



Considerations for the definition of remission criteria in psoriatic arthritis



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ABSTRACT

Objectives: Psoriatic arthritis (PsA) is an autoimmune disease that can cause progressive structural damage of the joints and irreversible disability. The potentially achievable results of biologic therapy for PsA has led to the view that disease remission should be the goal of treatment. However, the heterogeneity of disease manifestations and need for validated outcome measures makes defining remission in PsA challenging. This article evaluates proposed criteria for defining remission in PsA and discusses how these criteria can be applied in clinical practice.

Methods: A primary literature search was conducted in PubMed to identify articles discussing potential PsA treatment goals or targets, including minimal disease activity. English-language publications from the last 10 years were included in this assessment.

Results: There are 5 clinical domains in PsA that must be considered when evaluating remission: synovitis, enthesitis, dactylitis, spondylitis, and psoriasis/nail psoriasis. Due to variability in the completeness of remission and time to achieve remission with different therapies between these domains, remission should be measured clinically through a combination of objective measures, or a composite assessment tool. Composite measures are more efficient than unidimensional instruments in measuring remission, but remission rates differ between the available composite indices.

Conclusion: Although the concept of remission as a treatment goal in PsA is gaining acceptance among rheumatologists, further work is necessary to develop a broadly acceptable definition of remission.

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Introduction

Psoriatic arthritis (PsA) is an inflammatory condition of the joints that is commonly associated with the development of plaque psoriasis [1]. PsA has an annual incidence of 7.2 per 100,000 in the United States [2]. Further, as many as 30% of patients with psoriasis will develop PsA, and up to 15% of patients with psoriasis may have undiagnosed PsA [3–5]. Additionally, the incidence of PsA in patients with psoriasis is 1.87 per 100 [6]. The clinical manifestations of PsA are complex and heterogeneous. Symptoms of PsA include joint pain and stiffness, skin and nail

psoriasis, dactylitis, and persistent, painful enthesitis [1]. Although PsA was once considered a mild disease, it is now understood that progressive structural damage can begin early in the course of PsA due to effects of pro-inflammatory cellular infiltrate and elaboration of inflammatory cytokines [1,7]. Damage is evidenced by radiologic changes in up to 47% of patients at a median interval of 2 years and causes irreversible disability [8].

Treatments for PsA include nonsteroidal anti-inflammatory drugs; corticosteroids; conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs); biologic therapies including tumor necrosis factor (TNF) inhibitors; interleukin (IL)-17 inhibitors, and IL-12/23 inhibitors; and targeted synthetic DMARDs such as apremilast [9]. For patients with concomitant skin disease, topical treatments and ultraviolet light therapy are also commonly used. Given the heterogeneous nature of PsA manifestations, treatment should involve consideration of the disparate areas of disease involvement in individual patients [9]. Often, the intensity of therapy is driven by the disease manifestation that is considered to be most severe by the patient and treating physician, but treatment requires consideration of, and therapy for, all of the

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various areas of disease manifestation, even though clinical appearances of these individual features may not all occur simultaneously [10].

The potentially achievable results of highly effective biologic therapies that enable the treatment of multiple manifestations of PsA, and the improved treatment paradigms for PsA and other autoimmune disorders, has generated the growing consensus that disease remission should be considered the ultimate goal when treating patients with PsA [11]. The heterogeneity of disease manifestations and the need to validate outcome measures make defining remission particularly challenging. Although remission criteria and activity indices designed for rheumatoid arthritis (RA) have been used to assess PsA, they are limited in their ability to evaluate all PsA manifestations [10,12,13].

This article offers insight and perspective regarding the considerations and potential criteria for defining remission in PsA, and examines how rheumatologists can apply these criteria in clinical practice.

Search strategy

A primary literature search was conducted on May 16, 2016 in PubMed to identify articles discussing potential PsA treatment goals or targets, including minimal disease activity (MDA). English-language publications from the last 10 years were included in this assessment. Articles were deemed relevant if they included information on remission or MDA.

Domain-based assessment of PsA disease activity

Because the biological factors involved in PsA pathogenesis may differ across domains, effects of treatment and the time and degree of completeness at which remission is achieved in these domains can vary considerably. Therefore, it is important to understand which domains are affected in individual patients and how pharmacologic intervention impacts each domain [14].

Synovitis assessment

Assessment of objective remission in synovial tissue can be straightforward, requiring ascertainment of whether residual pain or swelling in joints is present and including the potential use of imaging to confirm the absence of disease activity. Musculoskeletal ultrasound or magnetic resonance imaging (MRI) can be used to visualize synovitis associated with PsA. To detect synovial changes in small joints (e.g., distal interphalangeal joints), high-resolution ultrasound is needed. Power Doppler sonography or MRI can be used to detect changes in synovial tissue inflammation and vascularity in response to treatment [15,16]. The Outcome Measures in Rheumatology Clinical Trials (OMERACT) psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS) can be used to quantitatively assess synovitis, bone edema, and erosions in hands. On MRI, OMERACT defines synovitis as increased post-gadolinium enhancement of an area in the synovial compartment that has a thickness greater than the width of the normal synovium [17].

