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Remission in PsA – where are we now?

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Abstract

Advances in treatments and treatment strategies for psoriatic arthritis (PsA) have led to many patients responding well to management of their disease, and targeting remission as a treatment goal is now a possibility. Treat to target (T2T) is a strategy aimed at maximizing benefit, irrespective of the type of medication used, by monitoring disease activity and using it to guide therapy. The measurement of response to treatment has been the subject of wide discussions among experts for some time, and many instruments exist. Comparisons of the different measures and their different strengths and weaknesses, is ongoing. The impact of modern imaging techniques on monitoring disease progression is also evolving, and advanced techniques using both magnetic resonance imaging (MRI) and ultrasound (US) have the potential to improve management of PsA through identification of risk factors for poor prognosis as well as accurate assessment of inflammation and damage, including subclinical disease. Increased understanding of the pathways that drive the pathogenesis of PsA will be key to identifying specific biomarkers for the disease and developing effective treatment strategies. Targets for response, considerations for use of a T2T strategy in PsA, different imaging techniques, and serological aspects of remission are all discussed in this review, and areas for further research are identified.

Introduction

The treatment goals for patients with psoriatic arthritis (PsA) are control of disease activity, improvement of physical function and quality of life, and prevention of structural damage to joints [1-3]. In the last few years, advances in pharmacological treatment of PsA, particularly the introduction of biologic therapies, have enabled excellent responses to be achieved in many patients [4]. However, PsA is a heterogeneous disease and measuring its response to treatment, both in the clinic and in clinical trials, has been the subject of wide debate.

Advances in treatment strategies for rheumatic diseases have also occurred. Treat to target (T2T) is aimed at maximizing benefit, irrespective of the type of medication used, by monitoring disease activity using the best current measures and remission criteria [5]. The Tight Control of disease activity in rheumatoid arthritis (RA), (TICORA) [6] study showed that escalating therapy in a T2T strategy could improve outcomes in RA. The study investigated an intensive treatment strategy consisting of frequent, objective assessment of patients, intensive use of intra-articular steroid injections if needed, and a structured protocol for the escalation of treatment in patients with active disease despite treatment. The targets in RA have become more stringent over time, related to a greater ability to achieve remission as new, better treatments are developed [7].

Evidence for T2T in PsA only began to emerge in 2013, and many treatments and outcome measures have been 'borrowed' from RA. There has been little agreement on what target(s) for response should be used in PsA [8], and a literature review by the European League Against Rheumatism (EULAR) showed that there were few relevant studies on T2T in PsA [8].

The use of magnetic resonance imaging (MRI), ultrasound (US), and computed tomography in the study of PsA has permitted a better understanding of the various pathologies of the PsA phenotypes. These sensitive imaging techniques have highlighted the high frequency of subclinical inflammation and added insights into the persistence of inflammation and structural damage after therapy [9-12].

This review provides an overview of the current status of targeting remission in PsA, including a focus on areas that need more research. It resulted from a consensus meeting with an expert panel of clinicians involved in PsA routine management and research in February 2016.

Considerations in Applying Treat to Target (T2T) in PsA Clinical Practice

Specific aspects and challenges of remission in PsA

In order to assess remission, it must first be defined. Remission implies that at a minimum, the inflammatory disease process will be controlled such that the patient has no symptoms and no long-term functional or structural joint consequences [13]. Even in clinical manifestations, PsA is a multi-faceted disease with varied rheumatological and dermatological presentations. Beyond this, PsA not only has clinical manifestations, but is also characterized by structural and immunologic changes. Therefore PsA remission may encompass more than remission of the clinical signs and symptoms of musculoskeletal and skin disease.

Core domains for assessment of PsA were defined by Outcome Measures in Rheumatology (OMERACT) in 2006 [14] and updated in 2016 [15, 16], and a core set of domains criteria for minimal disease activity (MDA) in PsA have also been defined [7, 17]. Ideally, the target for remission should be feasible for clinical use and, as PsA is a heterogeneous condition, should include assessment of all key different domains. As yet, there are no reliable serum markers of PsA disease activity.

