Review Article

The Clinical Utility of Musculoskeletal Ultrasound for Disease Activity Evaluation and Therapeutic Response Prediction in Rheumatoid Arthritis Patients: A Narrative Review

CME Credits

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Abstract

Rheumatoid arthritis (RA) is characterized by persistent synovitis and joint/bone destruction. There is an unmet need to predict the therapeutic response to disease-modifying anti-rheumatic drugs (DMARDs) and achieve a treat-to-target goal. Musculoskeletal ultrasound (MSUS) is widely used to identify structural change and assess therapeutic response in RA. This review aims to summarize the available evidence regarding the clinical application of MSUS in evaluating disease activity and predicting therapeutic responses to DMARDs. We searched the MEDLINE database using the PubMed interface and reviewed English-language literature from 2000 to 2022. This review focuses on the updated role of MSUS in assessing disease activity and predicting therapeutic responses to DMARDs in RA patients. MSUS is now widely applied to identify articular structural change and assess the disease activity of RA. Combined use of gray scale and power Doppler MSUS is also superior to clinical assessment and laboratory examination in evaluating disease activity of RA. With portable use, good viability, and high sensitivity to articular inflammation, MSUS would be useful in assessing therapeutic response to biologic/targeted synthetic DMARDs (b/tsDMARDs) in RA patients. Given MSUS could also detect subclinical inflammation in a substantial proportion of RA patients with clinical remission, it is recommended to assess b/tsDMARDs-treated RA patients who have achieved low disease activity or remission. Although substantial literature data have revealed clinical utility of MSUS for monitoring disease activity and evaluating therapeutic response in RA patients, the evidence regarding its predictive value for the effectiveness of b/tsDMARDs is limited.

Keywords: Disease activity, disease-modifying antirheumatic drugs, rheumatoid arthritis, therapeutic response, ultrasound

Introduction

Rheumatoid arthritis (RA) is a multifactorial chronic arthritis characterized by persistent synovitis, joint/bone destruction, and poor life quality.[1,2] The therapeutic drugs include conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic/targeted synthetic DMARDs (b/tsDMARDs).[1,3-10] Despite the therapeutic effectiveness of b/tsDMARDs, a substantial proportion (20%–30%) of RA patients still show poor response.[8,11] In pursuit of a treat-to-target goal[12] and reduction of the economic burdens of b/tsDMARDs, there is an unmet need for utilizing imaging modalities to properly assess disease activity or accurately predict the therapeutic effectiveness of b/tsDMARDs in RA patients.

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Musculoskeletal ultrasound (MSUS) is now widely applied to identify synovitis, tenosynovitis, bone erosion, and soft tissue changes in RA patients; therefore, it is helpful for early diagnosis of RA.[13-15] With the help of a high-frequency linear array transducer, grayscale MSUS helps visualize inflammatory activity and structural damage of the affected joints, even in small joints, in RA.[16,17] Doppler MSUS can further reveal blood flow on the synovial membranes and is a good tool for evaluating the inflammatory activity of joints in RA.[18-20]

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Although plain or conventional radiographic assessment of peripheral joints has served as a standard tool for documenting the extent of joint destruction in RA, there exist difficulties in evaluating the complex anatomical structure of the joints involved in an early stage. Currently, magnetic resonance imaging (MRI) is considered a sensitive imaging modality for detecting synovitis, joint effusion, and early bone erosions;[21] however, it has some disadvantages as it is expensive and not easily accessible.[22] With low cost, portable use, and good patient compliance, MSUS with power Doppler (PD) would be recommended as the first-choice imaging modality for RA patients.[23] Besides, MSUS is superior to clinical assessment and laboratory examination in identifying structural lesions and diagnosing early RA.[16,24-26] Therefore, the European League Against Rheumatism (EULAR) endorses the importance of MSUS in RA management, including diagnosis, prognosis, remission surveillance, and therapeutic response.[27]

Baseline RA disease activity is linked to the progression of joint damage[28,29] and is also a useful predictor of therapeutic response to csDMARDs.[29,30] Likewise, baseline MSUS may help predict disease flare after treatment.[31,32] or therapeutic responses in RA patients.[33,34] However, Sundin *et al*. revealed that the baseline MSUS does not improve the prediction models for disease remission in RA patients.[35] This review aims to summarize the current-related evidence to clarify the role of MSUS in assessing disease activity and evaluate the inconsistent results regarding its predictive value for therapeutic response in RA patients.