As with other PsA domains (discussed below), there is often poor correlation between joint pain and swelling associated with synovitis and imaging findings. For example, a recent study by Lackner et al. [18] found that ultrasound-verified inflammation had limited correlation with global assessment of disease activity. To truly be considered in remission, patients should have a complete absence of both clinical and radiographic disease activity. However, it is recognized that achieving and maintaining remission can be challenging, such that MDA in only certain domain(s),

“near remission,” or low disease activity might instead be appropriate goals [12]. In addition to the clinical definitions for disease activity, there is also an unvalidated definition for minimal ultrasound disease activity (MUDA), which may be an appropriate goal for some patients. MUDA is defined as a power Doppler signal of ≤ 1 for 68 joints, perisynovitis of metacarpophalangeal joint, tenosynovitis of wrists/ankles/small joints, and 14 entheses [19].

Enthesitis assessment

There are several domain-specific instruments available for assessment of enthesitis, including the Leeds Enthesitis Index (LEI) [20], the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index [21], the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [22], and the 4-point enthesitis measure (Table 1) [23].

LEI, which evaluates 6 sites for the presence of tenderness, was the first enthesitis measure to be developed and validated in PsA [20]. The SPARCC enthesitis index and MASES are used in general populations of patients with spondyloarthritis, and neither instrument has been validated specifically for use in PsA, although the SPARCC enthesitis index has demonstrated good response and discrimination characteristics in PsA [23]. The SPARCC enthesitis index evaluates 16 enthesal sites for the presence or absence of tenderness (maximum score of 16), and modified versions are available that assess 6 or 8 sites [21,23]. MASES evaluates 13 enthesal sites for signs of tenderness and is recommended by the Assessment of SpondyloArthritis International Society for use in clinical trials. The 4-point enthesitis measure assesses both the right and left Achilles tendons and plantar fascia insertions on a scale of 0–3, and effectively discriminated between placebo and biologic DMARD therapy in several clinical trials [23,25,26].

In comparisons of instruments that measure clinical enthesitis in patients with PsA, LEI performed better than MASES and 8-site SPARCC enthesitis index in identifying response to treatment, and instruments assessing a greater number of sites outperformed the 4-point enthesitis measure [20,27]. In a phase 2 clinical trial of the anti-IL-6 monoclonal antibody, clazakizumab, in which both LEI and the SPARCC enthesitis index were used to measure enthesitis, the SPARCC enthesitis index displayed greater responsiveness and discrimination [28].

Although enthesitis measures have performed effectively in clinical trials, distinguishing drug treatment from placebo effect

Table 1
Sites assessed in outcome measures for enthesitis [23,24]

Site	LEI	SPARCC	MASES	4 Point
First costochondral			L, R	
Seventh costochondral			L, R	
Supraspinatus insertion		L, R		
Lateral epicondyle humerus	L, R	L, R		
Medial epicondyle humerus		L, R		
Posterior superior iliac spine			L, R	
Anterior superior iliac spine			L, R	
Iliac crest			L, R	
Fifth lumbar spinous process			X	
Proximal Achilles	L, R	L, R	L, R	L, R
Greater trochanter		L, R		
Medial condyle femur	L, R			
Insertion plantar fascia		L, R		L, R
Quadriceps insertion patella		L, R		
Inferior pole patella		L, R		
Tibial tubercle		L, R		
Total number of sites evaluated	6	18	13	4

L, left; LEI, Leeds Enthesitis Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; R, right; SPARCC, Spondyloarthritis Research Consortium of Canada; X, single site present (not bilateral).

[25,26,28,29], a discrepancy has been shown between clinical examination and findings of inflammation on ultrasound, suggesting that asymptomatic inflammation is not uncommon in patients with PsA [30–32]. Specifically, several studies have shown that subclinical enthesitis persists on ultrasound based on assessment using the Glasgow Ultrasound Enthesitis Scoring System (GUESS) in patients without clinical signs of arthropathy [32–35]. To help standardize the use of ultrasound in evaluating enthesitis in spondyloarthritis, OMERACT has developed a consensus-based ultrasound definition that includes hypoechogenicity, increased thickness of the tendon insertion, calcifications, enthesophytes, erosions, and Doppler activity as core elementary lesions of ultrasound-detected enthesitis [36].

Dactylitis assessment

Dactylitis has been assessed in clinical trials by a number of methods. The simplest method is to assess whether a digit is fully swollen, aided by checking if there is an imbalance in swelling with the contralateral digit. To be counted as dactylitic, there should be tenderness with palpation of the shaft midway between joints, not at the joint line. If the digit is swollen, but not tender, it may be considered as “cold dactylitis,” that is, perhaps previously inflamed but not currently inflamed. Another method that has been used is the Dactylitis Severity Score, in which digits are scored from 0 (no dactylitis) to 3 (severe dactylitis). Such simple methods have demonstrated responsiveness in several clinical trials [37–40]. Additionally, Helliwell et al. [41] developed the Leeds Dactylitis Index (LDI), a quantifiable score that uses an instrument known as a dactylometer to measure finger circumference, along with assessment of tenderness.

Spondylitis assessment

Inflammatory spondylitis can be a component of PsA. Assessment of spondylitis remission is challenging and can have low accuracy because it can be difficult to determine whether back pain is due to inflammation or other causes such as degenerative spine disease or fibromyalgia. Because spondylitis is not present in all patients with PsA and reliable assessment with MRI in trials is expensive, formal assessment of spondylitis has not been pursued in PsA trials. Rather, patients with PsA are evaluated with instruments that have been validated for use in ankylosing spondylitis, including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [42], Bath Ankylosing Spondylitis Functional Index (BASFI) [43], and Bath Ankylosing Spondylitis Metrology Index [44]. BASDAI is a commonly used instrument, consisting of 6 VAS questions about fatigue, pain, and stiffness. A limitation of using BASDAI and BASFI in PsA is that these instruments do not discriminate well between axial and peripheral disease activity. Therefore, these instruments are best suited for use in patients with predominantly axial involvement [23].

