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Challenges in Implementing Treat to Target Strategies in Rheumatology

Julia A. Ford, MD,

Division of Rheumatology, Brigham and Women's Hospital, Boston MA, USA.

Daniel H. Solomon, MD, MPH

Division of Rheumatology, Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston MA, USA.

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Introduction

Rheumatology therapeutics have grown exponentially in the last several decades with the development of targeted biologic disease-modifying anti-rheumatic drugs (DMARDs), as well as the routine use of combination DMARDs. Thanks to an expanded and more effective treatment arsenal, the goal of achieving low disease activity or even disease remission in certain rheumatic diseases is now feasible, and should be the expectation of both rheumatologists and patients. A natural extension of this expectation is a treatment paradigm of targeting low disease activity or clinical remission in rheumatic diseases, especially RA. Treat to target (TTT) is a treatment strategy in which clinical management decisions are made with the goal of achieving and maintaining a pre-defined and sequentially measured target.

Outside of rheumatology, TTT approaches have been adopted in the management of chronic diseases such as diabetes and hypertension leading to better disease outcomes¹. However, despite a fairly strong evidence-base demonstrating the impact of TTT strategies in improving disease outcomes in RA for example, there is not widespread uptake of TTT in rheumatology clinics in North America. In this chapter, we examine the evidence supporting use of TTT strategies, discuss barriers to implementing TTT in clinical practice, and propose solutions and future directions for TTT implementation and research with a specific focus on RA. We briefly address key issues in TTT pertaining to other rheumatic diseases including systemic lupus erythematosus, psoriatic arthritis, and gout.

Correspondence: Julia A. Ford, 60 Fenwood Road, Boston MA, 02115, jrford@partners.org.

JAF: Julia A. Ford, Division of Rheumatology, 60 Fenwood Road, Boston MA 02115.

DHS: Daniel H. Solomon, MD, MPH, Division of Rheumatology, 60 Fenwood Road, Boston MA, 02115.

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Treat to Target Principles and Evidence-Base in RA

The TTT model for RA is based on the core principles and recommendations as outlined by an international working group^{2,3}. First, the physician and the patient should identify a disease activity target using shared decision-making; for most RA patients, the target should be clinical remission or in some cases, low disease activity. Low disease activity may be more appropriate for patients with many comorbidities or long-standing RA. Second, disease activity should be measured regularly using a validated composite measure to assess whether patient has achieved the pre-specified target. The choice of the measure is not explicitly defined, but most agree that it should be a validated disease activity measure (versus a clinician's impression, i.e., "disease active" or "doing well") and not a functional status score, such as the Health Assessment Questionnaire. Third, if the target has not been reached, the physician should adjust therapy at least every three months until the target is achieved.

Shared decision-making is a key element of the TTT approach and should be applied throughout its implementation. Shared decision-making consists of providers and patients discussing preferences and having a two-way conversation and risks and benefits of different treatment decisions. These decisions include the goals of treatment (i.e., what is the appropriate target), whether to change treatments when disease activity is not at target or side effects may be present, and what treatment changes might be best. To achieve shared decision-making, providers must inform patients based on evidence and ensure a reasonable level of patient understanding, but they also need to elicit preferences and answer questions. Through this process, patients and providers partner together to make treatment choices. Both the American College of Rheumatology (ACR)⁴ and European League Against Rheumatism⁵ have emphasized TTT principles and shared decision-making in RA management guidelines.

Though designs differ across randomized controlled studies comparing a TTT approach to routine care in RA, they consistently demonstrate improved clinical outcomes⁶. The Tight Control of Rheumatoid Arthritis (TICORA) study⁷ randomized 110 patients in National Health Services hospitals in the UK to Disease Activity Score (DAS)-driven treatment with monthly assessments compared to routine care with visits every three months; 82% of patients in the TTT arm achieved EULAR good response (DAS28 <2.4 and change in DAS by >1.2) at 18 months, compared to 44% in routine care arm, and also showed reduced progression of erosive disease and radiographic damage. The Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial⁸ randomized 299 RA patients in the Netherlands to monthly assessments and treatment adaptation via a computerized algorithm to achieve a composite target versus routine care, finding that significantly more patients in the targeted control arm (35%) achieved DAS28 remission compared to control arm (14%) at two years. Fransen et al⁹ randomized rheumatology clinics in the Netherlands to a TTT approach to care using DAS28 (12 clinics, 205 patients) versus routine care (12 clinics, 179 patients), with significantly more patients in the TTT clinics achieving low disease activity on DAS. Symmons et al¹⁰ randomized 466 RA patients in England to receive "symptomatic care" (home visits every 4 months aimed at symptom control) or "aggressive care" (hospital visits at least every 4 months with algorithm-based treatment

changes to control both clinical and laboratory evidence of inflammation); while both groups had similar HAQ scores at 36 months of follow-up, TTT group enjoyed better physician global assessment scores.

