Status Versus Changes, Onset of Action, and Sustainability
How Do We Define and Present These Concepts in Clinical Trial Reports in Rheumatology?

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Abstract
Since the main objective of therapies in rheumatology is not only to improve the patient condition but also to prevent a further disability and because of the emergence of new and very effective therapies, the outcome measures used to evaluate treatments in rheumatology have been revisited. The major changes are that in addition to the concept of improvement (achievement of a relevant level of change), other concepts have been recognized as important, such as status (achievement of an acceptable condition), onset of action (the quickest is the better), and sustainability. In order to evaluate these concepts, new tools have been recently elaborated (for example, the ACR-EULAR remission criteria in rheumatoid arthritis) and several statistical approaches can be used for an optimal presentation of the data observed in clinical trials (in particular to assess the concepts of onset of action and sustainability).

Due to the heterogeneity of the clinical presentation of rheumatoid arthritis (RA), as well as other rheumatologic conditions, a number of individual measures can be proposed to evaluate disease activity. For example, in RA, patient reported outcomes comprise the following nonexhaustive list: pain, function, fatigue, sleep disturbances, physical and psychological well being, and coping. Moreover, other individual measures assessed by physicians also can be collected, such as joint count and acute phase reactants (e.g., the so-called doctor-reported outcomes). In order to facilitate the interpretation of data observed in different clinical trials, core sets of individual measures were defined that should be reported in clinical trials of RA. In order to further facilitate the inter-trials comparison, composite indices also have been proposed; a composite index is a single parameter combining individual measures. Current questions related to the optimal composite index to evaluate disease activity in RA is not within the scope of this article:

1. Whether or not the composite index should include a functional impairment measure or not.
2. Whether or not the composite index should include only patient-reported outcomes, such as the RADAI (rheumatoid arthritis disease activity index) or also joint count and levels of acute-phase reactants, using indices such as the DAS (Disease Activity Score) and SDAI (Simplified Disease Activity Index). Contrastingly, we have the objectives in this current review to assess recently recognized concepts of interest for both a patient’s and a doctor’s perspective, namely attainment of an acceptable status, onset of action, and sustainability of a successful treatment.

Changes Versus Status
The conventional, main objective of any therapy in rheumatology is to improve the patient condition. Therefore, the first composite index used to assess therapies in clinical trials referred to the changes observed between baseline (before therapy) and final visit (after therapy). In the 1990s, the American College of Rheumatology (ACR) criteria were proposed based on the relative changes in core set variables (Table 1). In order to present the results at an individual level (e.g., percentages of responders), a threshold in these relative changes has been proposed. Originally, such a threshold had been defined by 20%. However, because of new, more effective therapies, other thresholds have been proposed (e.g., 50%, 70%, and 90%), resulting in the following des-
ignitions: ACR20, ACR50, ACR70, and ACR90 response criteria. Recent epidemiological studies have emphasized that, both from a patient’s perspective and a physician’s perspective, the capacity to attain a particular disease activity state was more important than to attain a particular disease activity change. This concept is summarized by the sentence: “It’s good to feel better but it’s better to feel good.” 10 As for the composite indices evaluating changes, thresholds in the composite indices evaluating status have been proposed, permitting presentation of the results in terms of a percentage of patients at a specific status of their condition (e.g., active, moderate, or low disease activity, remission). Table 2 provides such thresholds for the most commonly used composite indices evaluating a disease activity state in RA.

The current recommendations while reporting data collected in clinical trials is to refer to these composite indices and, in particular, to the conventional ACR20 response criteria to facilitate the inter-trials comparison. However, along with such practical considerations, the presentation of an index referring to the concept of percentage of patients in an acceptable state (e.g., remission or low disease activity state) also is highly recommended.11,12 For the researchers in charge of the design of clinical trials, the still remaining question is the choice of “the” primary outcome measure that will permit the sample size calculation and the primary statistical analysis. Based on post-hoc analysis of recently conducted trials in this area, the current (personal one of the author of this review) recommendation should be the following:

1. In proof of concept trials (in which the minimum number of patients has to be recruited), the mean changes in a continuous variable, such as the DAS, should be preferred.

2. In phase 2 clinical trials, the ACR20 response criteria should be preferred, since the number of patients needed according to this parameter is lower than the one needed according to the indices referring to the status.

3. In phase 3 clinical trials, there is a trend to use more relevant and stringent criteria, such as the DAS remission criteria.13

Onset of Action and Plateau of Efficacy

From a patient’s perspective, it is clear that a treatment with a quick onset of action is more desirable than a treatment with a similar magnitude of effect but with a delayed onset of action.8 However, there is still no consensus concerning how to approach this concept. In particular, for the practicing rheumatologist in charge of informing the patient of the fundamental action of a proposed treatment, the question is whether the information related to the time that the plateau of efficacy is achieved is more important than the estimated time the treatment is usually begins to be effective. One could argue that the most important information to be given to a patient in whom a therapy is initiated is the time he/she will have to “wait” during therapy before discontinuing such therapy because of inefficacy. This information is usually based on the time to achieve the plateau of efficacy observed in clinical trials. On the other hand, the concept of “onset of action” is also important, since the practicing rheumatologist can explain based on an evidence based approach that, despite the patient will have to stay on the treatment at least until the time of the plateau of efficacy, an improvement could be observed as rapidly as the time the onset of action was observed in previously conducted trials.