Skin and nail assessment

Because skin and nails are visible, they are generally easier for clinicians to assess than other PsA domains. Instruments commonly used to measure skin activity in PsA include the Psoriasis Area and Severity Index (PASI), static physician global assessment (PGA), and body surface area (BSA) involvement, which measure features such as erythema, induration, scaling, and the extent of skin affected [45]. It is debated whether achievement of remission in psoriasis should be defined as completely clear (i.e., PASI100 response and PGA = 0) or almost clear (i.e., PASI90 and PGA = 1) skin [46,47]. While PASI90 response is an acceptable treatment goal for many patients, achieving completely clear rather than

almost clear skin is associated with clinically important differences in health-related quality of life, especially for patients with psoriasis affecting highly visible areas (e.g., head and neck) and hands or feet [47,48]. Although there are shortcomings of PASI, especially in assessing non-plaque psoriasis, it remains the gold standard for measuring disease severity [48]. However, because BSA is much easier to use in clinical practice than PASI, current guidelines from the National Psoriasis Foundation state that BSA $\leq 1\%$ is an acceptable target response goal for patients initiating a new treatment [49].

The concept of molecular remission of skin disease has also been explored, and biopsies have shown that skin from areas in which lesions have cleared have a unique molecular signature of psoriasis activity [50]. However, this molecular evidence is not likely to be important because skin is no longer symptomatic, and it is generally considered impractical to take biopsy samples of clear skin for such purposes.

Up to 80% of patients with PsA have evidence of nail disease [51]. Nail disease activity can be measured in clinical trials using the Nail Psoriasis Severity Index (NAPSI), a simpler modified version of NAPSI (mNAPSI), and a nail VAS [52–54]. With these instruments, each fingernail is evaluated visually for characteristic features of disease (e.g., pitting, onycholysis, oil-drop dyschromia, nail plate crumbling, and leukonychia) [52,53]. NAPSI and mNAPSI scores are both simple-to-calculate quantitative measures that are sensitive to change and have been used reproducibly in clinical trials [23,45]. However, many clinical practitioners may not be aware of these scores, as they are predominantly used as research tools.

Assessment of remission and disease activity: use of composite measures

The concept of remission has been described as complete control of inflammation in all aspects of disease (including skin) to the extent that disease sequelae are avoided and quality of life is maintained [12]. As such, remission should be measured clinically using a combination of objective measures, such as tender joint count (TJC) and swollen joint count (SJC), skin and nail examination, and patient-reported outcomes, such as pain, function, and fatigue. Theoretically, imaging (e.g., X-ray, ultrasound, and MRI) and biomarker measurements could be used as quantifiable ways to measure disease activity, but such measures are not currently available, and generating such criteria would be complex because of the need to assess multiple clinical domains—synovitis, enthesitis, dactylitis, spondylitis, and psoriasis, including nail psoriasis—that may have varied responses to treatment [11]. Although there have been numerous attempts to define remission in PsA, a universal, accepted definition remains elusive [10,12].

More than a decade ago, Gladman et al. [55] proposed that remission is an absence of actively inflamed joints. This definition does not take into account the significant burden of extraarticular musculoskeletal disease and non-musculoskeletal features common to PsA. These other features were addressed in remission criteria proposed in 2008 by Cantini et al. [56] that were based on remission criteria developed in 1981 by Pinals et al. [57] for RA. Based on these criteria, remission in a patient would mean having no tender or swollen joints, no evidence of enthesitis, no active extraarticular features, 100-mm VAS pain and fatigue scores ≤ 10 , and normal acute-phase reactants. A threshold for skin response was not included in these criteria.

Identification and evaluation of the methods for measuring a patient's disease activity is a first step in understanding how to frame a definition for remission. Historically, many of the disease activity and clinical measures used in PsA have been adopted from

other inflammatory rheumatic diseases, such as RA, because of the similarities in joint symptoms and signs between these diseases. For example, the disease activity score for 28 joints (DAS28), originally developed for RA, can assess articular response in PsA and is often used in clinical practice [58]. DAS28 low-disease activity criteria (i.e., scores ≤ 3.2) perform well in clinical trials, indicating treatment response for active drugs vs. placebo, but when this cutoff point is lowered to DAS28 < 2.6 , the differentiation is often unclear [58]. A limitation of DAS28 is that only 28 joints are assessed, rather than assessment of 68 tender and 66 swollen joints (including distal interphalangeal joints of the hands but not the feet), as specified in the American College of Rheumatology (ACR) recommended measures for RA clinical trials, which are often referred to as the “gold standard” in PsA [59,60]. Although DAS28 performed well in clinical trials that included only patients with extensive polyarticular disease, it performed poorly in patients with oligoarticular PsA [61]. Therefore, this instrument is of limited usefulness in clinical practice in which many patients have oligo- or monoarticular disease activity predominantly in their feet or distal interphalangeal joints that DAS28 may fail to measure [58].

Over the past several years, initiatives have been undertaken to develop single-instrument PsA-specific composite assessments of relevant clinical outcomes across multiple domains (Table 2).

Scoring and different response thresholds for criteria such as remission and low, moderate, and high disease activity for these instruments is summarized in Table 3.

