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Rheumatoid Arthritis (Y Yazici, Section Editor)

Treat to Target, Remission and Low Disease Activity in the Treatment of Rheumatoid Arthritis

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Abstract

Purpose of this review Treat to Target (T2T) and disease activity measurements have changed the way rheumatologists treat patients, particularly those with rheumatoid arthritis. The author will address the history behind the development of T2T as well as some practical aspects around the use of T2T and disease activity measurement.
Recent findings The stated targets for disease activity are remission and low disease activity (LDA). However, given that these are "surrogate" measures, each individual measure may, in fact, be measuring a different level of disease activity. Ultimately, no single measure is better than any other. Despite this, recent work has demonstrated that patients in whom the target can be attained, there are better outcomes. How long to wait before making a change in therapy and how deep to push toward the absolute abrogation of disease remains unclear.
Summary Treat to Target is an attainable and acceptable goal for treating patients with rheumatoid arthritis. The deeper the response, the better the outcome, but a low level of disease activity may be acceptable. Treating patients to target will require that patients are evaluated, using a metric, and that changes are made in therapies, based on this metric and sound medical judgement.

Introduction

The treatment of rheumatoid arthritis has evolved from a physician-based "Gestalt" to a measurement and target-driven approach. This article will summarize the important milestones in this evolution

and will discuss the different measures available, the appropriate target for treatment, as well as the strengths and weaknesses of the Treat to Target approach.

Why measure

For decades, the evaluation of rheumatoid arthritis (RA) has been based primarily on "Gestalt", the general feeling that the treating physician was able to discern the level of disease activity, based on his or her clinical experience. [1•] When treatment options were limited to NSAIDs, gold salts, corticosteroids, and, perhaps, methotrexate (MTX), this might have been appropriate. However, with the development of newer agents, such as combination therapies and the biologics, low disease activity (LDA) and remission (REM) became a realistic outcome, and realistic target. [2, 3].

One of the first studies looking into this was the TICORA study [4••], a study in which patients were treated via two paradigms. Done in the pre-biologic era, a target-directed program using a prescribed treatment plan was compared with "standard of care" (SOC) for the treatment of patients with RA. Although blinded only to the assessor and criticized for the high doses of corticosteroids used to control the disease, the TICORA study clearly showed the superiority of a target-based treatment option compared with SOC, and opened the way for further studies of the concept. Other studies were to follow, using different treatment strategies [5, 6], but all demonstrated that the attainment of LDA and REM were realistic goals and that the goals were attainable regardless of which medications were used in the treatment.

Based on these studies, an international task force was created to set up best practices and guidelines for the treatment of RA [7, 8••]. As part of these guidelines, recommendations using a disease-measured approach to therapy and targets were established. In particular, it was felt that the preferred target for treatment would be remission ("the abrogation of disease"), but in many patients, particularly those with established disease, LDA was also an acceptable target. Patients should be monitored frequently, and medications were to be adjusted if and when patients did not reach the appropriate target. This treatment paradigm has been widely accepted in practice and by both the ACR and EULAR, representing one of the major changes in practice behaviors, since the addition of biologic agents to the treatment of RA.

How to measure

Once there is a movement away from "educated guessing/Gestalt" toward treating to a target, it becomes obvious that there has to be measurement tools used. These tools are all based on the ACR Core Data Set and include different components from this group (Table 1). The most commonly used include the DAS28 (ESR or CRP), CDAI, SDAI, and RAPID3, although this list is not intended to be exhaustive. Some physicians are relying on lab tests to monitor patients such as a multi-biomarker disease activity measure (MBDA), while others are using a combination of these measures to determine disease activity [9–13] (The author routinely uses both the CDAI and RAPID3 in clinical

Table 1. Components of the ACR Core Data Set used in the different disease activity measures

ACR Core Data Set	DAS28	SDAI	CDAI	RAPID3/PAS-II
Tender joint count	*	*	*	
Swollen joint count	*	*	*	
Physician global		*	*	
Pain				*
Patient global	*	*	*	*
Function				*
ESR/CRP	*	*		

practice.) All of these measures have their advantages and disadvantages, ranging from time to perform, requirements to perform formal joint counts, the availability of laboratory results, and the influence of patient vs. physician input. None of these measures are perfect and can be influenced by factors outside of the RA clinical activity, such as those related to the patient-reported components where non-inflammatory pain and disability may influence the results, those related to the inconsistencies of the physician-reported components where the vagaries and inconsistencies of joint exams become a factor, and those related to the confounding of lab exams where factors such as infections or other non-RA-related conditions can influence the results.

