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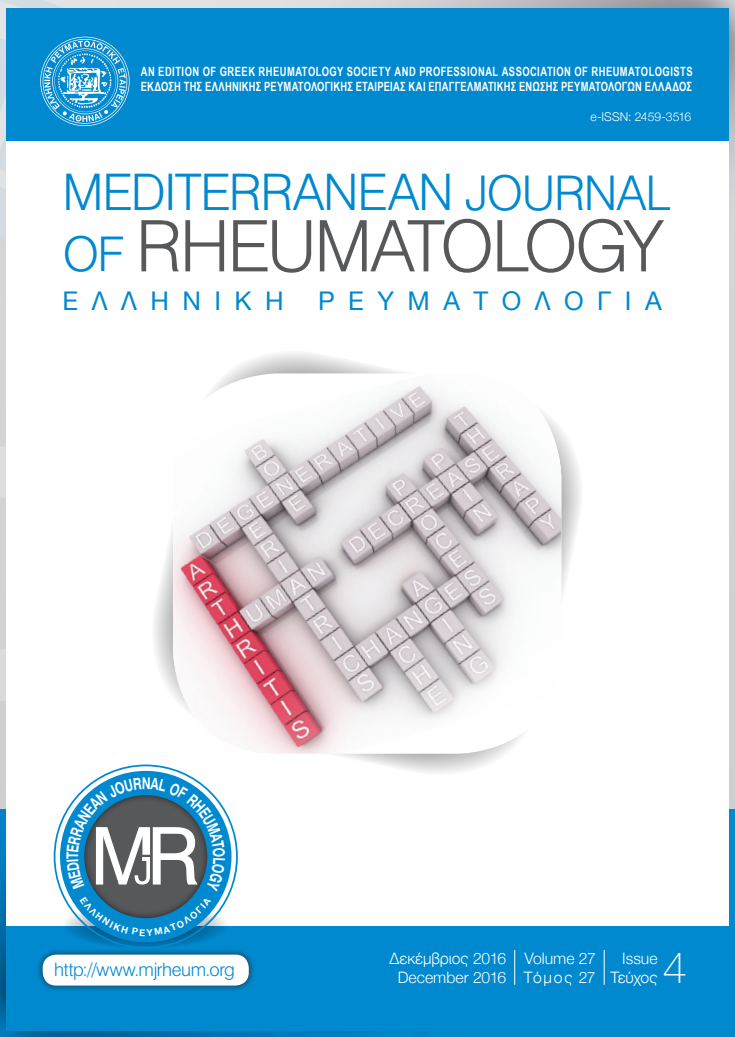

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EDITORIAL

Commentary: Musculoskeletal Ultrasound in Rheumatoid Arthritis: does it still deserve the same enthusiasm?

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ABSTRACT

Musculoskeletal ultrasound (MSUS) is thought as a major advance in the diagnosis and management of rheumatic diseases, predominantly inflammatory arthritides. The ability of the method to detect subclinical synovitis and guide treatment strategies accordingly has been indicated by several observational studies showing an association between MSUS-detected synovitis and eventual treatment outcome. However, two recent interventional studies have tested this hypothesis with largely negative results. The implications of these findings to routine clinical practice and future research areas are discussed in this commentary.

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There is no doubt that musculoskeletal ultrasound (MSUS) reflects a major advance in the imaging of rheumatic diseases. In inflammatory polyarthritis, the availability of portable ultrasound machines, non-ionizing radiation nature, "bedside" use, real-time dynamic examination and ability to evaluate multiple joints in one sitting, has rendered ultrasound a valuable diagnostic tool, facilitating the indispensable clinical examination. These advantages are hindered by some intrinsic limitations such as the need for experienced operators, significant inter- and intra-observer variability and the cost associated with the best possible quality of the equipment, which in several settings may not be adequately reimbursed.

Musculoskeletal Ultrasound is an additional tool that might help the clinician to differentiate true inflammatory arthritis from other painful conditions or comorbidities, such as osteoarthritis, fibromyalgia, etc. The expansion of the use of MSUS has coincided with the development and implementation of the Treat-to-Target (T2T) treatment strategies for rheumatoid arthritis (RA), that aim to achieve complete remission or at least low disease activity in all RA patients. In this context, ultrasound has been shown to be very sensitive in the detection of subclinical synovitis, which in turn has been associated with prediction of flares and progression of radiological damage.[1,2] Several studies have suggested that regular assessment of RA patients with MSUS could lead to alterations in treatment decisions in 25-40% of them,[3] either by intensifying treatment if "silent" subclinical synovitis is detected, or by de-escalating treatment if no evidence of subclinical synovitis is found. The question as to whether such an approach would alter eventual outcome remained open until recently.

