The Journal of Rheumatology Volume 45, no. 1

Minimal Disease Activity as a Treatment Target in Psoriatic Arthritis: A Review of the Literature

Laure Gossec, Dennis McGonagle, Tatiana Korotaeva, Ennio Lubrano, Eugenio de Miguel, Mikkel Østergaard and Frank Behrens

J Rheumatol 2018;45;6-13
http://www.jrheum.org/content/45/1/6

Review

Minimal Disease Activity as a Treatment Target in Psoriatic Arthritis: A Review of the Literature

Laure Gossec, Dennis McGonagle, Tatiana Korotaeva, Ennio Lubrano, Eugenio de Miguel, Mikkel Østergaard, and Frank Behrens

ABSTRACT. As in other inflammatory rheumatic diseases, the objective of psoriatic arthritis (PsA) treatment is the achievement of a defined target. Recent recommendations propose aiming for remission or low disease activity; however, a consensual definition of remission is lacking. A state of minimal disease activity (MDA) has been established and is defined by low activity assessed by tender/swollen joint counts, tender entheseal points, Psoriasis Area and Severity Index or body surface area, patient pain and global activity visual analog scale, and functional evaluation by Health Assessment Questionnaire. Since its development, MDA has been used increasingly in studies and clinical trials. In this article, the potential use of MDA as a treatment target in PsA is reviewed. The frequencies of MDA achievement with biologic disease-modifying antirheumatic drugs are summarized based on data from registries, observational studies, and clinical trials. Predictors and the prognostic effect of attaining MDA are also evaluated. (First Release November 15 2017; J Rheumatol 2018;45:6–13; doi:10.3899/jrheum.170449)

Key Indexing Terms:
REMISSION DISEASE ACTIVITY BIOLOGIC THERAPY PSORIATIC ARTHRITIS

Historically, treatment options for psoriatic arthritis (PsA) were limited to nonsteroidal antiinflammatory drugs (NSAID) and conventional synthetic disease-modifying antirheumatic drugs (csDMARD) such as methotrexate (MTX), sulfasalazine, and leflunomide. These drugs, originally developed to treat rheumatoid arthritis (RA), have shown some benefit in treating inflammation and the heterogeneous symptoms of PsA[1]. However, over the past decade, the availability of targeted synthetic and biologic DMARD, including tumor necrosis factor (TNF) inhibitors, phosphodiesterase 4 inhibitors, interleukin (IL)-12/23 inhibitors, and IL-17A inhibitors, has revolutionized treatment, offering effective disease control for patients with NSAID and csDMARD toxicity and/or lack of efficacy[2,3]. Further, the availability of a greater range of treatment options has led to significant advances in treatment strategies for PsA. Specifically, a "treat-to-target" (T2T) approach to PsA management has been proposed, following its successful application in other rheumatic diseases, such as RA[2,4,5].

Treating to target necessitates defining a quantifiable target; in PsA, this target is recognized as remission both by the international T2T task force and by the recently updated European League Against Rheumatism treatment recommendations[2,6]. Although the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations do not specifically recommend a treatment target, they do agree that

From Sorbonne Universités, UPMC Univ Paris 06; Department of Rheumatology, AP-HP, Pitié Salpêtrière Hospital, Paris, France; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and UK National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK; V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia; Dipartimento di Medicina e Scienze della Salute, Università degli Studi del Molise, Campobasso, Italy; Hospital Universitario La Paz, Rheumatology Department, Madrid, Spain; Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup; Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; Rheumatology University Hospital Frankfurt and Project Group Translational Medicine and Pharmacology TMP, Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Goethe University Frankfurt am Main, Frankfurt, Germany.

This article was drafted following a roundtable discussion funded by Novartis and attended by the authors, for which they received honoraria from Novartis.

L. Gossec, Professor, MD, PhD, AP-HP, Pitié Salpêtrière Hospital; D. McGonagle, Professor, PhD, FRCPI, NIHR-Leeds Musculoskeletal Biomedical Research Unit, Leeds Institute of Rheumatic and Musculoskeletal Medicine; T. Korotaeva, Professor, MD, PhD, Department of Psoriatic Arthritis, V.A. Nasonova Research Institute of Rheumatology; E. Lubrano, Aggregate Professor, MD, Academic Rheumatology Unit, Department of Medicine and Health Sciences, University of Molise; E. de Miguel, Associate Professor, MD, PhD, Academic Rheumatology Unit, Hospital Universitario La Paz; M. Østergaard, Professor, MD, PhD, Copenhagen University Hospital, and Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases; F. Behrens, MD, Head Clinical Research Rheumatology and Fraunhofer Institute IME.

