Treat-to-target: measures

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ABSTRACT
Current approach to rheumatoid arthritis (RA) treatment combines early and aggressive therapy, with methotrexate as the anchor medication and monitoring disease activity to achieve the best possible outcome for patients. To recognise which patients are responding treatment and reaching low disease activity levels or remission, an objective outcome measure needs to be utilised in routine clinical care. DAS28, SDAI, CDAI and RAPID3 are all validated and similarly functioning measures that can be of use in everyday care, allowing rheumatologists to treat-to-target. The main challenge remains getting all rheumatologists to start using one of these measures as part of the care they provide.

The treatment of rheumatoid arthritis (RA) has seen important changes over the last decade. Methotrexate (MTX) had emerged as a drug of choice in the mid-1980s, however, a majority of patients in those years were also treated with some combination of parenteral gold and other modestly effective drugs, such as penicillamine, sulfasalazine or hydroxychloroquine. Combination treatment, which is now considered the standard treatment option when patients fail their first disease-modifying anti-rheumatic drug (DMARD), was rarely used. The usual practice was to stop the ineffective DMARD and start a new one and repeat as needed. During early-to-mid 1990s a new and different paradigm evolved: rather than old methods of waiting for worsening and increasing disease activity, modern treatment has become more aggressive, starting as early as possible with DMARDs to increase the dose until a good therapeutic response has been achieved and closely follow the disease activity to match the aggressiveness of our treatment to the aggressiveness of the disease. Studies such as TICORA (1) and BeSt (2) have demonstrated that with tight control of disease activity by using standardised disease assessment instruments and adjusting treatment according to preset goals, it was possible to achieve high degrees of remission with traditional DMARDs.

Four important factors have led to this more aggressive approach in the modern treatment of rheumatoid arthritis:
1) the disease is now recognised to be associated with significant mortality, morbidity, diminished quality of life and disability
2) aggressive treatment has been shown to more effectively improve both symptoms and quality of life measures
3) DMARD treatments have been shown to effectively retard radiographic progression of disease
4) Currently used DMARDs, MTX and biologic agents are far more effective than the older DMARDs and also have far less side effects

RA treatment is a fast changing and advancing area. Not only are we getting better at using the drugs we already have, new medications are available to us and more are on the way. Our main challenge is still and will be to identify which patients are responding to our treatments and to objectively quantify this response or non-response. Without using the proper tools for this aim, we will fall short of providing the best chance for disease control for our patients. Previously mentioned studies such as TICORA, and BeSt have demonstrated the importance of close monitoring of RA patients. However, unfortunately this is not what happens in the real world. Rheumatologists still generally use few quantitative measures in making clinical decisions. Few rheumatologists use questionnaires in routine clinical care, and similarly small number perform a formal joint count at each visit that can be used as part of any composite index that uses joint counts (3).

Evidence-based medicine has become the holy grail of modern medical prac-
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Table I. Measures included in composite scores commonly used in RA.

<table>
<thead>
<tr>
<th></th>
<th>DAS28</th>
<th>SDAI</th>
<th>CDAI</th>
<th>RAPID3</th>
<th>Core Data Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen joint</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tender joint</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Physician global</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ESR/CRP</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Patient global</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Functional score</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pain</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Table II. Activity level cut offs for composite indices.

<table>
<thead>
<tr>
<th>Activity level</th>
<th>DAS28 (0–10)</th>
<th>SDAI (0–86)</th>
<th>CDAI (0–76)</th>
<th>RAPID3 (0–30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt;5.1</td>
<td>&gt;26</td>
<td>&gt;22</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.2–5.1</td>
<td>11–26</td>
<td>10.1–22</td>
<td>6.1–12</td>
</tr>
<tr>
<td>Low</td>
<td>2.6–3.2</td>
<td>3.3–11</td>
<td>2.9–10</td>
<td>3.1–6</td>
</tr>
<tr>
<td>Remission/near remission</td>
<td>≤ 2.6</td>
<td>≤ 3.3</td>
<td>≤ 2.8</td>
<td>≤ 3</td>
</tr>
</tbody>
</table>

practise however practicing clinicians often depend primarily upon their own impressions or the impressions of trusted colleagues of what has worked in the past, sometimes taking into account widely publicised RCT. Many physicians consider only data from RCT as “evidence” and commonly ignore data from routine clinical care.

