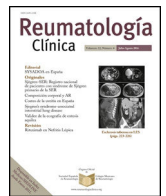




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Original Article

Recommendations for the Use of Ultrasound and Magnetic Resonance in Patients With Rheumatoid Arthritis[☆]



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ABSTRACT

Objective: To develop evidence-based recommendations on the use of ultrasound (US) and magnetic resonance imaging (MRI) in patients with rheumatoid arthritis (RA).

Methods: Recommendations were generated following a nominal group technique. A panel of experts, consisting of 15 rheumatologists and 3 radiologists, was established in the first panel meeting to define the scope and purpose of the consensus document, as well as chapters, potential recommendations and systematic literature reviews (we used and updated those from previous EULAR documents). A first draft of recommendations and text was generated. Then, an electronic Delphi process (2 rounds) was carried out. Recommendations were voted from 1 (total disagreement) to 10 (total agreement). We defined agreement if at least 70% of experts voted ≥ 7 . The level of evidence and grade or recommendation was assessed using the Oxford Centre for Evidence-based Medicine Levels of Evidence. The full text was circulated and reviewed by the panel. The consensus was coordinated by an expert methodologist.

Results: A total of 20 recommendations were proposed. They include the validity of US and MRI regarding inflammation and damage detection, diagnosis, prediction (structural damage progression, flare, treatment response, etc.), monitoring and the use of US guided injections/biopsies.

Conclusions: These recommendations will help clinicians use US and MRI in RA patients.

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Recomendaciones para el uso de la ecografía y la resonancia magnética en pacientes con artritis reumatoide

R E S U M E N

Palabras clave:

Artritis reumatoide
Ecografía
Resonancia magnética
Recomendaciones

Objetivo: Establecer recomendaciones, basadas en la evidencia, sobre el uso de la ecografía (US) y la resonancia magnética (RM) en pacientes con artritis reumatoide (AR)

Métodos: Las recomendaciones se consensuaron mediante metodología basada en grupos nominales. Un grupo de expertos (15 reumatólogos y 3 radiólogos) definió el alcance, usuarios, apartados del documento, posibles recomendaciones, revisiones sistemáticas a realizar (se utilizaron y actualizaron las revisiones de documentos de consenso previos de EULAR), y de la asignación de tareas. Los expertos delimitaron los apartados y redactaron las recomendaciones. El nivel de evidencia y grado de recomendación se realizó utilizando el sistema del Center for Evidence Based Medicine de Oxford. El grado de acuerdo se estableció mediante un Delphi a 2 rondas. Las recomendaciones se votaron según una escala de 1 (total desacuerdo) a 10 (total acuerdo), definiéndose el acuerdo como una puntuación ≥ 7 por al menos el 70% de los participantes. El documento completo fue revisado por los expertos y el proyecto coordinado por un metodólogo experto.

Resultados: Se emitieron 20 recomendaciones que cubren: la validez de la US y RM para la detección de actividad y daño estructural, capacidad diagnóstica, predictora (de progresión de daño estructural, de brote de la enfermedad, respuesta al tratamiento, etc.), utilidad en la evaluación y monitorización de estos pacientes que están en tratamiento, y uso de la US como guía (para infiltraciones o biopsias).

Conclusiones: Se presentan recomendaciones útiles para el manejo de la US y RM por los clínicos en pacientes con AR.

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Introduction

Ultrasound (US) and magnetic resonance imaging (MRI) are highly useful in the daily clinical practice of rheumatologists, both in the diagnosing process and in the therapeutic management of inflammatory diseases, among them, rheumatoid arthritis (RA). The development of new drugs and the establishment of criteria for better control of the inflammatory activity in this disease have led to a marked change in the utilization of the two techniques in the routine management of RA patients.¹ The reason for this change lies in both their ability to detect inflammation (with the possibility of intensifying the treatment and avoiding or reducing irreversible structural damage) and the increasing incorporation of US and the greater accessibility of MRI studies on the part of rheumatology departments.

Ultrasound has a great advantage in the fact that it can be performed at the point of care. This enables the immediate comparison with clinical data and findings from other studies in cases of diagnostic suspicion or doubts. As a consequence, it is essential to facilitate programmed learning according to a competitive curriculum for US in rheumatology, to gain access to a medium or high-range US machine and to become familiar with the settings. Magnetic resonance imaging may not be as accessible as US in rheumatology departments, but it is a highly useful imaging technique, both for diagnosis and for patient follow-up.

The incorporation of these imaging techniques into clinical practice should be based on valid scientific criteria, judgment and feasibility. Therefore, the main objective of this project was to draw up recommendations on the use of US and MRI in RA, based on the best available evidence, which serves as a reference for all of the professionals involved in caring for patients with rheumatic diseases. Our proposal was to reduce the variability in the use of these imaging techniques and to close the gaps between clinical practice and the best scientific evidence.

