Toward Treating to Target in Psoriatic Arthritis

Dafna D. Gladman

ABSTRACT. The concept "treat to target" in rheumatology was first developed for rheumatoid arthritis. A similar attempt to develop such an approach for spondyloarthritis was unsuccessful because the assessment tools and target of therapy had not been developed. In psoriatic arthritis (PsA), composite indices to assess disease activity, disease state, and responsiveness have been developed and can be used as targets. There are a number of definitions for remission, but none are widely accepted. However, a state of minimal disease activity has been defined. There is evidence now that the treat-to-target approach is feasible, using the minimal disease activity state as a target and devising a tight control approach, which is superior to standard of care. Further work will determine the best target and the best approach to reach it. (J Rheumatol Suppl. 2015 Nov;93:14–16; doi:10.3899/jrheum.150626)

Key Indexing Terms:
PSORIATIC ARTHRITIS TREATING TO TARGET MINIMAL DISEASE ACTIVITY

The concept "treat to target" in rheumatology was summarized by Solomon, *et al*[1] 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." This process should be proactive, with a clear endpoint (the "target"), and should be operationalized as a specific treatment algorithm; as well as supported by findings from many randomized controlled clinical trials that suggest benefits of early aggressive treatment approaches. In rheumatoid arthritis (RA), a treat-to-target strategy has been developed with the target being remission, for which there are definitions through the American College of Rheumatology (ACR) and the European League of Associations Against Rheumatism[2]. How does this concept apply to psoriatic arthritis (PsA)?

The Spondyloarthritis Treat-to-Target Approach

Recently an international panel considered the possibility of developing a treat-to-target approach for spondyloarthritis (SpA). A review of the literature suggested that little was known about the benefits of early aggressive treatment for SpA. What was provided was a list of items necessary for implementation of a treat-to-target approach for both SpA and PsA[3]. Briefly, proposed requirements included to:

- Develop composite measures that would be valid, with definitions of disease activity states and response categories[4]
- Develop a definition of remission
- Determine whether it is necessary to include all aspects of the disease or whether particular aspects would be sufficient
- Develop a treatment target and consider whether there would be different longterm outcomes when considering remission versus a low disease activity state
- Determine whether progression of joint damage would be different in different disease activity states
- Determine whether responsiveness is dependent upon disease duration
- Conduct therapeutic trials to determine, when treating to target, whether aiming at remission or aiming for a low disease activity state is better than standard of care
- Determine whether peripheral and axial disease in PsA will respond in a similar manner, and how enthesitis and dactylitis respond to different therapies
- Determine whether care of patients with SpA or PsA is better if carried out by rheumatologists or by nonrheumatologists
- Determine whether therapy might be reduced with the desired outcome maintained
- Determine the effect of patient education on outcome

PsA is an inflammatory musculoskeletal disease associated with psoriasis. Most investigators now consider PsA to consist of several domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail disease. All these domains must be included when assessing disease activity and response in this disease.

Composite Outcome Measures in PsA

As noted above, one of the recommendations of the treat-to-target effort was the development of composite outcome measures. Several composite measures have been developed for PsA. The PsA Joint Assessment Index (PsAJAI) was developed through an analysis of the pivotal trials for adalimumab, etanercept, and infliximab[5]. The PsAJAI thus includes joint counts and patient reported outcomes. However, the skin assessment was not included because it overshadowed any of the arthritis measurements and was considered an independent factor in assessing response in PsA. The composite PsA Disease Activity Index (CPDAI) was based on the treatment grid developed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)[6,7]. It includes all the domains of PsA, and assigns

From the University of Toronto, Psoriatic Arthritis Program, Western Research Institute, University Health Network, Toronto, Ontario, Canada.

D.D. Gladman, MD, FRCPC, Professor of Medicine, University of Toronto; Senior Scientist, Toronto Western Research Institute; Director, Psoriatic Arthritis Program, University Health Network.

Address correspondence to Dr. D.D. Gladman, Centre for Prognosis Studies in The Rheumatic Diseases, Toronto Western Hospital, 399 Bathurst St., 1E-410B, Toronto, Ontario M5T 2S8, Canada. E-mail: dafna.gladman@utoronto.ca

a weight, depending on the severity within each domain, for a potential total of 15 points. The instrument has face validity, is responsive, and very feasible, thus fulfilling the Outcomes in Rheumatology Clinical Trials (OMERACT) filter[8]. Moreover, a cutoff has been established such that a score of 6 would require an increase in therapy, thus addressing the issue raised by the treat to target in SpA group. However, a concern has been raised that this composite index may not allow patients with specific disease manifestations to reach the required score for change of therapy. The Disease Activity Index for PsA was developed by Schoels and colleagues[9]. It includes a number of joint assessment items but excludes skin assessment. Two composite indices for PsA were developed by Helliwell, *et al* through the GRAPPA Composite Exercise (GRACE) study[10]. These include the Psoriatic Arthritis Disease Activity Score, which was generated by principal component analysis from the data collected during the GRACE study and provides disease activity states as well as response criteria, and the GRACE instrument, which is based on the desirability function of the items considered important in the assessment of patients with PsA based on the core set developed at OMERACT. The GRACE instrument also provides activity states and response criteria. While both these tools fulfill the criteria of face validity and responsiveness, they are somewhat more complicated, because they require more transformation and calculations. Thus they are not as readily feasible at the bedside as the CPDAI.

