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Treat to Target in Rheumatoid Arthritis: Fact, Fiction or Hypothesis?

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The treatment armamentarium for rheumatoid arthritis (RA) has grown substantially over the last 15 years since the development of targeted biologic and non-biologic disease modifying anti-rheumatic drugs (DMARDs). These drugs have broadened the treatment possibilities and changed how rheumatic disease experts approach the clinical management of RA. The goal of reducing disease activity to very low levels (or remission) is now realistic, and emerging evidence suggests that treating to achieve these targets enhances long term structural and quality of life outcomes.(1–7) Consequently, "treat to target" (TTT) has become an attractive concept in the clinical management of rheumatoid arthritis (RA). TTT is generally defined as a treatment strategy in which the clinician treats the patient aggressively enough to reach and maintain explicitly specified and sequentially measured goals, such as remission or low disease activity. TTT is proactive, has a clear endpoint (the "target"), and can be operationalized as a specific treatment algorithm, simplifying the multitude of complex medication sequences that can be used to treat active RA. The emerging TTT paradigm is supported by findings from many randomized controlled clinical trials in the last decade, not designed as TTT strategy trials, that suggest the benefits of early aggressive treatment approaches.(5, 8, 9)

While TTT has many potential benefits, the rheumatology community needs to critically appraise its value in the treatment of RA. Put another way, is TTT a proven paradigm or a hypothesis requiring more complete testing? In this commentary, we first describe how TTT has been defined in RA and what data support its use. Second, we examine the conceptual roots of TTT, assessing how it has been used in conditions outside of rheumatology. Third, we examine current DMARD use patterns and barriers to TTT in clinical practice are

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examined. Fourth, we discuss data from the patients' perspective relevant to TTT and set out a research agenda to address identified gaps in knowledge.

I. Treat to Target in Rheumatoid Arthritis

Over the past 10–15 years, several randomized controlled clinical trials have demonstrated that a TTT strategy can achieve superior clinical outcomes compared with usual care. Studies included to support evidence for TTT can be divided into randomized strategy trials, assessing the efficacy of treating to a specific target versus routine care in the comparator arm; and treatment target trials in which all treatment arms have a defined target, but different treatment strategies to reach the target are compared. All TTT trials have included relatively frequent assessment with recommendations for intensifying treatment when patients have not reached target. These trials (reviewed in Table 1) have been primarily conducted in Western Europe.(1–7, 10) The number of subjects included in TTT trials ranges from 96–508. Some of the trials required subjects in the TTT arm to be treated according to specific treatment algorithms and others allowed treating physicians to decide on treatments but required a specific disease activity goal. Almost all randomized at the subject level. Treating providers were not blinded to assignment group in most studies, but many of the trials employed blinded assessors. Duration of follow-up ranged from 6–36 months and few trials accounted for the clustering of subjects within practices.

The treatment targets varied across trials, and the rates of attaining the targets in the intervention arms ranged from 31–82%. The intervention arms' rates of reaching target were enhanced compared to the control arms' in all but one study. The safety of TTT was comparable to the non-TTT arms with no greater rate of withdrawal due to adverse events. Several noted reduced progression in radiographic measures, but not all. Almost no information is available regarding the cost of a TTT strategy.(11)

Data on the prognostic importance of consistent control of disease activity gave birth to the TTT strategy. Achieving optimal outcomes and aiming for targets using treatment strategies with maximum benefit and minimal harms was the biggest motivation for developing recommendations for treatment of RA.(12) A recent international task force issued recommendations about TTT. While these recommendations are not uniformly accepted, several aspects of these TTT recommendations and principles are important to highlight (see Table 2). Remission is specified as the primary target, but the recommendations note that low disease activity may be an appropriate alternative target. The ACR RA treatment guidelines also point out the importance of these treatment goals.(13) It is further noted that the choice of the disease activity measure and target may be influenced by comorbidities and drug toxicities, and that patients must be appropriately informed about the treatment target. Furthermore, the TTT recommendations embed several important principles, including that RA treatment should be based on a model of shared decision making. They also appropriately note that many aspects of TTT are based on limited evidence.