The Psoriatic Arthritis Response Criteria (PsARC) was the first tool to be specifically developed and validated for PsA. This instrument was developed for use in 1996 in a randomized, placebo-controlled trial of sulfasalazine in PsA [68], but was not referred to as PsARC until 4 years later when it was used in a randomized controlled trial of etanercept [69]. PsARC consists of 4 items: patient global assessment (PtGA), PGA, TJC, and SJC; TJC and SJC are performed on 68 and 66 joints, respectively [23]. In clinical trials, PsARC has shown significant response differences between active treatment and placebo; however, it has not performed as well as ACR20 or European League Against Rheumatism (EULAR) criteria [58].

In recent years, 2 new arthritis-focused, PsA-specific measures of disease activity, the Psoriatic Arthritis Joint Activity Index (PsAJAI) and the Disease Activity in Psoriatic Arthritis (DAPSA), have been developed. PsAJAI, which was developed as part of the assessments for the effects of TNF inhibitors, provides a weighted

sum of 30% improvement in 6 measures: TJC, C-reactive protein (CRP), PGA, pain, PtGA, and the Health Assessment Questionnaire (HAQ) [70]. Response rates with PsAJAI are generally comparable to those observed using ACR20 criteria and PsARC [23]. DAPSA, which was developed as the Disease Activity Index for Reactive Arthritis (DAREA) [71] and later renamed [72], is an index of patient global and pain assessments, 68 TJC and 66 SJC assessments, and CRP level [73]. Advantages of DAPSA are that it weighs the contributions of musculoskeletal activity as well as pain and PtGA, and provides thresholds for low, moderate, and high disease activity and remission based on DAPSA score [67,74]. Limitations of DAPSA are that it focuses specifically on peripheral disease and does not contain domains for skin assessment, enthesitis, dactylitis, or axial disease [74].

Since 2004, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and OMERACT have been working toward development of PsA-specific composite measures of disease activity. A key part of this initiative is the long-term GRAPPA composite exercise (GRACE) project, which evaluated more than 450 patients using new and existing composite measures that capture information across clinical domains of PsA [23].

Two new composite measures developed as part of the GRACE project are the Psoriatic Arthritis Disease Activity Score (PASDAS) and the Arithmetic Mean of Desirability Functions, which was later renamed the GRACE Index [62]. PASDAS is a weighted composite score (range: 0–10) of measures of patient and physician global assessment on 0- to 100-mm VAS, the physical component summary of the Medical Outcomes Study Short Form-36 (SF-36), SJC, TJC, Leeds Enthesitis Count, tender dactylitis count, and CRP [62]. PASDAS score thresholds for high, low, and very low disease activity are 5.4, 3.2, and 1.9, respectively [64,65]. The GRACE Index measures 8 variables, including TJC; SJC; HAQ; patient VAS for global assessment, skin, and joints; PASI; and Psoriatic Arthritis Quality of Life (PsAQoL). These variables are transformed and combined using the arithmetic mean [62].

A separate initiative led by Coates et al. was undertaken to define a state of “minimal disease activity” as a target for treatment. As a result of this project, in 2010, the MDA criteria currently used in PsA were validated. These criteria define MDA as meeting 5 of 7 outcome measures, including entheses and skin assessments [75,76]. It is important to note that meeting 5 of 7 criteria means that patients may have residual disease activity in 1 or 2 areas, such as TJC, SJC, or skin, especially because MDA does not set a threshold value for the 2 criteria that are not met. As such, achieving MDA is not the same as being in remission [64]. In a study comparing quantitative measures to assess PsA disease activity, Acosta Felquer et al. [13] found that MDA criteria are more stringent than DAS28 and less stringent than ACR/EULAR Boolean remission criteria. However, MDA criteria can be made stricter by requiring patients to meet 6 or 7 outcome measures. Alternatively, MDA can be made more focused by mandating that patients achieve particular cut points. MDA of joints and skin requires that TJC, SJC, and skin BSA criteria are met along with 2 other criteria (MDA joints and skin). MDA-joints criteria require that the joint elements be met, and the skin component could also be mandated in MDA skin. In a recent study using data from the GRACE Project, Coates and Helliwell [64] showed that agreement between the original 5 MDA and MDA-joints criteria was almost perfect, and that an MDA score of 7/7 corresponds to very low disease activity, which is close to a real remission state. In clinical studies of infliximab, MDA criteria were shown to have predictive validity for improved ACR20/50/70 and PGA, and patients who achieved MDA using these criteria were significantly less likely to experience long-term radiographic damage than patients who did not achieve MDA [76]. A summary of findings from studies that have utilized MDA criteria is provided in Table 4. Similar

Table 2
Clinical domains included in composite measures of PsA disease activity [23,62,63]

Domain	PsARC	PsAJAI	DAPSA	PASDAS	GRACE	MDA	CPDAI
Peripheral arthritis	✓	✓	✓	✓	✓	✓	✓
Pain		✓	✓			✓	
Patient assessment	✓	✓	✓	✓	✓	✓	✓
Physician assessment	✓	✓		✓			
Skin					✓	✓	✓
Enthesitis				✓		✓	✓
Dactylitis				✓		✓	✓
Spine disease							✓
HAQ		✓			✓	✓	✓
CRP		✓	✓	✓			
SF-36 PCS				✓			
PsAQoL					✓		

CPDAI, Composite Psoriatic Disease Activity Index; CRP, C-reactive protein; DAPSA, Disease Activity for Psoriatic Arthritis; GRACE, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Exercise; HAQ, Health Assessment Questionnaire; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; PCS, physical component score; PsA, psoriatic arthritis; PsAQoL, psoriatic arthritis quality of life; PsAJAI, Psoriatic Arthritis Joint Activity Index; PsARC, Psoriatic Arthritis Response Criteria; SF-36, Short Form-36.

