

# The Role of Advanced MRI in the Development of Treat-to-Target Therapeutic Strategies, Patient Stratification and Phenotyping in Rheumatoid Arthritis

Ali Mobasher

State Research Institute Centre for Innovative Medicine <https://orcid.org/0000-0001-6261-1286>

Mark Hinton

Image Analysis Group

Olga Kubassova (✉ [olga.kubassova@ia-grp.com](mailto:olga.kubassova@ia-grp.com))

Image Analysis Group

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## Research Article

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## Abstract

In this commentary we discuss the potential of advanced imaging, particularly Dynamic Contrast Enhanced (DCE) magnetic resonance imaging (MRI) for the objective assessment of disease progression in rheumatoid arthritis (RA). We emphasise the potential DCE-MRI in advancing the field and exploring new areas of research and development in RA. We believe that different grades of bone marrow edema (BME) and synovitis in RA can be examined and monitored in a more sensitive manner with DCE-MRI. Future treatments for RA will be significantly improved by enhanced imaging of BMEs and synovitis. DCE-MRI will also facilitate enhanced stratification and phenotyping of patients enrolled in clinical trials.

## Commentary

Rheumatoid Arthritis (RA) is an inflammatory disease affecting about 1.3 million adults in the United States and many millions more across the world. RA causes pain, swelling, stiffness, and loss of function in synovial joints and has a huge socioeconomic impact due to the high morbidity associated with it. It is estimated that between 0.5 % and 1 % of the human population is affected worldwide, and between 25 and 50 new RA cases evolve in a population of 100,000 [1]. Several features distinguish RA from other kinds of arthritis. RA can manifest itself rapidly and often in a symmetrical pattern. This means that if one knee or hand is involved, the other one is also affected. The disease often affects the wrist joints and the finger joints closest to the hand, but it can also affect other parts of the body besides the joints. RA occurs in all races and ethnic groups [2]. The cause of RA is not known, but it is believed to be an autoimmune disease [3]. Although the disease often begins in middle age and occurs with increased frequency in older people, children and young adults also develop it. RA occurs much more frequently in women than in men.

New patients with RA require a rapid and definitive diagnosis and treatment initiation with disease-modifying antirheumatic drugs (DMARDs) to retard or stop progression, stimulate remission, control disease manifestations and reduce the overall disease burden [4]. This highlights the potential of advanced imaging, particularly magnetic resonance imaging (MRI) in disease diagnosis and management and in the evaluation new drugs in clinical trials. In a recent issue of JAMA, published on 5 February 2019, Møller-Bisgaard et al reported on whether the integration of MRI into clinical rheumatology practice can enhance strategies for monitoring disease activity and determining whether the therapy being tested is effective in slowing down joint damage and disease progression [5]. The key objective of this study was to determine whether an MRI-guided treat-to-target strategy versus a conventional clinical treat-to-target strategy improves outcomes in patients with RA in clinical remission. The study was part of the IMAGINE-RA randomized clinical trial, conducted in nine hospitals in Denmark. The presence of bone marrow edema (BME) in the wrist or MCP joints was used as a marker to escalate a predefined treatment algorithm versus a conventional clinical treat-to-target strategy can improve outcomes in patients with RA in clinical remission. BME occurs in various forms of inflammatory and non-inflammatory arthritis and probably represents infiltration of inflammatory cells and vascular perfusion changes within the bone marrow. BME is common in early RA and is associated with erosive progression and poor functional

outcomes [6]. It is also well established that the location and extent of BME in psoriatic arthritis (PsA) is different from those seen in RA and osteoarthritis (OA) [7, 8], suggesting that treatment monitoring strategies must incorporate MRI as a key imaging modality and biomarker. However, the recent study by Møller-Bisgaard and colleagues showed that MRI-guided treat-to-target strategy using BME compared with a conventional treat-to-target strategy did not result in improved disease activity remission rates and it did not reduce radiographic progression over 2 years in this particular patient cohort. Although this negative study does not support the use of BME as a biomarker in MRI-guided strategy for treating patients with RA in clinical remission and low disease activity, it does offer exciting opportunities for future research.