Address correspondence to Prof. L. Gossec, Hôpital Pitié-Salpétrière, Service de Rhumatologie, 47–83, Boulevard de l'Hôpital, 75013 Paris, France. E-mail: laure.gossec@aphp.fr

Full Release Article. For details see Reprints and Permissions at jrheum.org

Accepted for publication August 16, 2017.

the ultimate goal of therapy is to achieve the lowest possible level of disease activity in all domains of disease[3].

Clinical remission or inactive disease, defined as "the absence of clinical and laboratory evidence of significant inflammatory disease activity," is proposed as the major treatment target according to the T2T recommendations[6]. As remission by its most stringent definition may be difficult to attain in many patients, minimal or low disease activity has also been proposed as an alternative target for treatment[6].

Despite the evolution of treatment recommendations, universally accepted and validated definitions of low disease activity and remission are currently lacking. Further, there is no consensus on the best measure of disease activity in PsA. Studies often refer to the RA-derived American College of Rheumatology (ACR) response criteria and sometimes to the 28-joint Disease Activity Score[7]. Because PsA is a multifaceted disease that displays variability in both presentation and disease course, including not only synovitis but also extraarticular musculoskeletal inflammation (e.g., in the digits, entheses, and spine) and inflammation of the skin and nails, several PsA-specific composite measures of disease activity have been developed[8,9]. These include measures covering multiple domains of PsA (e.g., Composite Psoriatic Disease Activity Index[7], Psoriatic Arthritis Disease Activity Score[8], Psoriatic Arthritis Response Criteria[10], and the GRAPPA Composite Exercise Index[11]), and the Disease Activity index for PSoriatic Arthritis (DAPSA), a composite measure of articular disease[12]. These measures are continuous, with remission subsequently defined as a level below a set cutoff value.

Minimal disease activity (MDA) is a "state" of disease activity in PsA rather than a continuous measure. It is a simple, easy-to-use index that is widely used in clinical and observational studies[13], and has also been investigated as a treatment target in a randomized strategy trial[5,13]. The objective of our review was to summarize evidence gathered from clinical trials, observational studies, and registries regarding the achievement, and predictors thereof, of MDA in patients with PsA. The validity of MDA as a treatment target and the relevance of these data to the T2T strategy and to clinical practice are also discussed.

Our article was drafted following a Novartis-funded roundtable discussion attended by the authors and a patient representative in February 2016 to review the status of remission in PsA. The meeting included short presentations followed by moderated discussions. MDA featured prominently in these discussions, during which the authors identified a gap in the literature for a review article on this topic. Outcomes were analyzed thematically, with no formal method of gathering consensus.

The Concept of MDA

To our knowledge, MDA was first discussed for RA at the Outcome Measures in Rheumatology Clinical Trials (OMERACT) 6 conference in 2002, in response to challenges posed by targeting remission in its most stringent form. MDA was defined as "that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations[14]."

In PsA, MDA was developed based on the PsA core set of outcomes[13]. The operational definition of MDA in PsA was developed by a group of 60 experts, including both rheumatologists and dermatologists, who evaluated 40 patient profiles from an observational PsA database[13]. Statistical analysis allowed for cutoff points to be determined for several of the key core clinical components of PsA that were combined to form a single composite measure. In the resulting definition, a patient achieves MDA when 5 of the following 7 criteria are met: tender joint count ≤ 1; swollen joint count ≤ 1; Psoriasis Area and Severity Index ≤ 1 or body surface area ≤ 3%; patient pain visual analog score (VAS) ≤ 15; patient global disease activity VAS ≤ 20; Health Assessment Questionnaire (HAQ) Disability Index ≤ 0.5; tender entheseal points ≤ 1. Of note, MDA does not include acute-phase reactants and spondylitis activity.

Frequency of MDA in Randomized Controlled Trials

MDA has been assessed in several trials with biologic DMARD in PsA, including trials with TNF inhibitors, and more recently, the IL-17A inhibitor, secukinumab[15,16,17,18,19,20].

