

Rheumatoid Arthritis Relapse and Remission – Advancing Our Predictive Capability Using Modern Imaging

Lene Terslev^{1,2}
Mikkel Ostergaard^{1,2}

¹Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup, Denmark;
²Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Abstract: Clinical remission has become an achievable target for the majority of patients with rheumatoid arthritis, but subclinical inflammation as assessed by ultrasound and magnetic resonance imaging (MRI) has been demonstrated to be frequent in patients in clinical remission. Subclinical synovitis has been shown to be linked to both subsequent structural damage progression and a risk of flare, demonstrating that subclinical synovitis represents incomplete suppression of inflammation and questions whether it is appropriate only to use clinical composite scores as treatment target in clinical practice. Maintaining a state of remission has proven important as sustained clinical remission impacts long-term outcome regarding joint damage progression, physical function and quality of life. Treating subclinical inflammation has been attempted and has led to more frequent strict clinical remission and better physical function, but also to more adverse events. Thus, an overall benefit of incorporating imaging goals in treat-to-target strategies has not been documented. However, in patients in clinical remission on biological disease-modifying anti-rheumatic drugs, both ultrasound and MRI may aid in the clinical decision regarding whether drug tapering or even discontinuation should be attempted.

Keywords: ultrasound, magnetic resonance imaging, clinical remission, flare, tapering, subclinical synovitis

Introduction

As emphasized by the 2010 treat-to-target (T2T) recommendations, the treatment goal in patients with rheumatoid arthritis (RA) is to suppress inflammation and thereby prevent pain and joint destruction, and improve functional ability and quality of life. This should be obtained as quickly as possible and preferably within 6 months. Frequent clinical monitoring is suggested, ideally with an interval of 2–3 months, until the goal is achieved, which has been recommended to be set as clinical remission or at least low disease activity (LDA), assessed by the use of composite measures.¹ The T2T recommendations are further supported by the 2019 European League Against Rheumatism (EULAR) recommendations for the management of RA with conventional synthetic (cs) and biological (b) disease-modifying anti-rheumatic drugs (DMARDs).^{6,5}

Different composite measures for determining remission exist, and for many years the most frequently applied in routine care has been the composite Disease Activity Score based on 28-joint count (DAS28). The use of DAS28 <2.6 as a criterion for clinical remission has proved to be better than a conventional strategy not using a DAS28-targeted strategy.^{2,3} It does, however, allow for residual disease activity to

Correspondence: Lene Terslev
Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Valdemar Hansens Vej 17, Glostrup, 2600, Denmark
Tel +45-38632616
Email Terslev@dadlnet.dk

be present despite fulfilling the definition of clinical remission. Therefore, the updated 2016 T2T recommendations and the EULAR treatment recommendations from 2019 now favour American College of Rheumatology (ACR)/EULAR Boolean remission or the simplified or clinical disease activity index (SDAI or CDAI) over DAS28 remission.^{4,5} In particular, the stringent ACR/EULAR Boolean remission seems better to reflect the clinical perception of remission, ie the absence of any signs and symptoms of significant inflammatory disease activity. However, the fact that patient-reported pain is incorporated in the composite remission criteria may, in patients without clinical signs of disease activity, impact their ability to fulfil composite remission criteria.⁶ Although clinical remission has become an achievable target for the majority of RA patients, defining “true” remission can be difficult as the current composite criteria do not take physical function and structural damage progression into consideration. Regarding the latter, it has been demonstrated that erosive progression still occurs in 20–30% of patients in clinical remission, regardless of the composite remission criteria used (DAS28, CDAI, SDAI or ACR/EULAR Boolean remission criteria).^{7–11} Currently, imaging is not part of any composite scores for remission.

Is Clinical Remission a Sufficient Goal?