Two recent studies have provided new evidence and add significant controversy as to the usefulness of MSUS for monitoring disease activity in RA and modifying treatment decisions. The TaSER study[4] was the first randomized controlled trial of its kind, where two T2T treatment strategies were compared with each other, with the second one incorporating MSUS data in the evaluation of disease activity. In this study, 111 matched patients with RA or undifferentiated arthritis, with duration of symptoms <1 year, were randomized to a T2T treatment strategy in order to achieve low disease activity target, either according to the conventional DAS28 assessment (<3,2) or to a combined DAS28-ESR/MSUS assessment (total power Doppler joint count ≤1). Although the patients under MSUS monitoring received more intensive treatment with disease-modifying antirheumatic drugs (DMARDs), improvement in both clinical (DAS44) and imaging (RAMRIS) outcomes after 18 months of follow-up were the same between the two groups. Rate of adverse events was also similar. The only difference noticed was associated with remission outcomes (DAS44, but not with ACR/EULAR-Boolean), where the MSUS-assisted treatment strategy showed slightly better results (DAS44<1.6: control 43%- intervention 66%, p=0,03).

Similar findings were even more recently observed in another relevant study from Norway, the ARCTIC study.[5] In this, 122 RA patients with disease duration <2 years were randomized to either a conventional way of treatment escalation or to one based on MSUS assessment. After 16 and 24 months of follow up, there were no differences in clinical or radiological outcomes between the two groups, since similar percentages of patients (22% vs 19%) achieved remission. Serious adverse event rate was also the same in the two groups. Although there are a few differences between the two studies (e.g., disease duration, undifferentiated arthritis, power Doppler outcome, study duration, treatment steps), they both show that the addition of MSUS assessment to the conventional way of handling RA patients does not offer any significant advantage to patient outcomes, either in terms of (clinical or radiographic) efficacy or in terms of safety. This is very important for everyday clinical practice, since it has always been a dilemma how to handle patients in clinical remission with evidence of MSUS synovitis. Treatment escalation based on MSUS detected subclinical synovitis has never been formally tested previously, and based on the aforementioned findings, it appears that US assessment does not provide better clinical or imaging results. The percentage of patients that achieved DAS remission was arithmetically slightly higher in the US group in both studies; this fact should be taken into account, especially in view of the limitations of both studies such as the small number of patients and the highly selective population including early RA subjects. Whether these findings should be extrapolated to the broader should be determined in larger, international multicenter studies, recruiting patients with various disease stage in terms of RA duration, activity and severity.

Regarding power Doppler (PD) findings specifically in patients with clinical remission: should we just ignore them? According to these two studies, the answer is probably yes. Power Doppler subclinical synovitis seems to have dubious clinical importance. Although it has been shown that PD findings are indicative of radiological progression or disease relapse,[1,2] it seems that even if we treat these patents more aggressively, we may not achieve a better outcome. Furthermore, even if the PD signal holds a prognostic role for the development of erosions,[2] it seems that we cannot do much about this, since in both studies radiological progression was not halted by TNF inhibitor administration in the later treatment steps. In particular,

in the ARCTIC study, MSUS-guided treatment led to a greater number of patients' progression to biologic treatment with the associated increased cost without translating into any equivalent advantage in patient perspective. An interesting aspect still to be investigated is the role of MSUS in deciding treatment de-escalation, since neither of these studies evaluated which is the optimal handling of RA patients with clinical remission and positive MSUS findings. Therefore, further studies are also required to compare a strategy of lowering treatment level according to conventional vs MSUS-based evaluation.

At this point it seems that the role of MSUS might be limited to the diagnostic field, providing valuable information about the presence of synovial inflammation, or facilitating diagnostic arthrocentesis in difficult joints. Whether it is of value to intervention remains an open question as well: on the balance of existing evidence, its role in intervention appears dubious. Even where US-guided injections are concerned, at least 3 systematic reviews do not appear to confirm that they offer better results than "blind" landmark-guided injections, mainly for long term outcomes.[6,7,8]

In a very recent publication in *Ann Rheum Dis* (ARD), the prime European experts in MSUS, presented their proposed algorithms for the pragmatic use of MSUS in the management of patients with RA. They suggest that MSUS assessment should be involved in all phases of dealing with RA patients, from diagnosis to the introduction of DMARDs to the acquisition of a stable clinical state or loss of clinical response.[9] They do, however, admit that there is a huge open research agenda, including issues discussed above and others, such as: Is there a different definition of US remission in different stages of the disease? How frequently should RA patients be assessed with US? What is the impact of US assessment on long term outcomes?

The controversy about MSUS and its uses does and will continue to exist. In any case, we may just be discussing a pseudodilemma:[10] MSUS can provide important information about the joint and the adjacent tissues, but ultrasound specialists are the appropriate individuals to interpret the findings and implement them in clinical routine setting. Musculoskeletal ultrasound is just a diagnostic tool, complementing -but not replacing- physician's skills and clinical examination and rheumatologists' clinical view on patients' condition.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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