TNF inhibitor therapy. Across the randomized controlled trials with TNF inhibitors, the proportion of patients achieving MDA is variable (24–52%, Table 1)[15,16,17,18]. It is noteworthy that about 45–56% of patients in the randomized controlled studies with TNF inhibitors, including those receiving placebo, were receiving MTX and the vast majority of patients were naive to previous biologic therapy. Longterm data from these trials indicate that MDA response rates were sustained in patients who continued the therapy (Table 2)[15,18,21,22,23].

Secukinumab. To date, the fully human anti–IL-17A monoclonal antibody, secukinumab, is the only other approved biologic therapy with available data on MDA response rates[19]. In the FUTURE 2 study, treatment with secukinumab 150 mg and 300 mg resulted in 32% and 34% of anti–TNF-naive patients, respectively, achieving MDA at Week 16 versus 14% of patients with placebo (Table 3)[19]. In the roughly 35% of patients with a previous inadequate response or intolerance to anti-TNF therapy, 8% and 16% achieved MDA with 150 mg and 300 mg, respectively, versus 3% with placebo[19]. In the overall group, treatment with secukinumab 150 mg and 300 mg resulted in 23% and 28% of patients, respectively, achieving MDA at Week 16 versus 10% of patients with placebo. These response rates were all sustained through Week 52[19].

Higher MDA response rates were also observed in patients ≤ 2 years since diagnosis versus those > 2 years since

Table 1. Short-term achievement of MDA in patients with PsA treated with anti–TNF-α therapies.

Biologic Agent	Trial	Week	Anti-TNF Status of Patient Population	n	Dose	Patients with MDA, %	Reference
Randomized Controlled Trials							
IFX	IMPACT	16	Anti–TNF-naive	31	5 mg/kg	48*	Coates LC, *et al*, 2010[15]
				32	PBO	3	
	IMPACT 2	24	Anti–TNF-naive	77	5 mg/kg	52†	
				80	PBO	21	
CZP	RAPID-PsA	24	Anti–TNF-naive and -experienced	138	200 mg	33†	Mease PJ, *et al*, 2014[17]
				135	400 mg	34†	
				136	PBO	6	
GOL	GO-REVEAL	14	Anti–TNF-naive	285	50 mg/100 mg	24*	Kavanaugh A, *et al*, 2016[18]
				104	PBO	1	
ADA	ADEPT	24	Anti–TNF-naive	62	40 mg	39†	Mease PJ, *et al*, 2013[16]
				60	PBO	7	
Open-label Trial							
IFX	RESPOND	16	Anti–TNF-naive	57	5 mg/kg + MTX	59#	Baranauskaite A, *et al*, 2012[20]
				58	MTX 15 mg	24	

*p < 0.0001 vs PBO; †p < 0.001 vs PBO; #p < 0.05 vs MTX. TNF: tumor necrosis factor; PsA: psoriatic arthritis; ADA: adalimumab; CZP: certolizumab pegol; GOL: golimumab; IFX: infliximab; MDA: minimal disease activity; MTX: methotrexate; PBO: placebo.

Table 2. Longterm achievement of MDA in patients with PsA treated with anti–TNF-α therapies.