The discrepancy between ensuring clinical remission and still seeing continued structural deterioration in some RA patients has led to the exploration of potential persistent

silent inflammation, also called subclinical inflammation. Both ultrasound and magnetic resonance imaging (MRI) may be used to assess subclinical signs of inflammatory activity, as both imaging techniques are more sensitive than clinical evaluation for inflammation in joints, tendons and tendon sheaths.^{12–26} This is also the reason for acknowledging the use of ultrasound and MRI for joint assessment in the 2010 ACR/EULAR classification criteria for RA, facilitating an earlier fulfilment of the classification criteria.²⁷

A high number of studies has been able to demonstrate that subclinical inflammation seen by ultrasound and MRI is present in a substantial proportion of RA patients in clinical remission, in both joints and tendons^{12–21,24,25,28} (Figures 1 and 2). Subclinical synovitis is present independent of using DAS28, CDAI, SDAI or even the more stringent ACR/EULAR Boolean remission criteria for determining clinical remission, and its presence is found to be independent of the type of treatment given, ie csDMARD or bDMARD.^{19,23,25,29–32}

In the assessment of subclinical synovitis by ultrasound, the majority of studies applies a grey-scale synovial hypertrophy score >1 as a sign of pathology,^{21,24} as grade 1 synovial hypertrophy itself is a frequent finding in healthy controls^{33,34} and in RA patients with diverging ability to improve.^{34,35} However, most emphasis has been placed on the presence of Doppler activity, although this component is very dependent on the equipment used.³⁶ For optimal assessment of inflammation by MRI, the Outcome Measures in Rheumatology (OMERACT) group recommends that T1-weighted sequences are

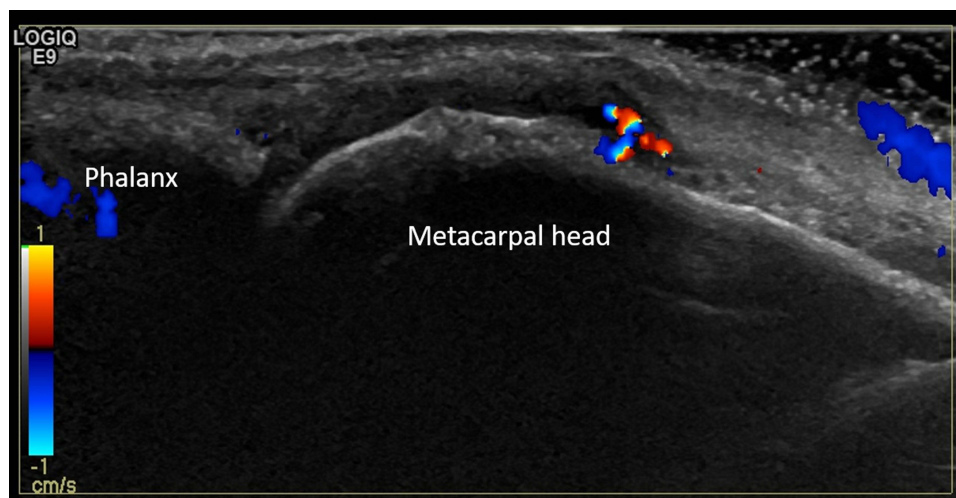


Figure 1 Patient with rheumatoid arthritis in clinical remission. The ultrasound image shows the third metacarpophalangeal joint with grade 2 synovial hypertrophy and grade 2 Doppler activity.