However, there is another important question that needs to be asked: what it is that is actually being evaluated by our current tools? Using the DAS28, a patient may have eight or more swollen joints, but could still be classified as being in "remission." Even the most stringent measure, Boolean remission, which allows for only one tender and one swollen joint, allows for some degree of disease activity. Thus, "remission" is more of a measurement target, rather than a true clinical state. The same can be said of low disease activity (LDA), as well.

It should also be recognized that most measures have defined values for different levels of disease activity; they are not identical in terms of what "true" physical state constitutes the measured low disease activity and remission (Table 2). The DAS28 allows for two different versions calculated using either the ESR or the CRP, with identical values being defined as REM (DAS28<2.8) or LDA (DAS28<3.2). However, a more careful examination reveals that values are not interchangeable. A study looking at the correlation between DAS28 (ESR) and DAS28 (CRP) suggests that, to be at the same level of disease activity, the DAS28 (CRP) target should be between 10 and 20% lower than the DAS28 (ESR) [14]. In terms of level of "disease activity," there are differences between the different measures. However, despite these differences, in terms of a target, any measures used consistently should suffice.

Some have suggested that the addition of an ultrasound (US) study to the clinical measures would increase the accuracy of the measure. However, the results of the ARCTIC study [15] were not encouraging. In this study of 963 visits in 130 patients, the addition of seven joint US evaluations did not result in any significant improvement and may have led to more rapid changing of medications without additional benefit and the potential of increased cost.

Table 2. Values for disease activity

	Remission	Low disease activity	Moderate disease activity	High disease activity
DAS28 (ESR or CRP)	<2.6	≥2.6 and <3.2	≥3.2 and <5.1	≥5.1
SDAI	≤3.3	>3.3 and ≤11	>11 and ≤26	>26
CDAI	≤2.8	>2.8 and ≤10	>10 and ≤22	>22
RAPID3	≤3	>3 and <6	>6 and ≤12	>12
PAS II	≤0.25	>0.25 and ≤3.7	>3.7 and ≤5.1	>5.1

Another study has looked at the value of adding an MMP-3 measure to the DAS28, to improve the accuracy of the measurement. In this study, 243 patients were randomized to receive treatment based on SOC ("R" n =62), DAS28 driven ("D" n =60), MMP-3 driven ("M" n =60) or DAS+MMP-3 driven ("T" (n =61)). After 56 weeks of treatment, while there were differences between the "R" and "T," there was no advantage to the addition of the lab test to a DAS-driven approach, in terms of number of patients in remission, number of patients with normal function, and number of patients without X-ray progression [16].

In the end, no measure, to date, is truly "better" than the other. In fact, looking at the ability to differentiate active drug from placebo, Bergman et al. were able to demonstrate that any composite measure using three or four components of the ACR core data set performed equally well [17]. Still, some measures have been more readily adopted than others, so using them, preferentially, would lead to more uniform and standardized practice patterns.

Recently, the American College of Rheumatology (ACR) working group evaluated the currently available disease activity measures to determine which ones met a minimum standard for use. The requirements for meeting this standard looked to see which measures (1) provided a numerical value, (2) categorized disease activity into, at least, three disease states, (3) were feasible for routine use, and (4) provided adequate psychometric properties [18]. While other measures met a minimal standard of acceptability, based on these requirements, the working group recommended that five measures be considered for routine clinical use. These were DAS28 (ESR), DAS28 (CRP), CDAI, SDAI, RAPID3, and PAS-II. Ultimately, the decision as to which measure or measures to choose, in a clinical setting, should be determined by the practice requirements, time constraints, and resources available to each individual site and practitioner.

Remission vs. LDA

The appropriate target for treating is felt to be remission. Studies have shown that patients achieving this level of disease activity fare better than those who have not [19–21]. This has been particularly true with respect to patient function, but also in terms of quality of life and productivity. In a study of 139 patient completing 1 year follow-up, patients who attained REM had a HAQ of

0.27±0.41 at 6 months and 0.22±0.35 at 12 months, compared with a HAQ of 0.49±0.5 at 6 months and 0.75±0.61, after starting from a baseline HAQ of 0.95 ±0.7 (p <0.05). [19]. In a similar study, Radner et al. found that patients achieving remission had a HAQ of 0.39±0.58 vs. 0.72±0.86 in those patients in LDA. In this same group, work impairment, as measured by the WPAI, was 11.8%± 18.7% vs. 26.8%±23.9% in the REM group vs. LDA and overall work activity impairment was 10.8%±14.1% vs. 29.0%±23.6%, respectively. Other measures of quality of life, function, and mental health, as measured by the EQ-5D and SF-36 physical and mental component scores, showed similar benefits of REM vs. LDA. There was also some evidence that there may have been an impact on cost [20]. However, despite the implications that attaining REM leads to better outcomes that being in LDA, few studies have looked at the benefit of treating patients who are in LDA more aggressively to attain REM. The CAMERA study, using a computer-based algorithm, was one such study. Although this study was done in the pre-biologic era and used cyclosporin as one of its medication, the results were not encouraging, showing that, although there was a small, but insignificant improvement in HAQ (0.1 point, which is below the MCID for this measure), there were increases in medication toxicities in the patients more aggressively treated [6]. Without additional studies, it is not known whether a patient who is in LDA needs to be "pushed" to REM or if it would be just as appropriate to allow patients who are responding at a level of LDA to remain at this level of disease activity.