Materials and Methods

Search strategy

The present review focuses on the existing evidence of MSUS as a modality for assessing disease activity and predicting therapeutic response to b/tsDMARDs in RA patients. We searched the MEDLINE database using the PubMed interface and reviewed the English-language literature up to November 30, 2022, from 2000 to 2022. The search keywords for this updated review included MSUS, ultrasound, sonography, clinical utility, prediction, predictor, disease activity, therapeutic response, csDMARDs, bDMARDs, tsDMARDs, Janus kinase inhibitors (JAKi), and RA. Duplicates and manuscripts with incomplete data have been excluded. The details of the search strategy are illustrated in Figure 1.

Study selection

Two authors (CC Chen and DY Chen) independently assessed the titles and abstracts identified by the search described above and retrieved the relevant full-text articles. One author (DY Chen) evaluated the full-text articles for eligibility. We selected articles, including clinical trials, RA cohorts, case reports, and case–control studies, if they were relevant to the clinical utility of MSUS in evaluating disease activity and the therapeutic response in RA patients.

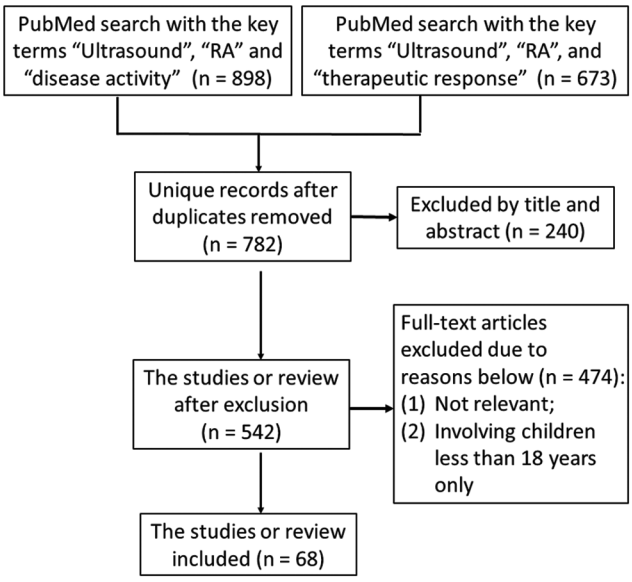

Figure 1: The flow diagram of the literature selection process [Search conducted on 30 November 2022]. Duplicates and manuscripts with incomplete data have been excluded

Data extraction

The authors extracted data from these studies electronically. From each study, we recorded Information regarding MSUS, ultrasound, sonography, clinical utility, prediction, predictor, disease activity, therapeutic response, csDMARDs, bDMARDs, tsDMARDs, JAKi, and RA. The csDMARDs consist of methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, and cyclosporine. The bDMARDs comprised tumor necrosis factor (TNF)-α inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab), non-TNF-α inhibitors (tocilizumab, abatacept, or rituximab), and JAKi (tofacitinib, baricitinib, and upadacitinib).

Results

The utility of musculoskeletal ultrasound for assessing disease activity and therapeutic response to disease-modifying anti-rheumatic drugs in rheumatoid arthritis patients

As illustrated in Table 1, MSUS is now widely applied to identify structural change and assess the disease activity of RA.[13-16,36,37] PD-MSUS offers extended dynamic range over that provided by conventional color Doppler imaging. Therefore, PD-MSUS could reveal synovial proliferation and vascularity,[18,38] and several studies demonstrated that PD-MSUS was useful for monitoring disease activity and therapeutic response to bDMARDs in RA patients.[38-40] Reiche *et al*. demonstrated that PD-MSUS could detect the onset of disease activity before worsening clinical manifestations in RA patients receiving therapy with rituximab, a monoclonal antibody directed against B-cell marker CD20.[41] Bellis *et al*. also reported that MSUS could detect tenosynovitis and might be the imaging predictor for disease flares in RA

Table 1: The studies indicating clinical utility of musculoskeletal ultrasound (MSUS) for disease activity evaluation and therapeutic response prediction in patients with rheumatoid arthritis (RA)

