

Clinical remission in rheumatoid arthritis and psoriatic arthritis

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ABSTRACT

It is currently recognised that remission can be an achievable target for several rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients by a treat-to-target approach. For RA different remission criteria have been proposed, depending on the disease activity scores used, on the importance given to the inclusion of patients' perspective into the definition of remission, and on their applicability in clinical practice, that generate highly different remission rates. Conversely, for PsA, remission is still insufficiently defined and represents a partially unmet need. For both conditions, several first- and second-line treatment strategies are now available – disease-modifying anti-rheumatic drugs (DMARDs) of synthetic and biologic origin – that make the achievement of remission or at least low/minimal disease activity a realistic goal. This paper is a narrative review of the different criteria of remission, in the light of the available treatment strategies for RA and PsA, and in the attempt to provide rheumatologists an opportunity to improve the outcome to the greatest extent possible in their clinical practice.

Introduction

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases, characterised by symmetrical, often erosive, inflammatory polyarthritis of the small and medium-sized joints, which can lead to decreased function and disability. Though primarily involving joints, RA should be considered a systemic disease that includes extra-articular manifestations, organ and vessel involvement and comorbidities. The natural history of RA used to be progressive, however, in the last decades, disease-modifying anti-rheumatic drugs (DMARDs), together with new treatment strategies, such as the treat-to-target (T2T) approach and the tight control

of disease activity (1-3), have shown to be able to reduce radiographic and disease progression and improve prognosis. Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis. The peripheral joint involvement of PsA is also progressive in the majority of patients, and patients also have functional impairment, worse quality of life (QoL), and significantly increased early mortality in comparison to the general population (4-7). The management of PsA consists of non-pharmacological and pharmacological measures, where DMARDs are cornerstones, being effective in reducing or reversing signs and symptoms, disability, impairment of QoL, work inability and joint damage progression (8, 9). In recent years, a T2T approach has been developed as a new treatment paradigm also for PsA and other spondyloarthritis (10). The primary goal of the T2T strategy in both RA and PsA is the achievement of a state of clinical remission of the disease, low-disease activity (LDA) being a possibly acceptable alternative therapeutic goal. However, different remission criteria have been published according to each disease activity score used, and the last several years have seen a re-evaluation and formal redefinition of the state of remission carried out by the American College of Rheumatology/European League Against Rheumatism for RA (ACR/EULAR) (11), whereas for PsA, remission is still insufficiently defined (10, 12, 13). Moreover, further critical issues have been identified about clinical remission of inflammatory arthritis, i.e. the need to include patients' perspective into definition of remission and to validate remission criteria for use in clinical practice (14-16).

This paper is a narrative review on the different criteria to define clinical remission in RA and PsA, also in the light of their feasibility in the rheumatological clinical practice and their possible

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achievement with the different available treatment options. This approach, by evaluating only the clinical aspects of remission in these two conditions, was chosen for a better management of these two diseases in real clinical settings. However, the absence of an assessment on the role of imaging and biomarkers for this review could be, to a certain extent, a limitation of the study.

Clinical remission in RA

Definitions

The advent of biologic agents (b-DMARDs), and especially their use in combination with conventional synthetic DMARDs (csDMARDs) like methotrexate (MTX) has allowed to think about new, more ambitious outcomes in RA (17-20). Consistently with all these progresses, the cornerstone of the 2010 T2T recommendations was the definition of an achievable treatment target, ie remission or at least low-disease activity (LDA) (1). However, heterogeneous definitions of remission were developed over time (21-26).

• The ACR/EULAR definitions of remission in RA

In the absence of a widely used definition of remission that was both stringent and achievable, the ACR and European League Against Rheumatism (EULAR) together with the Outcome Measures in Rheumatology Initiative (OMER-ACT) jointly constituted a committee to redefine remission in RA. In 2011 they proposed new definitions of remission suitable for use in clinical trials (11). Whereas EMA had regarded a DAS28 < 2.6 as remission, the ACR and EULAR introduced a new definition of remission based on SDAI (≤ 3.3) and Boolean criteria: any definition should include at least tender and swollen joint counts together with an acute phase reactant, while excluding therapy, duration of remission, and measures of physical function and damage. Patient reported outcomes (PROs), as patient global assessment (PtG) or patient pain, were also included; in fact, it was demonstrated that these measures add important information, since they are capable to discriminate between treatments after controlling for physician-reported and

