Treat-to-target and Improving Outcomes in Psoriasis: A Report from the GRAPPA 2014 Annual Meeting

Junko Takeshita, April W. Armstrong, Philip J. Mease, and Joel M. Gelfand

ABSTRACT. Treat-to-target strategies are part of routine clinical practice in cardiovascular medicine. This approach, however, is relatively new in rheumatology and dermatology and has not been widely applied to the management of psoriatic diseases. At the 2014 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in New York, New York, USA, several GRAPPA members summarized and participated in a panel discussion on the treat-to-target concept as it applies to psoriasis, its potential role in improving treatment outcomes, identification of specific treatment targets for psoriasis, and future directions for research. (J Rheumatol 2015;42:1037–40; doi:10.3899/jrheum.150128)

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At the 2014 GRAPPA Annual Meeting, the topic of treating to target and improving outcomes in psoriasis was addressed in an overview by Dr. Joel Gelfand, followed by a panel discussion with Drs. Gelfand, Philip Mease, and Junko Takeshita, and moderated by Dr. April Armstrong. Topics included treatment target options for psoriasis, timepoints for assessing those targets, and the importance of research to establish and support treat-to-target strategies for managing psoriasis. The audience was also polled for their opinions on treatment targets in psoriasis.

Treat-to-target: Definition, History, and Potential Role in the Management of Psoriatic Diseases

Dr. Gelfand summarized the concept of "treat-to-target" and discussed its potential applicability to psoriasis. Treat-to-target is not a new concept in medicine; the underlying principle is preventive therapy to improve patient outcomes by treating a disease until a prespecified objective measure is achieved. Treatment options generally have a strong evidence base with proven efficacy/effectiveness and safety data from randomized controlled trials (RCT) or observational studies. Treat-to-target originated and has become a well-established practice in cardiovascular medicine. However, appropriate treatment targets remain a matter of debate and continue to evolve across all medical specialties. Although treatment to a specified target is meant to improve outcomes, focused attention on 1 target may result in oversight of unintended consequences. For example, while 2 clinical trials of patients with type 1[1] and type 2[2] diabetes showed stricter glycemic control to be associated with reductions in late diabetic microvascular complications, a subsequent clinical trial of type 2 diabetics found intensive glucose-lowering therapy to be also associated with increased mortality[3]. The 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommendation to abandon previous cholesterol treatment targets in favor of fixed-dose cholesterol-lowering strategies[4] exemplifies another treatment target controversy.

Treat-to-target strategies are also being adapted for rheumatoid arthritis based on clinical trials that showed reduction of disease activity with set treatment goals[5,6,7,8,]. However, treat-to-target strategies have not been well-studied in psoriatic diseases. In a single open-label RCT of intensive management versus standard care in the treatment of early psoriatic arthritis (PsA; Tight COntrol of PsA; TICOPA)[9], preliminary analyses suggest that tight control of PsA is associated with improved joint outcomes. The tight-control group was more likely than the standard-care group to achieve American College of Rheumatology (ACR) 20 response at 48 weeks (OR 1.91; 95% CI, 1.03–3.55)[10]. However, adverse events were also more frequent among the tight-control group versus the standard-care group.

Unlike in the management of PsA, where treatment with tumor necrosis factor inhibitors is associated with reduction

From the Department of Dermatology and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; Colorado Health Outcomes Program (COHO), University of Colorado Denver, Denver, Colorado, USA; and Swedish Medical Center and University of Washington School of Medicine, Seattle, Washington, USA.

J. Takeshita, MD, PhD, Department of Dermatology and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine; A.W. Armstrong, MD, MPH, COHO, University of Colorado Denver; P.J. Mease, MD, Swedish Medical Center and University of Washington School of Medicine; J.M. Gelfand, MD, MSCE, Department of Dermatology and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine.

Address correspondence to Dr. J. Takeshita, Department of Dermatology and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, University of Pennsylvania, One Convention Ave., 1463 Penn Tower, Philadelphia, Pennsylvania 19104, USA. E-mail: Junko.Takeshita@uphs.upenn.edu

in radiographic progression of disease[11], the panelists noted that the benefits of psoriasis treatment, beyond objective improvement of skin disease, remain to be shown empirically. Particularly among patients with moderate to severe disease who are at increased risk of developing major adverse cardiovascular events[12,13,14,15], diabetes[16], and chronic kidney disease[17], culminating in an average 5-year shorter lifespan than patients without psoriasis, psoriasis therapies may provide benefits beyond the skin. The potential systemic benefits of psoriasis therapies have been suggested in some[18,19,20] but not all[21,22] observational studies, and experimental studies have yet to be completed. Thus, further research is required to definitively support and establish the benefits of treatment targets in psoriasis.

