Abstract
The treat to target approach to managing therapy in rheumatoid arthritis was only just formally proposed in 2010, yet it is clearly here to stay. While the original recommendations were based on a limited set of published data, subsequent studies have explored the role of the treat to target approach in a variety of clinical settings and have confirmed its value. Despite this, additional data is needed, and challenges still remain in the widespread implementation of the treat to target strategy. Some of these challenges are at the patient level, some are at the physician level, and some are at the system level. The identification of these challenges is in itself an opportunity to improve the treat to target paradigm in order to maximize the outcomes of patients with rheumatoid arthritis.

The Treat to Target (T2T) recommendations for management of rheumatoid arthritis (RA) were first published by an international task force in 2010. The rationale for developing these recommendations drew from the application of specific therapeutic targets to reduce the risk of organ failure in diseases such as diabetes and hypertension. In their publication, the task force laid out a set of 4 overarching principles and 10 specific recommendations for treating RA to target, defined ideally as remission of clinical disease activity. At the time, there was limited published evidence available to support the individual recommendations, so that most were based solely on expert opinion. Subsequently, a number of studies have demonstrated the value of treating to target in RA, as well as the superiority of this approach when compared to usual care of this disease.

The T2T recommendations were presented as an attempt to transform the clinical management of RA into a standardized approach, with the goal of improving both short and long-term outcomes. Three years after their publication, it seems appropriate to ask how this ambitious goal has translated into clinical practice. Interestingly, while it is difficult to argue with the T2T approach as a broad concept, it is less clear that each of the individual elements resonate with clinical rheumatologists. Members of the T2T task force recently surveyed 1,901 rheumatologists in 34 countries about their level of agreement with the individual recommendations. There was broad agreement with the 10 recommendations, and most respondents indicated that they were currently applying these recommendations to daily practice; however, a substantial percentage of those who were not applying some of the individual recommendations indicated that they were unwilling to do so. For example, among the 12.7% who indicated that they were not routinely reassessing patients with moderate or high disease activity on a monthly basis, 43% indicated that they would not be willing to do so. Responses such as these serve to highlight the challenges that remain in applying the T2T paradigm to clinical care.

The goal of this paper is to review some of the data that has become available on treating to target since the publication of the original recommendations and to identify some of the challenges that still remain in the adoption of this approach (Table 1).

When the task force developed the T2T recommendations, they referenced the evidence from a number of studies that examined the benefit of T2T relative to usual care. These studies, however, assessed the use of the T2T approach in a clinical trial setting rather than in routine clinical practice. For example, the TICORA study, frequently referenced as a clear example of the benefits of the T2T strategy, compared patients randomized to monthly visits employing treatment changes targeted at achieving low disease activity (DAS <
methotrexate and infliximab in early RA with efficacy of a T2T strategy have recently been published. The Two additional studies examining the comparative efficacy of a T2T strategy have recently been published. The IDEA study, a 78-week trial comparing initial therapy with methotrexate and infliximab in early RA with methotrexate plus a single dose of 250 mg IV methylprednisolone, employed a T2T approach targeted at low disease activity (DAS44 < 2.4). This trial also added a step down strategy, in which infliximab was discontinued in patients achieving sustained remission for 6 months (14 of 55 did so). The initial steroid group was treated with non-biologic DMARDs until achieving the target; their clinical and radiographic outcomes were similar to the infliximab group at 78 weeks, although approximately 10% exited the trial after meeting NICE criteria for biologic use (high disease activity). While this trial did not compare T2T with usual care, it did demonstrate the value of the T2T approach, showing that treating to target with non-biologic DMARDs can achieve comparable results to biologic therapy.

The STREAM trial extended the T2T approach from established RA to a population of early, undifferentiated arthritis with just two to five swollen joints. In this trial, which randomized 82 patients (60% with a positive ACPA antibody) to conventional therapy with non-biologic DMARDs or an aggressive T2T strategy aimed at DAS remission, the percentage of patients achieving remission, the improvement in function, and the degree of inhibition of radiographic progression were all similar at 1 and 2 years, even without biologic therapy in the usual care group. The apparent success of usual care in this trial may be due to its focus on the window of very early disease, when the introduction of almost any disease-modifying therapy may be sufficient to achieve meaningful results.

Subsequent to the publication of the T2T recommendations, the Dutch DREAM registry has been reported as the first study to specifically look at the outcomes and feasibility of employing a T2T strategy in routine clinical practice. In this trial, a series of early RA patients, enrolled as part of an inclusion cohort, were treated with a T2T regimen at a group of five Dutch rheumatology clinics. The DREAM cohort, which included the use of biologics as necessary to achieve the desired target, demonstrated not only that a T2T approach to therapy could be practical in clinical practice, but that it can achieve comparable results to those achieved in a clinical trial. EULAR good response at 1 year was achieved in 68% of patients, compared with 82% in the T2T arm of the TICORA trial, and DAS28 remission was 58%, compared with a DAS remission of 65% in TICORA. A recent comparison of a subgroup of patients from three centers in the DREAM cohort with a comparable group of early RA patients treated with usual care at two different Dutch clinics reported that the T2T regimen achieved better clinical results over a year, with 55% of those in the T2T group achieving DAS28 remission at 1 year compared with 30% of those receiving usual care.5 Median time to remission was 25 weeks for T2T compared with more than 52 weeks for usual care. Similar findings were seen when comparing a group of early RA patients treated in the French GUEPARD T2T study with a matched group of patients receiving usual care in the French ESPOIR registry. In this case, patient and physician global assessments, as well as the HAQ functional questionnaire, demonstrated the superiority of the T2T approach more clearly than joint counts alone.