Thus, the recommendations are both subtle and complex, requiring on the one hand that providers elicit patient's treatment goals and preferences, and on the other hand that providers pursue a standardized treatment algorithm with an objective treatment target.

While the algorithm will result in treatment that is no more aggressive than is typical for most patients and providers, some patients will experience an escalation in treatment beyond what would be typically prescribed.

II. Treat to Target Outside of Rheumatology

Treat to target has become a popular concept in the medical management of several common chronic conditions, including diabetes, hypertension, and hyperlipidemia. In its early formulation, TTT was used in the care of diabetes mellitus to design trials that focused on a HbA1c target, as opposed to specific treatment algorithms or combinations.(14) The impressive reductions in long-term diabetes-related complications and overall mortality seen in the DCCT (Type I diabetes) and UKPDS (Type 2 diabetes) studies solidified consensus around threshold target-based therapy.(15, 16) The concept spread rapidly to the hypertension and lipid arenas where similar studies were undertaken with explicit blood pressure and LDL goals, respectively. Strategy trials, employing a TTT approach, were undertaken and often utilized non-physician providers and explicit algorithms for medication use.(17, 18)

The substantial long-term outcomes data from trials focused on lowering LDL, blood pressure or HbA1c lay a strong foundation for TTT. For example, a large meta-analysis of 14 statin trials showed that reaching target LDL reduced mortality by 12%.(19) As a result of these data, the National Cholesterol Education Program's Adult Treatment Panel recommendations rest upon Level I evidence.(20) That said, in the context of a randomized controlled strategy trial, more aggressive treatment targets for HbA1c among diabetics with cardiovascular disease produced worse outcomes in the arm with a more aggressive target. (21)

The success of TTT in other chronic conditions serves as an important motivator to a TTT strategy in RA. RA is similar to these conditions in that all are chronic conditions with effective treatments, and combination therapy is frequently required to control the disease (Table 3).

While the similarities between RA and these conditions in which TTT has been employed are important, several differences are also notable (see Table 3). First, RA is generally symptomatic and consequently patients can report their disease activity using validated self-report measures. In stark contrast, diabetes, hypertension, and hyperlipidemia are often, but not always, asymptomatic. The lack of symptoms can contribute to "clinical inertia" in which providers and patients become reluctant to change therapies despite imperfect disease control as evidenced by numerical targets.(22)

Second, treatments for RA require substantial disease monitoring for potential harms, including the risk of infections, heart failure or liver disease. While the absolute risk of these treatments is not likely different than many treatments for other chronic diseases, they are perceived by most patients (and many providers) as "dangerous" drugs because of their effects on the immune system and black box warnings related to cancer and infection. As well, most RA treatments have accompanying recommendations for laboratory monitoring

which may add to the perception of risk. Such perceptions may create patient concerns about increasing doses, adding, or changing treatments.

Third, the evidence linking tight disease control with long-term improved outcomes is less robust for RA than it is for diabetes, hypertension or hyperlipidemia. Several studies suggest that tight long-term control in RA is more likely to help a patient achieve clinical remission and minimize radiographic damage than routine care, but efficacy ranges across patients and many still incur radiographic damage over time.(1–6) In contrast, the association between achieving target disease control in diabetes, hypertension, and hyperlipidemia and reduced long-term morbidity has been studied in many thousands of patients over several decades. It is noteworthy that along with beneficial effects, tight control of hyperglycemia and hypertension have also been associated with serious risks such as symptomatic hypoglycemia or hypotension, and even increased mortality in some multi-morbid sub-groups.(21)

III. Barriers to Treat to Target in Rheumatology

If we accept the benefits of a TTT paradigm in RA, many formidable challenges limit incorporating it into typical practice. First, it appears that many patients with RA do not even receive a DMARD. Population-based studies (not ones performed in rheumatology practice) demonstrate that 35–60% of patients with at least two diagnoses of RA do not have record of filling prescriptions for DMARDs.(23) It is likely that some of these patients do not have RA, have very mild disease, or have contra-indications to DMARDs. However, the sizable proportion of RA patients not receiving DMARDs suggests that widespread deployment of a TTT strategy will be challenging.