Table 3
Scoring/response criteria for composite measures of PsA disease activity [23,62–67]

Instrument	Response criteria
PsARC	2 of the following: $\geq 30\%$ improvement in TJC or SJC and/or PtGA or PGA improvement of ≥ 1 point on a 5-point Likert Scale
PsAJAI	Weighted sum of $\geq 30\%$ improvement in 6 measures <ul style="list-style-type: none"> • Weight of 2 given to TJC, CRP, and PGA • Weight of 1 given to pain, PtGA, and HAQ
DAPSA	Sum of patient global and pain VAS, TJC, SJC, and CRP Cut-off values of ≤ 4 for remission, > 4 and ≤ 14 for low disease activity, > 14 and ≤ 28 for moderate disease activity and > 28 for high disease activity
PASDAS	Weighted composite score (range: 0–10) patient and physician global skin and joint VAS, SF-36 PCS, SJC, TJC, LEI, tender dactylitis count, and CRP. Thresholds for high, low, and very low disease activity are 5.4, 3.2, and 1.9, respectively
GRACE	Measures 8 variables: TJC; SJC; HAQ; patient VAS for global assessment, skin, and joints; PASI, and PsAQoL. Cut points are assigned for remission, low, moderate, and high disease activity for each of the 8 variables measured
MDA and VLDA	MDA is classified as achievement of ≥ 5 of these 7 criteria and VLDA is classified as achievement of 7 of these 7 criteria: <ul style="list-style-type: none"> • TJC ≤ 1 • SJC ≤ 1 • PASI ≤ 1 or BSA ≤ 3 • Patient pain VAS ≤ 15 • Patient global activity VAS ≤ 20 • HAQ ≤ 0.5 • Tender enthesal points ≤ 1
CPDAI	5 domains scored as none (0), mild (1), moderate (2), or severe (3), and summed <ul style="list-style-type: none"> • Peripheral arthritis assessed using TJC, SJC, and HAQ • Skin assessed using PASI and DLQI • Enthesitis assessed using number of sites affected and HAQ • Dactylitis assessed using number of fingers affected and HAQ • Spine disease assessed using BASDAI and ASQOL Scores of 2, 4, and 8 are defined as thresholds for very low, low, and high disease activity, respectively

ASQOL, Ankylosing Spondylitis Quality of Life Questionnaire; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BSA, body surface area; CPDAI, Composite Psoriatic Disease Activity Index; CRP, C-reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; DLQI, Dermatology Life Quality Index; GRACE, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Exercise Index; HAQ, Health Assessment Questionnaire; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PCS, physical component score; PGA, physician global assessment; PsA, psoriatic arthritis; PsAJAI, Psoriatic Arthritis Joint Activity Index; PsAQoL, Psoriatic Arthritis Quality of Life; PsARC, Psoriatic Arthritis Response Criteria; PtGA, patient global assessment; SF-36, Short Form-36; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale; VLDA, very low disease activity.

observations to those reported in clinical trials have also been noted in an observational cohort study of patients with PsA [77]. Overall, MDA criteria can be easily incorporated into clinical practice and adjusted (i.e., requiring different criteria to be met) based on individual patients' treatment goals.

Another established composite measure of PsA disease activity evaluated in post hoc analyses is the Composite Psoriatic Disease Activity Index (CPDAI) [64]. CPDAI assesses PsA disease activity, patient function, and health-related quality of life across 5 domains (i.e., peripheral joints, skin, enthesitis, dactylitis, and spinal involvement) on a scale from 0 to 15 [94]. CPDAI has demonstrated greater sensitivity in the measurement of treatment response compared with DAPSA and DAS28, supporting the importance of assessing multiple domains when measuring disease activity [62,95]. A CPDAI score of 2 correlates well with the definition of very low disease activity, while scores of 4 and 8 are defined as thresholds for low and high disease activity, respectively [64,65].

PASDAS, CPDAI, and MDA have been shown to be highly sensitive and specific, and scores are well correlated between instruments. When different composite measures of PsA disease activity were compared using data of a TNF inhibitor, PASDAS and the GRACE Index were better at distinguishing treatment effect than modified CPDAI, DAPSA, or DAS28, and reflected effects of treatment on a wide range of PsA domains [96]. Overall, composite measures are considered to be more efficient than unidimensional instruments in measuring disease activity and therefore remission [10,12,13]. However, data have shown that estimates of remission rates differ for the available composite indices of PsA disease activity [66]. A limitation of composite indices is that such single measures encompassing multiple diverse domains may lose the

ability to differentiate between responses in individual domains. Furthermore, while numerous instruments (PASDAS, CPDAI, MDA, and DAPSA) are used in clinical trials to assess remission, it is more common in clinical practice to use instruments such as Routine Assessment of Patient Index Data 3 (RAPID3), MDA, and DAPSA because they are less complex to administer.