laboratory measures. Finally, Boolean based definitions were proposed, requiring tender joint count (TJC) and swollen joint count (SJC) ≤ 1 , levels of C-reactive protein (CRP) ≤ 1 mg/dL and a PtG ≤ 1 (11). These changes were mainly due to the observation that with the DAS28 cut-off accepted as remission criterion actually a significant disease activity could still be present. Furthermore, as Smolen pointed out (27) the formula used to calculate DAS28 gives too much weight to acute phase reactants, “possibly giving an unfair advantage to IL6-inhibiting agents”. For example, it was shown that patients treated with tocilizumab had reached a DAS28 < 2.6 without meeting ACR70, and sometimes not even ACR50 response criteria (28, 29). On the other hand, JAK-inhibitors were shown to result in dramatic differences between remission rates assessed by DAS28-ESR and DAS28-CRP, as discussed below in this paper (30, 31).

Subsequent analyses of trials suggested that roughly 9–12% of patients in the trials the committee had studied would have achieved remission based on the 2011 ACR/EULAR definitions and that those rates were similar for the SDAI and for Boolean definitions. The committee concluded that the proposed definitions of remission in RA were stringent but achievable and should be a major outcome for trials.

• Validation of RA remission definition in clinical practice

The ACR/EULAR committee stated that variants of their definitions of remission may be utilised in every day settings, provided additional research validating these outcomes in practice settings would be performed (32). A first validation attempt was to analyse the effectiveness of these criteria based on clinical trials in observational studies performed in the clinical practice (15). The authors examined remission in the US Veterans Affairs RA (VARA) registry including 1,341 patients (91% men) undergone 9,700 visits and a community rheumatology practice (ARCK) of 1,168 patients (28% men) undergone 6,362 visits. Not surprisingly, remission probability was different according to the definition of remission adopt-

ed. However, differences were rather small and in line with the probabilities emerged from the clinical trials considered in the ACR/EULAR remission paper (11). The authors underlined that the major differences between their results and those of ACR/EULAR consisted in the tenuous and sporadic nature of remission: only 3% of patients had a remission that lasted at least 2 years.

Subsequently the ESPOIR cohort from a French observational study was used to validate the performance of the provisional ACR/EULAR RA remission criteria for use in practice and test their predictive validity (33). The method was to match each person in remission with a person not in remission and to compare x-ray stability and health assessment questionnaires (HAQ) between the two groups. The authors concluded that the ACR/EULAR definitions of remission were also appropriate and valid for observational studies in RA and for the clinical practice. In addition, those definitions showed high predictive validity for good outcomes in clinical practice. Finally, the ESPOIR cohort analysis validated the practice-based definitions suggested by the ACR/EULAR committee, that were focused on definitions not including acute phase reactants, since these were considered difficult to obtain during a clinic visit.

The NOR-DMARD study examined, in clinical practice, the frequency of 6 definitions for remission and 4 definitions for low disease activity (LDA) after starting a DMARD in patients with RA and analysed factors predictive of achieving remission within 6 months (34). Remission and LDA were calculated by the Disease Activity Score-28 joints (DAS28), the CDAI, the SDAI, the Routine Assessment of Patient Index Data (RAPID3), and both the ACR/EULAR Boolean remission definitions, 3 and 6 months following DMARD prescriptions (approximately 5,000) in patients included in the Norwegian register NOR-DMARD. The results showed that, in daily clinical practice, the definitions based on DAS28 and RAPID3 identified remission about twice as often as the ACR/EULAR Boolean, SDAI, and CDAI. Factors predicting remission were similar across the dif-

ferent definitions, and included lower age, male sex, short disease duration, high level of education, current non-smoking, non-erosive disease, treatment with a biological DMARD, being DMARD-naïve, good physical function, little fatigue, and LDA.