Biologic Agent	Trial	Week	Data Analysis	n	Dose	Patients with MDA, %[a]	Reference
Open-label Trials							
IFX	IMPACT	50	Observed	63	5 mg/kg IV	42	Coates LC, *et al*, 2010[15]
		98	Observed	37	5 mg/kg IV	30	
	IMPACT 2	54	Observed	157	5 mg/kg IV	40	
CZP	RAPID-PsA	48	NRI	138	200 mg	40	Mease PJ, *et al*, 2015[21]
				135	400 mg	38	
		96	NRI	138	200 mg	40	
				135	400 mg	42	
		216	NRI	138	200 mg	38	Mease PJ, *et al*, 2016[22]
				135	400 mg	41	
		216	Observed	98	200 mg	53	
				87	400 mg	63	
GOL	GO-REVEAL	52	Observed	96	PBO-GOL 50 mg/100 mg	30	Kavanaugh A, *et al*, 2016[18]
				262	GOL 50 mg/100 mg	42	
		104	Observed	87	PBO-GOL 50 mg/100 mg	37	
				250	GOL 50 mg/100 mg	43	
		256	Observed	77	PBO-GOL 50 mg/100 mg	44	
				205	GOL 50 mg/100 mg	52	
ADA	ADEPT	48	Not reported	116	40 mg	41	Mease PJ, *et al*, 2015[23]
		96	Not reported	104	40 mg	39	
		144	Not reported	88	40 mg	43	
Observational Studies							
Anti–TNF-α therapy	—	68	Multiple imputed	226	Not reported	64[b]	Haddad A, *et al*, 2015[26]
Anti–TNF-α therapy (ADA, ETN, or GOL)	—	52	Observed	75	ADA 40 mg, ETN 25/50 mg, GOL 50 mg	61	Perrotta F, *et al*, 2016[27]
IFX or GOL	BioTRAC	52	Observed	196	Not reported	45	Zummer M, *et al*, 2015[28]
Standard care, including DMARD and biologic agents	—	52	Observed	344	Not reported	60[b]	Coates LC, *et al*, 2010[15]
ETN, ADA, IFX, or TCZ	—	260	Observed	197	Not reported	40	Theander E, *et al*, 2014[29]

[a]Percentage of patients with MDA at stipulated timepoints are shown unless stated otherwise; [b]MDA achieved on at least 1 visit through stipulated timepoint. ADA: adalimumab; CZP: certolizumab pegol; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; GOL: golimumab; IFX: infliximab; IV: intravenously; MDA: minimal disease activity; NRI: nonresponder imputation; PBO: placebo; PsA: psoriatic arthritis; TNF: tumor necrosis factor; TCZ: tocilizumab.

Table 3. Short-term and longterm achievement of MDA in patients with PsA treated with secukinumab in the randomized controlled trial, FUTURE 2.*

Biologic Agent	Week	Anti-TNF Status of Patient Population	n	Dose	Patients with MDA, %	Reference
Secukinumab	16	Anti–TNF-naive	65	300 mg	34	Coates LC, *et al*, 2016[19]
			63	150 mg	32	
			58	PBO	14	
		Anti–TNF-IR	32	300 mg	16	
			37	150 mg	8	
			30	PBO	3	
		Overall	97	300 mg	28	
			100	150 mg	23	
			88	PBO	10	
	52	Anti–TNF-naive	63	300 mg	41	
			59	150 mg	39	
		Anti–TNF-IR	30	300 mg	23	
			29	150 mg	21	
		Overall	93	300 mg	35	
			88	150 mg	33	

* In the FUTURE 2 study, 397 patients with active PsA were randomized to subcutaneous secukinumab (300 mg, 150 mg, or 75 mg) or placebo at baseline, weeks 1, 2, and 3, and every 4 weeks from Week 4. Placebo patients were rerandomized to secukinumab 300 mg or 150 mg every 4 weeks from weeks 16 or 24, depending upon clinical response. The overall population includes both patients who are anti–TNF-naive and those who have previously used up to 3 anti-TNF agents but have had an inadequate response or stopped treatment because of safety or tolerability reasons. Data presented are as observed. Data from the 75 mg are not reported because that is not an approved dose of secukinumab. IR: inadequate responders; MDA: minimal disease activity; PBO: placebo; PsA: psoriatic arthritis; TNF: tumor necrosis factor.

diagnosis[19]. MDA response rates were in fact highest among anti–TNF-naive patients with disease duration ≤ 2 years who were treated with secukinumab 300 mg (50% at Week 16). Because skin involvement is one of the aspects that often prevents patients achieving MDA[24], the high proportion of patients achieving MDA with secukinumab treatment may be a result of its superior efficacy in psoriasis[25].

Frequency of MDA in Observational Studies

A number of real-world clinical studies have assessed MDA in patients with PsA (Table 2)[26,27,28,29,30]. In these observational and open-label cohorts, the proportion of patients treated with TNF inhibitors meeting MDA criteria at least once in 12 months ranged from 44% to 64%. With standard care, 60% of patients were found to achieve MDA on at least 1 visit, and 34% achieved MDA on consecutive visits for at least 12 months[30]. In an early PsA observational cohort, the Swedish Early PsA Register, 40% of patients achieved MDA at the 5-year followup, following treatment with predominantly DMARD or biologic therapies (etanercept, adalimumab, infliximab, or tocilizumab)[29].