Treatment to target

Treat to target (T2T), defined as the frequent assessment of disease activity and adjustment of therapy until a state of low disease activity or remission is achieved, is a frequently used strategy in the management of numerous diseases, such as diabetes mellitus. In rheumatic diseases, this approach is increasingly employed in the management of RA, and now PsA and other types of inflammatory arthritis [97–99]. The concepts of tight disease control and T2T were developed initially in RA as a result of imaging studies investigating the relationship between inflammation and damage, most notably the Tight Control for Rheumatoid Arthritis (TICORA) study [97]. As this relationship has become firmly established and studies have shown that tight control is associated with improved outcomes (e.g., clinical, structural, functional, quality of life, productivity, and morbidity/mortality endpoints), T2T has become a standard of RA management [98,100]. In PsA, the Tight Control in Psoriatic Arthritis (TICOPA) study showed that patients were significantly more likely to achieve the primary outcome of ACR20, as well as secondary outcomes of ACR50, ACR70, and PASI75, after 48 weeks of tight control treatment strategies aiming for MDA compared with standard care [80,101]. However, there is still much less information available on the value of defining therapeutic

Table 4
Findings from clinical trials of MDA in patients with PsA

Trial	Number of patients	Treatment	Results
<i>Randomized, double-blind, controlled trials</i>			
IMPACT 1/ IMPACT 2 [76]	IMPACT 1:63 IMPACT 2:157	<ul style="list-style-type: none"> IMPACT 1: infliximab (5 mg/kg) at week 0, 2, 6, and 14 followed by blinded infliximab therapy to week 46 and an open-label treatment from week 50–98 IMPACT 2: infliximab (5 mg/kg) at week 0, 2, 6, 14, and 22 	<ul style="list-style-type: none"> IMPACT 1: At week 16, 48% of patients receiving infliximab achieved MDA, compared with 3% receiving placebo ($P < 0.0001$) IMPACT 1: At week 50, all patients were receiving infliximab and 42% were categorized as MDA IMPACT 1: At week 98, 30% of patients achieved MDA IMPACT 2: At week 24, 52% of patients receiving infliximab achieved MDA, compared with 21% receiving placebo ($P < 0.001$) IMPACT 2: At week 54, 40% of patients receiving infliximab achieved MDA
GO-REVEAL [78]	405	<ul style="list-style-type: none"> Golimumab 50 mg, or golimumab 100 mg every 4 weeks 	<ul style="list-style-type: none"> At weeks 14, 24, and 52, respectively, 23.5%, 28.1%, and 42.4% of patients receiving golimumab achieved MDA Approximately 50% of patients treated with golimumab achieved MDA at least once by week 256 Baseline HAQ DI score was a significant predictor of patient's ability to achieve persistent MDA <ul style="list-style-type: none"> Patient with 1-unit higher baseline HAQ DI score had a lower likelihood of achieving MDA at consecutive visits (≥ 3 and ≥ 4)
FUTURE 2 [79]	397 TNF-naïve or TNF-IR patients	<ul style="list-style-type: none"> Secukinumab 300 mg, 150 mg, or 75 mg at baseline, week 1, 2 and 3, and then every 4 weeks from week 4 	<ul style="list-style-type: none"> 23% of patients receiving secukinumab 150 mg and 28% of patients receiving secukinumab 300 mg achieved MDA at Week 16 <ul style="list-style-type: none"> In TNF-naïve patients at week 16, MDA was achieved by 32% of patients receiving secukinumab 150 mg and 34% of patients receiving secukinumab 300 mg In TNF-IR patients at week 16, MDA was achieved by 8% of patients receiving secukinumab 150 mg and 16% of patients receiving secukinumab 300 mg Response rates sustained through week 52 (33% for secukinumab 150 mg and 35% for secukinumab 300 mg) <ul style="list-style-type: none"> In TNF-naïve patients at week 52, MDA was achieved by 39% of patients receiving secukinumab 150 mg and 41% of patients receiving secukinumab 300 mg In TNF-IR patients at week 16, MDA was achieved by 21% of patients receiving secukinumab 150 mg and 23% of patients receiving secukinumab 300 mg
<i>Open-label, randomized, controlled trial</i>			
TICOPA [80]	206 with early PsA of < 2 years	<ul style="list-style-type: none"> 101 patients received tight control (seen by physician every 4 weeks—if MDA was not reached, treatment with DMARDs or TNF inhibitors was increased to maximum dose) 105 patients received standard care (generally reviewed every 12 weeks with no formal measure of MDA used to make clinical decisions) 	<ul style="list-style-type: none"> In the tight-control group, 24% of patients reached MDA by week 12 In the tight-control group, 72% of patients reached MDA at least once between week 12 and 48 and 56% of patients attained MDA on 2 or more consecutive visits
<i>Open-label trials</i>			
ADEPT [81]	136	<ul style="list-style-type: none"> Adalimumab 40 mg every other week 	<ul style="list-style-type: none"> 39% of patients receiving adalimumab reached MDA at 24 weeks compared with 7% of patients on placebo ($P < 0.001$) 37% of patients treated with adalimumab achieved MDA_{PGA1} at 24 weeks compared with 5% of patients on placebo ($P < 0.0001$) 39% of patients treated with adalimumab achieved MDA_{PGA2} at 24 weeks compared with 8% of patients on placebo ($P < 0.0001$)
STEREO [82]	412 (268 with active disease followed for MDA)	<ul style="list-style-type: none"> Adalimumab 40 mg every other week 	<ul style="list-style-type: none"> At week 12, 17.9% of patients reached MDA 7.8% of patients obtained all 6 requirements of MDA
<i>Prospective registry</i>			
SwePsA [83]	197	<ul style="list-style-type: none"> 61% of patients received DMARDs at some point during the 5-year study 16.8% of patients received methotrexate continuously Etanercept, adalimumab, infliximab, and rarely tocilizumab were used when needed throughout the study 	<ul style="list-style-type: none"> At study initiation, 18.2% of men and 7.7% of women achieved MDA ($P = 0.023$) <ul style="list-style-type: none"> At 5 years, 50% of men and 32.7% of women achieved MDA ($P = 0.017$) Factors at study initiation associated with MDA after 5 years: <ul style="list-style-type: none"> Univariate analysis: male sex, short delay between onset of symptoms and inclusion in trial, axial disease, low SJC and TJC, lower disease activity, lower patient global and pain VAS, low HAQ, and MDA at inclusion Multivariate analysis: Shorter delay of symptom duration before inclusion in trial and low HAQ score at inclusion were both independent predictors of MDA. In women, symptom duration before entering trial and low HAQ were predictors of MDA. In men, low pain VAS was predictive of MDA