Second, few non-rheumatologists are comfortable managing DMARDs, and relatively few patients with RA have easy access to rheumatologists. A recent American College of Rheumatology workforce study demonstrated that 83% of urban areas in the US with populations between 10,000 and 50,000 have no rheumatologist; in those regions, the median distance to the nearest rheumatologist is 159 miles.(24) We also know that the strongest predictor of receiving DMARDs for a patients with RA is a visit with a rheumatologist.(25–27) Thus, without better access to rheumatologists, much of the RA population will likely not have a chance of being treated with a TTT strategy.

Third, even if patients can access a rheumatologist, many patients may not want to pursue a TTT strategy. As noted in Table 2, enlisting patients as partners in TTT is an important principle. However, it appears that a sizable portion of patients are reluctant to change treatments if they feel “ok” despite having active arthritis. In one study of more than 6000 subjects from the National Data Bank on Rheumatic Diseases, 77% indicated they were satisfied with their medications, yet 71% of these satisfied respondents had moderate or greater disease activity as assessed by their Patient Activity Scores and Health Assessment Questionnaire score. These observations demonstrate discordance between patients’ treatment preferences and their perceived pain and function.(28) Similar work from other researchers also demonstrates discordance between rheumatologists’ ratings of disease activity and their patients’ ratings.(29) Several possible explanation for this discrepancy may

be that patients observe improvement in their disease state, even though they have not reached the desired target for disease activity. As well, patients may not be convinced that changing treatments will actually improve outcomes.

Fourth, TTT requires frequent visits and the use of structured RA disease activity measures, two potential impediments for rheumatologists with busy practices. While return visits for patients who have not reached target disease activity should be brief, frequent visits may be difficult for patients. Consistent use of structured disease activity measures (CDAI, SDAI, DAS28, RAPID) is required for a TTT strategy, but it is unclear that most rheumatology practices use them consistently.

Finally, since TTT requires rapid treatment escalation in the face of ongoing active disease, medications must be available without long delay. As any US-based provider knows, gaining approval for expensive treatments in RA is not quick and often burdensome. This barrier, plus expensive patient co-payments, is not likely to lessen as the pressure to reduce health care costs continues.

IV. Patient Perspectives on Treat to Target

One of the principles for TTT described by the International Task Force includes engaging the patient in a discussion about their goals for treatment. Relatively little has been written about RA patients' understanding or attitudes regarding TTT. However, other chronic conditions where TTT has been used present some information regarding the patient's perspectives.

It is clear despite well-documented campaigns to spread the provision of targeted diabetic therapy to achieve goal HbA1c levels, patient buy-in and adherence is still sub-optimal.(30) A host of patient-level barriers exist, including medication ease of dosing, cost, inconvenience, lack of disease symptoms, medication side effects, or disinterest in frequent monitoring necessary for glycemic control. Similar issues exist for both hypertension and hyperlipidemia.

While we do not yet have studies specifically focusing on patient's attitudes towards TTT, several studies suggest that implementing and adhering to TTT strategies in clinical practice will be challenging. Findings from the National Data Bank on Rheumatic Diseases found that many patients are satisfied with their current medications despite having levels of disease activity that would warrant escalation of care according to TTT algorithms. Moreover, patients may be reluctant to change treatment regimens not only because of the fear of side effects associated with new medications, but because of a fear of losing control of their disease. Recent data suggests that high disease activity (as indicated by RAPID4 scores) is predictive of future escalation only in patients who also report that their illness has a significant physical and/or emotional impact on their quality of life.(31) Thus, patients who have adapted to their disease may not have changes on patient reported outcome measures and may be unlikely to be willing to escalate treatment, regardless of their disease activity score.(32) Data from TTT trials related to improvements in outcomes that patients can relate to, such as quality of life, would likely help patients understand the value of TTT.