While the available evidence does support improved clinical outcomes with TTT compared to routine care, the precise treatment strategy to reach a target is not clear. Several treatment target trials have compared different therapeutic strategies to reach a specified target. The FIN-RACo trial¹¹ randomized 195 early RA patients in Finland to treatment with combination therapy (sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone) or single DMARD therapy with target of ACR remission at one year; 38% of patients treated with combination therapy achieved the target versus 17% of patients on DMARD monotherapy, which was a significant difference, and no increase in adverse events was observed in the combination therapy group. In the BeSt trial¹², 508 patients in the Netherlands were randomized into four different treatment strategies (sequential DMARD monotherapy; step-up combination therapy; initial combination therapy with high dose prednisone; or initial combination therapy with infliximab) and treated to target of low disease activity on DAS44. At two years, significantly more patients treated with initial combination therapy including either prednisone or infliximab achieved low disease activity compared to patients treated initially with monotherapy. Saunders et al¹³ randomized 96 RA patients in the United Kingdom to receive step-up therapy (initiating sulfasalazine, followed by methotrexate and subsequently hydroxychloroquine) or triple therapy at onset and treated to target of remission per DAS28. At one year, both groups achieved similar percentages of patients in remission (45% in step-up therapy group and 33% in parallel triple therapy group). As the aforementioned studies illustrate, there is not one single agreed-upon treatment strategy to achieve low disease activity or clinical remission in RA.

Barriers to Implementation of TTT

Access to Care

A major challenge to more widespread implementation of TTT in clinical practice is access to rheumatology subspecialty care. A systematic review of observational studies of patients with early and established RA reported that, even after publication of ACR guidelines supporting universal DMARD use in active RA, only 30–73% of RA patients in administrative or population-based studies (who were not necessarily under the care of a rheumatologist) were prescribed a DMARD; DMARD use in studies of patients in RA-specific cohorts or registries (who received rheumatology subspecialty care) ranged from 73–100%¹⁴. Furthermore, in a study examining data from the National Ambulatory Medical Care Survey, only 47% of visits with a diagnosis code for RA had an associated DMARD prescription, with a visit to a rheumatologist doubling the likelihood of being prescribed a DMARD¹⁵.

The fact that DMARD use is more prevalent in RA patients under the care of a rheumatologist is not surprising. Primary care physicians and other non-rheumatologists are generally not comfortable with treating RA, with a survey of approximately 1,000 primary care physicians in the U.S. finding that only one-third of respondents felt very comfortable managing this condition, and only 9% feeling comfortable initiating a DMARD¹⁶. Factors

contributing to this discomfort may include lack of continuing medical education on RA beyond medical school, lack of clear-cut treatment algorithms, and lack of familiarity with DMARDs which are perceived as having dangerous side effects particularly in medically complex patients.

Given what we know about non-rheumatologist discomfort with RA management and DMARD use, it is difficult to imagine TTT strategies being effectively implemented outside of rheumatology subspecialty care. Unfortunately, many RA patients do not have easy access to a rheumatologist, with regional disparities in the US. An American College of Rheumatology membership database study found that 84% of micropolitan areas in the US (population between 10,000 and 50,000) did not have a practicing rheumatologist¹⁷. As demand for rheumatology care is anticipated to exceed supply in coming years¹⁸, the access to care problem will likely worsen.

Physician Factors

Despite being under the care of a rheumatologist, RA patients do not always receive treatment changes in the face of active disease. In a study of biologic-naïve RA patients in the Consortium of Rheumatology Researchers of North America (CORRONA) RA registry, approximately half of patients with moderate or high disease activity received treatment changes consistent with ACR recommendations for use of biologic and non-biologic DMARDs over 6–12 months¹⁹.

In preparation for a randomized controlled trial of TTT implementation, one of this chapter's authors (DHS) conducted qualitative interviews with twelve rheumatologists exploring use of TTT in their clinical practice²⁰. Despite all interviewees believing they engaged in TTT, almost none truly followed a TTT strategy: only 3 of 12 regularly assessed a disease activity measure, 4 of 12 documented the treatment target in the medical record, and 1 of 12 engaged the patient in choosing the treatment target. This suggests that physicians may lack education on the core principles of TTT (particularly shared decision-making), or believe that their clinical “gestalt” of a patient's disease activity is equivalent or superior to a validated disease activity measure. We also suspect that some reluctance to “buy into” TTT among physicians may stem from resistance to standardization and algorithm-based care in medicine, which some physicians perceive as reducing their autonomy and devalues their clinical expertise.