Another major factor affecting quality of life for PsA patients is comorbidity, and this aspect needs to be considered when setting realistic expectations of disease remission. A large proportion of PsA patients have comorbidities, which are often under-recognized and undertreated, which may influence treatment, prognosis and outcomes; they include cardiovascular disease, obesity, metabolic syndrome, depression, uveitis and cancer [18, 19]. One study has found that 42% of PsA patients have three or more comorbidities; however, the incremental effects of comorbidities on quality of life relate more to the type rather than the number of comorbidities [20]. Targeted treatment is therefore an important concept in achieving patient-defined remission.

Patient perspectives on disease activity, treatment and remission in PsA

Patients with PsA and their physicians may view the disease differently, and there is a discrepancy between patient and physician assessment of joint activity [21]. An analysis of 565 patients found that patients scored their disease worse than physicians, with the discordance greater for joints than for skin parameters. Similar discrepancy is well-documented in RA [22], but has been less well-studied in PsA.

Patient education in PsA is often not optimal and PsA patients are less empowered than those with RA [23]. However, a recent study showed that the difference between patients and physician global assessment of disease activity as well as the difference between tender and swollen joint count were associated with a reduced risk of achieving remission, both in PsA and RA [24].

Results of the Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey [25] showed that 59% of surveyed PsA patients were receiving no treatment or only topical treatment. This is partly due to low expectations on the part of patients that dermatologists or rheumatologists will be able to offer effective treatments.

For patients, the impact of disease on quality of life and function is important. Although individuals may have very different expectations of how their disease is managed, aspects of disease and treatment that are important to patients are not adequately covered by the self-report measures (both patient reported outcomes [PROs] and existing composite scores) most often used in PsA patients [26]. These include the impact of environmental factors, societal attitudes towards individuals with psoriasis (PsO) or PsA, the increased feeling of isolation from social activities, and treatment burden, resulting in, for instance, lack of leisure time. Expectations are an important factor in disease management. For example, there is evidence that RA patients consider remission more as a feeling of returning to normality, rather than an absence or reduction of symptoms [27]. Treatment clearly impacts quality of life for PsA patients, and there is evidence that treatment early in the course of the disease (< 2 years disease duration) led to greater improvements in arthritis scores and quality of life measures compared with those treated after having the disease for more than 2 years [28].

Clinical remission in PsA: How to measure it

Comparison of different instruments used to assess disease activity and measure outcomes

The composite measures used to assess disease activity are compared in Table 1, built by author consensus while writing the paper. These composite measures combine individual measures of disease activity into a single score and, while this may be a more efficient approach than comparing across individual scores, the ability to distinguish between changes in disease activity in individual clinical features may be lost [29]. Different outcome measures may be used in clinical practice from those used in clinical trials although, if being used to guide treatment decisions in a trial, these measures must be feasible. A joint count assessing 68 joints for tenderness and 66 joints for swelling is employed in virtually all randomized controlled trials (RCTs) to constitute the primary outcome measure and is endorsed by OMERACT [14]. However, the Disease Activity Score 28 (DAS28) developed for RA [30] is an often-used measure of disease activity and remission in PsA in clinical practice around the world and is a secondary measure used in RCTs. However, it was not developed for PsA patients, it is purely a measure of joint inflammation and confined to 28 joints and it does not assess disease in common domains of PsA involvement, i.e., distal interphalangeal joints, feet or ankles, skin, and nails.

Work is ongoing to compare different measures. The GRACE (GRAppa Composite Exercise) project aimed to develop new composite measures in PsA and compare them with existing indices [31]. The new indices included the psoriatic arthritis disease activity score (PASDAS) and the GRAPPA composite index, which uses the arithmetic mean of desirability functions. These have been compared with existing indices such the Composite Psoriatic arthritis Disease Activity Index (CPDAI), Disease Activity for PSoriatic Arthritis (DAPSA), and DAS28.

A recent study in patients with active PsA demonstrated that different remission criteria provide different results [32], while the performance of six composite activity indices was compared in a real-world study [33]; all six showed good discriminant capacity, but the proportions of patients classified in the disease activity levels differed and, in particular, the rate of patients in remission was clearly different among the indices. Of note, none of the existing composite measures, including MDA, capture the original (2006) [14] nor the updated (2016) [15, 16] PsA core set.

Is Treat to Target applicable in PsA?

The preferred 'target' (state) of a T2T approach is remission or inactive disease as the primary goal and low disease activity or MDA as the secondary goal.