Despite the study's conclusion that making treatment decisions based upon BME on MRI, is not clinically helpful, there are alternative and more promising possibilities.

As stated earlier, it is established that BME is an important predictor of the disease progression in patients with inflammatory arthritis such as RA and can be better understood with more advanced imaging sequences such as Dynamic Contrast Enhanced (DCE)-MRI [9]. This MR sequence of rapidly acquired images after the Gadolinium-based contrast agent injection was collected as a part of the IMAGINE-RA imaging protocol. Due to its dynamic as opposed to static nature, DCE-MRI visualises the vascularisation levels of the oedema lesions, thus looking into the oedema's level of perfusion and inflammation, as though it was a heterogenous tumor. Published work by Brown et al has provided compelling evidence to suggest that the best predictor of progressive erosion in RA is Doppler ultrasound, implicating a key role for BME and perfusion in driving diseases progression[10]. As previously shown by Hodgson et al[11, 12], DCE-MRI can be used to quantify the perfusion and treatment changes in the bone compartment. This approach can potentially help to distinguish between inflammation, repair or trauma in the bone, which all look oedema-like on static MRI sequences and reveal treatment responses as measured with the AI-driven methodologies that are based on the objective quantitative assessment of DCE-MRI time vs intensity curves [9]. It has been shown that the perfusion measured this way is predictive of treatment response, despite unchanged or persistent BME.

These studies and emerging evidence in the literature would seem to indicate an opportunity to use DCE-MRI image datasets from the same or similar trials to explore the heterogeneity of BME and synovial perfusion/inflammation in order to better phenotype RA patients and show vascular responses following various treatment regimens that can complement the widespread and validated static scoring systems such as RAMRIS. There is also a unique opportunity to examine the overlap between RA and cardiovascular diseases that impact on vascular perfusion, especially in bone, implicating endothelial dysfunction and angiogenesis impairment in the cardiovascular system [13] and the ageing vasculature of arthritic joints [14].

In summary, we believe that advanced imaging has the potential to facilitate disease diagnosis, monitor disease progression and enhance clinical trials of new RA treatments. We propose that bone marrow is an important site for looking at pathological changes that drive joint damage and destruction in RA and

other joint diseases such as PsA and even in the inflammatory phenotypes of OA [15, 16]. It has been proposed that imaging remission should only be selected as a target if it can be convincingly demonstrated that it can be treated and that the clinical outcome for patients will be improved by trying to achieve imaging remission in addition to clinical remission [17]. Our hypothesis is that different grades of BME and synovitis examined with DCE-MRI will be predictive of erosive progression regardless of treatment strategy in patients with RA in clinical remission and low disease activity. We would advocate the importance of using more sensitive imaging modalities such as DCE-MRI to test, in a more targeted way, precision treatments in RA. We propose that existing and future treatments guided by imaging, biomarkers and deeper phenotyping of the patients will deliver better outcomes in smarter clinical trials and in the rheumatology clinics of the future. We are confident that this concept will appeal to a broader audience in rheumatology research and clinical practice especially regarding the importance of using more sensitive measures and biomarker tools to better phenotype arthritic diseases and stratify patients for smarter clinical trials. Advances and new directions in the field of MRI [18] will reflect potential treatment changes in future RA treatments, guided by DCE-MRI.

## Declarations

Declarations of interest: Olga Kubassova is CEO and shareholder in IAG, Image Analysis Group and has received consultancy, speaker and travel fees from various biotechnology and pharmaceutical companies. Ali Mobasher is President-Elect of the Osteoarthritis Research Society International (OARSI), an employee of a government of Lithuania and European Commission funded research institute and a consultant to IAG, Image Analysis Group.

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