Patient Factors

Patient involvement is a crucial aspect of the TTT strategy. However, patients may be unwilling to escalate treatment if they are generally satisfied with their degree of disease control, despite not having reached the pre-specified treatment target. A study of over 6,000 RA patients found that 77% were satisfied with their RA medication regimen, even though 71% of these satisfied patients had moderate or high disease activity according to Patient Activity Score and 47% had moderate or high functional limitations on HAQ score²¹. Satisfaction with degree of RA control, fear of side effects, and fear of loss of control of disease with medication changes were among reasons described by patients for unwillingness to change therapy. A qualitative study of 48 RA patients identified the

following themes regarding motivations to resist treatment regimens: fear of medications, maintaining control over health, denial of sick identity, disappointment with treatment, and feeling overwhelmed by cognitive burden of deciding²². Themes associated with motivations to accept treatment included a desire to return to normal life, and a fear of future disability due to RA.

In addition to being willing to escalate therapy to achieve treatment targets, patients must also adhere to therapy for TTT to be successful. A retrospective study of RA patients using Medicare claims data comprised of 141 infliximab users, 853 etanercept users, and 1668 methotrexate users found >80% adherence (defined as number of therapy administrations or filled prescriptions divided by expected number) in 81%, 68% and 64% of users, respectively²³. Clearly, there are gains to be made in the area of ensuring patient adherence to prescribed therapies.

Systems Issues

Even in the scenario in which both patient and provider are motivated to pursue a TTT approach, constraints within the US health care system provide challenges to successful implementation. Visits every 1–3 months may be required to assess disease activity and adjust therapy, which may be difficult for patients to attend and for rheumatologists (who, as previously discussed, are in demand) to accommodate in their schedules. Furthermore, the pressure to see more patients and therefore shorten appointment times particularly for follow-up visits makes it difficult for rheumatologists and patients to engage in shared decision-making and have meaningful conversations about changes in care. Tracking disease activity measures on a consistent basis, an essential principle of TTT, is perceived as time-consuming for busy providers and is usually not systemically incorporated into a practice's workflow. Lastly, the often lengthy and involved process of obtaining insurance approval for DMARDs can result in delays to escalating therapy and therefore to achieving treatment targets, and may stand in the way of busy providers making necessary medication changes.

Possible Solutions to Challenges in TTT Implementation

Clearly, successful implementation of a TTT strategy in RA care faces multiple challenges. Possible solutions and strategies for mitigating these barriers are presented in Table 1. Improving access to RA care will be essential to more widespread uptake of TTT. The rheumatology community would benefit from expanding and improving medical education for non-rheumatologists in RA diagnosis and management, starting at the medical school level and extending into residency and continuing medical education particularly for primary care and general practitioners, who are on the front lines of care. Particularly as we anticipate increasing demand for rheumatology care, we should be attracting young physicians to the specialty and increasing fellowship positions to train them. Midlevel providers (physician assistants (PAs) and nurse practitioners (NPs) with rheumatology training) should be increasingly integrated into care teams, and the data supports the effectiveness of these providers in caring for patients with RA. A nationwide survey of 174 midlevel providers in rheumatology showed that over 90% felt comfortable diagnosing RA and prescribing DMARDs²⁴. In a study of over 300 RA patients cared for in practices

with our without midlevel providers, patients seen in practices with NPs or PAs had lower RA disease activity²⁵.

Mitigating physician, patient, and systems barriers to TTT first requires education of all involved parties regarding the rationale for such an approach. Once both physicians and patients “buy into” the TTT approach, redesign of care delivery and practice workflows in the clinic may be required to facilitate successful implementation. The use of patient-reported outcomes, integration of technology to track disease activity, and learning collaboratives (see below) are possible solutions to different aspects of this problem.

Patient Reported Outcomes

Patient reported outcomes (PROs) are signs or symptoms reported by the patient without the interpretation of a third party²⁶. An example of PROs in RA is the Routine Assessment of Patient Index Data 3 (or RAPID3), a fairly widely used disease activity index comprised of PROs across three domains (physical abilities, pain, and overall health) that correlates with DAS28 and the Clinical Disease Activity Index (CDAI), with the benefit of not requiring a formal joint count. How best to incorporate PROs into TTT approaches is an important question under investigation, particularly given the emphasis on shared decision-making and patient involvement in TTT. The Patient-Reported outcomes Measurement Information System (PROMIS) pilot study²⁷ is examining the use of PROs in specific PROMIS domains (Pain Interference, Fatigue, Depression, Physical Function, and Social Function) using computer adaptive tests at clinic visits in RA patients being treated with a TTT strategy at an academic medical center. Baseline data has demonstrated the feasibility of incorporating PROs using PROMIS questionnaires into practice workflow²⁷.