TTT recommendations specify the importance of adhering to a shared decision making model. Given the structure inherent to the TTT approach, this model requires that patients are fully informed of the specific algorithms to be used and that they agree to increased burden of monitoring and likely escalations of care (even in some cases when they don't feel that additional medications are required). Shared decision making may be easier to implement in TTT strategies using specific targets as opposed to those requiring the use of specific medications, since the former enables physicians to incorporate their patients' treatment preferences. There has been some effort to make TTT recommendations more patient friendly;(33) this effort needs to continue.

It is important to consider the patient perspective in other diseases where TTT has been employed. Some literature suggests that while patient function may improve employing a TTT strategy, other data suggest that the burden of treatment (checking blood sugar, more needle sticks) can increase depression scores.(34, 35) In the setting of RA, the targets for treatment mix both objective scores (joint counts and inflammatory markers) with the patient experience (patient global). Thus, TTT in RA relies on treating towards a physiological target, but the patient must experience the target as a steppingstone to enhanced quality of life. Patients must be educated adequately to fully endorse the target in a TTT approach.

V. Conclusion

In conclusion, TTT in RA faces many challenges limiting its widespread acceptance. Some of these challenges are scientific due to a relatively sparse evidence-base. We have outlined some of the major questions facing TTT (see Figure 1). These can be fit into several categories of research: biologic, clinical, and health services. These topics may serve the rheumatology community well as areas for research proposals.

Other barriers include potential conceptual mis-match: patients know how their arthritis affects their body and what they want from their treatments; their goals may not align with an objective target of low disease activity or remission. Further, some patients may be too fearful of the potential risks of aggressive therapy to engage in TTT. Moreover, access to rheumatic disease expertise limits the use of DMARDs in the US and certainly will limit dissemination of TTT. We believe that there is a continued need for testing and refining many of the concepts underpinning TTT in RA. We look forward to a robust research effort in response to the important potential posed by TTT. Clearly, TTT in RA holds promise with substantial evidence. However, many aspects of TTT need more data to push it from a hypothesis to a fully proven treatment strategy.

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Basic Science Questions

1. Is there a biologic “window of opportunity” during which aggressive immunosuppression as part of TTT will change the long-term biology of RA?
2. Are there biomarkers that predict which patients will be able to successfully reach the target in a TTT strategy?

Treatment/Clinical Questions

1. Is there one (or several) most effective TTT strategy?
2. Should the target for TTT be the same in all patients?
3. Is TTT associated with improved long-term function and reduced morbidity/mortality?
4. Is TTT associated with long-term extra-articular benefits, such as reduced cardiovascular disease and less osteoporosis?
5. Is TTT associated with a higher rate of drug side effects?

Health Services Questions

1. What are the economic costs of a TTT strategy?
2. How can rheumatology practices best deploy a TTT strategy?
3. What is the potential role of mid-level providers (nurse practitioners and physician assistants) in TTT?
4*. What is the patient perspective on TTT? In what areas is there “buy-in” from patients, and what areas is there concern?
5*. What are the optimal methods to communicate risk/benefit balancing in TTT?
6*. How can TTT best fit in a shared decision-making framework?

Figure 1.

Research Agenda for Treat to Target in Rheumatoid Arthritis

* These questions might be considered “patient-centered.”