Authors	No. of the patients	Main results	Ref. No.
		Role for evaluating disease activity or therapeutic response	
Naredo *et al*. [2005]	94 patients	(1) MSUS detected more joints with effusion than clinical examination; (2) MSUS findings correlated better with CRP and ESR than clinical measures.	[16]
Ceccarelli *et al*. [2022]	102 patients treated with JAKi (41 tofacitinib and 61 baricitinib)	(1) A significant reduction in both total and PD-MSUS scores parallels the decrement of activity; (2) PD-MSUS and tenosynovitis scores significantly correlated with changes in DAS28-CRP.	[34]
Kaeley *et al* [2016]	309 patients with inadequate response to methotrexate therapy	After 24-week adalimumab therapy, (1) PD-MSUS synovial scores correlated poorly with DAS28, and (2) 70% patients with remission had US-detected synovial vascularity.	[38]
Naredo *et al* [2008]	278 patients treated with TNF-α inhibitors	A significant parallel improvement in PD-MSUS scores and DAS28 was found during 12-month follow-up period.	[39]
Sarzi-Puttini *et al* [2018]	132 active patients treated with certolizumab	MSUS showed rapid improvement in synovial proliferation and PD signal at week 8, and maintained to week 52.	[40]
Reiche *et al* [2014]	20 patients treated with rituximab	(1) MSUS synovitis scores significantly decreased after 6- and 12-month therapy; (2) PD-MSUS could detect the flare of disease activity before worsening of clinical symptoms.	[41]
Bellis *et al*. [2016]	427 patients in clinical remission	(1) The presence of tenosynovitis was 52.5% was detected by GS-MSUS and 22.7% by PD-MSUS; (2) the presence of synovitis was 71.6% by GS-MSUS and 42% by PD-MSUS; (3) The presence of radiographic erosions was associated with GS- and PD-<SUS synovitis.	[42]
Mortada *et al*.[2021]	140 patients	(1) The U9 MSUS scale was significantly associated with CDAI, DAS28-ESR, and functional status (HAQ); (2) The U9 scale could distinguish different grades of RA activity; (3) A significant parallel decrease was detected in clinical and MSUS scales at the follow-up assessment.	[49]
Zhou *et al*. [2017]	151 patients (22 patients treated with certolizumab, CZP)	(1) After CZP therapy, US7 scores and MMP-3 levels were significantly decreased at week 2; (2) The mean changes in US7 scores at week 12 and 24 were significantly higher in responders (ACR50 and ACR70) than the non-responders.	[50]
Aga *et al*. [2016]	118 early RA and 212 established RA	The MSUS in RA 9 joint/tendon (USRA9) score could be useful for monitoring articular inflammation	[51]
Epis *et al*. [2014]	6 active patients treated with tocilizumab	The results of MSUS evaluations mirrored that of clinical parameters (DAS28-ESR, DAS28-CRP, VAS score, and HAQ).	[52]
Kawashiri *et al*. [2021]	59 patients treated with abatacept	MSUS scores and clinical disease activity were significantly reduced after 6-month abatacept therapy.	[53]
Germano *et al*. [2022]	52 patients treated with tofacitinib	(1) MSUS joint and tendon scores significantly reduced at week 2, 4, 12, and 24; (2) The decrement of MSUS joint scores was correlated with the reduction of CRP at week 24.	[54]
D'Agostino *et al*. [2016]	89 patients treated with abatacept	The earliest PD-MSUS sign of improvement in synovitis was at week 1, with continuous improvement to week 24.	[62]
Leng *et al*. [2016]	82 patients treated with infliximab	(1) The 7-joint US (US7) scores were significantly correlated with that of 12-joint US (US12); (2) Strong correlations were observed between US7 scores and DAS28, HAQ, and CRP levels.	[78]
		Role for predicting therapeutic response	
Naredo *et al* [2015]	77 patients treated with bDMARDs, in sustained clinical remission	Baseline global score of PD-MSUS synovitis as an independent predictor of bDMARDs tapering failure.	[32]
Razmjou *et al* [2020]	25 patients treated with tofacitinib	Baseline PD-MSUS and multi-biomarker disease activity score could predict CDAI and DAS28 responses at week 12.	[33]
Naredo *et al* [2008]	278 patients treated with TNF-α inhibitors	Time-integrated values of joint PDMS-US signal could predict the progression of radiographic erosion and total radiographic score.	[39]
Christensen *et al*. [2014]	120 patients scheduled for treatment with DMARDs	Central pain sensitization and inflammation detected by PD-MSUS scores as prognostic factors for therapeutic response.	[59]
Christensen *et al*. [2016]	103 patients scheduled for treatment with DMARDs	(1) Baseline MSUS scores could predict DAS28 response; (2) MSUS score was significantly correlated with change in DAS28.	[60]
Morris *et al*. [2021]	54 patients treated with tocilizumab	(1) Baseline and 12-week PD-MSUS change could predict clinical activity CDAI at week 24; (2) Baseline 34-joint PD-MSUS score was associated with DAS28-ESR ≧1.2 response.	[61]
Kawashiri *et al* [2017]	39 patients treated with bDMARDs	The change of GS/PD MSUS scores at week 12 could predict DAS28 response at week 24.	[63]