Target Endpoints: Disease Activity and Other Targets

Disease activity targets rely on measures that capture psoriasis severity. Several such measures exist[23,24], but each has important limitations to consider. The panelists discussed characteristics of ideal disease activity measures, including ready incorporation into the clinical setting (i.e., easy and quick measurements), accountability for both overall extent of involvement and the component characteristics of psoriatic lesions, applicability to different psoriasis types, and utility as both a single static measure and a measure of change over time.

Primary clinical trial efficacy endpoints have traditionally included the Psoriasis Area and Severity Index (PASI)75, defined by ≥ 75% improvement in PASI score; and physician's global assessment (PGA)-defined clear or almost clear skin, typically corresponding to scores of ≤ 1[25]. With the development of increasingly efficacious therapies, PASI90 and 100 are also being reported[26,27]. In the real-world clinical setting, however, treatment endpoints remain poorly defined. Guidelines with suggested treatment goals have been established in Canada[28], Europe[29,30], the United Kingdom[31], and Australia[21] and are largely based on expert opinion. Most recommendations identify PASI75 as a primary treatment goal despite the PASI score being time-consuming and cumbersome to calculate and having little significance as a single score. Less intensive assessments — used more readily in the clinic — are percent body surface area (BSA) of psoriasis involvement and PGA; however, each measure has its limitations. BSA involvement does not assess the severity of individual psoriatic lesions (i.e., extent of erythema, induration, and scale); whereas PGA does not incorporate BSA involved by psoriasis. These limitations may be overcome by using the product of BSA and PGA [Simple-Measure for Assessing Psoriasis Activity (BSA × PGA)], which has been highly correlated to PASI scores in initial studies[31a] and may be a promising disease activity measure in the clinical setting. The PASI, BSA, and PGA scores are further limited by their inability to adequately capture disease activity for non-plaque types of psoriasis. Thus, the panelists emphasized the need to develop additional disease activity measures for other psoriasis types (e.g., the Brigham Scalp Nail Inverse Palmoplantar Psoriasis Composite Index; B-SNIPI)[32].

With an increasing focus on patient-centered medicine[33] and the importance of including the patient perspective, the panelists also discussed patient-reported outcomes (PRO) as targets for improving psoriasis care. Many treatment guidelines[29,30,31,34] also incorporate a patient-reported dermatology-specific health-related quality of life (QoL) measure, most commonly the Dermatology Life Quality Index (DLQI)[35,36], where suggested secondary treatment goals include ≥ 5-point improvement in DLQI score[31], DLQI ≤ 1[29] (i.e., no effect of patient's skin disease on QoL), or DLQI ≤ 5[30,37] (i.e., no effect to small effect on QoL). In general, objective data supporting the use of PRO or objective disease activity measures as targets in psoriasis are sparse. Few studies have evaluated the effect of low skin disease burden on patient-reported QoL. Secondary analyses of data from 2 phase III adalimumab RCT[27] found significantly greater improvement of DLQI and Medical Outcomes Study Short Form-36 (SF-36) scores among patients who achieved PASI90 and 100 versus patients with lower levels of PASI response. Similarly, secondary analyses from a phase II brodalumab RCT[37] showed significantly greater improvement of DLQI and Psoriasis Symptom Inventory (PSI) scores among patients who achieved PASI100 versus those who achieved PASI75 but not PASI100; additionally, patients who achieved complete skin clearance (PGA = 0) were more likely to report DLQI and PSI scores of zero (i.e., no effect of skin disease on QoL, and no psoriasis-related symptoms, respectively) versus patients with almost clear skin (PGA = 1). Further, in a clinic-based, multicenter, cross-sectional study of patients with moderate to severe psoriasis with clear or almost clear skin, 76% of patients with clear versus 44% with almost clear skin reported no effect of their skin disease on QoL (i.e., DLQI ≤ 1). In fully adjusted analyses, patients with clear versus almost clear skin were 60% more likely to report no effect of their skin disease on QoL, independent of basic demographic and clinical factors, psoriasis history, and current therapy for psoriasis[38]. Thus, complete skin clearance (PASI100 or PGA score of zero) is an important treatment target from the patient perspective. However, none of the aforementioned studies assessed the relative safety and cost effectiveness of such treatment strategies. Further studies are therefore necessary before implementing physician- or patient-reported treatment targets in routine practice.

