# Can remission be maintained with or without further drug therapy in rheumatoid arthritis?

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**Key words:** Rheumatoid arthritis, remission, TNF antagonist therapy, DMARDs, withdrawal of therapy.

**ABSTRACT**

*Remission is now the accepted goal of management in rheumatoid arthritis (RA). This article highlights the controversies surrounding the definition of remission and reviews the potential of current treatment options to achieve remission.*

*Defining "true" remission can be difficult based on current criteria, which do not consider structural and physical function. Nonetheless, considerable advances in recent years have made the concept of remission a realistic goal.*

*In early RA, substantial and largely irreversible radiographic damage is seen in 60% of patients within the first 2 years of diagnosis. Early therapeutic intervention would ideally lead to reduction in long-term disability in RA and likelihood of inducing and maintaining remission.*

*Long-term maintenance therapy with disease-modifying antirheumatic drugs (DMARDs) has been shown to be effective in preventing flares of disease. Stopping therapy for short periods does not necessarily lead to flares, but the effect on long-term radiographic damage and potential to achieve similar levels of disease control following reinstatement of therapy is not established.*

*Early use of tumour necrosis factor (TNF)–antagonist therapy (e.g. infliximab) has been shown to lead to significant improvement in disease activity measures (clinical and radiologic outcomes) when compared to monotherapy or combination DMARD and corticosteroid therapies. Response was shown to be sustained in 70% of patients receiving TNF-blocking therapy 1 year after stopping treatment. This suggests the significant role of TNF-blocking therapy in enabling sustainable remission without need for long-term administrations, which has important implications for favourable health economics.*

*At present, little published evidence exists on the effects of withdrawal of TNF-blocking therapy in patients with established RA in remission. In conclusion, evidence indicates that remission is a realistic goal, but more evidence is required to establish optimal treatment strategies and define criteria for remission that include imaging and immunological as well as clinical assessment of the disease state.*

## Introduction

The availability of new therapies and treatment strategies in rheumatoid arthritis (RA) has encouraged rheumatologists to consider the concept of remission. With remission now a distinct possibility, the accepted goal of management should embrace a complete return to normality in patients with early disease and the arrest of joint damage and disability progression in patients with established disease. Remission has become the focus of many clinical trials over recent years. However, the definition of remission has been a controversial one, ranging from the complete absence of disease activity that persists after stopping therapy (drug-free remission) to various definitions of low disease activity.

The currently available validated measures of disease activity—that is, European League Against Rheumatism (EULAR) disease activity score (DAS) (1, 2) and the American College of Rheumatology (ACR) criteria (3)—are not ideal for describing remission. The ACR criteria have been regarded as too rigorous and consider remission as a dichotomous variable, not a spectrum of disease activity (4). Neither ACR nor DAS criteria consider structural damage and physical function. The DAS criterion has recently been criticised for having low sensitivity and specificity (5). The cut-off values for DAS and DAS28 have also been controversial (6), and the appropriateness of the DAS28 in remission assessment has been questioned (5, 7, 8). Age and co-

morbid conditions can affect self-report of pain and global health assessment, and the impact of these covariates must be taken into account when using measures like patient visual analogue scales to help determine whether patients are in remission (9). Despite the absence of a gold standard definition of remission, the concept is becoming increasingly important as more patients with both early and established RA are expected to achieve this goal.

Advances in recent years have enabled the early diagnosis of RA and the development of highly successful and effective therapies, leading to changes in the management of RA. The modern management of RA involves early diagnosis and rapid, aggressive control of inflammation to prevent long-term joint damage. This involves early use of disease-modifying antirheumatic drugs (DMARDs) and combination strategies (10-12). Since substantial, largely irreversible radiographic damage is seen in 60% of patients with RA within the first 2 years of diagnosis, this approach is essential to achieving the goal of remission (13). In early RA, disability assessed by Health Assessment Questionnaire (HAQ) scores shows an initial fall followed by an increase over 4 years. Whilst in early RA, radiologic damage does not necessarily correlate with immediate loss of function as assessed through HAQ score progression, its cumulative effect can lead to increased disability and reduced likelihood of achieving remission (14, 15). With this in mind, it is accepted that the greatest potential for therapeutic intervention is prior to the diagnosis of RA, that is, in patients with undifferentiated inflammatory arthritis as diagnosed by known markers of persistence or in RA patients at the time of first presentation. This maximises the benefits of the "window of opportunity" that may be open early in the disease process, a time when therapeutic intervention has a disproportionate impact on outcome (16-18). In clinical terms, management of early RA could now be described as involving remission induction followed by remission maintenance after withdrawal of therapy.