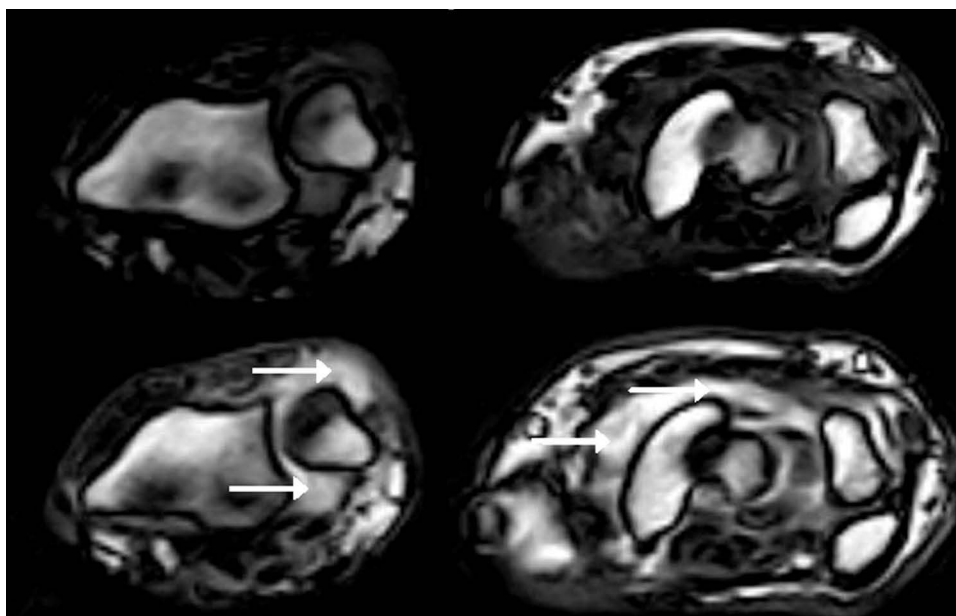


Figure 2 Patient with rheumatoid arthritis in clinical remission. Axial T1-weighted MR images of two sections of the wrist (left: distal radioulnar joint; right: intercarpal joints) with pre-contrast images in the upper row and post-contrast (after intravenous gadolinium contrast injection) images in the lower row. Images show considerable synovitis (arrows).

obtained before and after intravenous injection of gadolinium-containing contrast agent (optimal for assessment of synovitis and tenosynovitis), supplemented with a T2-weighted, fat-suppressed (T2FS) sequence or short tau inversion recovery (STIR), reflecting water content (optimal for bone marrow oedema/osteitis and also well suited for tenosynovitis).^{37,38} Synovitis scores of 1 are frequently seen in healthy controls, while bone marrow oedema is absent or very rare, when the most appropriate T2FS/STIR sequences are used, while less suitable sequences may provide different results.^{39–41}

In subclinical synovitis, the presence of Doppler activity in particular, but also the presence of grey-scale synovial hypertrophy, is related to erosive progression in csDMARD-treated patients, and the absence of ultrasound inflammation (no Doppler signal, grey-scale score ≤ 2) is associated with no radiographic progression.⁴² Furthermore, both subclinical synovitis and tenosynovitis in cs/bDMARD-treated patients have been shown to be related to a risk of flare.^{7,13,14,20,32,43–45} Finally, subclinical synovitis is also related to unsuccessful tapering of bDMARD treatment.^{45,46} In most studies, only the hands were assessed for signs of subclinical synovitis, but some studies have included both large and small joints – up to a total of 42 joints.^{13,14,21,23,30–32,46} Currently, there is no agreement on a reduced joint set for assessing RA patients in remission; however, a study from 2017 found that by

performing ultrasound examination of the hands only, it was possible to capture $\geq 90\%$ of patients with subclinical inflammation, and this approach appears feasible for use in clinical practice for evaluating the disease state in RA patients in remission.²⁴ The ability for MRI to predict erosive progression seems to be related less to the presence of subclinical synovitis than to the presence of osteitis and tenosynovitis, which have both been demonstrated to be independent predictors of 2-year MRI damage progression in RA patients in clinical remission.^{13,17,45,48}

Can Subclinical Synovitis in Remission Be Prevented?

Research has investigated whether adding imaging to the T2T regimen in RA patients could abrogate subclinical disease activity in the state of remission. The randomized controlled ARCTIC trial⁴⁹ investigated whether adding ultrasound information to the treatment decisions in early RA was better than clinical strategy alone, and found that the majority of patients in remission in both groups had subclinical synovitis by ultrasound and MRI after 1 year.²⁸ However, a randomized controlled trial in patients in clinical remission on csDMARDs investigated an MRI T2T strategy, aiming at eliminating osteitis, compared with a clinical T2T strategy.⁵⁰ The study found statistically significantly higher improvements in osteitis, tenosynovitis and total inflammation, and a trend

towards higher improvement in synovitis, in the MRI T2T arm compared to the clinical T2T arm,⁵⁰ although subclinical inflammation was not totally eliminated.