To approach these concepts in the reports of clinical trials, the conventional technique is to present the changes observed in continuous variables (e.g., pain on a 0-100 visual analogue scale or disease activity score) and to perform different tests to detect a statistically significant treatment effect at different

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### Table 1

<table>
<thead>
<tr>
<th>American College of Rheumatology Rheumatoid Arthritis Response Criteria*</th>
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<tbody>
<tr>
<td>A patient is considered as a responder if he or she fulfills the following:</td>
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<tr>
<td>IMPROVEMENT of AT LEAST 20% in:</td>
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<tr>
<td>Tender Joint count</td>
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<tr>
<td>AND</td>
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<tr>
<td>Swollen Joint count</td>
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<tr>
<td>AND</td>
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<tr>
<td>At least three of the following five:</td>
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<tr>
<td>1. Physician’s assessment of disease activity</td>
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<tr>
<td>2. Patient’s assessment of disease activity</td>
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<tr>
<td>3. Patient’s assessment of pain</td>
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<td>4. Patient’s assessment of physical function</td>
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<tr>
<td>5. Levels of acute phase reactants</td>
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</tbody>
</table>


### Table 2

<table>
<thead>
<tr>
<th>Composite Index</th>
<th>Remission</th>
<th>Low Disease Activity</th>
<th>Moderate Disease Activity</th>
<th>High Disease Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28-ESR5</td>
<td>&lt; 2.6</td>
<td>2.6 to 3.2</td>
<td>3.3 to 5.1</td>
<td>&gt; 5.1</td>
</tr>
<tr>
<td>SDAI5</td>
<td>&lt; 3.3</td>
<td>3.3 to 22</td>
<td>22 to 26</td>
<td>&gt; 26</td>
</tr>
<tr>
<td>CDAI6</td>
<td>&lt; 2.8</td>
<td>2.8 to 10</td>
<td>10 to 22</td>
<td>&gt; 22</td>
</tr>
<tr>
<td>RADA13</td>
<td>&lt; 3</td>
<td>3.1 to 6.0</td>
<td>6.1 to 12</td>
<td>&gt; 12</td>
</tr>
</tbody>
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intermediate visits (Fig. 1).14

In order to facilitate the interpretation of the results in this field, a presentation at the individual level has been proposed (e.g., percentage of patients with a success (either a degree of change or a level of status) at different time points. For this purpose, the life table analysis approach can be used where the “event” is defined by the first time the success is observed in individual patients (Fig. 2).15

Sustainability
Sustainability of a treatment success is also a concept of interest obviously important from a patient’s perspective but also from a physician’s perspective. In RA, a sustained (in comparison to an intermittent) low disease activity state is correlated with less long-term structural damage.16

Here again, there is no consensus concerning how to report the analysis of such a concept. Two different conventional approaches are commonly used:

1. The Food and Drug Administration (FDA) has proposed as the definition of a “major clinical response,” a response observed during 24 consecutive weeks during a trial. As an example, a major clinical response defined by an attainment of an ACR70 response during 24 consecutive weeks was achieved by 12% of psoriatic arthritis patients receiving infliximab during a 54-week period.17

2. As for the onset of action, the changes over time of continuous variables can be presented (Fig. I). The main criticism of this technique while evaluating the concept of sustainability is the difficulty in interpretation of the results because of missing data due to treatment discontinuation over time.

Other approaches have been recently proposed; such as for the onset of action, a life table analysis technique can be proposed defining the “event”—not as the time the patient is attaining a pre-defined success for the first time, but the time the patient is attaining the pre-defined success with sustainability observed at subsequent visits.15,18
The so-called continuity rewarded (ConRew) score consists in according one point to a patient attaining the pre-defined success at a specific visit and calculating the number of points acquired during the time of the trial. In order to emphasize that the interest is an observation of success during consecutive visits, an extra point can be given to a patient attaining a success at a specific visit where a success also occurred at the previous visit. Such a system is called a weighted ConRew score.19 Such a scoring system appeared to be very discriminant between treatment groups in the post hoc analysis of the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) trial that compared both etanercept and methotrexate and the combination (Fig. 3).18

Conclusion
The two major international societies in rheumatology, ACR and EULAR (European Union Against Rheumatism), have recognized the importance in revisiting the recommendations of reporting data collected in clinical trials of RA.11,12 Such recommendations include the three concepts discussed in this review (status, onset of action, and sustainability). Further studies are required in order to clearly provide recommendations concerning the technique to use in order to optimally approach these concepts and, in particular, the ones of onset of action and sustainability. Finally, the three concepts discussed in this review can be summarized by the following sentence: “It’s good to feel better but it’s better to feel good… as soon as possible… for as long as possible.”

Disclosure Statement
The author has received research grants to conduct clinical trials and has participated at symposia organized by Pfizer, Pharmacia, and Wyeth.

References

Figure 3 Evaluation of the concepts of sustainability according to different techniques (e.g., major clinical response, unweighted and co-weighted ConRew scores): the example of the post-hoc analysis of the TEMPO trial in RA. (Adapted from van der Heijde D, Klareskog L, Boers M, et al; TEMPO Investigators. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis. 2005;64:1582-7; Epub 2005 Apr 28. With permission.)

![Graph showing ACR20/MCR (% patients) and ConRew scores](image-url)