• Patient-perceived remission

Treatment should be aimed at achieving outcomes that are relevant to patients, therefore it is important to understand the patients' perception of remission, verifying whether the current definition of remission adequately reflects such perception. The ACR/EULAR definition of remission included only the 3 patient-reported outcomes (PROs) incorporated in the initial RA core outcome measurement set: PtG, pain, and physical function (35, 36). A first OMERACT workshop (OMERACT 10) on remission from the patient's perspective revealed great interest in a concept of remission shared by patients, physicians, and researchers, that takes into account measures that patients consider important (37). Nine focus-group discussions in Austria, The Netherlands and UK, including patients in ACR/EULAR remission, self-declared remission and moderate-to-high disease activity, were aimed at collecting patients' experience with remission (16). From these discussions, 26 aspects of remission were identified and grouped into 3 major themes of patient-perceived remission: absence or reduction of symptoms, decreased daily impact of their condition, and feeling of a return to normality. A subsequent OMERACT workshop (OMERACT 12) on patient perspective on remission in RA was initiated in the attempt to reduce the number of domains from 26 to a manageable number (38). The results of a qualitative research conducted by Van Tuyl *et al.* (16, 39) to determine the importance of specific symptoms, aspects of disease impact and normality in defining remission in RA from the patient's perspective revealed that patients expressed remission as lack of pain and fatigue and recovered independence.

• Sustained remission

Sustained remission is clinically more relevant than point remission in RA

but it remains so far a poorly reported outcome. Shidara *et al.* (40) evaluated long-term functional outcomes in RA, calculating the number of times that the ACR/EULAR or the DAS28 remission criteria were fulfilled, in a Japanese cohort of patients with RA in clinical practice. The results indicated that to continually fulfil any of the remission criteria is hard but more predictive of better functional outcome. Though not conclusive due to the analytical methods of the study, the results suggested that fulfilling the ACR/EULAR remission criteria appears to be preferable compared with the DAS28 remission criteria for avoiding future progression, particularly among patients with a shorter disease duration. Indeed, the study showed that more frequent achievement of ACR/EULAR remission as a treatment target was more likely to prevent progression of functional disability for 2.5 years. Results from the Canadian Early Arthritis Cohort (CATCH) (41) showed that female sex, greater pain, and lack of early DMARD therapy were poor predictors of sustained remission, while a rapid onset of remission appeared as a good predictor of long-term remission. Hamann *et al.* (42) undertook a systematic review of the literature to identify factors predicting sustained remission. Six studies were identified, not including the CATCH (43-48). The only favourable predictor of sustained remission was the concomitant use of MTX, while baseline high disease activity, tender joint count, age, disease duration, functional disability and female gender appeared as poor predictors.

• Drug-free remission

DMARD-free sustained remission is defined as the absence of synovitis after cessation of DMARD therapy, and is therefore different from remission outcomes that are assessed to measure treatment efficacy (49). Medication-free remission can be only achieved in a small subset of patients, however it is a relevant target in clinical practice, since it may decrease the risk for drug side effects as well as the economic burden of RA. Observational studies and clinical trials have reported that DMARD-free sustained remission can be achieved in

approximately 10–15% of the patients with RA (50-54). However, it is not clear whether drug-free remissions are primarily due to the natural course of the disease or to the early therapeutic intervention, and if the current treatments may interfere with this chance (55, 56). Moreover, the optimal time to discontinue therapies in RA is still under discussion (57).

Drug-free remission has been described in several patient groups, as reviewed in details by Nagy *et al.* (56). Briefly, in the BeSt study, cessation of infliximab was successful in 52%, success rates were higher in patients initially treated with infliximab, and the rate of progression of the joint damage progression did not increase during the year following treatment cessation. Of the 48% who flared, 84% regained LDA. Thirteen percent of the patients were still in drug-free remission after 4 years (58-60). Male gender, lack of anti-citrullinated protein antibodies (ACPA) and short symptom duration were associated with drug-free remission. The British Early Rheumatoid Arthritis Study (ERAS) cohort and the Leiden Early Arthritis Clinic (EAC) cohort, showed medication-free remission (defined as no synovitis after terminating the DMARD therapy) in 15% and 9.4% of the patients, respectively (61). Short symptom duration, seronegativity, acute onset, and minimal radiographic damage were associated with drug-free remission in both cohorts. The EMPIRE trial (Etanercept and Methotrexate in Patients to Induce Remission in early Arthritis), was conducted in DMARD-naïve patients with early inflammatory arthritis treated with etanercept plus MTX or MTX monotherapy (62). In both groups, 3.6% of patients achieved sustained drug-free remission by week 78. In the PRIZE study (63), 22% of patients who had achieved remission with 50 mg etanercept and MTX were still in remission more than 1 year after discontinuation of both drugs. In the AVERT (Assessing Very Early Rheumatoid arthritis Treatment) trial (abatacept in ACPA-positive patients with early RA) (64), the proportion of patients in remission (DAS28 <2.6), 12 and 18 months after treatment cessation, were 14.8% in the abatacept plus MTX arm, 12.4%