The TICOPA (Tight Control of Psoriatic Arthritis) study [34] has recently shown that treating to target by escalating therapy, with a greater use of combination disease-modifying anti-rheumatic drugs (DMARDs) and biologics in the tight control arm of the study significantly improves joint outcomes for newly diagnosed patients (Fig. 1) [34]. In the Standard Care arm patients were reviewed every 12 weeks in a general rheumatology outpatient clinic supervised by a consultant rheumatologist. No formal measures of disease activity were used to guide treatment decisions and there was no restriction on prescribing. By contrast, in the Tight Control arm patients were seen every 4 weeks by the study physician and treated according to a predefined treatment protocol. At each visit, patients were assessed for MDA criteria. Those not achieving MDA had their treatment escalated to the maximum dose according to the protocol. Patients achieving the MDA criteria continued on their current therapy.

Patients who received tight control treatment did experience more treatment-related adverse and serious adverse events than those receiving standard care, reporting more colds, nausea, fatigue and gastrointestinal upsets than those in the control arm (only partly explained by more frequent visits and recording of adverse events). However, despite larger doses of methotrexate in the tight control arm, liver enzyme abnormalities were similar in both arms. Patients in the tight control arm also required 27% more tumor necrosis factor inhibitor (TNFi) usage compared with those on standard care.

Patients in the TICOPA study were selected for early disease, and current T2T concepts may be more appropriate for newly diagnosed patients, and may be more difficult to apply in patients with longer disease duration with relatively more damage. This damage may affect the optimal primary target as patients with longstanding disease may be unable to meet these stringent criteria.

TICOPA is the first trial of strategy in PsA and further strategy trials are needed to weigh effectiveness against safety, since adverse events were also higher in the tight control arm of the TICOPA study compared with the standard of care (SOC) arm.

In two additional studies, a delay in diagnosis and intervention by 6 months demonstrated an impact on structural damage and long-term functional outcomes [35-37]. Data from the Swedish Early Psoriatic Arthritis Register (SwePsA) [38]suggest that a shorter time between onset of symptoms and diagnosis is associated with better clinical outcomes at 5 years. It therefore appears that, as is the case with RA, early intervention combined with a tight control strategy is important to prevent irreversible damage.

Insights from Modern Imaging

Much less information is available on the use of ultrasound (US) and magnetic resonance imaging (MRI) in PsA compared with RA, and imaging outcomes for remission in PsA are still evolving. What is clear is that MRI and US have the potential to improve PsA management [39]. Both techniques offer capability for assessing both inflammation and damage, with MRI enabling visualization of the spine in axial disease. Both may evaluate peripheral joints, with US being more patient friendly while providing multiple joint examinations in real time, though it is unable to visualize intra-bone pathology (osteitis). MRI can evaluate only one joint or a joint area during one session, and may be less acceptable to patients due to the enclosed nature of the technique.

Although there are no typical US patterns characterizing PsA synovitis, with the exception of possibly more intense intra-articular vascularization seen in inflamed tissue, US has demonstrated good accuracy in assessing synovitis in PsA [10, 39-42]. In addition, the presence of US-detected synovitis has been shown to be associated with long-term radiographic erosion progression and poor outcomes [23] Recently, Ficjan et al. [11] in a prospective and longitudinal study, developed an US composite score for the assessment of inflammatory and structural lesions in PsA, which demonstrates good metric properties including good sensitivity to change. US has also shown to be of added value in assessing enthesitis and dactylitis. US can also be used for visualizing structural changes and inflammatory activity at the psoriatic skin and nail level; thickening of both the epidermis and dermis is the most constant US pathologic finding in psoriatic plaques, whereas the hypoechoic band in the upper dermis is associated with Power Doppler (PD) activity (an expression of neoangiogenesis) and is particularly detectable in the active stages of the disease [43, 44].

Recommendations on imaging in spondyloarthritis (SpA) have been proposed by EULAR, including use of X-rays, US or MRI [45]. In axial SpA, the recommendation is for disease activity to be monitored with MRI of the sacroiliac (SI) joints and/or the spine, whereas conventional radiography should be used for long-term monitoring of structural damage. Similarly, for peripheral SpA, the recommendation is for US and MRI to be considered when monitoring disease activity (particularly synovitis and enthesitis), and conventional radiography is recommended to monitor structural damage.

