

# Drug-free remission: the goal of the future in management of patients with rheumatoid arthritis

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## Abstract

Management of patients with rheumatoid arthritis according to the “treat-to-target” strategy requires achievement of remission or low disease activity when remission cannot be achieved (mostly in patients with advanced disease). The assessment of remission and low disease activity is based on a number of definitions depending on the applied instruments which do not always correspond to one another.

The role of biomarkers and imaging techniques (ultrasound and magnetic resonance imaging) in predicting the risk for disease relapse after achieving remission and tapering disease-modifying antirheumatic drugs treatment are presented. The concept of achieving the full control of inflammation including residual synovial inflammation and drug free-remission is discussed.

**Key words:** rheumatoid arthritis, therapy, remission.

## Introduction

Management of patients with rheumatoid arthritis (RA) is based on “treat-to-target” strategy. The aim of the strategy is achievement of remission or low disease activity when bringing off remission remains impossible within a half of year of treatment. Remission is attained mostly in patients with early RA or those with a short time of the overt disorder. Achievement of remission in patients with advanced disease remains more difficult and in some of them accomplishment of low disease activity is considered as successful goal of management. Such strategy is used in all recommendations [1–5]. Rheumatoid arthritis treatment is based on adherence to this strategy. The “treat to target” strategy involves obtaining a significant response to treatment in the third month and the treatment goal in the sixth month. There is however a number of definitions used to assess remission and low disease activity depending on the instruments applied that do not always correspond with each other.

## Different definitions of remission and assessment results

Remission is defined using several indices, including DAS28-ESR < 2.6 (Disease Activity Score based on 28

joint count and erythrocyte sedimentation rate) DAS28-CRP < 2.6 (Disease Activity Score based on 28 joint count and serum C-reactive protein level), SDAI ≤ 3.3 (Simplified Disease Activity Index), CDAI ≤ 2.8 (Clinical Disease Activity Index), and a definition developed by ACR/EULAR 2011 (American College of Rheumatology/European League Against Rheumatism). According to them, low disease activity is identified if DAS28-ESR ≤ 3.2, DAS28-CRP ≤ 3.2, SDAI ≤ 11, CDAI ≤ 10 [6–8]. All definitions of remission and low disease activity involve a number of tender and swollen joints along with global assessment of disease activity made by a physician and/or a patient. Acute phase reactants, ESR or CRP, are used in the following definitions: DAS28-ESR, DAS28-CRP, SDAI (CRP ≤ 10 mg/dl) and ACR/EULAR 2011 (CRP ≤ 1 mg/dl). CDAI definition does not include acute phase reactants but is comprised of a total number of tender and swollen joints and global assessment of disease activity made by a physician and a patient using VAS. ACR/EULAR 2011 remission criteria focus on a number of tender and swollen joints, global assessment of disease activity made by a patient and CRP concentration. Values of particular parameters must be lower than or equal to 1 (≤ 1). Remission is achieved if total value amounts to ≤ 4 [9]. Definition of remission based on DAS28-ESR does not

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correspond to actual remission, because it is associated with progression of destructive joint lesions, concomitant diseases and persistent minimal disease activity [10]. If remission is classified according to DAS28-ESR and DAS28-CRP, this leads to high incidence of false-positive results, in particular while using drugs that affect biochemical acute phase markers which in fact results in a considerable difference in DAS28-OB and DAS28-CRP results.

It has been reported that remission with inhibited joint progression assessed based on a long-term follow-up is associated with lower DAS28-CRP, namely DAS28-CRP < 2.3 [11].