MRI and ultrasound currently appear to have limited validated value as an addition to routine clinical examinations for preventing subclinical synovitis in patients in remission.

Defining Imaging Remission

There is no international agreement on what constitutes imaging remission. For ultrasound, remission is generally perceived as an ultrasound disease state without Doppler activity (Doppler remission) and has been reported to be related to stable remission,⁴³ but different studies put varying emphasis on the presence of synovial hypertrophy by grey-scale ultrasound. Strict ultrasound remission (ie no synovial hypertrophy and no Doppler activity in any joint) has been reported in 7–35% of patients in remission, whereas Doppler remission is more frequent and has been reported in 46–76% of patients.^{19,29,31,32} This indicates that clinical treatment with or without a T2T approach is more likely to result in Doppler remission than a complete absence of imaging signs of synovial hypertrophy.

Also, for MRI, there is no international consensus on how remission should be defined. It could be based on the absence of certain imaging findings, such as absence of MRI synovitis,¹³ potentially not considering grade 1, or lack of bone marrow oedema,^{39,50} or it could be data driven, eg a state in which radiographic progression rarely occurs in RA patients in general (defined by Baker et al,⁵¹ and by Ahmad et al⁵² as synovitis score <3, osteitis score <3 or total inflammation score [osteitis double-weighted] <9) or in RA patients in clinical remission (defined by Gandjbakhch et al,¹⁷ in a cohort of 254 RA patients in clinical remission or LDA, as a synovitis score ≤5), or it could be defined as a state in which clinical flare is rare if a drug is tapered (defined by Brahe et al⁵³ as a total inflammation score <3 based on a sum score of synovitis found in the wrist and metacarpophalangeal joints 2–5).

Treating Subclinical Synovitis in Remission

Treating subclinical inflammation should ideally halt the progression of structural joint destruction and, not least, improve patient outcome over and above a treatment strategy based on conventional clinical and biochemical assessments⁵⁴ (see Box 1). Although it is recognized that

Box 1 Steps for Evidence-Based Documentation of the Relevance of Incorporating Imaging Goals into Treat-to-Target Goals in RA

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| <p>Step 1: Establish that subclinical inflammation can be detected by MRI and/or ultrasonography</p> <ul style="list-style-type: none"> • Document that MRI and/or ultrasonography demonstrate subclinical inflammation in patients with RA in clinical remission |
| <p>Step 2: Establish that subclinical inflammation detected by MRI or ultrasonography is clinically important</p> <ul style="list-style-type: none"> • Document that MRI and/or ultrasonography findings of subclinical inflammation predict any or all of: subsequent structural damage progression; clinical flares during continued therapy; and clinical flares in patients who taper or discontinue therapy • Document that absence of MRI and/or ultrasonography findings of subclinical inflammation predict any or all of: absence of subsequent structural damage progression; absence of clinical flares during continued therapy; and absence of clinical flares in patients who taper or discontinue therapy |
| <p>Step 3: Demonstrate that subclinical MRI or ultrasonography-detected inflammation can be improved by treatment and that the use of this improves key endpoints</p> <ul style="list-style-type: none"> • Document that an imaging-guided treatment strategy (involving therapeutic adjustments in case of certain imaging findings) will improve patient outcome over and above a treatment strategy based on conventional clinical and biochemical assessments |

subclinical synovitis is present in a large majority of patients in remission, only a few studies are available in which treatment of subclinical synovitis has been attempted.