in the abatacept monotherapy arm, and 7.8% in the MTX monotherapy arm. In two studies with tocilizumab, the ACT-RAY (65) and the DREAM (66) studies, 6 and 10% of patients respectively achieved drug-free remission. In the DREAM study, low matrix metalloproteinase 3 and low serum IL-6 levels were identified as predictors of LDA. Even if there are only few trials specifically conducted to assess drug free remission, it appears that biological therapies may increase this possibility. Ajeganova *et al.* (49) specifically investigated whether drug-free sustained remission is actually influenced by treatment, by comparing current treatment strategies with treatments that were used one or two decades ago. They also explored if the sustained remission status reflects resolution of symptoms and disability (49). DMARD-free sustained remission was defined as the absence of synovitis after DMARD cessation during the total follow-up that should be at least one year. The results showed that specific and more intensive treatment strategies were significantly associated with achieving remission, and increased the probability of a sustained DMARD-free remission, indicating that treatment can affect RA chronicity. Patients with RA achieving DMARD-free sustained remission had a normalised functional status, and VAS scores for pain and fatigue lower than the reference values, suggesting that important RA-related symptoms as pain and fatigue had resolved. Together, these observations suggest that DMARD-free sustained remission is a disease outcome reflecting health state close to expected in the general population with regard to functioning and several RA-related symptoms.

Treatment strategies to achieve remission in RA

Reversing inflammation, that is the major driver of clinical symptoms, joint damage, disability, and comorbidity in RA, is the main therapeutic target (67). Reaching this target may require regular assessment of disease activity to drive therapeutic adaptations in accordance with the final goal to achieve clinical remission or at least LDA (10). Composite measures of disease activity that include

joint counts are preferred to assess treatment effectiveness in the T2T approach. The degree of improvement after 3 months of therapy is predictive of target achievement; if the improvement is small, therapy should be adapted, balancing the risk of escalating therapy with treatment risks and patient-related factors (10, 68).

DMARDs are the drugs that target inflammation and reduce structural damage progression. There are two major classes of DMARDs: synthetic and biological. Biological DMARDs (bDMARDs) include TNF-inhibitors (TNFi), inhibitors of T-cell costimulation, B-cell depleting agents, interleukin-1 inhibitors, interleukin-6 receptor inhibitors. Synthetic DMARDs include the so-called conventional synthetic (csDMARDs), whose modes of action are still largely unknown, and the targeted synthetic (tsDMARDs) that have been developed to modulate a particular target implicated in the generation of inflammation. This is the case of Janus kinase (JAK) inhibitors, such as tofacitinib or baricitinib.

• *First line therapies*

According to EULAR recommendations (69), treatment should be initiated with a csDMARD, ideally MTX, plus short-term glucocorticoids (GC). Though not conclusively demonstrated to be superior to other csDMARDs, MTX is the preferred DMARD, over sulfasalazine and leflunomide (69, 70). Clinical data about the use of csDMARDs combinations are uncertain, as it seems that there might be no added efficacy compared to monotherapy at the potential cost of more toxicity (71-73), and the latest ACR and EULAR guidelines no longer recommend the early use of csDMARD combination (70).

• *Second line therapies*

A biological DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARD) are recommended by the latest EULAR recommendations when the first treatment fails, in patients with negative prognostic factors, as high disease activity despite the previous treatment, autoantibodies (ACPA or rheumatoid factors, especially at high titers), and early radiological damage.

The choice of the therapy is mainly left to the clinician's and patients' preference, but current practice would be to start a bDMARD (69). Clinical and structural efficacy is similar across all types of biological DMARDs. This has been shown in meta-analyses, as well as in few head-to-head studies (75-77). In terms of disease remission, comparisons among TNFi are available from the nationwide Danish DANBIO registry (78). Among over 2000 RA patients treated with adalimumab (29%), etanercept (22%) or infliximab (49%), infliximab had the lowest, and adalimumab the highest rates of remission, whereas etanercept had the longest drug survival rate. Subsequent data from the US-CORRONA registry showed no differences in rates of remission among the same three TNFi (79), but showed that response and remission outcomes were consistently inferior for patients who switched TNFi compared to biologically naïve patients.