ACR: American College of Rheumatology; ACR50: an improvement of at least 50% of the initial ACR composite index; ACR70: an improvement of at least 70% of the initial ACR composite index; bDMARDs: biological DMARDs; DMARDs: disease-modifying anti-rheumatic drugs; CDAI: clinical disease activity index; CRP: C-reactive protein; DAS28: Disease activity score for 28-joints; ESR: erythrocyte sedimentation rate; GS-MSUS: gray scale-MSUS; HAQ: Health Assessment Questionnaire; JAKi: Janus kinase inhibitors; PD-MSUS: power Doppler-MSUS; TNF-α: tumor necrosis factor-α

patients.[42] Therefore, MSUS would be an optimized tool for diagnosing, monitoring, and treating tenosynovitis in RA patients.[43] Besides, PD-MSUS combined with an intravenous ultrasound contrast agent may also help evaluate synovial inflammation and therapeutic response in RA patients.[44] Schueller-Weidekamm *et al*. revealed that contrast-enhanced pulse-inversion harmonic imaging and PD sonography enabled the detection of synovial perfusion change after intra-articular corticosteroid therapy.[45]

MSUS is more precise than clinical examination in identifying structural lesions,[16,25,26] and thereby superior to the 28-joint disease activity score that underestimates radiographic progression risk in nearly 20% of RA patients.[46] With portable use, good viability, and high sensitivity to articular inflammation, MSUS would be useful in assessing disease activity[16-20,47] and evaluating therapeutic response to DMARDs in RA patients. Currently, there are many proposed sets of MSUS scores.[48] Mortada *et al*. demonstrated that the U9 MSUS scale including eight joints showed a good construct (convergent and discriminative) validity and could be used to assess disease activity and monitor therapeutic response in RA patients.[49] Zhou *et al*. revealed that 7-joint MSUS scores could effectively reflect disease activity and therapeutic response to certolizumab pegol, one of the TNF-α inhibitors.[50] Aga *et al*. also reported that the 9-joint tenosynovitis score could help monitor inflammation in RA patients.[51] Epis *et al*. demonstrated that the responsiveness to tocilizumab therapy assessed by MSUS mirrored that assessed with clinical parameters in six patients with active RA.[52] Kawashiri *et al*. also evaluated the therapeutic effectiveness of b/tsDMARDs in RA patients based on clinical response, MSUS findings, and biomarker assessment. They found that serum bone biomarkers levels could help predict the ultrasonographic response to abatacept.[53] Germanò *et al*. assessed therapeutic response to tsDMADs (tofacitinib) in RA patients using the EULAR-the Outcome Measures in Rheumatology (OMERACT) US scoring system and observed a persistent reduction of MSUS inflammation signs paralleling clinical improvement.[54]

Given the clinical utility of MSUS for assessing disease activity and therapeutic response to DMARDs in RA patients, D'Agostino *et al*. proposed the novel algorithms incorporating MSUS to monitor disease activity and assess RA's therapeutic response.[55] Möller *et al*. also recommended using MSUS to evaluate disease activity and therapeutic effectiveness in RA patients.[56]

The utility of baseline musculoskeletal ultrasound for predicting therapeutic response to disease-modifying anti-rheumatic drugs

It is worth researching whether baseline MSUS can help predict the therapeutic response to b/tsDMARDs to improve the cost-effectiveness of medication. Naredo *et al*. revealed that the baseline global score of PD-MSUS synovitis was identified as an independent predictor of bDMARDs tapering failure.[32] Christensen et al. used a summed Doppler score, incorporating Szkudlarek's Doppler score[57] and a semiquantitative assessment of tenosynovitis,[58] to predict therapeutic response to bDMARDs in RA.[59] Christensen *et al*. also observed that baseline PD-MSUS was a useful predictor for the change in disease activity or clinical response in "real-life" RA patients.[60] Morris *et al*. revealed that baseline PD-MSUS and 12-week PD-MSUS change could predict clinical response to the ensuing 24 weeks of tocilizumab therapy.[61] D'Agostino *et al*. demonstrated that early improvement of Global OMERACT-EULAR Synovitis Score at week 12 could predict therapeutic response to abatacept at week 24.[62] Razmjou *et al*. revealed baseline PD-MSUS score as a predictor of clinical response to tofacitinib, one of the tsDMARDs, in RA patients.[33] Ceccarelli *et al*. observed that combined use of PD-MSUS and tenosynovitis scores could predict the therapeutic response to JAKi.[34] Interestingly, poor improvement of MSUS synovitis scores had a good predictive value for nonresponse to bDMARDs therapy assessed at week 24.[63]