The EULAR recommendations reflect the benefits of advanced imaging in assessing inflammation rather than assessing damage on X-rays, which has previously been an issue for trials conducted over short periods of time and trials that are not placebo controlled, where there is little radiographic structural progression. The recommendations and recent evidence from clinical trials suggest that the field could be moving towards a time when X-rays are of limited value for imaging in SpA clinical studies.

Using imaging to monitor disease activity

Multiple studies have shown that MRI and US can detect inflammatory and structural lesions [46] and identify risk factors for poor prognosis in PsA [39, 47]. In terms of quantifying change, most US composite scores have been developed for the assessment of inflammatory and structural lesions in PsA (in terms of quantifying change), and they have demonstrated construct validity, sensitivity to change, reliability and feasibility [11]. The OMERACT PsA MRI Score (PsAMRIS) has similarly demonstrated good performance metrics [11, 48]. Several studies have now demonstrated the use of imaging to monitor disease activity and therapeutic response. A study of more than 300 SpA patients being treated with TNFi showed that PD US is a reliable method to monitor therapeutic response by measuring enthesitis [49], while US had a pivotal role in differential diagnosis and treatment monitoring in a patient with early PsA undergoing an aggressive tight control treatment program and being monitored by US [50]. Similarly MRI has demonstrated responsiveness in PsA clinical studies [51].

Imaging of subclinical disease and remission

In line with the concept of subclinical disease first described in RA (inflammation detected by modern imaging but not examination), studies have found discrepancies between modern imaging and clinical findings, uncovering issues with accurate detection and clinical assessment of inflammation [9] and enthesitis, tenosynovitis or perisynovitis (i.e., extracapsular inflammation) in PsA patients in clinical remission [52]. In a study of newly diagnosed PsA comparing clinical examination with US in 49 patients, three-quarters were found to have sub-clinical synovitis, most frequently in the wrist and knee (Fig. 2) [53]. In patients on treatment, subclinical synovitis has been detected using US in patients classified as being in remission (as defined by MDA or DAS28) [9, 52]. There is some evidence that US detected synovitis might predict short-term flares in PsA patients in remission. However, it is not clear how important these US-detected manifestations really are and whether a T2T approach based on imaging would be superior to one based on clinical assessments. Some studies have shown that US can detect inflammatory and structural lesions and identify risk factors for poor prognosis in PsA [47]. Most of the studies have found discrepancies between US and clinical findings, uncovering issues with accurate detection and assessment of inflammation [9] and enthesitis, tenosynovitis or perisynovitis in PsA patients in clinical remission [52].

Enthesitis is another key, but often underestimated, feature of PsA, and therefore assessment of enthesitis with imaging is important, particularly as clinical measurements are often unreliable. Enthesitis may be predictive of flares, can predict clinical outcome, and can be present, although at a lower level, in remission or low disease activity states [54, 55]. A number of studies have been published supporting the validity of US in the assessment of entheses [56-60]. A recent study in newly diagnosed PsA found that three-quarters had sub-clinical synovitis, most frequently in the wrist and knee (Fig. 2).

Using contrast-enhanced US to detect persistent joint inflammation among patients in clinical remission showed that this technique is sufficiently sensitive to identify the presence of synovitis and thereby monitor remission [61]. Although there are limited data, there is some evidence that US detected synovitis might predict short-term flares in PsA patients in remission [62]. While Power Doppler US assessment may have an important role in monitoring treatment, its use at every clinic visit may not be feasible due to expertise required, time and financial constraints [63, 64]. However its use at specific time points where accurate assessment of inflammation is critical (e.g. evaluation of true remission state) may add value to usual care. Further developments such as whole-body MRI could be an additional tool for use in clinical decision making, allowing the assessment of disease activity in axial and peripheral sites, and improving the detection of inflammatory changes in PsA in locations that are difficult to assess clinically [65]. Again, feasibility is an important consideration given the equipment required and the costs associated with scanning.

Serological and Immunological Aspects of Remission in PsA

Two hypotheses have been formulated for the pathogenesis of PsA: firstly, that PsA is a classic autoimmune disease, or alternatively, that it begins with microtrauma at the enthesis, which then initiates innate immune events. [66]. A better understanding of the key pathologic pathways that drive progression from skin to bone involvement is needed in order to develop more effective treatment strategies.