In the BRASS study the authors [12] assessed incidence of remissions throughout a year according to different definitions and average duration of remission in 871 patients with advanced RA treated with classical synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs). Remission occurred in 35.4% of cases according to DAS28-CRP and in 19.5%, 19.2% and 18.1% of patient according to SDAI, CDAI and ACR/EULAR 2011, respectively. Studies showed that the percentage of patients with remission varies significantly according to the assessment method used. Follow-up in the subsequent year revealed that the disease exacerbated in more than a half of the patients who had achieved remission. Mean duration of remission has not differed depending on its definition and amounted to approx. 1 year. No significant differences in the relationship between sex, age, and duration of disease, seropositivity and duration of remission have been noted, however it was observed that remission is less common in older patients (> 50 years) and lasts for a shorter time [13].

Another study [14] analysed percentage of patients who achieved treatment goal in the sixth treatment month, i.e. remission or low disease activity, according to various definitions among 2483 patients. This analysis was based on pooled data from 6 randomised, controlled studies on the efficacy and safety of different biologic drugs. Using SDAI, 11.4% of patients achieved remission. Similar results were obtained using CDAI – 11.8% of patients. In contrast, 23% and 19.7% of patients achieved remission using DAS28-CRP and DAS28-ESR, respectively. The investigators highlight a significant discrepancy in the incidence of remission assessed in clinical studies depending on assessment methods applied. The percentage of patients with low disease activity also showed differences, though they were not as significant as in the case of remission. Low disease activity in the sixth treatment month was noted in 41.3%, 40.3%, 29.1% and 19.7% of patients according to SDAI, CDAI, DAS28-CRP and DAS28-ESR, respectively. The

study demonstrated that assessment of remission according to ACR/EULAR 2011 is consistent with the ones according to SDAI and CDAI.

There is a number of causes leading to different incidence of remission depending on definitions used. A number of swollen joints is of key importance. According to ACR/EULAR 2011, SDAI and CDAI, it ranges from 0.5 to a maximum of 1.7, whereas in the case of DAS28 it amounts to approx. 6 joints [15]. The DAS28 score is the weakest index for remission and does not correspond to inhibited joint progression and maintained functional capacity. Nevertheless, it is DAS28 that is used most frequently in clinical practice to assess disease activity and remission.

Other significant causes of differences in assessment of remission and low disease activity are the follows: patient population with regard to duration of the disease, inclusion criteria, csDMARDs and bDMARDs used in monotherapy and in combined therapy. Early RA patients respond to treatment faster and more of them achieves remission compared with advanced RA patients. If the disease is very active at baseline, activity markers after 6 months of treatment are higher than in the case of lower activity. It is also more difficult to reach treatment goal. Compared with combination treatment, monotherapy plays a significant role in assessing whether treatment goal has been achieved. Several studies revealed that treatment goal is more frequently achieved during combination treatment of a bDMARD or csDMARD, mainly with methotrexate (MTX), than during monotherapy [16]. Approximately 30% of patients are treated with bDMARDs in monotherapy. It should be also noted that both csDMARDs and bDMARDs exhibit different effect on acute phase proteins which may have impact on the assessment of disease activity in line with definitions based on ESR and CRP. CRP is a homogenous protein the concentration of which is rapidly decreased by drugs that inhibit its release, whereas ESR involves a number of proteins the release of which is a much more complex process.

Concomitant diseases, such as infections, diabetes or cardiovascular disorders also affect disease activity as well as incidence of remission and low disease activity. It has been shown recently that obesity has a significant negative impact on disease activity and chances of remission [17]. Adipokines have a pro-inflammatory effect. Fatty tissue affects the persistence of inflammation and its chronic nature. A significant relationship between obesity and disease activity, radiological progression, functional capacity, depression, mental functions, sex and pain has been observed. Obese patients are at higher risk of death due to cardiovascular disease.

Prince et al. [12] assessed predictive value of response to treatment in the third month on treatment goal (remission or low disease activity) reached in the sixth month. Analysis showed that predictive value of treatment goal amounted to 33% in the case of DAS28-ESR and 80% in the case of SDAI, indicating a significantly higher usefulness of this index in assessment of actual remission or low disease activity.

