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Introduction

Rheumatoid arthritis (RA) is an incurable chronic inflammatory disease associated with significant functional impairment and disability, linked to inflammatory and structural articular and peri-articular damage. The main objective in RA management is to stop or to prevent the progression of joint damage and subsequently to reduce the degree of disability. Articular and peri-articular inflammatory process suppression represents the first step in limiting structural damage. Therefore, the start of an early, tailored treatment with synthetic and/ or biological disease-modifying anti-rheumatic drugs (DMARDS), corticosteroids, coupled with a ‘treat to target’ (T2T) strategy aiming remission, represents the ultimate goal [1,2].

Measuring disease activity in RA

The measurement of the disease activity in RA in clinical practice shows a trend in achieving a more standardized approach and includes, in the last years, a variety of instruments relying basically on various types of joint counts, laboratory blood analysis (inflammatory parameters, etc.), global assessment scales, pain scales, fatigue, etc [3,4]. Currently, there are several validated instruments available which combine a variety of parameters into different composite scores, allowing a standardized way to quantify the level of disease activity, according to their threshold level. The most popular activity scores used in clinical practice are: disease activity score counting 28 joints (DAS 28), simplified disease activity index (SDAI), and clinical disease activity index (CDAI). These scores are based on the clinical joint assessment [5-7]. Despite being a routine assessment, the detection of joint synovitis by palpation is still a subjective method with moderate inter-performer agreement. Indeed, clini-
The concept of remission and low disease activity in RA

The main therapeutic objective in RA patients is to achieve remission status [10-12]. True remission should define the absence of symptoms, of inflammation and radiologic progression along with a stabilized functional status. Low disease activity (LDA) is a state characterized by minimal progression of joint damage and physical function and is a good alternative for patients who cannot attain remission because of comorbidities or other patient’s factors and drug related risks [11]. Notably, patients who achieve sustained remission status or LDA present better functional outcomes and a better quality of life in parallel with a reduction in radiologic progression [2].

Traditionally, remission was defined according to the modified ACR criteria [13]. In time, several composite scores were developed such as DAS, DAS 28 [5,14], SDAI and CDAI, the last two with more strict threshold values in comparison to DAS 28 [7]. Of further note, these remission criteria were developed to assess therapy responsiveness and outcomes for clinical trials purposes and work more effectively at a ‘group level’. However, at ‘patient level’, clinical remission criteria are unable to perform accurately due to several factors such as clinical assessment insensitivity, modified patients pain tolerance (possibly influenced by other comorbidities) or lack of inflammatory parameters elevation. There is general agreement that these criteria may define LDA rather than true remission [15].

Independently from the instrument used to define remission, a significant percentage (25-50%) of RA patients treated with synthetic DMARDs may continue to present radiological progression [16-19]. Actually, persistent active synovitis (subclinical) is one of its explanations and main predictor [20-22]. Indeed, 50 % of the RA patients achieving remission will present flares in the next 24 months [17]. In this context, clinical remission was recently redefined as a result of an ACR and EULAR collaboration initiative. The actual ACR/ EULAR 2011 remission criteria are still based on clinical evaluation of inflammatory joint modifications but has more restrictive requests. The Boolean and index based definitions are fulfilled when a patient’s scores on the following measures are \(\text{all } \leq 1\): tender joint count (TJC), swollen joint count (SJC), C reactive protein, and patient global assessment or when a patient’s score on the SDAI is \(\leq 3.3\) [23]. In the last years, significant effort has been made for better identification of early RA patients, in order to tailor an earlier treatment and to implement a monitoring schedule in accordance with T2T strategies. This approach may contribute to making remission a feasible target [11,24-29].

Musculoskeletal ultrasound use in RA

The easier access and acceptable healthcare costs for new, high resolution, imaging methods such as musculoskeletal ultrasound (MSUS) and MRI facilitates a more accurate depiction of inflammatory and structural multi-tissue lesions, in comparison to clinical examination (CE) [30-40]. In fact, in RA, there is a very good correlation between imaging delivered information and laboratory inflammation parameters, allowing a better disease activity assessment when using these tools [41].