When a patient does not achieve the treatment target on a biological DMARD (plus MTX), then any other bDMARD or a tsDMARD can be used (69). Even sequential use of TNFi, following lack of response to the first one administered, seems to provide similar outcomes as switching to biologics that target other molecules (74, 79, 80).

Though having different mechanisms of action, Tocilizumab (IL-6 inhibitor), Abatacept (T-cell costimulation inhibitor) and Rituximab (anti-CD20) seem to have similar efficacy (76). Actually, all the above mentioned biologics (in combination with MTX) show similar response rates that decrease with increasing previous drug experience (74, 76, 79). The real-life factors influencing the first-line choice or the switching strategy, focusing on the prescription of abatacept or tocilizumab compared to TNFi were analysed from an Italian registry, the Lombardy Rheumatology Network (LORHEN) Registry, on 1,900 patients enrolled from 2010 (81). It emerged that higher age and comorbidities influence the choice towards abatacept and tocilizumab compared to TNFi, with abatacept being preferred in case of suspension of previous treatments due to adverse events. After failure of a first-

line TNFi, switching to a different mechanism of action was more common.

Tofacitinib, the first JAK-inhibitor developed for the treatment of autoimmune diseases, inhibits JAK1 and JAK3 and, to a lesser extent, JAK2. It has been the first approved targeted synthetic DMARD in the world, and it is now approved for use also in the EU. As a JAK-inhibitor, tofacitinib interferes with IL-6, granulocyte-monocyte colony stimulating factor, interferons (type I and type II), and common γ -chain cytokines (such as interleukin 2 or interleukin 15) signalling (82). The efficacy of tofacitinib (5 mg BID) plus MTX appears to be similar to that of biologics (83), but, unlike most bDMARDs, tofacitinib in monotherapy showed to be clinically superior to MTX (84). Baricitinib is a JAK 1/2 inhibitor and has got approval by the EMA; in phase 3 clinical trials it has shown a similar efficacy as the biological DMARDs and tofacitinib. Interestingly, however, baricitinib plus MTX elicited a superior clinical and functional, but not structural, outcome compared with adalimumab plus MTX (85).

Smolen *et al.* evaluated remission rates obtained with tofacitinib across five phase 3 randomised controlled studies by remission criteria (31). Tofacitinib was given either as monotherapy, or with background MTX or other csDMARDs. In the over 3000 RA patients analysed, remission rates varied by criteria, with higher rates for DAS28-4(CRP) than other scores. Across the studies, DAS28-4(CRP) criteria generated 2- to 5-fold higher remission rates compared with DAS28-4(ESR), while remission rates determined using SDAI and CDAI were consistently similar to each other. The surprising discrepancy between DAS28-4(CRP) and DAS28-4(ESR), two variants of the same type of score, were hypothesised by the authors to be due to different effects of tofacitinib – that interferes with IL-6, the major activator of acute-phase reactants (86) – on ESR and CRP. Tofacitinib reduces CRP concentrations to a level that, when entered into the DAS28-4(CRP) formula, may result in values below the remission threshold, despite residual joint and patient global activity, while ESR is not affected to a similar extent.

Impact of early diagnosis and treatment on remission

During the last decade, early diagnosis and early treatment have been emphasised as a window of opportunity to achieve complete suppression of disease activity, that is, remission (87-91). There is evidence of the benefits of very early DMARD initiation in early chronic inflammatory arthritis, preferably before the onset of erosions, in reducing and also preventing the risk of joint damage progression and disability (67, 92, 93). Moreover, tight monitoring is particularly useful in patients with early arthritis, allowing to promptly adapt the therapeutic strategies (2, 93). Clinical remission and prevention of joint destruction must be the treatment targets especially in early RA (ERA).

The 2010 ACR/EULAR classification criteria for RA (94) redefine the paradigm of RA based on the early disease characteristics that are associated with persistent and/or erosive disease, and allow for an earlier treatment of the disease. The aim of this classification was to draw attention on the importance of earlier diagnosis and earlier start of an effective disease-modifying therapy. The criteria have been validated in many settings and offer 21% higher sensitivity than the former ACR criteria, at the cost of 16% lower specificity (95, 96). In light of the 2010 ACR/EULAR criteria, the European Medicines Agency (EMA) has published a new guideline on the clinical investigation of medicinal products other than non-steroidal anti-inflammatory drugs for the treatment of RA (97). This revision had been long awaited, the former guidelines dating back to 2003 (98), and it clearly divides RA patients into two populations, those with early RA and those with long-standing RA, to keep in line with the new ACR/EULAR RA classification criteria, allowing patients to be included at an earlier stage of their disease than before. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), invited by the EMA to provide comments on the new guideline (99), set-up a workgroup of experts in the field of RA and clinical trial methodol-

