, consider the “result column” and the “% of max” column for each core measure, and indicate (with an “x”) whether you think this patient is in MDA; 2) When you have completed scoring in the first step, go back to the profiles you scored as being in MDA and consider the “If yes” part of the question. Indicate how much any single measure could increase (“highest result tolerated”), given the others stay the same, before MDA would be lost in your opinion.

The 60 profiles were completed by 38 respondents. There was considerable consensus among the respondents on the profiles that were felt to represent patients in MDA. There was absolute agreement on 10 profiles: these were considered to be in MDA by all the respondents. Lowering the threshold of agreement yielded more profiles in MDA: there was ≥ 90%, ≥ 80%, and ≥ 70% agreement that 15, 17, and 22 profiles were representative of patients in MDA. The ≥ 80% agreement was selected for classifying the profile to correspond to a patient in MDA.

Two aspects were considered to derive a definition for MDA: determination of a “cutpoint” that consisted of a maximum value for each of the core measures; and consideration of the count of core measure results that must not exceed the cutpoint for the patient to be in MDA. Cutpoints were derived as follows: in the set of MDA profiles, summary statistics were calculated for each core set measure. Seven potential cutpoints for the core set were derived from these statistics, based on (for each measure): the mean, the rounded mean, the upper 95% confidence limit, the rounded upper 95% confidence limit, the maximum, the mean of highest tolerated value for each core measure, and the rounded mean of highest tolerated value. For example, the upper 95% confidence interval (CI) cutpoint would be the seven numbers corresponding to the upper 95% confidence limit for each measure. Considering the count of core measures that must meet (i.e., have a result no higher than) their individual cutpoint in order for the patient to be in MDA yields seven variations: 7/7, 6/7, 5/7, 4/7, 3/7, 2/7, and 1/7 where n/7 indicates that n or more of the core measures have a result at or below the cutpoint. This procedure generated 49 possible candidate definitions for MDA when the seven possible statistics that could be used in defining a cutpoint were combined with the seven variations in the count of the core measures that could be used to meet the cutpoint.

For those profiles in MDA, summary statistics were calculated and cutpoints were determined for the core measures. For each definition sensitivity and specificity was calculated. It was noted that as the value for the cutpoint in the definition decreases (i.e., becomes more strict, less disease activity), and likewise as the count of core measures (n) to be satisfied in the definition increases, sensitivity will decrease and specificity will increase. After reviewing the receiver operating characteristic (ROC) curves, three candidate definitions for MDA based on the core set were identified and presented to the participants for their consideration, namely: the rounded mean, rounded upper 95% confidence limit, and the maximum. In addition, participants
were asked to determine the best level of DAS28, equivalent with the preferred core set MDA definition.

OMERACT 7 module
In the opening module plenary, the goal of the module and concepts associated with MDA were reviewed, results of the survey of stakeholders were presented, and the charge to the breakout groups was made. Following the plenary, the conference participants divided into 10 breakout groups (each group consisted of 10 to 20 participants with a chair and rapporteur). During the breakout session, each breakout group reviewed the definitions of MDA with two tasks in mind: first, consider and discuss the operational definitions of MDA determined from the results of the survey of stakeholders and the comfort level with each definition as an initial definition for MDA; and second, consider a set of 10 profiles with respect to each of the candidate definitions. Each breakout group generated a report from their session and the rapporteur for each group reported back in the second module plenary. In reporting back, the tasks were to describe the process that was followed, provide a summary of the discussions, list the key concerns and issues raised, and provide a ranking of the candidate definitions.

The reports of the breakout groups generated specific issues that needed to be addressed by the MDA working group. The feedback was recorded and reviewed, taking an approach of clarifying the purpose, identifying misunderstandings, and addressing concerns raised. With access to the RAES database (13) and the Vienna’s profile survey (14), on-site consideration of these issues was possible prior to the vote at final conference plenary. One issue on misclassification had a direct and immediate impact on the candidate definitions. The concern was that patients with a chronic pain syndrome but low RA disease activity would be misclassified as high disease activity due to high scores in pain, tender joint counts, and patient global assessment. In theory, a DAS definition of MDA should be less sensitive to this problem because pain is not a component and patient global assessment carries only a small weight in the index. To address this problem, the tree approach was suggested: a decision node placed before the definition to better classify patients with MDA but high pain scores deemed unrelated to disease activity. This node would have to be very strict to avoid introducing new misclassification problems. The node suggested was as follows: if SJC = 0, TJC = 0, and ESR ≤ 10 then the patient is considered to be in MDA, regardless of the results of other core set measures. Most patients meeting this node would in fact be in remission.