So then, if a T2T strategy is so clearly more effective for the treatment of RA, what are the challenges inherent in employing this strategy in clinical practice? The first question often raised is one of practicality—is this an approach that patients and physicians are willing to adhere to? Indeed, there are no published data that prospectively examine the use of the T2T approach in the USA rheumatology practices. USA rheumatologists may be wary of embracing the T2T approach because of concern over finding time in the visit to focus on treating to an objective target, particularly when

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| Table 1 Challenges to Implementation of Treat-to-Target Strategy in Rheumatoid Arthritis |
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| Willingness of physicians to implement in a busy clinical practice |
| Setting appropriate targets for individual patients |
| Acceptance by patients |
| Appropriately valuing patient reported outcomes in setting targets |
| Identifying the relative importance of non-clinical targets (imaging, biomarkers) |
| Payer restrictions on access to higher cost therapies |
| Identifying potential long-term cost benefits |
other encounter elements may be required in order to meet regulatory or documentation requirements. One solution might be to focus on easily obtainable patient reported outcomes when assessing progress towards a target. Indeed, the investigators of the comparison of the GUEPARD T2T study and the ESPOIR usual care cohort suggested that use of the RAPID3, which includes patient reported measures only, might be an effective approach in a busy clinical practice.9

Like physicians, patients may be wary of embracing the T2T strategy although their engagement is critical to its success. In fact, when laying out their initial T2T recommendations, the task force was careful to note the importance of patient involvement in the process and later published a version of these recommendations that was designed to be understandable to patients, so that they could actively participate in their care.10 Despite this, the success of the T2T strategy in clinical trials has been based strictly on clinical disease activity measurements, primarily remission. Several investigators have suggested that patient concerns about the value and costs of their therapy, as well as patient centered outcomes, such as work ability, have not been adequately considered in the process of implementing T2T strategies in clinical care.11,12 There is also data to suggest that patients and physicians consider different aspects of disease when making treatment decisions.13,14 While the T2T strategy was intended to apply to all RA therapies, for some biologic therapies, incremental benefits in disease activity scores may not correspond to similar improvements in the patient centered outcomes that the patient really cares about, so that some may not see the benefit in changing therapy in an attempt to further lower disease activity state.15

Just as some have questioned whether the T2T strategy may place too much emphasis on quantifiable disease activity scores, it is also possible that an emphasis on even more objective measurements might lead to better outcomes. In one study, the addition of a biomarker target, matrix metalloproteinase 3 levels, led to more patients achieving clinical remission at a year than targeting clinical endpoints alone.16 Others have proposed that targeting resolution of ultrasound evidence of disease activity might lead to better overall outcomes than targeting clinical disease activity alone.17

Finally, the greatest challenge to fully implementing the T2T approach may lie in its cost. In the TICORA trial, there was actually a trend towards lower total medical costs in the T2T arm; higher medication costs were balanced by lower hospitalization costs than in the usual care group.1 However, this trial utilized only non-biologic therapy. An aggressive T2T approach will very likely lead to greater use of more expensive biologic therapies. While improved outcomes may translate into lower costs of care in the long run, as joint surgeries, hospitalizations, and even cardiovascular complications could be reduced, the short-term costs of care may be higher, leading to push back from payers. This is not a situation that is unique to the USA; even in the UK, where the National Health Service provides universal care, there is concern that payment guidelines will not support the T2T approach, especially in later stage RA, where there is less evidence for the benefit of treating to target.18 The solution to this challenge is likely to be the same in both the USA and the UK. Additional evidence needs to be developed to demonstrate the value of treating to target in clinical practice for all stages of RA, and data needs to be collected to demonstrate the downstream cost benefits that can accrue from the better clinical outcomes achievable with a T2T strategy.

In essence, the challenges associated with implementing a T2T strategy are also the opportunities. More information is clearly needed on the practicality of T2T in routine clinical care, on the selection of the most appropriate targets for both patients and rheumatologists, and on the potential cost savings to be realized by achieving improved outcomes in RA therapy. Recognizing the need for these data is also an opportunity, however, as such data could pave the way to improve the T2T approach, so that it more effectively achieves the ultimate goal—better outcomes for patients with RA.

Disclosure Statement
Eric M. Ruderman, M.D., is a consultant for AbbVie, Amgen, BMS, Celgene, Janssen, Lilly, Medac, Pfizer, and Vertex and has provided paid expert testimony for Pfizer.

References