ogy in order to discuss the appropriate design of clinical trials in early RA. The experts agreed that also in clinical studies of new drugs for the treatment of RA, particular attention is recommended in the definition of early RA population and in the choice of the endpoints for such a population (99). The workgroup also considered that patients who have already taken DMARDs usually respond less than DMARD-naïve patients, regardless of disease duration, and should preferably be studied differently and with different primary endpoints. They suggested to define as early RA patients DMARD-naïve patients with no more than 1 year of disease duration from diagnosis. Even though this definition does not comply with the definition of early RA (not more than 6 months) given in the 2015 ACR recommendations for the treatment of RA, it was considered more appropriate to characterise and select patients for clinical research (99).

Achieving remission in PsA

Pharmacological management of PsA is an area that has witnessed an important expansion in the last few years. With the advent of the biological therapies, trials started to be conducted specifically in patients with PsA – instead of deriving the experience gained from trials in RA – even though mostly with drugs that had previously demonstrated efficacy in RA. More recently, randomised controlled trials have demonstrated the efficacy of new compounds that are not used for the treatment of RA (100-105). In 2015, both the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the EULAR presented updated recommendations on the management of PsA (106, 107), with new therapies, assessments and increasing evidence on comorbidities requiring substantial revision of treatment strategies. Both groups assessed efficacy of therapies in different domains of disease, allowing physicians to select the optimal therapy based on disease activity in each domain. In 2014, an international task force published T2T recommendations also for PsA and other spondyloarthritis, defining remission or LDA as treat-

ment targets, though the participants were aware that there was no strong evidence base for this and that further research was needed (10).

Definitions of remission in PsA

PsA is a complex disease and, when assessing disease activity, all its clinical features should be considered: involvement of peripheral and axial joints, skin and nails, enthesitis and dactylitis, as well as extra-articular manifestations, such as uveitis and inflammatory bowel disease. It has also to be considered that disease activity may be different in different domains of PsA (13). PsA remission criteria and some composite activity indexes (Boolean criteria, DAS28) have been borrowed from RA, even if they do not include manifestations that are peculiar to PsA. Initially, Gladman *et al.* (108) defined remission as no actively inflamed joints on at least 3 consecutive visits, in patients with PsA treated with csDMARDs. However, it has been objected that criteria for remission in PsA should address all the various dimensions of the disease (109). Therefore, a number of disease activity measures and definitions of remission have been later developed, such as the Disease Activity Index for Psoriatic arthritis (DAPSA), the Composite Psoriatic Disease Activity Index (CPDAI), the Psoriatic Arthritis Disease Activity Score (PASDAS) (110-112). In 2010, Coates *et al.* developed and validated composite outcome measure taking into consideration most disease domains (113, 114): the definition of minimal disease activity (MDA) requires the fulfilment of five of the seven criteria comprising musculoskeletal and skin manifestations and patient-reported outcomes (113-115). Data obtained from post-hoc analysis, registries, and longitudinal observational studies showed that MDA and sustained MDA are achievable targets in PsA patients (116-123). MDA is achieved in approximately 60% of patients with TNFi (117, 123) and maintained in about 12% of patients following drug discontinuation, and predictors of MDA have been identified in male sex and normal ESR values (117). Sustained MDA – defined as MDA for more than 12 months at consecutive control visits – was shown