Several studies on the origins of PsA have revealed signs of subclinical synovitis and enthesitis by MRI and US examination in the joints of patients who have psoriasis but not PsA [67-70], although the significance of these findings is not clear. Enthesitis has also been documented in healthy controls [59], and in patients with psoriasis without arthritis [71].Psoriasis patients also have a greater risk of developing entheseophytes than healthy controls [72]. There is also evidence to suggest that skin-bone interactions are triggered by IL-17, and interleukin-17 (IL-17) overexpression in mice with chronic skin inflammation induces bone loss through inhibition of osteoblast-mediated bone formation [73]. Finally, recent data show that body mass index (BMI) may also have an effect on the development of enthesitis, with overweight patients having less chance of fulfilling MDA criteria for tender entheseal points [74].

There may be differences in the pathologies of the various phenotypes of PsA, in terms of presence of certain cytokines/immune cells in synovitis and enthesitis; for example, T-cell concentration changes or abnormalities in early disease may be predictive of progression and/or response to therapy [75]. Genetic factors, such as IL-23R polymorphisms, may also predispose to exaggerated cytokine production and a hyperproliferative response, which can combine with mechanical stress factors into clinically apparent skin disease and clinically unapparent entheseal proliferation [76].

Biochemical markers of inflammation

The concept of immunological remission in PsA is only beginning to be understood. Standard biomarkers of inflammation are not particularly helpful in judging inflammatory disease activity in PsA. Unlike the situation in RA, there are few established biomarkers for immunological pathology in PsA. As the IL-17 pathway is integral in psoriasis and psoriatic disease [77], the IL-17–IL-23 pathway may provide more reliable markers for PsA in future and recently, changes in CD3+ T-cell expression in PsA synovium have been shown to correlate with clinical response to treatment [75]. Biomarkers are under review as part of the OMERACT/GRAPPA initiative and several new biomarkers for PsA have been proposed, including calprotectin, SAA and MRP, although none has been extensively validated to date. In the future, newer approaches such as proteomics may reveal better biomarkers of disease activity for PsA.

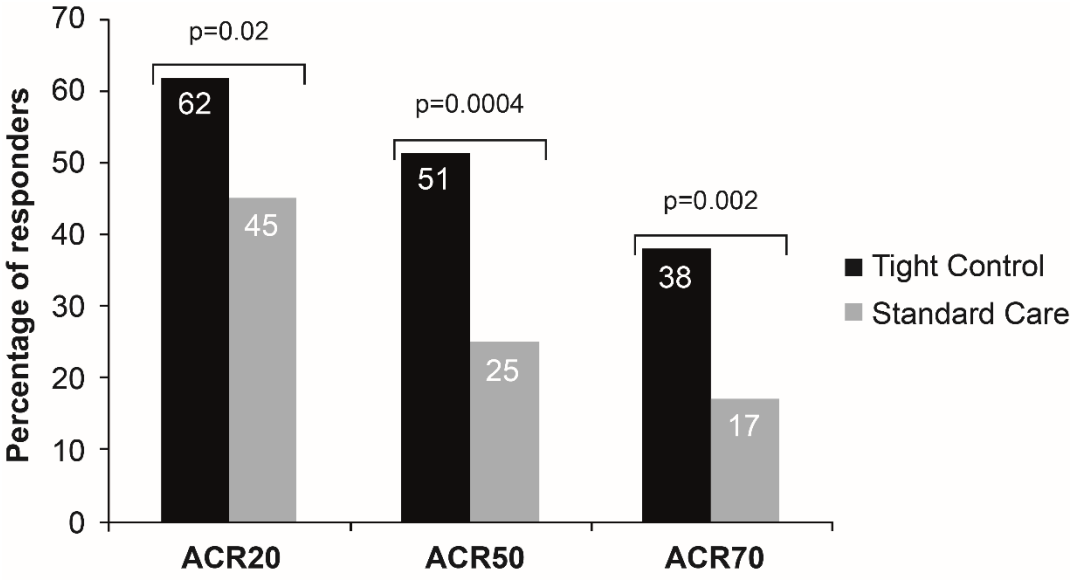
Conclusions

Advances in the treatment of PsA, particularly the introduction of biologic therapies, have allowed the disease to be controlled in many patients; however, measuring response to treatment in PsA patients is widely debated, partly caused by the heterogeneity of the disease. Changes have also occurred in treatment strategies for rheumatic diseases and the development of Treat to Target approaches have led to a change in the established treatment paradigm.