Material and Methods

The preparation of this document was an initiative of the Working Group on Ultrasound of the Spanish Society of Rheumatology

(ECOSER). The purpose of the present article was to provide recommendations concerning the use of US and MRI in RA patients. The development involved the utilization of the Delphi method and the nominal group technique.² The entire process of writing the document was performed through the distribution of tasks and comments among those participating, with the additional aid of several consensus documents published by the European League Against Rheumatism (EULAR) and the critical evaluation and the subsequent update of their systematic literature reviews (SLR).^{3–5} The process and final document were reviewed and validated by the Spanish Society of Rheumatology (SER).

Selection of the Panel and Assignment of Tasks

The first step was the formation of a panel of 18 experts (15 rheumatologists and 3 radiologists), selected through a search in MEDLINE for Spanish professionals with publications in indexed journals on the utilization of US and/or MRI in RA. The panel was constituted on the basis of the results of that search, the demonstrated experience of the professionals and their interest in the subject, also taking into account criteria concerning geographic representativeness. The entire process was coordinated by a methodologist with demonstrated experience in the Delphi method and SLR.

In the first meeting of the nominal group, the clinical questions to be developed were selected and the scope, objectives and sections of the document were decided. The clinical questions were formulated following the PICO format: patient, intervention, comparison and outcome. It was ultimately decided to carry out the SLR on different aspects of US and MRI in RA, and postpone the assignment of tasks to the panelists until the results of the SLR had been obtained. Given that these clinical questions had been previously formulated in the abovementioned EULAR consensus documents, it was decided that they be critically evaluated and updated.

Systematic Literature Reviews

The critical evaluation and updating of the SLR were performed with the help of an expert Spanish documentalist. For this, we

contacted those responsible for carrying out the SLR of the consensus documents published by EULAR on RA, to evaluate the questions and search strategies.³ The evidence tables and conclusions were also critically evaluated. In the SLR of that EULAR document, we screened for the following bibliographic databases: MEDLINE (from inception to June 2011), EMBASE (from inception to June 2011) and Cochrane Library (from inception to June 2011). The present document was updated from those dates to December 2014. Subsequently, using clinical queries, the bibliography was updated to May 2015. The search strategies of the EULAR documents were constructed combining terms in MeSH-like subject headings and free text, in order to improve and achieve a balance between the sensitivity and specificity. The expert documentalist evaluated them and considered them suitable, but introduced certain new terms to improve their yield. The inclusion and exclusion criteria were those used for the EULAR document. Regardless of the evidence tables of said document, which were considered suitable, we began with the selection of articles with the search completed (that corresponding to the EULAR document and that of the update). The process of selecting the articles (using a reference manager) was done by 2 independent reviewers (the SLR were distributed by pairs, for a total of 11 for 3 reviewers—EL, GM and FG), who also analyzed in detail the articles retrieved with the search strategies, utilizing a data collection form designed for that purpose. The methodological quality of the studies included was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool⁶ and that of the Centre for Evidence-Based Medicine of Oxford,⁷ and a series of questions to evaluate the risk of biases and the applicability of the studies. In the end, we analyzed the level of evidence (LE) and the level of agreement (LA) of each of the studies using the Oxford criteria because of the large volume of studies and the heterogeneity of the aspects evaluated (diagnosis, monitoring, etc.). The results of the SLR were also employed to establish the grade of recommendation (GR). All of the information in the studies was extracted from evidence tables. This entire process was supervised by an expert methodologist and 2 rheumatologists who were expert in the use of these imaging techniques.

Delphi Study

The different sections of the document were distributed among the members of the panel who were to draw them up and prepare them for the corresponding recommendation(s). They received a report of the results of the corresponding SLR to provide support for their drafts. Once drawn up and edited, the recommendations underwent the evaluation of the LA by means of a Delphi survey. For this, we sent the panelists an online questionnaire (<http://www.surveymonkey.com>) with the complete recommendations, together with the necessary instructions for voting by sending their LA for each of them (first Delphi round). The LA was assessed by voting using a Likert scale from 1 (totally in disagreement) to 10 (totally in agreement), and agreement was defined by a score ≥ 7 voted by at least 70% of the participants. The overall results of the Delphi were sent to all of the panelists (modified Delphi). The recommendations with a LA of less than 70% were reedited and voted in a second round, in pertinent cases. In the first round, it was also possible to include new recommendations to eventually be voted in the second round.