In the last 15 years MSUS has gained an increasingly important role in the evaluation and treatment monitoring of RA. B-mode or grey scale (GS) scanning allows direct visualizing of the morphology and quantity (hyper trophy) of the synovial tissue. Doppler techniques such as power Doppler (PD), color Doppler (CD), and spectral Doppler identify in real time the increased synovial micro-vascular blood flow. These parameters correlate with the level of disease activity at one given point in time [42-47]. Apart from GS and Doppler assessment of different structures, MSUS shows several other advantages such as high accessibility (it is routinely used in many rheumatology departments in and out-patient clinics), low cost in comparison to MRI, CT, and safety- i.e. lack of ionizing radiations [48]. The possibility to perform repetitive joint scanning, without any exposure to radiation, is ideal to maintain a tight control during the monitoring process [49,50].

Longitudinal studies demonstrate that MSUS is able to detect response to therapy more rapidly in comparison to clinical examination or different clinical scores [36,51-53] and that MSUS monitored patients become more compliant to therapy and follow up schedule [54].

Imaging acquisition

MSUS assessment assumes joint and peri-articular structures evaluation in GS and Doppler modalities, using the standard EULAR protocol [55]. Doppler methods are essential for identifying inflammatory lesions at baseline (previous to treatment commencement/ change of therapeutic strategy) and during follow up. In clinical remission status, the Doppler activity may show the presence of subclinical joint modifications.
Any peripheral joint can be assessed by ultrasound. Doppler techniques are more sensitive for superficial structures and on the dorsal area in comparison to the volar/plantar area. PD technique is preferred in clinical practice. It displays the total integrated Doppler power in color showing an increased sensitivity for low velocity flow detection, being independent of angulation and aliasing artifacts. PD evaluation is carried out by selecting the target (interest) region that has to include the cortical bone, joint space and a variable quantity of adjacent tissue. The color box should include all superficial layers (also the skin) thus avoiding misinterpretation of movement artifacts. Several parameters have to be set in order to increase the sensitivity of Doppler signal detection. The pulse repetition frequency (PRF) should be low, around 500-800 Hz, the Doppler frequency should be the highest possible for superficial structures and lower for profound tissues, the gain will be adjusted below the threshold to noise artifacts and the wall filter should be low. These parameter settings should be adjusted in accordance with the target region and from patient to patient, if needed. For longitudinal, correct, assessments and multicenter studies it is advisable to keep the same set-up and the same ultrasound machine [56]. Qualitative, semi-quantitative and quantitative scoring systems have been used for assessing synovitis by GS and/or PD in a different number of joints [57]. In practice the most frequently used is the 4 grade semi-quantitative scoring system for GS and PD developed by Szkudlarek et al (Table I) [58].

### The discriminative capacity and validity of MSUS in RA

The successful application of the MSUS assessment in RA patients in clinical practice and trials relies in its ability to correctly identify, quantify and monitor changes in time. Its discriminative capacity (one of the three main pillars of the OMERACT filter), helpful in differentiating between normal and pathological findings, in assessing the efficacy of different medications and in evaluating the active or inactive disease status, is supported by the concepts of reliability (reproducible result) and responsiveness (sensitivity to external change, independent from changes generated by machine differences, image acquisition and interpretation experience) [41,58-60].

The validity of MSUS in identifying inflammatory lesions is underpinned by correlations between the PD signal intensity and histopathology or contrast MRI of the same tissue [44,45,58,61-66]. Both, synovial histopathology and MRI are considered ‘gold standard’ methods for joint/peri-articular tissue examination.

Sensitivity to change of MSUS defines the utility in monitoring RA treated patients and was demonstrated by now by a series of important studies on different therapies [36,43,51,52,67-71].