To this end last several years have seen new recommendations about which tools to use in routine care, with the hope of implementing the treat-to-target concept. The last two ACR recommendations, in 2008 (4) and the latest in 2012 (5) recommend composite indices that have been validated and have been shown to work similarly in many different RCT data and in clinical settings. One important aspect to keep in mind is that no measure is perfect and that we should not make trying to get to perfect the enemy of the possible.

Composite scores are usually required in rheumatology in general but especially in RA because there is no one measure that can be used in all patients. Hence various different outcome measures are used in RCT and are recommended for use in clinical care. ACR and WHO/ILAR collaboration led to the Core Data set, developed to provide a consistent set of outcome measures for RA. ACR20, 50 and 70 responses have been used and are good tools, with some differing opinions as to which one is more clinically relevant, however as a group are cumbersome to use in real world clinical care. These are also change scores requiring one to know the starting disease activity level to determine what amount of change has happened. This has led to alternatives to be developed for both RCT and clinical care.

Disease activity score (DAS) and its derivatives, DAS28 (with a 28 joint count), DAS28-CRP (using CRP in place of ESR) are widely used in RCT. The DAS28 includes 4 measures, a 28 swollen and tender joint count as well as patient global estimate, and a laboratory test, either ESR or CRP (total score 0–10). The advantage of providing a score for current disease activity, rather than a change score, as in ACR20, 50 and 70, is that it makes this a more “true” reflection of disease activity. However, it requires a calculator to compute the score using a complicated formula. A website also provides a scoring tool, however this and the fact that at least a 28 joint count is required for the score, has led to it being used rarely in clinical practice. Further criticism has come from the fact that it is possible to be in remission range of DAS28 but still have several swollen and tender joints. In addition, the 28 joint count leaves the feet out and some have suggested that the exclusion of the feet does not provide a true picture of remission, even though a recent study showed that it did not make a significant difference (6).

The simplified disease activity index (SDAI) and its simpler version (no acute phase reactant needed) clinical disease activity index (CDAI) have been developed and used (7). Both are strongly correlated with DAS, but since they share most of the components of DAS, this is to be expected. CDAI has the advantage of calculation right at the time of patient visit since it does not require a laboratory test. Both are simple addition of the 5 and 4 measures, respectively, that make up the composite score. SDAI involves compilation of a swollen joint count (0–28), tender joint count (0–28), physician global estimate (0–10), patient global estimate (0–10), and CRP and CDAI is the same except a laboratory test is not included. This is simpler for the clinician yet a 28 joint count is still required for both measures.

One of the common reasons given for focusing on the swollen and tender joint counts is the belief that anything done by a physician is more “objective” and “scientific”, yet there are data to suggest that in fact patient measures are at least as good if not better in differentiating active treatment from placebo, (8) in addition to identifying response earlier than physician measures of swollen and tender joint counts (9).

Routine assessment of patient index data (RAPID3) was developed with the aim of solving an important problem in monitoring of patients in clinical care; the fact that the instrument needs to be easy to use for both the patients and rheumatologists, while performing as well if not better than the other available scores. This index of only 3 patient reported outcome measures from the core data set – physical function, pain, and global estimate, distinguishes active from control treatments in clinical trials as effectively as ACR or DAS measure (10, 11). The calculation of the score requires no gadgets, no blood test results or a joint count. It takes shorter time than a 28 joint count, DAS28 or HAQ scoring and is highly correlated in the routine care setting with DAS28 and CDAI (12).

The need to use a tool to assess our patients is obvious and all of the measures discussed above perform within the same range of response and are robust. They are part of the ACR RA treatment guidelines of 2008 and 2012 and have been incorporated into
the Physician Quality Reporting Initiative by Medicare for RA in 2009. The most user-friendly measure has a better chance of succeeding and improving both patient care and rheumatologists’ efficient use of time. The RAPID3 is used at the NYU Hospital for Joint Diseases clinics and some of the private practices, and the rheumatology fellows are thought the same. With more hands-on experience most rheumatologists, I feel, would find this a useful and acceptable tool.

For now, our best strategy for treating RA patients arguably is to start with MTX, with or without low dose steroids and treat aggressively. In addition, to achieve the best disease control that we can and document it, we need to monitor patient response with one of the tools that are available, the DAS28, SDAI, CDAI, or RAPID3 or the like, and adjust treatment according to these scores. Patients with inadequate responses after 3–6 months should have one of the biologic agents added to MTX to optimize treatment. However, the recognition of when a change is needed and if it achieves the desired effect can only be documented in an objective fashion with the use of one of the disease activity measures. It is time to start measuring in all our patients, all the time.

References
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