Results obtained with definition according to SDAI are basically equivalent to the ones related to ACR/EULAR 2011, which is the most appropriate and accurate for assessment of remission and should be used both in clinical studies and everyday practice. It pertains to current EULAR 2017 recommendations [18].

## Alternative remission assessment methods

Apart from definitions according to DAS28, CDAI and SDAI, ACR 2015 guidelines list also PAS (Patient Assessment Scale), assessed by patients determined in VAS (Visual Analogue Scale), and RAPID3 (Routine Assessment of Patients Index Data 3) as alternative remission assessment methods [19]. RAPID3 consists of three elements: assessment of physical function, pain and global health defined by patients. Each element has a scale from 0 to 10. Total score amounts to 30. Range of values defines disease activity: high activity < 12; moderate activity 6.1–12; low activity 3.1–6; remission ≤ 3. RAPID3 does not account for a number of tender and swollen joints which often is subjective, while assessment of physical function and pain made by a patient is a much more objective indicator. RAPID3 is easy to use and does not consume much time. As demonstrated in studies [20], it is a better predictor for maintaining physical function and lack of radiological progression than other indices used. Authors point to the possibility of using greater number of indices to assess disease activity. Their choice should depend of physician's decision [20].

Recent studies show that patients mostly define treatment goal as improvement of quality of life, including: pain relief, lack of fatigue, maintained physical function, capacity to work and have social life [21]. Improvement of symptoms and health-related quality of life is significantly more important for patients than assessment of clinical and serological characteristics. Patients with chronic disease who have not responded to several csDMARDs and bDMARDs are at high risk of progressive impairment of functional capacity and quality of life. RA sequelae are currently assessed by patients as a significant part of treatment aimed at improvement quality of life.

Patient-reported outcome (PRO) refers to global health in many aspects of life and is currently being evaluated in clinical trials [22]. It includes a number of parameters: duration of morning stiffness (min.), pain (VAS), assessment of disease activity made by a patient (VAS), functional capacity (HAQ-DI), fatigue (FACIT), sleep disorders, quality of life related to physical and mental functioning (SF-36), productivity (WPAI-RA) and health-related quality of life (HRQL). Treatment goal recommended by numerous experts, remission or low disease activity results in significant differences related to quality of life and socio-economic consequences when assessed by patients according to PRO. Differences in quality of life, occupational and social activity assessed by patients, and costs in patients with remission were compared with the ones with low disease activity in a group of 356 RA patients with different disease severity, who were treated with biologics in everyday practice [23]. SDAI was applied to assess remission and low disease activity. Authors attempted to answer whether patients believe that better outcome makes up for high treatment costs. Study demonstrated a significant difference between remission and low disease activity in terms of: functional capacity, health-related quality of life, productivity, impact on social life and indirect costs. Analysis of costs revealed that their amount and level of disability are correlated with each other. It was shown that treatment aimed at maintaining functional capacity and occupational activity is cost-effective, using bDMARDs. Therefore, remission is an optimal treatment goal also in socio-economic sense. If remission cannot be achieved, too intensive treatment after low disease activity is achieved may be dangerous for a patient and result in undesirable effects.

## Assessment of remission with the use of imaging tests

Joint progression is one of significant aspects of the assessment of remission [24]. Treatment should slow down or stop the joint damage progression and minimize or reverse impairment of functional capacity. In clinical practice, radiographic images of joints are taken once a year and the results are assessed. Radiological assessment of disease progression focusing on the number of erosions and the joint space narrowing which is primarily used in clinical studies is more sensitive but is not commonly applied in clinical practice.