These composite indices function reasonably well and could be used to measure response in a "treat-to-target" effort in PsA.

"Target" in PsA

The main issue, then, is what should be the target for tailored treatment in PsA. Ideally, a state of remission should be used as the target. How do we define remission in PsA?

A number of attempts to define remission in PsA have been published. The first was based on joint assessment alone, and was defined as no actively inflamed joints for a period of at least 12 months[11]. Based on this definition, 17.6% of 514 PsA patients achieved remission, which lasted, on average, 2.6 years. Male patients and those with a lower actively inflamed joint count at presentation to clinic were more likely to achieve a state of "remission." However, these criteria did not include skin disease or patient-reported outcomes.

In an early arthritis clinic in Dublin, Kane, *et al* used the ACR remission criteria for RA to determine remission among patients with PsA[12]. These include morning stiffness < 15 min duration, no fatigue, no joint pain history, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, and an erythrocyte sedimentation rate (ESR) < 30 mm/h for women and < 20 mm/h for men. They found that 26% of 119 patients achieved remission at Year 1 of followup, and 21% of 97 patients followed for 2 years achieved remission.

Cantini, *et al* also used the ACR remission criteria for RA but added that patients should have no enthesitis, dactylitis, or other extraarticular features except those related to the skin[13]. They also included a normal C-reactive protein. Of 236 patients requiring second-line drugs, 24.1% achieved remission, which lasted 13 ± 9.4 months. Remission was more common among patients treated with anti-tumor necrosis factor (TNF) agents than other disease-modifying antirheumatic drugs (60.5% vs 19.4%; $p < 0.001$).

Another study used a different definition for remission: the 28-joint Disease Activity Score (DAS28) < 2.6 at any visit[14]. They found that 58% of the patients had such a remission at 12 months. They found that patients with PsA were more likely to achieve remission than patients with RA, even after selecting individuals matched on baseline DAS28 scores. Predictors for remission were male sex, Health Assessment Questionnaire (HAQ), patient global assessment, and morning stiffness. HAQ at baseline remained the only independent factor associated with remission on linear regression.

It is clear that the DAS28 is not a proper measure in PsA because it excludes joints that are commonly affected in this disease and therefore would overestimate remission in this patient population. Remission should include resolution of all aspects of the disease and not only the peripheral arthritis. Thus, only definitions that include all aspects of the disease should be considered as a target for therapy in PsA.

Because the definition of remission has yet to be accepted, Coates, *et al* developed a definition for minimal disease activity (MDA)[15]. This definition includes both various domains of PsA and patient-reported outcomes. The MDA criteria were developed through an exercise involving GRAPPA members, and clearly have face validity. Patients are classified as in MDA when they meet at least 5 of 7 of the following criteria: tender joint count ≤ 1; swollen joint count ≤ 1; Psoriasis Activity and Severity Index ≤ 1 or affected body surface area ≤ 3; patient pain visual analog scale (VAS) ≤ 15; patient global activity VAS ≤ 20; HAQ ≤ 0.5; and tender entheseal points ≤ 1. Based on these criteria, 61% of 344 patients followed prospectively achieved a state of MDA on 1 or more visits, while 34% achieved a state of MDA that was sustained for at least 1 year and on the average lasted 28 months[16]. Twelve patients (10%) experienced flare of their disease after an average 34 months in MDA. Importantly, patients in MDA had less progression of radiological damage, suggesting that a state of MDA has important implications for outcome. Among patients treated with anti-TNF agents, 64% of 226 patients achieved a state of MDA. Male sex and a normal ESR at baseline were predictors for MDA[17]. Obesity and the presence of metabolic syndrome are associated with a lower likelihood of achieving MDA[18,19].

In the IMPAC 2 (Infliximab Multinational Psoriatic Arthritis Controlled Trial 2), 52% of 77 infliximab-treated patients achieved MDA at Week 24, compared with 21% of 80 receiving placebo ($p < 0.001$). At Week 54, 78% of those patients who achieved MDA had no radiologic progression, compared with 57% of those who did not achieve MDA ($p =$

0.009), again demonstrating a better outcome associated with achieving a state of MDA[20]. Similar observations were noted analyzing the ADEPT trial (ADalimumab Effectiveness in Psoriatic Arthritis Trial) with adalimumab[21].