Smartphone Applications

Mobile health (or mHealth) is a growing field which uses mobile devices (particularly smartphone applications, or “apps”) to support health care. Creating apps to help RA patients monitor their disease activity and share that information with their providers has clear implications for TTT. The currently available apps intended for use by RA patients predominantly offer symptom tracking, and areas for improvement include educational content, user security, and functionality to connect to health care providers²⁸.

Learning Collaboratives

Given the multifaceted nature of TTT strategy requiring the coordination and cooperation of health care providers (physicians, as well as nurses, medical assistants and clinic staff) along with patients, one of the authors (DHS) and colleagues pursued a Learning Collaborative approach for improving TTT implementation in RA. A Learning Collaborative utilizes a “test, learn, and share” approach consisting of sequenced learning sessions in which care teams (along with expert faculty) exchange information and brainstorm ideas, and action periods during which care teams test these ideas in their practices; successful ideas and changes can be shared at other participating sites²⁹. The Treat-to-target in RA: Collaboration To Improve adOption and adhereNce (TRACTION) trial²⁰ tested the effectiveness of such an approach to improving TTT implementation in rheumatology clinics. Eleven clinical rheumatology sites in the US were randomized to Learning Collaborative approach in the

first nine months (Phase 1) or the wait-list control group. Intervention sites had nine learning sessions involving expert faculty, and tested small changes in their practices and observed their effects, adopting helpful changes (in “plan-do-study-act” cycles). The primary outcome was a composite TTT implementation score determined through medical record review.

In TRACTION³⁰, five sites (with 23 rheumatology providers) were randomized to intervention arm and six sites (with 23 rheumatology providers) to the wait-list control. Among a sample of several hundred patients with RA, the mean TTT implementation score was 11% at baseline in both arms; at the end of the nine-month study period, the mean TTT implementation score had increased to 57% in the intervention group and 25% in the wait-list control group, which was a statistically significant difference. There was no observed increase in resource utilization or adverse events in the intervention arm. Overall, TRACTION supports the use of an educational collaborative to improve TTT implementation in rheumatology clinics, a process that requires care delivery redesign and adapting practice workflows across care team members.

Treat to Target in Other Rheumatic Diseases

Spondyloarthritis

In contrast to RA, there are not randomized controlled trials comparing TTT to routine care in spondyloarthritis (including peripheral and axial spondyloarthritis and psoriatic arthritis)³¹. However, international task force guidelines³² embrace a TTT approach in spondyloarthritis with recommended target of clinical remission, with alternative target of low disease activity and acknowledging importance of extra-articular aspects of these diseases. Potential barriers to effective implementation of TTT in spondyloarthritis are the heterogeneity of the patient population and the difficulty in capturing extra-articular manifestations such as psoriasis, inflammatory bowel disease, and uveitis into disease activity measures.

Systemic Lupus Erythematosus

Morbidity and mortality in systemic lupus erythematosus (SLE) remain unacceptably high, so there is much interest in improving care processes for these patients. An international task force on TTT in SLE published a set of overarching principles and recommendations³³ emphasizing shared decision making, multidisciplinary care, ensuring survival, prevention of organ damage, and prevention of flares. However, defining a good outcome or treatment target in a disease with such protean manifestations, and that affects different organ systems with varying degrees of severity, is challenging. Accrual of organ damage and adverse effects of therapies (particularly glucocorticoids) also confound the picture when assessing disease activity. The lupus community awaits validated definitions of lupus low disease activity state (LLDAS) and remission in SLE, which would be critical to implementation of TTT in this disease³⁴.

Gout

Lowering serum urate levels to prevent crystallization of monosodium urate and crystal deposition in joints resulting in gout has long been a principle of chronic gout management.

Treating to a target serum urate is currently endorsed by major rheumatology professional guidelines^{35,36,37} with recommendation for serum uric acid <6.0 mg/dL; however, the American College of Physicians guideline³⁸ contrasted substantially with the others, citing insufficient evidence for TTT in gout. While there is not a robust evidence base demonstrating efficacy of TTT serum urate approach in reducing gout flares, a 2017 EULAR abstract³⁹ showed promising results: Doherty et al randomized 517 gout patients in the UK to nurse-led care targeting serum urate <6.0 mg/dL, versus routine general practitioner care. Patients receiving nurse-led TTT care had significantly higher allopurinol dosages, significantly greater percentage of patients achieving serum urate <0.6 mg/dL, and importantly, significantly lower frequency of gout flares at the end of two years compared to the routine care group. More TTT strategy trials are needed in this disease.