Numerous clinical studies demonstrated that symptoms of persistent synovitis are visible in ultrasound and magnetic resonance imaging of patients with clinical remission assessed in accordance with DAS28 [25–27]. Persistent inflammation is observed in patients with

synovitis investigated using the power Doppler ultrasonography who also negatively respond to a reduced dose or discontinuation of bDMARDs. Such patients are at higher risk of relapse compared to those without persistent synovitis [27]. Investigators suggest that power Doppler ultrasonography is a more sensitive assay than assessment using DAS28 as far as occurrence of recurrences is concerned. Similar results were obtained by other investigators [28] who demonstrated that the synovial hyperplasia is associated with a high risk of relapse after dose reduction or discontinuation of medication with TNF- $\alpha$  inhibitors. At the same time, they revealed that lack of the synovial hyperplasia observed in ultrasonographic imaging is associated with minimal histopathological lesions in the synovial membrane indicating that this imaging technique detects persistent disease activity. Thus, clinical and ultrasonographic assays used together for assessing remission could become a significant indicator for reduction or discontinuation of the treatment after achieving persistent clinical remission. Unfortunately, ultrasonography of numerous joints is expensive and time-consuming method and it limits its application in clinical practice [29]. Magnetic resonance imaging identifies bone marrow oedema as predictor and possible location of early erosions, through it was demonstrated that erosions correlate with clinical joint swelling. Furthermore, it was revealed that many healthy individuals have signs of synovitis showing evidence of vasculopathy detected in ultrasonographic and magnetic resonance imaging which may lead to errors in assessment of remission achieved in RA patients and to their overtreatment [30].

### Perspectives in assessment of remission

As far as serum biomarkers of the disease activity are concerned, anti-citrullinated protein antibodies are the best studied predictive factor of relapse. RETO study showed that anti-citrullinated protein antibodies pose high risk of relapse similar to a short duration of persistent remission [31]. BEST, HIT-HARD and POET studies confirm this observation [32–34].

Inflammation is driven by persistent autoimmunity as it was confirmed in studies reported by Tanaka et al. [35]. They demonstrated that persistent high level of anti-citrullinated protein antibodies and rheumatoid factor is a negative predictive factor for long-term remission after discontinuation of medication with TNF- $\alpha$  inhibitors. It was suggested that immunological activity should be also determined with serum assays while assessing remission. CRP level, commonly estimated for assessing the disease activity does not

reflect inflammation in the joints and progressing destruction of the joints.

A combined multibiomarker for possible relapse has recently been used in RETO study. It consists of acute phase reactants, cytokines and metalloproteinases [36]. Persistent positive serum biomarker for inflammation in patients with negative anti-citrullinated protein antibodies increased a risk of recurrence from 13% to 32% in one year. The risk of relapse significantly increased up to 76% in patients with anti-citrullinated protein antibodies and persistent positive serum biomarker for inflammation. The study showed that serum biomarkers for inflammation were useful predictors for selection of subtypes of the patients whose medication dose may be reduced or treatment can be discontinued as well as the patients whose therapy should be changed. Current RA treatment focuses on controlling inflammation however the high frequency of relapses after clinical remission highlights the need of elaboration of more effective therapy with greater focus on the disease pathogenesis. In future, treatment should be mostly aimed at maintaining remission, detecting subclinical disease activity and differentiating between recovery and incomplete suppression of inflammation. Type of remission should be identified.

Clinical remission (lack of clinical signs of arthritis), imaging remission (negative results of ultrasonography, magnetic resonance imaging and serum markers of inflammation) and immunological remission (negative immunological tests, seroconversion) should be distinguished from each other. Currently, remission is assessed based on clinical signs, i.e. joint pain and swelling, without taking into account inflammation in synovial membrane. Subclinical disease activity is not taken into account while assessing remission based on DAS28. Immunological process remains present within the joints, leading to their destruction and clinically overt relapse which indicates that after achieving clinical remission it may be more appropriate to reduce a drug dose than to discontinue treatment. Changing treatment goal to attaining of immunological remission remains a subject discussion. In the current state of knowledge, remission should involve: no signs of arthritis (pain, swelling), seroconversion (rheumatoid factor/anti-citrullinated protein antibodies), and negative findings of imaging studies related to arthritis (ultrasonography, magnetic resonance imaging) and acute phase reactants restored to normal condition [37]. Such remissions raise hope for a long-term drug-free remission.

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