Predictors of Achieving MDA

If MDA is to be adopted in a real-world setting, it is imperative to understand which patient populations will be most likely to achieve MDA. To this end, predictors have been evaluated from both interventional and observational data from patients treated with biologic therapies.

In registries and observational studies, demographic characteristics such as younger age and male sex, lower functional impairment at baseline (assessed by the Bath Ankylosing Spondylitis Functional Index and HAQ), low disease activity at baseline, and other factors such as shorter symptom duration and greater general well-being (assessed by global VAS) have been reported as predictors of achieving MDA upon treatment with TNF inhibitors[24,26,31,32].

Predictors of achieving sustained MDA include lower functional impairment, lower disease severity, lower enthesitis count, and absence of dactylitis at baseline[28,30,33]. The relationship between a low HAQ score at baseline and an increased likelihood of achieving MDA has been substantiated in a clinical trial setting with both golimumab (GOL)[17] and adalimumab[34], with evidence from the Adalimumab Effectiveness in Psoriatic Arthritis trial (ADEPT) also supporting the correlation between low baseline enthesitis and achievement of MDA. It remains unclear whether inflammatory burden, as measured by erythrocyte sedimentation rate and C-reactive protein (CRP), is a predictor of achieving MDA[27,30,32].

A range of common comorbidities in PsA have also been identified as negative predictive factors for achieving MDA, including metabolic syndrome, increased weight, hepatic steatosis, carotid plaques, and coexistence of fibromyalgia[35,36,37,38]. There is also some evidence that successful weight loss may improve the attainment of MDA with anti-TNF therapies[39].

Prognostic Relevance and Patient-relevant Effect of MDA

Emerging evidence suggests that achieving MDA may be of prognostic relevance. Sustained achievement of MDA has

been shown to be associated with improved prognosis in terms of joint damage progression in both observational studies and registries[15,31]. Further, in a randomized controlled study with GOL, the 36% of patients who had MDA for ≥ 3 consecutive visits had significantly less radiographic progression compared with patients who did not reach MDA at 5 years[18]. Patients also experienced greater longterm functional improvements and improved patient global assessment of disease activity when they attained persistent MDA[5]. While low skin symptoms have been observed in patients with MDA in some trials[5], achievement of MDA does not necessarily correlate with more improvements in skin symptoms[15] because MDA is a multidomain outcome score.

The triad of persistent joint swelling, raised CRP, and baseline radiographic damage are all key for determining the longterm prognosis of patients with PsA[31,40]. Further research is required to assess the effect of MDA attainment, or lack thereof, on longterm prognosis of PsA.

MDA as a Treatment Target: The Tight Control in Psoriatic Arthritis Trial

To our knowledge, the first treatment strategy trial in spondyloarthritis was Tight Control in Psoriatic Arthritis (TICOPA), which had MDA as the treatment target[5]. In this trial, 206 patients with PsA were enrolled and randomly assigned to receive tight control or standard care. For the tight control strategy, patients were assessed at monthly intervals and had their treatment adjusted according to a strict treatment protocol based on whether they achieved MDA. Patients in the standard care arm were followed at 3-month intervals and managed according to the treating rheumatologist[5].

At 12 weeks, 24% of patients in the tight control arm of the study had achieved MDA. Following escalation of treatment in 71% of the patients in this arm, the proportion of patients reaching MDA at least once through Week 48 increased to 72%[5]. In patients who were treated with MTX only, 22% achieved MDA at 12 weeks and continued with MTX monotherapy throughout the study[41].

Serious adverse events were more frequent in the tight control group than the standard care group, and no differences were observed between the 2 treatment arms in radiographic progression, perhaps as a result of the overall low rate of progression in the relatively short duration of the study (48 weeks)[5]. Overall, the TICOPA trial provides evidence of the benefits of a T2T approach using MDA as a target in patients with early PsA. The T2T strategy significantly improved not only the primary clinical outcome, which is the ACR20 response criteria, but also more stringent clinical outcomes[5]. However, although the TICOPA study indicates that steering therapy toward MDA improves patient outcomes, this may also be achieved with other T2T measures that have not yet been tested, including objective measures of inflammation and/or other composite indices, some of which are mentioned below.