Table 1

Selected Treat to Target Randomized Controlled Trials in Rheumatoid Arthritis

Reference	Study Cohort	Target	Algorithm for TTT; follow-up interval	Duration of follow-up (mos)	Randomization	Blinded assessment	Results
Strategy Trials (one group with a target and another without)							
Grigor, 2004 (TICORA) (1)	N = 110; 2 National Health Service hospitals in UK	EULAR good response (DAS28 (ESR) <2.4 & change from baseline DAS by >1.2) at month 18	Yes; 4 weeks	18	Patient-level	Blinded metrologist	EULAR good response: TTT: 82% Control: 44% (p<0.0001)
Verstappen, 2007 (CAMERA) (2)	N = 299; 6 rheumatology departments in the Netherlands	>20% improvement of SJC and ESR, TJC, PGA at year 2	Yes; 4 weeks	24	Patient-level	No; open-label trial	DAS28 remission: TTT: 35% Control: 14% (p<0.001)
Fransen, 2005 (3)	N = 384; 24 rheumatology departments in the Netherlands.	DAS28 (ESR)<3.2 (low disease activity) at week 24	No; none	6	Practice-level	Unclear from publication	DAS28<3.2: TTT: 31% Control: 16% (p=0.028)
Symmons, 2005 (7)	N = 466; 5 rheumatology departments in England	No active tender or swollen joints; CRP < 2x ULN at year 3	No; 4 months	36	Patient-level	Assessor blinding	HAQ: TTT: 1.45 Control: 1.40 (p = NS)
Treatment Target Trials (all groups with target but strategies to achieve target differ)							
Mottonen, 1999 (FIN-RACo) (36)	N = 195; from Finland	Induction of ACR-remission* at year 1	No; 12 weeks	24	Patient-level	No; open-label trial	ACR Remission Criteria: Triple therapy: 38% Monotherapy: 17%
Saunders, 2008 (5)	N = 96; 3 National Health Service hospitals in UK	DAS28(ESR) <3.2 (low disease activity) at year 1	Yes; 12 weeks	12	Patient-level	Blinded metrologist	DAS28 remission: TTT: 45% Control: 33%
Goekoop-Ruiterman, 2007 (BeST) (6)	N = 508; 20 rheumatology departments in the Netherlands	DAS44 (ESR) <2.4 (low disease activity) at year 2	Yes; 12 weeks	24	Patient-level	Blinded metrologist	Low disease activity: Initial combo with IFX: 40% Initial monotherapy: 22%

Abbreviations: UK, United Kingdom; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; SJC, swollen joint count; TJC, tender joint count; PGA, physician global assessment; EULAR, European League Against Rheumatism; IFX, infliximab; ULN, upper limit of normal

*ACR remission criteria 1981

Table 2

Selected EULAR Recommendations and Principles of Treat to Target

Recommendations

- The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.
- While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.
- The patient should be appropriately informed about the treatment target, the strategy planned to reach this target under the supervision of the rheumatologist, and the risks and benefits of a TTT approach. The patient should be involved in refining the target to ensure that it is congruent with the patient's values and preferences.

Principles

- The treatment of RA must be based on a shared decision between patient and rheumatologist.
- The primary goal of treating the patient with RA is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, and normalization of function and social participation.

Adapted from Reference (12).

Table 3

Rheumatoid Arthritis Characteristics Compared with Other Chronic Conditions in Which Treat to Target is Accepted Paradigm

	Rheumatoid arthritis	Other chronic conditions (diabetes, hypertension, hyperlipidemia)
SIMILARITIES		
1. Chronic disease	Almost always	Almost always
2. Outcome measures	Continuous scales, e.g., DAS, CDAI, RAPID	Continuous blood measures, e.g., blood glucose, blood pressure, lipid panel
3. Treatment benefits	Effective but disease flares common	Effective but often requires changes in therapy
4. Combination therapy	Very frequent	Frequent for diabetes and hypertension
DIFFERENCES		
1. Disease course	Symptomatic with “flares”	Often without symptoms; “flares” are not common
2. Treatment safety	Relatively safe; requires substantial monitoring	Generally safe; little monitoring for most medications except subcutaneous insulin, which requires daily monitoring
3. Evidence for tight control	Relatively weak evidence for long-term benefits	Strong evidence for long-term benefits, some evidence of risks