The advent of tumour necrosis factor (TNF) antagonist therapy has revolutionised the management of RA. The majority of patients receiving TNF antagonist therapy have established RA and have failed at least two traditional DMARDs. These patients tend to have significant radiographic damage and joint deformity prior to starting therapy. Nonetheless, many such patients achieve low disease activity states with TNF antagonist therapy (19). Once effective therapy is commenced in these patients, continuing it indefinitely is usual, ceasing only for adverse events. This is not an optimal management strategy in terms of health economics. Little research has been published on withdrawal of TNF antagonist therapy in patients with established RA in remission. However, evidence suggests that remission in patients with established RA is generally not sustained after withdrawal of DMARD therapy.

Whether long-term sustained remission without therapy is an achievable goal is not yet known. Drug-free remission has been researched in patients with established RA who take DMARDs, patients with early inflammatory arthritis, and patients with early RA. These studies are described below.

**Remission in established RA patients who take DMARDs**

The quest for a drug-free remission for RA patients is longstanding. It was especially significant when therapeutic options were limited by significant toxicity and poor patient compliance. Several small randomised controlled trials (20-25) published in the 70s and 80s, suggested that long-term maintenance therapy with DMARDs was effective in preventing flares of disease. More recently a 52-week randomised, double-blind, placebo-controlled, multicentre study (26) was conducted to assess the effect of stopping DMARD therapy in 285 RA patients. Eligible patients had to meet 5 out of 6 ACR criteria for clinical remission, have stable disease for at least 1 year, and have received therapy for at least 2 years with hydroxychloroquine, parenteral gold, d-penicillamine, sulphasalazine, azathioprine, or methotrexate (MTX). Patients were randomised to either continue the second-line drug (DMARD) or switch to placebo. The primary study end point was flare of disease, as defined by recurrence of clinical synovitis, at which point protocol medication (DMARD/placebo) was discontinued and therapy with original DMARD was commenced.

Disease flares occurred in 53 patients from the placebo group and in 30 patients from the continued treatment group. The cumulative incidence of flare after 52 weeks was 38% for placebo and 22% for continued treatment ($p = 0.002$). For the sulphasalzine and antimalarials, the difference in flare rate between placebo and continued therapy was significant. However, statistical differences from placebo were not seen in patients treated with MTX and azathioprine, likely due to small numbers. Interestingly, patients who continued treatment with d-penicillamine had the same rate of flare as those who discontinued it.

This result is not consistent with results of another randomised controlled trial of d-penicillamine withdrawal (22). Significant risk factors for flare included randomisation to placebo group, high maintenance dose of DMARD, presence of painless swollen joints, and positive rheumatoid factor (RF). The results of this study suggest that patients in remission on DMARDs should continue with drug therapy, but "drug-free holidays" may be possible as 62% of patients in the placebo group went a full year without experiencing a flare. However, the effect on long-term radiographic damage and the outcome of reinstatement of therapy would require consideration.

The latter point was addressed by the same research group in a follow-up study of the 51 patients whose RA flared after discontinuation of DMARD therapy while in remission (27). These patients received a second course of the drug. Re-institution of the DMARD was found safe and well-tolerated; 50% of patients achieved the same level of disease activity parameters as before treatment discontinuation, in terms of duration of early morning stiffness, Ritchie articular score, and swollen joint count. Only 25% of the responders

achieved the same level of erythrocyte sedimentation rate. The authors concluded that the overall result was favourable. However, a large proportion of patients clearly never regained the same level of disease control as they achieved with the original course of therapy. It appears unlikely that this result would be acceptable to patients and rheumatologists 10 years later, particularly as recent evidence suggests that patients with low disease activity on DMARD therapy continue to have significant radiographic progression (28).

**Remission in patients with early inflammatory arthritis**

As the benefits of early intensive therapy become clearer, recognition and treatment of patients has shifted towards the first few months of symptoms rather than the first few years (29). A diagnosis of early RA can be difficult in the early phase, and not all patients may fulfil ACR criteria for RA. To support an early diagnosis of RA, Emery and colleagues (30) developed an early referral algorithm for newly diagnosed RA. Rheumatology referral was encouraged for any patient with the presence of any of the following: 3 or more swollen joints, metatarsophalangeal/metacarpophalangeal involvement by squeeze test, and morning stiffness of 30 minutes or more.