Table 4 (continued)

Trial	Number of patients	Treatment	Results
<i>Observational studies</i>			
Haddad et al. [84]	226	<ul style="list-style-type: none"> TNF inhibitors (infliximab, etanercept, adalimumab, golimumab) 	<ul style="list-style-type: none"> 64% achieved MDA after a mean \pm SD duration of 1.30 ± 1.51 years Male sex (OR = 1.65, 95% CI: 1.08–2.53; $P = 0.02$) and normal ESR (OR = 2.27, 95% CI: 1.22–4.17; $P = 0.009$) increased the odds of achieving MDA
Lubrano et al. [85]	124	<ul style="list-style-type: none"> TNF inhibitors (adalimumab, etanercept, and golimumab) were prescribed as recommended by the Italian Society of Rheumatology 	<ul style="list-style-type: none"> After 4 months, 28.5% achieved MDA After 8 months, 55.2% achieved MDA After 12 months, 64% achieved MDA The concordance between PtGA ≤ 20 mm and MDA was good at 4, 8, and 12 months
Perrotta et al. [86]	75	<ul style="list-style-type: none"> Patients received TNF inhibitors (adalimumab, etanercept, or golimumab) and were evaluated every 4 months for 1 year in a clinical practice setting 	<ul style="list-style-type: none"> MDA was achieved in 61.3% of patients No difference between TNF inhibitors was found Predictors for MDA: <ul style="list-style-type: none"> Male sex High CRP High ESR Low HAQ
Iervolino et al. [87]	146	<ul style="list-style-type: none"> Patients received TNF-α inhibitors 	<ul style="list-style-type: none"> Age, CRP, and BASFI at baseline were predictors for MDA after 3 months
Di Minno et al. [88]	270	<ul style="list-style-type: none"> 80 patients received adalimumab (40 mg every 2 weeks) 111 patients received etanercept (50 mg/week) 79 patients received infliximab (5 mg/kg every 8 weeks) 	<ul style="list-style-type: none"> After 12 months, 36.3% of patients achieved MDA <ul style="list-style-type: none"> 41.8% of patients receiving infliximab 36.9% of patients receiving etanercept 30.0% of patients receiving adalimumab Of the patients who reached MDA after 12 months, by 24 months, 17.3% relapsed Male sex ($P = 0.001$), younger age ($P = 0.042$), longer disease duration ($P = 0.004$), higher ESR ($P < 0.001$), higher CRP ($P < 0.001$), lower TJC ($P < 0.001$), and lower TEC ($P = 0.003$) were predictors of achieving MDA vs those who did not achieve MDA MetS, carotid plaques, and hepatic steatosis ($P < 0.001$) were more common in patients who did not achieve MDA vs. patients who did achieve MDA
Eder et al. [89]	557 (36.2% classified as overweight and 35.4% as obese)	<ul style="list-style-type: none"> Patients were followed every 6–12 months from 2003 to 2012 	<ul style="list-style-type: none"> 368 (66.1%) patients achieved sustained MDA Patients with high pain, high HAQ, and high TJC scores did not frequently achieve MDA <ul style="list-style-type: none"> 79.4% with a high pain score did not achieve MDA 59.4% with a high HAQ score did not achieve MDA 48.1% with a high TJC score did not achieve MDA In a univariate regression analysis, patients with higher BMI were less likely to achieve sustained MDA vs. patients with low BMI <ul style="list-style-type: none"> BMI: 25–30, OR = 0.65, $P = 0.002$ BMI: > 30, OR = 0.52, $P < 0.0001$ High BMI category was associated with a lower probability of achieving sustained MDA in each of the following categories: <ul style="list-style-type: none"> TJC (OR = 0.77, $P = 0.003$) Psoriasis activity as measured by PASI or BSA (OR = 0.29, $P < 0.0001$) Pain score (OR = 0.43, $P < 0.0001$) PGA (OR = 0.35, $P < 0.0001$) HAQ (OR = 0.61, $P < 0.0001$)
Costa et al. [90]	330 (134 without MetS and 196 with MetS)	<ul style="list-style-type: none"> TNF-α inhibitors 	<ul style="list-style-type: none"> At 24 months, 47.8% of patients achieved MDA 77.4% who did not achieve MDA had MetS Univariate analysis: patients with MetS were less likely to achieve MDA than patients without MetS (OR = 0.45, $P < 0.001$) MetS was associated with a lower probability of achieving MDA in each of the following criteria: <ul style="list-style-type: none"> TJC (OR = 0.63, $P = 0.015$) SJC (OR = 0.42, $P < 0.001$)