The three candidate definitions of MDA were considered by all the breakout groups. Although the definition with the cutpoints based on the maximum values and requiring all seven of the criteria to be satisfied had the best combination of sensitivity and specificity, the participants at OMERACT 7 indicated that this definition did not have great face validity, and it was not scored highly in the breakout sessions. Also, because of the specific nature of this definition, only patients who are close to remission would be classified as being in MDA. Of the three definitions, the definition with the cutpoints based on the upper 95% confidence limits and requiring 5 or more of the 7 criteria to be satisfied, garnered the greatest support.

Based on the reports of the breakout sessions, two operational definitions of MDA were formulated. It was noted that two sets of outcome measures were currently used as primary end points in RA clinical trials: the World Health Organisation/International Liege Against Rheumatism (WHO/ILAR) core set (corresponding ACR response criteria) 3 and the DAS28 (corresponding EULAR response criteria) 4. To follow current practice in trial methodology, two equivalent preliminary definitions of MDA for use as secondary outcome measures in clinical trials in RA were proposed. Researchers applying these definitions first need to choose whether to use the DAS28 or the core set definition, because each selects a similar proportion in a population but not always the same patients.

Core set definition (Fig. 2): For this definition, a patient with no tender or swollen joints and an ESR ≤ 10 would be considered to be in MDA, otherwise the full set of core measures is considered. If 5 of the following 7 criteria are met, then the patient is considered to be in MDA:

1. Pain (0-10) ≤ 2
2. SJC (0-28) ≤ 1
3. TJC (0-28) ≤ 1
4. HAQ (0-3) ≤ 0.5
5. physician global assessment of disease activity (0-10) ≤ 1.5
6. patient global assessment of disease activity (0-10) ≤ 2
7. ESR ≤ 20

Otherwise, the patient is not in MDA.

DAS-based definition (Fig. 3): For this definition, a patient with no tender or swollen joints and an ESR ≤ 10 would be considered as MDA, otherwise the DAS28 would be considered. The DAS28 definition places the patient in MDA when DAS28 ≤ 2.85.

The two operational definitions of MDA were presented, voted on, and endorsed as preliminary definitions of MDA at the conference plenary. The question posed to the OMERACT 7 participants at the conference plenary was Do you agree that both the core set definition and the DAS-based definition have sufficiently passed the OMERACT filter to be recommended as preliminary definitions of MDA for use in randomised clinical trials, to be further validated in other data sets and long-term outcome databases?

These preliminary definitions for MDA satisfy the OMERACT filter (5) for truth, discrimination, and feasibility. Truth is the opinion of the physician being met by the proposed definition, in the setting of randomised clinical trials; all important issues have been considered, with no fatal issues remaining, and a large research agenda identified for other issues. Discrimination in classification criteria is subsumed under truth. Feasibility of using the definitions in a trial setting is achievable.

Prospective validation
The objective of the OMERACT 7
module for MDA was to seek consensus on a definition of MDA that could be recommended as a secondary end point in randomised clinical trials and could be further validated in other data sets and long-term outcome databases. In particular, MDA has been validated by the authors in two study data sets. The first is the Combination Therapy in Early RA (COBRA) study evaluating the efficacy and safety of step-down prednisolone, MTX, and sulphasalazine, with sulphasalazine alone in early RA. Patients were randomised to receive combined treatment comprised of sulphasalazine, MTX, and high/low oral prednisolone in the first 28 weeks with tapering and withdrawal of prednisolone and MTX in the second 28 weeks, or sulphasalazine. The results for MDA mirrored the clinical results of the COBRA study with significant differences between the combination treatment and sulphasalazine alone at 6 months but not at 12 months. It was found that the more often patients were in MDA, the better the radiographic progression. Further, sensitivity analysis indicated that the cutpoints chosen for the definition were reasonable, and the initial node in the definitions did not lead to substantive differences in the results (15). The second data set consisted of two randomised, double-blind, placebo-controlled trials of abatacept in patients with active RA: a 6-month trial (Abatacept Trial in Treatment of Anti-TNF Inadequate responders [ATTAIN]) comparing treatment with abatacept to placebo on a background of disease-modifying anti-rheumatic drug (DMARD) therapy in patients for whom anti-TNF therapy failed; and a 12-month trial (Abatacept in Inadequate responders to Methotrexate [AIM]) comparing treatment with abatacept to placebo on a background of MTX therapy. It was found that significantly more patients treated with abatacept were in MDA compared to control, and that the more often patients were in MDA, the better the radiographic progression (16). The authors will continue to evaluate and validate the MDA and encourage other researchers to include MDA as a secondary end point in their randomised clinical trials to further validate MDA in other data sets and long-term outcome databases.

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