Incorporating MDA into Clinical Practice and Its Limitations

Several concerns remain regarding the validity of MDA as well as its incorporation into clinical practice. Further, although outside the scope of our review, the debate surrounding the most appropriate measure of disease activity in PsA is ongoing. Further studies to establish the relative merits of MDA versus other disease measures, particularly DAPSA-defined remission, are required (Table 4).

Content validity. There are 3 potential issues with content validity for MDA. First, overlap between MDA and patient-reported outcomes needs to be addressed[42]. Second, the lack of acute-phase reactants as objective measures of inflammation could be considered a hindrance to the face validity of MDA. Finally, MDA includes a low level of HAQ, which may be difficult to achieve in an established disease irrespective of disease activity levels.

Relationship with imaging remission. Conflicting evidence has been shown regarding the relationship between ultrasound (US) remission and MDA[43,44]. Although a recent study suggested that MDA was predictive of US remission[44], another study has shown the presence of US-verified active inflammation at PsA-specific sites in patients with MDA[42]. There is evidence that alternative measures of disease activity such as DAPSA may correlate better with US remission than MDA[43]. Magnetic resonance imaging (MRI) offers an alternative imaging tool for measuring disease activity in PsA, and unlike US, it can measure all disease manifestations, including osteitis[45]; however, the relationship between MRI and MDA has yet to be investigated.

Feasibility in clinical practice. Although our review has indicated reasonable percentages of patients achieving MDA in published studies, there is still the question of how low the target should be regarding inflammation. A variant of MDA (very low disease activity) has recently been proposed but remains to be validated[9]. Remission, and indeed MDA, may be an unattainable treatment goal in patients with particularly

Table 4. MDA research agenda.

• What is the optimal measure of disease activity in PsA?
• Do MDA components all reflect the inflammatory process? Are they all needed or are there issues of overlap?
• Does MDA correlate with inflammation (biomarker and imaging)?
• What are the longterm effects of achieving MDA on structural progression?
• Does MDA adequately capture the patient perspective on treatment targets?
• What is the optimal treatment strategy for obtaining and maintaining MDA?
• Are there any additional biomarkers for achieving MDA?
• Does achieving MDA correlate with improved health-related quality of life?
• Is MDA an appropriate measure of disease in patients with axial PsA?

MDA: minimal disease activity; PsA: psoriatic arthritis.

aggressive or established PsA, and the question of how to treat such patients also remains to be answered. Low disease activity may be a more attainable goal under these circumstances.

On top of these theoretical limitations, it also remains to be seen how practical MDA will be for everyday treating rheumatologists in clinical practice. Consultation times are often limited, so the relative simplicity or complexity of the MDA criteria versus other scores needs to be considered. MDA is certainly simpler than some other measures in PsA; however, it does necessitate a formalized assessment of enthesitis and skin involvement, as well as the HAQ Disability Index score in all patients. This full clinical assessment and the inclusion of HAQ may be limited in some clinics where such assessments are not routinely performed.

MDA and the patient's perspective. The importance of shared decision making between the patient and the rheumatologist is well established[2]; although MDA may be deemed an appropriate target by the treating physician, this may not necessarily be the preference of a particular patient[5]. Recent data do indicate a link between MDA and patient-reported outcomes[46,47], but further research is warranted. Patients may also have difficulty understanding MDA; initiatives to educate patients on the T2T strategy and simple definitions of measures and targets may therefore be beneficial to ensure its use in clinical practice.

Treatments strategies and MDA. The optimal treatment strategy for obtaining and maintaining MDA, in terms of treatment sequencing, combination, and tapering, is currently unclear. Additional strategy trials are required to investigate this topic. As alluded to previously, further longterm data assessing the relevance of MDA are also required. The prognostic relevance of MDA through 5 years has been assessed with GOL in a clinical trial setting[18], but more data are required with greater numbers of patients treated with additional agents and in a real-world setting. Exactly what MDA and other composite outcomes are measuring, and to what degree reversible inflammatory disease is being evaluated, remains to be determined.

Limitations

The outcomes presented in our discussion are subject to some limitations. The key themes are based on the opinions of individuals with an interest in MDA, and gaps in the evidence may exist. A detailed review of other composite measures of disease is outside the scope of this article. Of the composite indices mentioned, DAPSA is covered in slightly more detail because of its inclusion as a target in the 2017 T2T recommendations[6].