Another issue is the time necessary to reach the defined target. The T2T task force recommended that patients be monitored frequently and that the target should be attained within 3 months. However, a recent study, looking at treatment trajectories in 174 patients treated with baricitinib, demonstrated three distinct treatment responses. One group (n =55) responded very quickly and well, while another group (n =55) essentially never attained a low CDAI target. However, there was a middle group (n =29) who had a more erratic and a less predictable response [22]. For these patients, a longer time frame may be necessary. Determining who these patients are, at the onset of treatment, remains a challenge.

One way is to measure the rate of response, during the first 6–12 weeks of treatment. In a study by van der Heijde et al. patients treated with certolizumab pegol who had a <0.6 point change of the DAS28 (ESR) by week 6, only 2.4% were able to attain LDAS at 1 year. If the DAS28 (ESR) did not improve by at least 1.2 points by week 12, only 22.3% were in LDAS at 1 year. [23]. From a practical standpoint, in the authors' opinions, these data imply that as long as the patient is making continued progress toward LDA or REM, with steady improvement from each visit to the next, the current regimen can be maintained. On the other hand, if essentially no response has been seen by week 6 and/or only minimal response is seen at 3 months, a strong consideration should be made toward changing therapies. This is not always easy for patients who feel "better" on their current medications than they did when they started.

As a result, the clinician often is presented with the situation of wanting to change a medication in a patient who is reluctant to do so. A recent study [24] using data from the MONARCH study adalimumab (ADA) vs. sarilumab (SARI) in MTX incomplete responders took a novel approach to look at how to address this issue. Patients who had improved, but had not reached low CDAI, were either switched from ADA to SARI or continued SARI, in an open-label

extension. At the end of the study, 57% of those who switched improved, 37% had no changes, but most importantly, only 6% of patients worsened. This provides some reassurances to the patient that there is only a minimal risk of "going backwards." However, ultimately, the choice of treatment will remain a joint decision between the patient and the physician, as recommended by the T2T guidelines.

While patients may be reluctant to change medications, an additional obstacle to T2T is physician reluctance. The reasons for this are myriad and run the gamut of lack of time during the clinical visit, lack of belief in the validity and benefit of T2T, and routine disease monitoring, systems issues which do not facilitate the integration, such as the RAPID3 or CDAI, into the medical record, to simply a lack of desire or understanding of the need for disease measurement. Ultimately, it will be up to the clinician to determine if and when to integrate this concept into clinical practice. On a sobering note, in a small study looking at the benefit of US in monitoring 21 patients with RA and 12 patients with PsA, Kitchen et al. found that despite all patients being determined to be in "remission" by the attending academic clinician, only 22% of these patients were in "remission" by US criteria (power Doppler score ≤10). However, just as importantly, when a disease activity score was employed (DAS29 (CRP)), only 51% were actually in remission. As good as clinical "gestalt" may be, measurement is superior [25].

Conclusion

With the availability of advanced therapies, the ability to have patients attain level of low disease activity or remission is clinically realistic. The consequence of this will be better long-term outcomes, with better function and quality of life. To get to this level of disease activity, it will be necessary for clinicians to adopt and use, on a consistent basis, disease activity measures. While a number of measures are available, and recognizing that no single measure is superior to any other nor is it always an accurate reflection of disease activity, some degree of standardization is beneficial. To this effect, the ACR has provided a list of "preferred" measures which, while not intended to be exhaustinve nor immutable, are both feasible and sufficiently accurate for widespread use. With these measures, clinicians will be able to treat to a predetermined target. Based on the work of the T2T task force, this target is felt to be remission, although low disease activity may be an acceptable target, particularly in established disease. While an improved outcome has been predicted with this concept, the use of targets and guidelines are not meant to be dogmatic. Ultimately, the aggressiveness of treatment remains a joint decision between the physician and the patient.

Compliance with Ethical Standards

Conflict of Interest

Dr. Bergman reports personal fees from Abbvie, Amgen, Genentech, Janssen, Pfizer, Gilead, Novartis, Sanofi/Regeneron, Sandoz, and Merck outside the submitted work.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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