Discussion

RA, a chronic autoimmune arthritis, is characterized by synovial inflammation and hyperplasia, cartilage degradation, and bone erosions.[1,2] To achieve the tight control strategies,[12] there is an unmet need for utilizing imaging modalities to assess disease activity and predict the therapeutic effectiveness of DMARDs in RA patients. Combined use of gray scale and PD-MSUS is useful to depict structural (i.e., bone erosion, cartilage damage, articular effusion, and tendon lesion) and inflammatory abnormalities (i.e., synovitis and tenosynovitis) in RA.[13-15,27,42,43,64,65] Recently, the EULAR-OMERACT-EULAR ultrasound taskforce develop an international, consensus-based, RA synovitis scoring system evaluating gray scale and PD components and their combination and demonstrated the system is highly reliable.[27,66] Considering that no ideal MSUS scoring system has been identified as yet, imaging-based predictor models do not perform significantly better than models based on clinical and laboratory assessment in RA patients.[35] Thereby, MSUS is still not included in the standard procedures recommended by ACR or EULAR for predicting therapeutic response to b/tsDMARDs in RA patients.[67]

Given that MSUS could detect subclinical inflammation in a substantial proportion of RA patients in clinical remission,[68-71] D'Agostino *et al*. recommended using MSUS to assess b/tsDMARDs-treated RA patients who have achieved low disease activity or remission.[55] If there is subclinical synovitis detected by MSUS, a change or optimization of the DMARDs regimens should be considered.[55] Therefore, MSUS appears to be the most feasible measure to detect inflammatory activity in difficult-to-treat patients in whom there is a doubt about the presence of inflammation, particularly in those with obesity or concomitant fibromyalgia.[72]

Currently, there is no standard for the number of joints to be examined by MSUS in RA patients. Naredo *et al*. demonstrated that a simplified 12-joint PD-MSUS score compared to a

comprehensive 44-joint examination of 160 RA patients was valid, feasible, and responsive to change.[73] Hammer and Kvien analyzed the results from studies examining the different numbers of joints and observed similar sensitivity between examining 7 joints and 78 joints.[74] Although the simplest and convenient evaluation system is the 7-joint MSUS,[75] the minimal number of joints included in an MSUS assessment remains unclear.[76] These discrepancies may hamper the use of a sum score to determine the overall level of disease activity in RA patients. In comparison with contrast-enhanced MRI, MSUS is operator dependent. However, Albrecht *et al*. reported good-to-excellent interobserver and moderate intermachine reliability of PD-MSUS in assessing disease activity and therapeutic response in a longitudinal arthritis study.[77]

There are some limitations in this review. Regarding the quality of the searched literature data, some included articles were case reports, case series, or small-sized cohorts. Due to the various definitions of structural damage detected by MSUS and the different numbers of joints examined and evaluated for synovial inflammation,[73-75,78] there exists an added heterogeneity in the clinical utility of MSUS for assessing disease activity in RA. Finally, the different MSUS scoring systems employed in the clinical setting in the literature data led to another heterogeneity in the therapeutic response assessment in RA patients in this review.

Conclusion

Although substantial literature data have revealed the clinical utility of MSUS for monitoring disease activity and evaluating therapeutic response in RA patients, the evidence regarding its predictive value for the effectiveness of DMARDs is limited. In the future, we look forward to an algorithm combining the MSUS scoring system and clinical assessment or serological markers to help optimize DMARDs therapy and achieve a treat-to-target goal. Besides, with the progressively improving resolution of MSUS images and more sophisticated integration of artificial intelligence with accumulating literature data, MSUS will become ever more instrumental in rheumatology practice.

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Conflicts of interest

Prof. Der-Yuan Chen, an editorial board member at *Journal of Medical Ultrasound*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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