Status of MDA

Evidence from clinical trials and registries suggests that MDA may be an attainable treatment outcome in PsA. Data from the TICOPA trial provide proof of the concept that tight control of disease activity in PsA results in better outcomes than standard care[5]. Nevertheless, several open issues remain, including the longterm significance of achieving and maintaining MDA and whether MDA is the optimal treatment target in PsA. The treatment paradigm for PsA is likely to evolve further over the coming years and the key goal will be to identify the optimal treatment strategy to ensure the best outcomes for patients.

ACKNOWLEDGMENT

This article was drafted based on a gap in the literature identified by the authors during a roundtable discussion funded by Novartis to review the status of remission in PsA. We thank David Trigos, a patient representative, for providing his input during the initial discussion. Medical writing support was provided by Antonia Bowman, Ben Drever, and Saira Zaman, medical writers from Seren Communications, an Ashfield Company, part of UDG Healthcare PLC. Novartis provided funding for the writing.

REFERENCES

1. Ramiro L, Smolen JS, Landewé R, van der Heijde D, Dougados M, Emeryet P, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis 2016;75:490-8.
2. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75:499-510.
3. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Acosta-Felquer LM, Armstrong AW, et al. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol 2016;68:1060-71.
4. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3-15.
5. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet 2015;386:2489-98.
6. Smolen J, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman D, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update to recommendations by an international task force. Ann Rheum Dis 2017 Jul 6 (E-pub ahead of print).
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. Ogdie A, de Wit M, Callis Duffin K, Campbell W, Chau J, Coates LC, et al. Defining outcome measures for psoriatic arthritis: a report from the GRAPPA-OMERACT Working Group. J Rheumatol 2017;44:697-700.
9. Coates LC, Helliwell PS. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. J Rheumatol 2016;43:371-5.
10. Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis: a department of Veterans Affairs cooperative study. Arthritis Rheum 1996;39:2013-20.
11. 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.
12. 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.
13. 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.
14. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 2005;32:2016-24.
15. Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res 2010;62:965-9.
16. 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.
17. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis 2014;73:48-55.
18. Kavanaugh A, van der Heijde D, Beutler A, Gladman D, Mease PJ, Krueger GG, et al. Radiographic progression of patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy: results through 5 tears of a randomized, placebo-controlled study. Arthritis Care Res 2016;68:267-74.
19. Coates LC, Mease PJ, Kirkham B, McLeod LD, Mpofu S, Karyekar C. et al. Secukinumab improves minimal disease activity response rates in patients with active psoriatic arthritis: data from the randomized phase 3 study, FUTURE 2 [abstract]. Ann Rheum Dis 2016;75 Suppl 2:605.
20. Baranauskaite A, Raffayová H, Kungurov NV, Kubanova A, Venalis A, Helmle L, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. Ann Rheum Dis 2012;71:541-8.
21. Mease PJ, Deodhar A, Fleischmann R, Wollenhaupt J, Gladman D, Leszczyński P, et al. Effect of certolizumab pegol over 96 weeks in patients with psoriatic arthritis with and without prior antitumour necrosis factor exposure. RMD Open 2015;1:e000119.
22. Mease PJ, Fleischmann R, Wollenhaupt J, Deodhar A, Gladman D, Hoepken B, et al. Certolizumab pegol for the treatment of psoriatic arthritis: 4-year outcomes from the RAPID-PsA trial [abstract]. Ann Rheum Dis 2016;75 Suppl 2:608-9.
23. Mease PJ, Kavanaugh A, Coates LC, McInnes I, Hojnik M, Zhang Y, et al. The prediction of long-term minimal disease activity and its benefits in patients with psoriatic arthritis [abstract]. Arthritis Rheumatol 2015;67 Suppl 10:651.