To better understand this potential early stage of RA, Green *et al*. (31) designed a study to assess persistence of mild inflammatory arthritis. Sixty-three patients with an early, mild, untreated, inflammatory polyarthritis were given a single dose of corticosteroid at presentation. The primary outcome measure was clinical disease remission or persistence of arthritis at 6 months following injection. Remission was defined as the absence of symptoms or signs in a patient receiving no anti-inflammatory drugs. At 6 months, 78% of patients had persistent inflammatory joint disease and the other 22% had disease remission. Of the patients recruited, 51% satisfied ACR criteria for RA. The three most significant predictors of outcome were: disease duration >12 weeks; RF positivity, and shared epitope positivity. When all three of these adverse outcome predictors were present, 100% of the patients had persistent disease at 6 months. Conversely, when these factors were absent, patients had a 98% chance of remission.

The major conclusion of this study was that patients who fulfil ACR criteria for RA, with symptoms for <12 weeks, have a 50% chance of disease remission when treated with a single dose of corticosteroid. Information on the long-term outcome of these patients and whether this remission is sustainable would have significant value for clinical practice. Nonetheless, the diagnosis of RA with a duration <12 weeks should be made with caution.

A 2-year randomised study by Svenson *et al*. (32) examined DMARD-naive patients within a year of diagnosis of RA and found that low dose prednisolone and DMARD combination therapy led to significant reduction of joint damage in early RA and high remission rates, defined as DAS28 scores < 2.6. Whilst this has important implications for clinical practice, the relevant benefit of using glucocorticoids on a medium- to long-term basis in treatment remains debatable.

**Remission in patients with early RA treated with TNF antagonist therapy**

Quinn *et al*. (33) performed a 12-month, double-blind, randomised, placebo-controlled trial of infliximab with MTX, with the aim of inducing remission in patients with early poor prognosis RA. The primary end point was synovitis as measured by magnetic resonance imaging (MRI). This was one of the first studies to analyse the effect of a course of TNF antagonist therapy in early RA, although an earlier pilot study of high-dose infliximab given for just 6 months led to relapse after discontinuation in all patients assessed. At 1 year, all MRI scores were significantly better, with no new erosions in the infliximab/MTX group. The latter group also achieved higher ACR50 and 70 responses when compared to the placebo/MTX group. Importantly, one year after stopping induction therapy, response was sustained in 70% of patients from the active treatment arm, with a median DAS28 of 2.05.

These results suggest that the early use of aggressive TNF antagonist therapy may have a specific effect on the long-term process that controls inflammation in active RA, thus enabling sustainable remission on maintenance MTX monotherapy without TNF antagonist therapy. Preventing early erosive disease also increases the likelihood of future remission and may decrease the likelihood of long-term disability.

The results and concepts highlighted in Quinn's study were confirmed by a large single-blind study from the Netherlands (34). This study sought to determine the optimal treatment strategy for patients presenting with RA. A total of 508 patients with < 2 years of symptoms were recruited into a multicentre, randomised clinical trial. Patients were allocated to 1 of 4 treatment strategies: 1) sequential DMARD monotherapy starting with MTX; 2) step-up combination therapy from MTX; 3) initial combination DMARD therapy with tapered high-dose prednisolone; and 4) initial combination therapy with infliximab and high-dose MTX. Patients in all the groups were assessed regularly (every 3 months) with the aim of rapidly reducing disease activity to DAS44 < 2.4. A clear benefit was seen in the patients from strategies 3) and 4) with a significantly greater and more rapid improvement in function (as measured by HAQ). These patients also had significantly less progression of radiologic joint damage than patients treated with sequential monotherapy or step-up combination therapy, with 46% of patients from the infliximab group showing no radiologic progression at 1 year.

Most importantly, this study (35) showed that after TNF antagonist therapy had produced remission for 6 months, it was possible to withdraw the TNF antagonist agent and maintain remission in the second year. Remarkably, a proportion of patients were able to cease their MTX therapy also. This has considerable future implications as it represents the ultimate concept of remission, equating to cure (36).

**Conclusions**

"Prevention," "remission," and "cure"

are words now commonly used when discussing the management of patients with RA. These high but realistic goals have been made possible by decades of research. However, more research is required into achieving a drug-free remission, which has been shown to be a possibility. The difficulty lies in the absence of objective criteria for defining remission that includes imaging and immunologic assessment of the disease state, thereby enabling accurate detection of patients who are in "true" remission. These are likely to be the patients who are able to sustain a drug-free remission.

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