to be associated with prolonged reduced Rx progression (115). However, it has been questioned whether MDA may really define a state of remission or near remission (113), and subsequent efforts were aimed at describing the cut-off values of these indices and their validity in defining PsA remission (124). Stringent criteria for a ‘very low disease activity’ (VLDA) score were identified in a ‘full’ MDA score of 7/7 and a PASDAS ≤ 1.9 (118, 119). Not surprisingly, while about 60% of patients were shown to reach the ‘classic’ MDA criteria (5/7), the above defined VLDA was reported to be achieved in a lower percentage of patients, *i.e.* less than 40% (120). Since the previous edition of the EULAR PsA management recommendations, T2T recommendations had been developed also for PsA (10, 125), recommending clinical remission/inactive disease of musculoskeletal involvement (arthritis, dactylitis, enthesitis, axial disease) as major treatment target, but also taking extra-articular manifestations into consideration; low/minimal disease activity is proposed as an alternative treatment target. However, it has not been established whether achieving a state of remission leads to better long-term outcomes than LDA, so this item remains somewhat controversial (10). Furthermore, there is no clear definition of remission for extraarticular musculoskeletal manifestations, such as enthesitis or dactylitis. Also, there are so far no sufficient data on the relationship between remission of musculoskeletal symptoms and of skin disease in PsA. This is the reason why the first recommendations to T2T states ‘a major’ rather than ‘the major’ treatment goal, and expands the term ‘clinical remission’ to the slightly less stringent term ‘inactive disease’, in order to acknowledge the lack of data. It is worth underlining that the group referred the terms ‘remission/inactive disease’ mainly to the musculoskeletal features of PsA and not to the extramusculoskeletal alterations, although eventually recommending not to neglect the latter when making decision about therapy. In order to clarify the definition of remission, the 3rd T2T recommendation for PsA and other spondyloarthritis provides a definition for remission as the absence

of clinical and laboratory evidence of significant inflammatory disease activity. The recommendations use the term ‘clinical remission’ to underline that the definition of remission should consider clinical rather than imaging measures. However, since joint damage progression correlates with the number of swollen joint counts and dactylitis (126, 127), it can be expected that in patients in clinical remission structural damage will not progress.

Clinical remission, stringently as it was defined above, may be difficult to achieve in clinical practice, especially in patients with established/long-standing disease (128-131), given that the factors associated with higher remission rates appear to be younger age, lower functional impairment and, in some cases, higher C-reactive protein levels (122). This is the reason why LDA/MDA are considered useful alternative targets, since physical function and QoL should not be much worse than in remission, and progression of structural damage should be minimal or even absent. In PsA clinical trials, the greatest improvement in all outcome measure is generally achieved between 3 and 6 months (132-134), therefore, the T2T task force defined in 6 months the time lapse to reach LDA or remission; however, they recommend that if no significant reduction in disease activity is observed within 3 months, therapy should be promptly adapted (10). Regarding joint involvement, the Disease Activity index for Psoriatic Arthritis (DAPSA) has been recently defined and validated as a specific LDA criterion in PsA (135). The DAPSA was used to define patients in DAPSA remission, namely those with DAPSA ≤ 4 , and its validity in discriminating different degrees of functional impairment and different extents of joint damage progression in patients with PsA was assessed (136). Indeed, the DAPSA score showed to be discriminant and sensitive to changes regarding two of the most important outcomes of PsA, namely disability and damage, thus promising to be highly valid for future use to define endpoints in clinical trials or treatment target in clinical practice. MDA has been shown in one study to be predictive of reduced

structural damage progression, and to be a valid treatment target, as demonstrated in the recent 'Tight control in PsA' (TICOPA) trial (137, 138). Interestingly, a recent study pointed out the discordance between PtG and physician's global assessment (PhG) in PsA, that was particularly frequent in patients in remission (139), possibly because patients may have different expectations regarding their disease status compared to their physicians, in particular in states of LDA. Indeed, an observational study showed that PtG can estimate the LDA status and can be considered as a surrogate outcome measure for the assessment of global disease activity in PsA patients during routine clinical practice (140).

Factors associated with discordance fell within psychological rather than physical domains of health. The meaning of remission from the patient's perspective is probably worth further exploration also in PsA. Better definition of remission and identification of predictors of remission, as well as possible PROs to be included, are topics for further research.

Treatment strategies to achieve remission in PsA

As mentioned before, the 2016 EULAR recommendations for the management of PsA state as first recommendation that treatment should be aimed at reaching the target of remission or, alternatively, MDA/LDA. Monitoring and tight control have also been expanded from RA to PsA (2, 10, 125). The only randomised trial that specifically evaluate a tight control approach in PsA is the TICOPA trial (137, 138), which showed that the group undergoing tight control had more favourable outcomes.