Lastly, with multiple potential disease activity measures, PRO, and comorbidities, particularly PsA, the panelists discussed the need to consider multiple treatment targets (e.g., simultaneous disease activity and QoL targets or combined skin and joint disease targets) and to prioritize targets. For example, in a patient with both psoriasis and PsA,

should reaching joint disease targets supersede that of skin disease? Should objective disease activity or QoL be prioritized in managing patients with psoriatic diseases? It will be important to address these questions and to also elicit and incorporate patients' opinions regarding these and other issues, including acceptable risk-benefit ratios and assessment frequency, as treat-to-target strategies for psoriasis are established.

Time to Treatment Targets

Two treatment phases should be considered when assessing treatment targets: induction and maintenance. The induction phase is the time from initiation of therapy to maximal response; maintenance is the time period after induction. Assessment timepoints may vary depending on the treatment phase. Historically, clinical trials assess efficacy at 12 weeks after therapy initiation — the time at which the majority of patients reach maximal response to most moderate to severe psoriasis therapies. In the absence of large-scale RCT to guide the identification of optimal outcome assessment frequency, existing guidelines suggest assessing initial response up to 16 weeks after initiation of therapy or up to 24 weeks for therapies with slower onset of action[29,30]. Ideal assessment frequency during maintenance is even less clear, with guidelines suggesting routine followup as directed by the specific therapy, which may be as frequent as 2 months for systemic medications[30].

Audience Responses to Psoriasis Treatment Target and Priorities Questions

Following the presentation and panel discussion, audience members were polled for their answers to 6 questions with instructions to choose a single best response. Questions and answers are summarized in Table 1.

The majority of respondents were PsA researchers or healthcare providers. The majority chose disease activity targets that reflected complete skin clearance or minimal disease activity, and PRO targets that reflected no effect of skin disease on QoL. Prioritization of treatment targets favored PsA over psoriasis, reflecting the identification of the majority as PsA researchers or healthcare providers. Further, most deemed QoL to be more important than psoriasis or PsA disease activity as treatment targets, emphasizing the ongoing trend of increasing incorporation of PRO in the practice of medicine. Importantly, stratification of responses by respondent category revealed that patients or patient advocates had strong preferences for skin clearance (i.e., PASI100, PGA = 0) as treatment targets, with all prioritizing QoL targets over objective disease activity targets.

Treat-to-target strategies are increasingly being incorporated into management of chronic diseases. Further studies are necessary to establish the benefit of incorporating treat-to-target concepts into routine dermatologic practice.

Table 1. Audience responses to psoriasis treatment target and priorities questions. Responses are n (%).

1. What is your primary role? (Total responses N = 125)	
a. Psoriasis researcher/healthcare provider	28 (22)
b. PsA researcher/healthcare provider	88 (70)
c. Patient/patient advocate	9 (7)
2. What is an appropriate target regarding change in PASI? (N = 149)	
a. ≥ PASI75	84 (56)
b. ≥ PASI90	54 (36)
c. PASI100	11 (7)
3. What is an appropriate target regarding BSA? (N = 148)	
a. ≤ 10%	11 (7)
b. ≤ 5%	17 (11)
c. ≤ 3%	48 (32)
d. ≤ 1%	64 (43)
e. 0%	8 (5)
4. What is an appropriate target regarding PGA? (N = 152)	
a. At most mild (i.e., mild, almost clear, or clear)	16 (11)
b. At most almost clear (i.e., almost clear or clear)	99 (65)
c. Clear	37 (24)
5. What is an appropriate target regarding DLQI? (N = 135)	
a. ≤ 5 (i.e., no to small effect on QoL)	24 (18)
b. ≤ 1 (i.e., no effect on QoL)	93 (69)
c. 0 (i.e., no effect on QoL)	18 (13)
6. This is how I would prioritize "targets" in the treat-to-target approach (N = 137)	
a. Psoriasis disease activity > QoL > PsA disease activity	2 (1)
b. Psoriasis disease activity > PsA disease activity > QoL	8 (6)
c. QoL > psoriasis disease activity > PsA disease activity	21 (15)
d. QoL > PsA disease activity > psoriasis disease activity	62 (45)
e. PsA disease activity > psoriasis disease activity > QoL	23 (17)
f. PsA disease activity > QoL > psoriasis disease activity	21 (15)

PsA: psoriatic arthritis; PASI: Psoriasis Area and Severity Index; BSA: body surface area; QoL: quality of life; DLQI: Dermatology Life Quality Index; PGA: physician's global assessment.

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