Di Minno et al. [91]	270 patients (135 obese, 135 normal weight)	<ul style="list-style-type: none"> • 29.6% adalimumab • 41.1% etanercept • 29.3% infliximab 	<ul style="list-style-type: none"> ◦ TEC (OR = 0.73, $P = 0.007$) ◦ PASI (OR = 0.51, $P < 0.001$) ◦ HAQ (OR = 0.66, $P = 0.015$) • No association between MDA and sex, age, or smoking • After 12 months, obesity was the strongest predictor for the risk of not achieving MDA (HR = 4.90, $P < 0.001$) • After 24 months, obesity was associated with a high risk of relapse for patients who had achieved MDA after 12 months (HR = 2.04, $P = 0.014$) • Predictors for achieving MDA in patients with obesity: <ul style="list-style-type: none"> ◦ Low TJC (HR = 1.15, $P < 0.001$) ◦ Male sex (HR = 2.25, $P < 0.001$) ◦ High CRP (HR = 1.18, $P < 0.001$)
Di Minno et al. [92]	126 overweight/obese patients	<ul style="list-style-type: none"> • 46.8% etanercept • 26.2% adalimumab • 27.0% infliximab • Patients were randomized to a hypocaloric diet or a free self-managed diet 	<ul style="list-style-type: none"> • Regardless of diet, after 6 months of treatment, $\geq 5\%$ weight loss was a predictor for MDA (OR = 4.20, $P < 0.001$) • $< 5\%$ weight loss: 23.1% achieved MDA • 5–10% weight loss: 44.8% achieved MDA • $> 10\%$ weight loss: 59.5% achieved MDA • $\geq 5\%$ weight loss was a predictor of achieving MDA in patients with axial PsA (OR = 8.16, $P = 0.014$) and in patients with axial and peripheral PsA (OR = 4.16, $P = 0.013$), but not patients with just peripheral PsA (OR = 1.94, $P = 0.525$)
Lubrano et al. [93]	58 patients with predominately axial PsA	<ul style="list-style-type: none"> • 25.8% adalimumab • 51.7% etanercept • 22.5% golimumab 	<ul style="list-style-type: none"> • Independent predictors of MDA: <ul style="list-style-type: none"> ◦ Male sex (OR = 3.4, $P = 0.045$) ◦ Age (OR = 21.0, $P = 0.040$) ◦ Disease duration (OR = 3.4, $P = 0.045$) ◦ Low HAQ score (OR = 15.23, $P = 0.01$)

BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; BSA, body surface area; CI, confidence interval; CRP, C-reactive protein; DI, disability index; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HR, hazard ratio; MDA, minimal disease activity; MetS, metabolic syndrome; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PGA, physician global assessment; PsA, psoriatic arthritis; PtGA, patient global assessment; SD, standard deviation; SJC, swollen joint count; TEC, tender entheses count; TJC, tender joint count; TNF, tumor necrosis factor; TNF-IR, previous inadequate response/intolerance to TNF inhibitors; VAS, visual analog scale.

targets for PsA than for RA. An international task force was formed to discuss and develop consensus recommendations for treatment targets for PsA and other spondyloarthritis [99]. This task force has recommended that a treatment target should be remission of all clinical domains. Low-disease activity was also recommended as an alternative goal of treatment when remission could not be achieved because of such factors as fixed deformities, treatment side effects, and patient preferences [99].

As awareness of the value of T2T in PsA has grown, rheumatologists are becoming increasingly familiar and experienced with performing quantitative assessments of disease activity. When using a T2T approach, it is important to consider individual patient characteristics when starting a new therapy and setting treatment goals. For example, patients who may be predisposed to known side effects of aggressive biologic treatment, such as elderly patients with a tendency for recurrent sinusitis or urinary tract infections, are not good candidates for dogged pursuit of remission, and low disease activity may be satisfactory and sufficient. Patients from the TICOPA study had early disease, so current T2T concepts may have greater applicability in newly diagnosed patients than in those with disease of longer duration. Additionally, patient preferences, such as anxiety over taking different biologics due to concerns about safety, drug access, cultural beliefs, and natural stoicism, may preclude pursuit of remission. Furthermore, measurement of imaging goals for remission may not be feasible or practical based on economic factors, lack of access to advanced imaging technologies, or physical location of affected joints.

As goals are being set for individual patients, use of available quantitative tools can be modified accordingly. For example, in patients with early signs of disease and limited joint damage, it may be possible to achieve very low-disease activity (VLDA) as measured by MDA (i.e., meeting all 7 criteria), whereas for patients with established disease and irreversible damage, meeting 5 of 7 MDA criteria may be a more realistic treatment goal. Ideally, more comparative studies of different treatment targets will be performed to help guide practitioners in setting goals.

Conclusions

The establishment and validation of PsA outcome measures have allowed improved assessment and quantification of disease activity in multiple clinical domains. Measures of individual domains and composite measures, such as the MDA criteria, have been used successfully in clinical trials, and the US Food and Drug Administration is placing greater importance on these criteria when evaluating new drugs. In addition, the measures being used in clinical trials are increasingly accessible and practical for use in daily rheumatology practice, suggesting that their real-world utilization will increase.

Furthermore, attaining remission as a treatment objective for certain patients with PsA is gaining acceptance within the rheumatology community. However, pursuit of remission is not appropriate for all patients, and T2T decisions should take into consideration patient preferences for target levels, disease activity, and the means required to achieve such levels.

Additional work is needed to develop a definition of PsA remission that is broadly acceptable to researchers, clinicians, regulatory agencies, and patients. The ideal definition should represent achievement of a state that avoids disease progression and future damage, and maintains optimal functionality and quality of life.

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