Both MRI and US techniques have the potential to improve PsA management, and imaging outcomes for remission in PsA are still evolving. The concept of immunological remission in PsA is only just beginning to be discussed and biomarkers for the disease are yet to be fully identified.

While remission is the ultimate goal for PsA patients and their physicians, questions on what exactly we should aim to achieve still remain; this review has examined the current status of targeting remission in PsA, with a focus on areas that need more research.

Figures



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408 *FIG 1: Proportion of patients achieving an ACR response at 48 weeks in TICOPA (tight control vs SOC) [34]*

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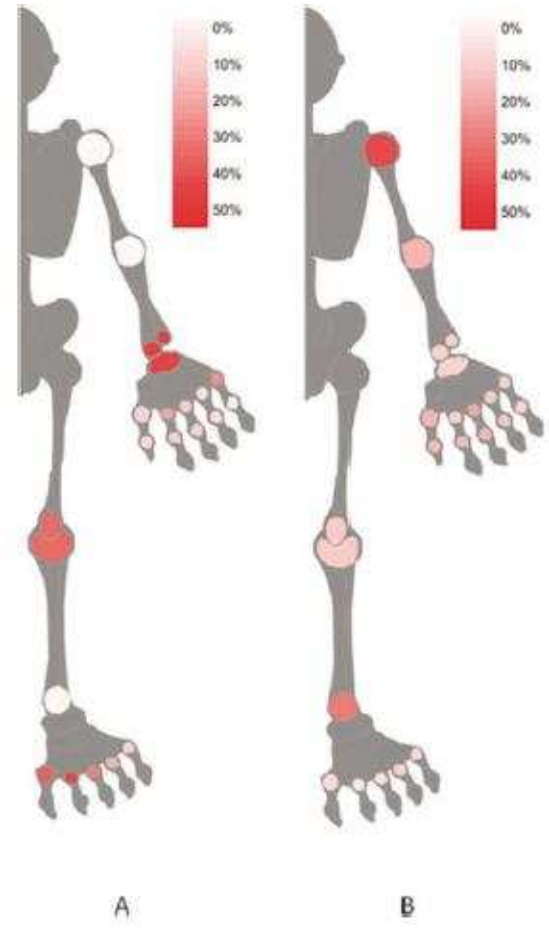

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411 *FIG 2: Subclinical synovitis in 49 patients with early PsA [53].*
412 *A: US positive, clinical exam negative; B: US negative, clinical exam positive.*

Instrument:	**MDA** [7, 29, 55]	**PASDAS** [31]	**CPDAI** [78, 79]	**DAPSA** [80, 81]	**RAPID 3** [82]	**PsAID*** [83]	**DAS28** [30]
Developed for PsA?	Yes	Yes	Yes	Yes	No - Generic	Yes	No - RA
Approx time for patient to perform	2-5 mins	2-5 mins	5-10 mins	1-2 mins	2-5 mins	2-5 mins	1-2 mins
Approx time for assessor to perform	5-10 min	5-10 min	5-10 min	5-10 min	1 min	1 min	3-5 min
Complex calculation required	No	Yes	No	No	No	No	Yes
Continuous measure of disease activity	No	Yes	Yes	Yes	Yes	Impact not activity*	Yes
Measures peripheral arthritis	Yes	Yes	Yes	Yes	No	Impact*	Yes
Measures enthesitis	Yes	Yes	Yes	No	No	Impact*	No
Measures skin disease	Yes	Within global only	Yes	No	No	Impact*	No
Sensitive to change in PsA	Yes	Yes	Yes	Yes	Yes	Yes	Polyarticular only
Additional comments		Requires SF-36 and CRP	Development not evidence based	Requires CRP Cutoffs based on physician opinion only, peripheral arthritis only	No physician exam	Impact measure rather than activity	Peripheral arthritis only and measures only 28 joints.

415 **TABLE 1. Comparison of features of clinical remission instruments**

*PsAID measures the impact of the disease on the patient rather than disease activity but identifies impact of the disease in many domains including MSK and skin.

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