Evidence for Treat to Target in PsA

A study tested the concept of treat to target in PsA. The TICOPA trial (Tight Control of PsA) was designed to test whether intensive management of PsA according to a prescribed treatment plan with the target being MDA (tight control) would be superior to standard-of-care therapy[22]. The tight-control group were seen at 4-week intervals, and treatment was increased if the MDA target was not met. Treatment was initiated with methotrexate (MTX) 15 mg per week, and if MDA was not achieved, MTX was increased to 10 mg for 2 weeks, then 25 mg for 2 weeks, and maintained for another 4 weeks, at which time if MDA was not achieved, sulfasalazine was added, up to 2 g per day. If MDA was not achieved, either cyclosporine or leflunomide was added for 8 weeks. If there were still 3 tender and swollen joints, anti-TNF agents were introduced. If MDA was not achieved after 12 weeks of the first anti-TNF agent, a second agent would be tried. In the standard-of-care group, therapy was provided according to the treating physician without a prescribed followup or escalation of therapy. The study included 206 patients; 101 were randomized to tight controls and 105 to standard of care. At 48 weeks the tight-control group demonstrated much better outcomes in terms of disease activity, although there were more side effects, and there was not a detectable difference in radiographic progression between aggressive therapy and standard of care. This study demonstrates that the treat-to-target approach is feasible and desirable in PsA, and additional studies are necessary to further determine the exact therapy that should be used.

The treat-to–target approach is an important therapeutic concept in rheumatology, and is certainly appropriate for PsA. Several instruments to determine disease activity and responsiveness have been developed that can serve as targets toward which therapeutic interventions should be directed. One study has already demonstrated that this approach is not only feasible but desirable. Further trials are necessary to evaluate the best treatment approach to achieve tight control of the disease, and its effect on longterm outcome in PsA.

REFERENCES

1. Solomon DH, Bitton A, Katz JN, Radner H, Brown EM, Fraenkel L. Review: treat to target in rheumatoid arthritis: fact, fiction, or hypothesis? Arthritis Rheumatol 2014;66:775-83.
2. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
3. Schoels MM, Braun J, Dougados M, Emery P, Fitzgerald O, Kavanaugh A, et al. Treating axial and peripheral spondyloarthritis, including psoriatic arthritis, to target: results of a systematic literature search to support an international treat-to-target recommendation in spondyloarthritis. Ann Rheum Dis 2014;73:238-42.
4. Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis 2014;73:6-16.
5. Gladman DD, Tom BD, Mease PJ, Farewell VT. Informing response criteria for psoriatic arthritis (PSA). II: Further considerations and a proposal – the PsA joint activity index. J Rheumatol 2010; 37:2559-65.
6. Ritchlin CT, Kavanaugh A, Gladman DD, Mease PJ, Boehncke WH, de Vlam K, et al. Treatment recommendations for psoriatic arthritis. Ann Rheum Dis 2009;68:1387-94.
7. Mumtaz A, Gallagher P, Kirby B, Waxman R, Coates LC, Veale JD, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis 2011;70:272-7.
8. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67:745-53.
9. Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis 2010;69:1441-7.
10. Helliwell PS, FitzGerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis 2013;72:986-91.
11. Gladman DD, Ng Tung Hing E, Schentag CT, Cook R. Remission in psoriatic arthritis. J Rheumatol 2001;28:1045-8.
12. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology 2003;42:1460-8.
13. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Criteria, frequency, and duration of clinical remission in psoriatic arthritis patients with peripheral involvement requiring second-line drugs. J Rheumatol Suppl. 2009 Aug;83:78-80.
14. Saber TP, Ng CT, Renard G, Lynch BM, Pontifex E, Walsh CA, et al. Remission in psoriatic arthritis: is it possible and how can it be predicted? Arthritis Res Ther 2010;12:R94.
15. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48-53.
16. Coates LC, Lee KA, Chandran V, Cook R, Gladman DD. Frequency, predictors and prognosis of minimal disease activity in an observational PsA cohort. Arthritis Care Res 2010;62:970-6.
17. Haddad A, Thavaneswaran A, Ruiz-Arruza I, Pellett F, Chandran V, Cook RJ, et al. Minimal disease activity and anti-tumor necrosis factor therapy in psoriatic arthritis. Arthritis Care Res 2015;67:842-7.
18. Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. Ann Rheum Dis 2015;74:813-7.
19. Costa L, Caso F, Ramonda R, Del Puente A, Cantarini L, Darda MA, et al. Metabolic syndrome and its relationship with the achievement of minimal disease activity state in psoriatic arthritis patients: an observational study. Immunol Res 2015;61:147-53.
20. Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res 2010;62:965-9.
21. Mease PJ, Heckaman M, Kary S, Kupper H. Application and modifications of minimal disease activity measures for patients with psoriatic arthritis treated with adalimumab: subanalyses of ADEPT. J Rheumatol 2013;40:647-52.
22. Coates LC, Navarro-Coy N, Brown SR, Brown S, McParland L, Collier H, et al. The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis. BMC Musculoskelet Disord 2013;14:101.