#### Clinical remission versus imaging remission

There is a continuous concern regarding the performance of the actual remission criteria. The question is whether they really do reflect the remission status. Several studies report a significant discrepancy between clinical and imaging findings in RA patients achieving clinical remission. In these circumstances, the question to be answered is if clinical remission is followed also by imaging remission [18,20,27,72-84]. In fact, a variable percentage (25-50%) of RA patients continue to present active synovitis (detected by MSUS and MRI) and high disease activity scores during clinical remission, independently from the type of the applied remission criteria (more lax or restricted). The persistence of subclinical inflammation seems to be correlated to angiogenic factors elevation and to radiologic progression in patients with clinical remission or LDA [18,20,77].

In line with these findings, a number of studies highlight that the number of PD positive joints at baseline represents a predictor factor for future disease relapses. Likewise, the degree of the PD signal at baseline is a predictor for radiologic progression in early RA [22,36,65,79,85,86] as well as in longstanding RA [52,69,87-90]. In this respect, subclinical active synovitis could be considered a surrogate marker to define the disease activity or a complete remission status in treated RA patients [18,79,91-93].

When adequate therapy is early prescribed (‘window of opportunity’) a higher percentage of patients achieve remission. Likewise, a higher percentage have chances

<table>
<thead>
<tr>
<th>Grade</th>
<th>GS synovitis</th>
<th>PD synovitis</th>
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<tbody>
<tr>
<td>0</td>
<td>absence of synovial thickening</td>
<td>absence of signal, no intra-articular flow</td>
</tr>
<tr>
<td>1</td>
<td>mild synovial thickening</td>
<td>mild, 1-2 vessels signal for small joints and 2-3 for large joints</td>
</tr>
<tr>
<td>2</td>
<td>moderate synovial thickening</td>
<td>&lt; 50 % of normal synovial area</td>
</tr>
<tr>
<td>3</td>
<td>marked synovial thickening</td>
<td>marked vessels’ signals in &gt; 50% of the synovial area</td>
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for sustained remission after biologic DMARDs tapering or arrest attempts in comparison to patients with delayed start of the therapy [76,94-98]. Early RA patients in remission (DAS<1.6) had lower PD scores and absence of imaging synovitis (GS and PD) in 43% in comparison to only 17.4% of those with long standing RA [74].

Patients who receive first line biologic therapy have GS synovitis in a significantly lower percentage in comparison with the groups treated with biologics according to the present recommendations (failure to 2 synthetic DMARDs) but the number of PD positive joints remain comparable between the groups. This observation led to the conclusion that GS synovitis correlates with disease duration (duration of inflammation and subsequent fibrotic changes) and PD positive synovitis is an independent parameter and a better marker for inflammation at one point in time [18,77].

Remission at one point must be differentiated from sustained remission (>18 months), the last one being correlated to joint scores, radiologic progression, and residual disfunction reduction [99,100]. This information is important when readjustment of treatment strategy (tapering/ arrest) is discussed [77,101].

**Number of monitored joints, type of joints, and MSUS scoring systems**

In clinical practice, it is advisable to follow the EULAR guidelines for MSUS evaluation in GS and PD [55], to be familiarized with Doppler techniques [56,102], and with actual scoring systems and composites instruments for disease activity assessment [103].

Developing scoring systems for synovitis is important for several reasons. Firstly, it facilitates homogenous therapeutic decisions in a certain moment of disease evolution (therapy commencement, tapering process, or arrest) and secondly, it allows longitudinal efficacy evaluation for specific therapies. In time, the first scores developed were independent MSUS scores (GS, PD), targeting single joints. Afterwards, global scoring systems quantifying inflammation at patient level were elaborated [57]. Furthermore, there were attempts to incorporate MSUS information in composite scores as DAS [71] or to develop multimodal scores consisting of a combination between clinical and MSUS information. In this respect, subclinical inflammatory lesions, low degree or borderline lesions difficult to be identified by clinical examination, may add new information and optimise medical decisions [104,105].