Questions and Future Directions

Many questions remain surrounding TTT in RA, and we present a proposed research agenda in Box 1. A particularly interesting question is whether there is a therapeutic “window of opportunity” early in the course of RA during which aggressive treatment could meaningfully alter the disease trajectory and reduce chronicity or the need for long-term immunosuppression. A systematic literature review⁴⁰ of 18 cohort studies and randomized controlled trials reporting outcome data in early RA showed that prolonged symptom duration was associated with lower chance of DMARD-free sustained remission, lending support to the idea of a window of opportunity in RA. One can imagine how a TTT approach could be highly valuable in this setting.

Another question of interest is whether TTT in RA is associated with improved clinical outcomes in extra-articular aspects of disease. There are some data^{41,42} that suggest that lower disease activity is associated with reduction in cardiovascular risk, but this has not been demonstrated in a randomized controlled trial.

Conclusion

Though TTT for RA is supported by evidence and endorsed by major rheumatology professional organizations, this strategy for care has not been widely embraced in the US. Creative solutions are needed at the individual provider and patient level, as well as at a systems level, to propagate a TTT approach.

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Box 1**Proposed research agenda for treat-to-target in rheumatoid arthritis***Basic science questions*

1. Is there a window of opportunity during which aggressive treatment with TTT strategy can alter the course of RA?

Clinical questions

1. What is the most effective treatment strategy to reach a target of low disease activity or remission?
2. What is the optimal disease activity measure for TTT?
3. Is TTT associated with improved long-term outcomes, including reduced radiographic progression?
4. Is TTT associated with better extraarticular outcomes in RA, such as reduced cardiovascular risk?

Health services questions

1. How can mobile health technologies be optimized for TTT?
2. What are the economic costs of TTT versus routine care?

Key Points

- Treat to target (TTT), as defined in RA, utilizes shared decision making between physicians and patients to select a disease activity target, routinely assess disease activity, and adjust therapy accordingly to achieve and maintain the target.
- Despite evidence demonstrating improved clinical outcomes in RA using a TTT strategy, it is not widely used in rheumatology in North America.
- Access to rheumatology care, physician and patient engagement, and systems issues provide barriers to successful implementation of TTT in RA.
- Implementation of TTT in rheumatology practice requires multi-faceted interventions involving the whole care team.

SYNOPSIS

Despite evidence that treat to target (TTT) approaches lead to better disease outcomes in RA, TTT is not widely implemented in rheumatology clinics in North America. In this chapter, we discuss the barriers (including access to care, patient and physician factors, and systems issues) to implementing TTT in the clinic, and propose possible solutions and future research directions.

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Table 1

Barriers to treat-to-target implementation in rheumatology clinics and possible solutions and strategies for improvement

Barrier	Possible Solutions or Strategies
Access to Care	
Nonrheumatologists are often not comfortable initiating or managing DMARDs	Bolster medical school and CME training in RA and DMARDs
Many RA patients do not have easy access to a rheumatologist	Increase funding for rheumatology fellowship positions
	Integrate midlevel providers (NPs and PAs) into care teams
Physician Factors	
Lack of physician education on TTT principles	Integrate TTT in fellowship education and continuing medical education (CME)
	Develop learning collaboratives to encourage multidisciplinary team approach and patient engagement in TTT
Physician feels clinical gestalt is equivalent or superior to TTT	Educate practicing rheumatologists on TTT evidence base
	Collect disease activity measures and share across providers in a clinic site
Patient Factors	
Patients express satisfaction with disease control despite having active disease on validated measures	Educate patients on importance of optimizing disease control
Adherence to medications	Leverage pharmacist, nursing, and family support; reminder programs through automated programs (apps and SMS text)
Systems Issues	
Frequent visits for disease assessment difficult in busy practices	Use midlevel providers for follow-up visits
Documentation of disease activity measures is time-consuming	Use patient self-reported outcomes, including use of apps and mobile health tools
	Engage clinic staff (medical assistants) to assist in collection and recording
Time pressures impede shared decision-making	Develop patient-friendly resources that discuss different therapeutic options
Insurance issues delay changes in therapy	Lobby to reduce barriers to insurance coverage for patients with chronic disease