In 2015, a study evaluated the effects of intensifying treatment to prevent joint damage in RA patients in clinical remission (DAS28 <2.6) with a least one Doppler-positive joint.⁵⁵ The patients were randomized 1:1 either to continue the existing treatment with methotrexate or to increase the methotrexate dose. The study found that the Doppler score decreased significantly and the modified total Sharp score (mTSS) on X-ray was significantly suppressed at 52-week follow-up in the group where treatment was intensified compared to the group that continued on the same dose. Although the data are promising, the study has still only been presented as a congress abstract. Ongoing studies (TURA and REVECHO) are currently exploring the role of ultrasound in treating subclinical synovitis, but no data are available at this time.

Regarding MRI, an MRI-guided T2T strategy, aiming at absence of osteitis, was investigated in RA patients in clinical remission and compared with a conventional T2T strategy, aiming at clinical remission. In this randomized controlled clinical trial (IMAGINE-RA), the MRI-guided

T2T strategy did not result in improved DAS28 remission rates or reduce radiographic progression, compared with the conventional T2T strategy.⁵⁰

However, patients who followed the MRI-targeted treatment strategy had improved chances of achieving more stringent remission across all definitions (such as CDAI, SDAI and ACR/EULAR Boolean remission) after 2 years. This also indicates that the achievement of a “deeper” (ie more stringent) state of remission is an achievable goal in patients in DAS28 remission.^{48,56} This is relevant since patients who achieve sustained SDAI and ACR/EULAR Boolean remission have a better long-term outcome (>10 years) regarding joint damage progression, physical function and quality of life.^{57–61} However, it should be noted that the MRI T2T treatment strategy used in the IMAGINE-RA study also led to a higher number of serious adverse events, which were likely to be related to the more intensive treatment administered.

Predicting Flare in Remission

Once remission has been achieved, it is important to maintain remission and avoid flares. Flares are episodes of increased disease activity and involve a deterioration in patient-reported outcomes, such as functional ability and general health, pain and morning stiffness.^{44,60–63} However, flares may also result in more objective changes such as structural damage.

The lowest risk of flares is seen in patients with persistent ACR/EULAR Boolean remission⁶⁴ but, in general, patients with short-term remission (remission interrupted by flares) are more likely to experience radiographic erosive progression compared to patients who achieve persistent remission.⁶⁵

Flares are frequent in RA patients, with 30–50% experiencing a disease flare within the first 2 years of remission.^{60,66} In a study published in 2020, patient-reported flares were associated with increased disease activity by clinical examination and by ultrasound, ie they were demonstrated to be true (objectively confirmed) flares.⁶⁶ Serial imaging by ultrasound and MRI after self-reported flares found the flares to be related to synovial and tenosynovial inflammation, followed by delayed-onset bone marrow oedema.⁶⁷

An important question is whether flares can be avoided. Several studies have investigated the ability of imaging modalities to predict flares in DMARD-treated RA patients.

One study demonstrated that the presence of subclinical tenosynovitis in RA patients in clinical remission was associated with flare. If the tenosynovitis had both grey-scale and Doppler activity present, it was associated with shorter duration of remission (<12 months).²⁰

In another study, subclinical synovitis, defined as the presence of Doppler signal, was associated with an increased risk of flare,²¹ and the presence of concurrent Doppler-positive tenosynovitis and joint synovitis has been shown to predict flare in RA patients in remission, with an odds ratio (OR) and 95% confidence interval (95% CI) of 2.75 (1.45 to 5.20) in crude analyses and 2.09 (1.06 to 4.13) in adjusted analyses.^{21,68} Thus, Doppler-negative joints have been reported to increase the chance of not experiencing a flare,^{43,44} and Doppler-positive findings in at least one joint have been shown to be the main predictor of flare.⁴³ This demonstrates that subclinical synovitis represents an incomplete suppression of inflammation.

Tapering Therapy in Patients in Remission

As remission has become an obtainable goal, there has been interest in assessing the ability to taper or even discontinue DMARD treatment. There are very scarce data in relation to stopping versus continuing cDMARDs in RA patients in clinical remission. One older trial assessed the ability to stop cDMARDs in RA patients in remission, and found that drug discontinuation was associated with a significant increase in flare rate compared to patients continuing their csDMARD treatment;⁶⁹ furthermore, the study found that patients experiencing a flare had difficulties in regaining remission.^{69,70} Although tapering of csDMARDs may be considered,⁵ since it will be successful in some patients, the frequent difficulty in stopping csDMARDs illustrates that RA often is a life-long (incurable) disease requiring continuous therapy.