Any quantification system used has to pass the OMERACT filter and confirm validity, discriminative capacity and to prove feasibility. Feasibility implies also the possibility to explore the smallest number of joints and tendons which will offer enough information for inflammation amount evaluation.

There is no consensus yet regarding the number of joints to be included in an efficient synovitis scoring system. Reduced joint number scoring systems like 12 joints [52], 7 joints [106], 6 joints [107] perform similarly to the extended ones in terms of clinical and laboratory variables [70,105,108,109,110].

Future studies are necessary to clarify this aspect. Up to now, MSUS evaluation is considered to be superior (more accurate) to clinical examination but its sensitivity to change is not [41,111], possibly due to the fact that clinical scores and composite clinical- MSUS scores measure the same pathological finding- synovitis. Recent studies showed already the importance of separate synovitis and tenosynovitis (accurately detected with MSUS) monitoring under biologic therapy [67,112]. In this regard, multimodal composite scores have not been tested yet [104,113].

In practice, large joints are less important for disease monitoring in comparison to small joints. For remission assessment, main studies included wrist area and MCP of the dominant hand as a minimal set [110].

**The relevance of MSUS lesions for diagnosis and remission**

There is an ongoing debate regarding the relevance of MSUS lesions for diagnosis and remission [92,103,114,115].

Defining total imaging inflammation abolition (absence of GS and PD signal) is an exigent target. In this regard, a more feasible desideratum seems to include only sufficient diminution or abolition of PD activity. The minimal accepted synovial activity threshold is still not clearly defined but the median scores in grey scale less then 1 and in PD less then 0.5 based on 5 joint scanning (MCP 2-5 and wrist of the dominant hand 4 grade semi-quantitative score) correlate with a negative radiologic evolution [18].

**Follow up frequency**

The follow up frequency for MSUS evaluation has to be further clarified. In the short term MSUS has proved to be a feasible tool in synovial perfusion change induced by different therapies (biologics, CS) [36,43,53,67,116]. Long term studies (>1 year) are few [113]. Statistical significance was obtained only at 30-38 weeks due to the low patients number included in the studies [117,118].
Ankle and feet synovitis in RA remission assessment

Ankle and feet synovitis is present in about 36% of the RA patients [119]. There is clear underestimation of joint involvement when applying remission criteria such as DAS 28- ESR, SDAI, CDAI in comparison to ACR 1981 or ACR/EULAR 2010 criteria which count all joints [120]. Residual synovitis is present in 20% of these patients drawing in a subsequent high risk for radiological progression. Hence, actual recommendations (not firmly required) are to include ankle and feet in the routine joint evaluation [23,121].

Grey scale - grade I synovitis

Approximately 56% of all evaluated synovitis are grade I. Clinical examination cannot identify this modification which is not accompanied by swelling or pain. Currently, grade I synovitis is considered nonspecific for RA, being present in about 15% of the controls and without therapeutic relevance according to some authors opinion [114]. Indeed, a low PD grade associated to GS grade I may not necessarily reflect active synovitis [117]. On the contrary, according to a recent published study, GS grade I synovitis is not encountered in healthy subjects [122]. Future agenda has to define the acceptable or reasonable MSUS synovitis and the limit up to which treatment is unnecessary. This issue has to be clarified in regard to biologic tapering attempts or over- treatment risk [123].

Conclusions

MSUS, especially PDUS activity monitoring in target joints is a feasible and patient friendly method, complementory to clinical examination, helpful in guiding clinicians to chose the right treatment strategy and to strictly monitor it in patients with RA. Current EULAR recommendations on the use of imaging in RA, based on the best available research evidence and expert opinion, include MSUS as a valuable tool for clinical practice [124].

Conflict of interest: none

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