The first-line recommended pharmacological approach are csDMARDs, preferably MTX. Following an inadequate response to at least one csDMARD, administered for an appropriate length of time (usually 3–6 months), therapy with a bDMARD, usually a TNFi, should be commenced (107). Among bDMARDs, it is the opinion of the experts, that TNFi should be currently be the first choice treatment, given the long-term experience with them, and their well-established

efficacy/safety balance in PsA. All the currently available originator TNFi (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) have demonstrated to be effective in PsA on both skin and joint involvement, and in preventing radiographic damage (141). Overall, TNFi have made LDA or remission achievable targets in up to 50–60% of PsA patients (110). Most published data on TNFi effectiveness in PsA did not have remission or MDA as endpoints; however, post-hoc analysis and observational studies following TNFi treatment have reported 28 to 52% of patients reaching MDA, depending on the study, the drug and the duration of follow-up (114, 116, 142). In particular, the GO-REVEAL long-term study showed that remission or a near-remission status, such as MDA, are achievable by many PsA patients (141). Recent data suggest that a combination therapy with csDMARD and TNFi, especially mAbs, is beneficial in achieving and maintaining a good level of response in PsA patients, while it is worth noting that drug survival on etanercept is not affected by the combination with MTX (143–145).

bDMARDs targeting interleukin (IL) 12/23 (ustekinumab) or IL-17 pathways (secukinumab) may be considered if TNFi are not appropriate. It should be remembered that both agents were shown to be less effective in patients who had previously received TNFi compared with those who had only received csDMARDs. However, there are not enough long-term safety data to fully appreciate the benefit/risk profile of these newer drugs (107).

Among tsDMARDs, apremilast, a PDE4-inhibitor, may be considered in case of inadequate response to at least one csDMARD, or inappropriateness of bDMARDs, but apremilast has shown only a moderate effect size, so that the achievement of remission or LDA may be unlikely (107). Since the JAK and signal transducer and activator of transcription (JAK-STAT) signalling pathway is implicated in the pathogenesis of PsA, a recent study investigated and demonstrated the effect of tofacitinib in differentially regulating JAK-STAT signalling (146), further supporting a role

for blockade of JAK-STAT signalling pathways in the treatment strategy for PsA. In clinical studies, tofacitinib has shown a questionable benefit/risk profile in the treatment of psoriasis (147, 148), whereas positive results in PsA have emerged from a recently completed phase 3 clinical trial, showing a clinical response maintained over 1-year period of treatment, without radiographic structural damage progression in more than 90% of the patients (149, 150). A Japanese phase 3 trial has shown short-term efficacy of tofacitinib at both 5 and 10 mg twice daily, and maintenance of efficacy for 52 weeks with a manageable safety profile in patients with moderate to severe plaque psoriasis and/or active psoriatic arthritis, though in this study the number of patients with PsA was very limited (151).

Comparison between clinical remission in RA versus PsA

The comparison between RA and PsA with regard to clinical remission is due to the fact that both diseases are common in real clinical practice, showing that clinical remission is an achievable target. However, the description of clinical remission in this review of two conditions characterised by joint involvement but with some other important differences has been outlined and differentiated. In fact, RA and PsA have been assessed with some instrument tailored for each single disease or, sometimes, "borrowed" from one to the other (usually RA to PsA).

Conclusions

It is now widely accepted that a T2T approach allows to obtain better outcomes than a conventional approach in treating both RA and PsA, and that remission can be an achievable target for several patients. However, remission according to the stringent definitions proposed by the current recommendations may not yet be a realistic goal for most patients (1, 11, 13, 107, 152). LDA/MDA are considered possibly alternative goals, and several different remission criteria have been proposed, based on the disease activity scores used, on the importance given to the inclusion of patients' perspective into the definition of remis-

sion, and on their applicability in clinical practice, with different criteria generating highly different remission rates. Moreover, compared to RA, for PsA remission is probably still insufficiently defined, still representing an at least partially unmet need. However, despite the relatively small number of studies and the difficulty in objectively defining remission in such a complex disease, TNFi have shown to achieve a condition of remission or at least MDA.

Selecting appropriate criteria and measurement tools has important implications for both clinical trial design and clinical practice. This paper reviewed the different criteria of remission, taking into account all these aspects and in the light of the available treatment strategies for RA and PsA, in the attempt to provide to all rheumatologists an opportunity to improve the outcome to the greatest extent possible in their clinical practice. Further real-world studies and data obtained from registries will provide more useful data about remission or LDA/MDA in inflammatory arthritis and hopefully offer more information about predictors and biomarkers that will help in better defining the treatment approaches most likely to achieve remission for patients with RA and PsA.

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