Deriving an Operational Definition of Low Disease Activity State in Rheumatoid Arthritis

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ABSTRACT. This article summarizes the process proposed to come to a definition of low disease activity in rheumatoid arthritis (RA). The purpose of this definition is to aid the interpretation of trial and longitudinal study results. A conceptual proposal is "a disease activity state that is deemed a useful treatment target by both physicians and patients." An operant definition can be derived by judgmental (opinion-based) or statistical (data-based) approaches, but the first seems more appropriate. Once a few candidate definitions have been selected, their usefulness and prognostic validity can be tested in longitudinal datasets. (J Rheumatol 2003;30:1112–4)

Key Indexing Terms:
DISEASE ACTIVITY RHEUMATOID ARTHRITIS
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Introduction

As a start, it should be mentioned that this article takes as a given the current core set of disease activity measures, as well as the 2 existing response criteria — the American College of Rheumatology (ACR) and the Disease Activity Scale (DAS)[2,3]. This approach is limiting in the sense that other measures possibly useful for such a definition, such as fatigue or quality of life, are not considered. We feel discussion on the inclusion of other measures reflects back to discussions over the core set itself. Also, our approach pays little attention to the time dimension that makes the definition of a low disease activity state most useful, for example, the duration of time spent in the state. These and other decisions to enable the process to move forward rapidly were open for discussion at the conference.

To derive a definition of low disease activity state, a 4-step process is required, that is, the determination of: a conceptual definition, an operant definition, a prospective validation, and a final definition. This article describes the process of moving from a conceptual definition to an operant definition of a low disease activity state related to RA.

Procedures

Conceptual definition. Both the qualifications of "important" (improvement) and "low" (disease activity state) are part of the mindset of the rheumatologist and the patient, anchored to their experience with the disease. For the physician, they are linked to treatment decisions in the 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 a 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.

For example, one suggestion might be to define low disease activity as that state which is deemed a useful target of treatment by both physician and patient, given current treatment possibilities and limitations. With this suggestion, we follow the example set by the Nijmegen and Groningen groups in The Netherlands when they started the process of defining the DAS in the 1980s[4]. They reasoned that any index of disease activity should reflect clinical practice, and they defined high as the level of activity demonstrated at a clinic visit where the physician decided to initiate or change treatment, and low as the level at a visit where the physician did not change treatment policy. The DAS index then resulted from a discriminant function that optimally distinguished between these 2 states.

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 agreed-on definition is limited in time. The last decades have seen increased willingness of rheumatologists to treat earlier and more aggressively, reflecting a movement towards lower disease activity (and more improvement) as treatment target. Thus, the DAS definitions are most 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: the DAS is a continuous measure of disease activity that can be used to set stricter treatment targets. The validity of the index will come into question only when new

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measures are introduced into the treatment decision process (such as prognostic markers currently not in routine use).

We reiterate that the starting point is the core set and the 2 improvement criteria. When we move to the operant definition, we should include all available tools to derive the candidate definition. Thus we feel the definition of low disease activity should probably be expressed as a range, defined both in terms of the core set and the DAS.

We note that an important aspect of any desirable state is the time spent in that state. Irrespective of the definition, other questions need to 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, this aspect is complex and requires longitudinal studies that record disease activity repeatedly and in sufficient detail. For now, we feel the definition of the time component should be addressed at a later stage. Proposed conceptual definition of low disease activity: that state deemed a useful target of treatment by both physician and patient, given current treatment possibilities and limitations.

Operant Definition

To go from concept to something that is expressed as a quantity requires a data-driven consensus process. The chosen definition needs to pass the test of the OMERACT filter (truth, discrimination, feasibility)[5]. As noted in the development of the RA core set[2], both a judgmental and a statistical approach can be considered. Often a combination is used.

Judgmental approach. In the judgmental approach, all parties (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: what rheumatologists *say* they do is not necessarily what they really do[6]. Probably more than one option should be used to compare and converge upon a single definition.

A way must be found to incorporate the tradeoffs present in any decision in practice, such as the increasing chance of serious toxicity when methotrexate (MTX) dose is increased, or the costs of high versus low dose anti-tumor necrosis factor therapy. This could perhaps be done in the setting of a utility questionnaire (e.g., rating scale or standard gamble with selected scenarios).

The exercise would need to be limited to one or only a few drugs (e.g., MTX at the highest tolerated dose of up to 30 mg/week, or MTX at a 15 mg/week increase, or MTX continued at present dose). Also, other co-factors such as age and duration of RA would have to remain constant. Although the state we try to define should not be situation-specific or be specific to a treatment, the example needs to 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. The target will become outdated as soon as future therapy allows lower disease activity states with similar or lower toxicity.

Statistical Approach

If this definition were primarily intended for use in trials, we could follow the example of the ACR improvement process. That is, a range of definitions of disease state that could be applied in existing trial datasets, to determine which definition best distinguishes placebo from active, or weak from strong, treatment. Although the length of trials has recently increased, trials usually have limited numbers of repeated measurements and are thus not well suited to studying the time component. Probably only the attainment of the disease state can be studied, and not the length of time in which this state is enjoyed. On the whole, we feel the statistical approach is less suited to arrive at a definition.

Once a definition has been agreed on, it could be tested on trial datasets. 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 improvement criteria ACR 50 or ACR 70 or the EULAR "good response" definitions are often less discriminative than their counterparts that require less treatment response (ACR 20 and EULAR "moderate"). Nevertheless, they have their own validity issues with respect to 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. Proposed approach to develop the definition: the judgmental approach, i.e., eliciting opinions in several ways and merging these in a consensus process.

Next Steps

After one (or a few) candidate definitions have been proposed, we would determine (in longitudinal datasets) whether being in this state for a certain period leads to benefits, in terms of disability and damage, compared to not being in this state. This test will prospectively validate the definition, a compromise opinion on what constitutes a useful treatment target. 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 the state over time is "better" than measuring disease activity continuously and using an area under the curve approach. However, circularity must be avoided: the suggested process starts from a clinical perspective because

it is felt to be useful to have an intermediate state between active disease and remission. 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. We suggest that a full discussion on the purpose and process of validation need not take place now.

A final definition is extremely unlikely. Examples from the past teach us that the qualifier "preliminary" can be applied almost indefinitely. More important, as described in the introduction, low disease activity as a treatment target is likely to be defined differently with every new development in treatment.

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