24. Marin J, Acosta Felquer ML, Ferreyra Garrot L, Ruta S, Rosa J, Soriano ER. Patients with psoriatic arthritis fulfilling the minimal disease activity criteria do not have swollen and tender joints, but have active skin. J Rheumatol 2016;43:907-10.
25. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med 2014;371:326-38.
26. 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.
27. Perrotta FM, Marchesoni A, Lubrano E. Minimal disease activity and remission in psoriatic arthritis patients treated with anti-TNF-α drugs. J Rheumatol 2016;43:350-5.
28. Zummer M, Rahman P, Arendse R, Starr M, Kelsall J, Avina-Zubieta JA, et al. Predictors of early minimal disease activity in PsA patients treated with anti-TNF in a real-world registry [abstract]. Arthritis Rheumatol 2015;67 Suppl 10:2870.
29. Theander E, Husmark T, Alenius GM, Larsson PT, Teleman A, Geijer M, et al. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). Ann Rheum Dis 2014;73:407-13.
30. Coates LC, Cook R, Lee KA, Chandran V, Gladman DD. Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. Arthritis Care Res 2010;62:970-6.
31. Geijer M, Lindqvist U, Husmark T, Alenius GM, Larsson PT, Teleman A, et al. The Swedish early psoriatic arthritis registry 5-year followup: substantial radiographic progression mainly in men with high disease activity and development of dactylitis. J Rheumatol 2015;42:2110-7.
32. Iervolino S, Di Minno MN, Peluso R, Lofrano M, Russolillo A, Di Minno G, et al. Predictors of early minimal disease activity in patients with psoriatic arthritis treated with tumor necrosis factor-α blockers. J Rheumatol 2012;39:568-73.
33. Mease PJ, Karki C, Etzel CJ, Kavanaugh A, Ritchlin CT, Malley W, et al. Clinical characteristics and disease activity in psoriatic arthritis patients with dactylitis or enthesitis: results from Corrona registry [abstract]. Arthritis Rheumatol 2015;67 Suppl 10:678.
34. Mease PJ, Kavanaugh A, Coates LC, McInnes I, Hojnik M, Zhang Y, et al. The prediction and benefits of minimal disease activity in patients with psoriatic arthritis in the ADEPT trial [abstract]. Ann Rheum Dis 2015;74 Suppl 2:355.
35. Brikman S, Furer V, Wollman J, Borok S, Matz H, Polachek A, et al. The effect of the presence of fibromyalgia on common clinical disease activity indices in patients with psoriatic arthritis: a cross-sectional study. J Rheumatol 2016;43:1749-54.
36. 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.
37. 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.
38. Di Minno MN, Peluso R, Iervolino S, Lupoli R, Russolillo A, Tarantino G, et al. Hepatic steatosis, carotid plaques and achieving MDA in psoriatic arthritis patients starting TNF-α blockers treatment: a prospective study. Arthritis Res Ther 2012;14:R211.
39. Di Minno MN, Peluso R, Iervolino S, Russolillo A, Lupoli R, Scarpa R. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor α blockers. Ann Rheum Dis 2014; 73:1157-62.
40. Gladman DD, Mease PJ, Choy EH, Ritchlin CT, Perdok RJ, Sasso EH. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. Arthritis Res Ther 2010;12:R113.
41. Coates LC, Helliwell PS. Methotrexate efficacy in the tight control in psoriatic arthritis study. J Rheumatol 2016;43:356-61.
42. Lubrano E, Perrotta FM, Parsons WJ, Marchesoni A. Patient's global assessment as an outcome measure for psoriatic arthritis in clinical practice: a surrogate for measuring low disease activity? J Rheumatol 2015;42:2332-8.
43. Husic R, Gretler J, Felber A, Graninger WB, Duftner C, Hermann J, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. Ann Rheum Dis 2014;73:1529-36.
44. Michelsen B, Diamantopoulos AP, Hammer HB, Soldal DM, Kavanaugh A, Haugeberg G. Ultrasonographic evaluation in

psoriatic arthritis is of major importance in evaluating disease activity. Ann Rheum Dis 2016;75:2108-13.
45. Tan AL, McGonagle D. The need for biological outcomes for biological drugs in psoriatic arthritis. J Rheumatol 2016;43:3-6.
46. Queiro R, Cañete JD, Montilla C, Abad M, Montoro M, Gomez S, et al. Minimal disease activity and impact of disease in psoriatic arthritis: a Spanish cross-sectional multicenter study. Arthritis Res Ther 2017;19:72.
47. Coates LC, Mease PJ, Gossec L, Kirkham B, Rasouliyan L, Mpofu S, et al. Patients with active psoriatic arthritis achieving minimal disease activity with secukinumab treatment demonstrate sustained improvement of function and quality of life [abstract]. Arthritis Rheumatol 2016;68 Suppl 10:1741.