More attention has been given to the ability to taper bDMARDs, as this is relevant both in relation to reducing costs and regarding safety issues.^{71,72} Hence, according to the EULAR recommendations for the management of RA with csDMARDs and bDMARDs, it is suggested to taper bDMARDs before attempting to taper csDMARD treatment in RA patients on combination therapy.⁵

There is consensus that tapering or discontinuation of bDMARDs should only be attempted in patients in persistent remission, but no clear definition exists on what constitutes “persistent remission”.⁵ Successful dose tapering, and even

discontinuation, has been reported in several clinical trials, but is not achievable in all patients^{73–79} but there is a risk of flare related to both tapering and discontinuation.^{73–80} However, discontinuing bDMARDs is also associated with radiographic progression,^{80,81} which has not been reported when tapering bDMARDs to a lower dose than the standard dose.^{53,81} In the latter study, comprising patients in low disease activity or remission on tumour necrosis factor (TNF)-inhibitor therapy, no radiographic progression (no increase in hands and feet Sharp–van der Heijde score) was found after 48 weeks in 90% of the patients continuing on standard dose and, similarly, no erosive progression was seen in 75% of the patients receiving half of standard dose and in 55% of the patients discontinuing TNF-inhibitor therapy (progression in the group with discontinued therapy was statistically significantly higher than in patients continuing the standard dose, even though all patients in tapering/discontinuation groups resumed the full standard dose in case of flare).⁸¹

Tapering may be obtained by spacing the treatment intervals or by reducing the actual drug dose. Both ultrasound and MRI, based on their ability to detect subclinical signs of inflammation, have been investigated for their value for selecting patients who could successfully taper or even discontinue bDMARD treatment. Most studies apply a tapering approach when investigating the possibility for discontinuation,^{46,47,53} but some studies discontinue treatment without prior tapering.⁸² In studies investigating tapering of bDMARDs in the attempt to discontinue, it has been shown that low baseline MRI combined inflammation score and low baseline MRI combined damage scores are independent predictors for successful tapering to half or two-thirds of standard dose at 2-year follow-up.⁵³ The absence of Doppler activity in joints has been reported both to be predictive of successful tapering and to be without predictive value.^{23,46}

Furthermore, a lower Doppler sum score of 24 joints prior to tapering may predict successful discontinuation of bDMARDs at 2-year follow-up.²³ In this study, a one-unit increase in Doppler 24-joint sum score decreased the odds for achieving successful discontinuation at 2 years by 56%.²³

Only one study attempted discontinuation of bDMARD treatment without prior tapering,⁸² and found a significant difference in the degree of residual inflammation at the time of discontinuing bDMARDs between patients who could successfully discontinue treatment and those who could not, with higher residual inflammation in the latter group. However, the predictive value could not be established owing to the too small sample size.

In the imaging studies where imaging parameters were incorporated as potential predictors, demographic data, such as short disease duration, a maximum of one previous bDMARD and male gender, have also been reported to be predictors of successful tapering.^{53,82–84} Furthermore, one study found the DAS28 level prior to tapering to be predictive of successful tapering.⁴⁶

Conclusion

Ultrasound and MRI are sensitive imaging modalities, which have demonstrated that subclinical synovitis, tenosynovitis and osteitis are frequently present in RA patients in clinical remission and may impact erosive progression and the risk of flare. This questions whether it is appropriate to use clinical composite scores alone for establishing remission. Treating subclinical inflammation has led to more frequent strict clinical remission and better physical function, but also to more adverse events. Thus, an overall benefit of incorporating imaging goals in T2T strategies has not been documented. Both MRI and ultrasound appear promising in aiding in the decision on whether tapering or discontinuing bDMARD treatment will be successful.

Disclosure

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