Edition of the Final Document

Once the Delphi study was completed, the sections and recommendations were integrated and edited. The complete document

was then sent to the group of panelists for the introduction of the corrections and the necessary comments, which resulted in a final report for the preparation of the definitive document. The methodologist participated in the assignment of each of the recommendations, the LE and the GR according to the Centre for Evidence-Based Medicine of Oxford,⁷ and the LA (from Delphi). Once the process was concluded, everything was sent to 2 external reviewers, a clinical rheumatologist and a medical epidemiologist with extensive experience in the validation of imaging techniques.

Results

The recommendations generated, which appear in [Table 1](#), are described below.

Utility of Ultrasound and Magnetic Resonance Imaging in the Evaluation of Inflammatory Activity

Recommendation 1. The use of ultrasound should be considered for the detection of synovitis in RA patients in whom the results of physical examination were questionable or negative (LE 2a; GR B; LA 80%).

Ultrasound provides added value for the detection of synovitis and can be highly useful in patients with questionable findings on joint examination or in cases requiring a more accurate assessment of inflammatory activity in those patients.

Synovitis detected by US (gray-scale [GS] and Doppler mode) has been found to have a good correlation with histological evidence of synovitis.^{8–16}

When compared to MRI (as a reference method), US has been shown to have high sensitivity and specificity for the detection of synovitis in small joints.^{14,17–34} Sensibility is less marked in the case of tenosynovitis, although specificity is high.^{17,18,26,34} Magnetic resonance imaging is also more sensitive than US for the detection of synovitis in large joints.¹⁷

On the other hand, in general, study results demonstrate greater sensitivity of US for the detections of synovitis (in large and small joints) in comparison with physical examination, regardless of the duration of RA.^{28,32,35–43} With respect to activity markers, US has been found to have a good correlation with erythrocyte sedimentation rate^{14,42,44–48} and endothelial growth factor.¹³

Recommendation 2. Magnetic resonance imaging can be utilized to evaluate inflammatory activity in RA (LE 2a; GR B; LA 80%).

The use of MRI can be evaluated in patients with RA and inconclusive clinical activity (for example, with spinal involvement) or when the results of MRI may implicate a change in the therapeutic approach.

Synovitis detected by MRI has shown a good correlation with evidence of synovitis revealed by a histological study.^{16,49–56} Moreover, there is an association between the bone marrow edema (BME) observed in MRI and the presence of inflammatory cell infiltrates (osteitis) in medullary bone.^{51,53,57} Finally, synovitis detected by MRI is also related to clinical and biological markers of inflammatory activity.^{49–51,58}

Like US, MRI has also been seen to be more sensitive than physical examination for the detection of synovitis and tenosynovitis in hands and feet, regardless of the duration of RA.^{30,58–66} The same trend appears to be observed in large joints, although the results are less conclusive, probably because we have access to a smaller number of studies.⁶⁷

The authors of some reports have compared the value of high-field and low-field MRI^{57,66,68–71} for the detection of synovitis and/or BME in carpi and metacarpophalangeal (MCP) joints,

Table 1
Definition of the Recommendations Together With the Level of Evidence, Grade of Recommendation and Level of Agreement, for Rheumatoid Arthritis, in Relation to Ultrasound and Magnetic Resonance Imaging.

#	Recommendations	LE; GR; LA
1	The use of US should be considered for the detection of synovitis in RA patients in whom the results of physical examination are questionable or negative	LE 2a; GR B; LA 80%
2	MRI can be utilized to evaluate inflammatory activity in RA	LE 2a; GR B; LA 80%
3	It is recommended that patients with RA and neurological and/or radiological symptoms indicative of cervical instability undergo MRI of the cervical spine	LE 3a; GR B-C; LA 87%
4	US can be utilized rather than plain radiography to detect erosions in accessible small joints of hands and feet	LE 2b; GR B; LA 100%
5	MRI can be utilized to detect erosions in patients with normal radiological findings, especially in early RA	LE 2a-b; GR B; LA 93%
6	MRI can be utilized, if necessary, to detect structural damage of cartilage and tendons in RA patients	LE 2b; GR B-C; LA 93%
7	US (presence and grade of synovitis in GS and Doppler mode, like the presence of erosions) is a useful aid in the diagnosis of RA, together with the clinical, analytical and radiological evaluation	LE 2a; GR B; LA 100%
8	US examination for diagnostic purposes should include at least the wrists and MCP and MTP joints, especially the 5th (target of early erosions)	LE 2a; GR B; LA 100%
9	US can be useful in RA for the differential diagnosis with regard to other inflammatory arthritides, such as psoriatic arthritis or crystal arthropathy	LE 5; GR D; LA 87%
10	MRI can contribute to the diagnosis of RA in patients with undifferentiated arthritis in whom the differential diagnosis is of special relevance, for example, in cases of negative autoantibodies and possible nonautoimmune/inflammatory arthritis	LE 2b; GR B-C; LA 80%
11	US data (especially the presence of a synovial Doppler signal, but synovial proliferation as well, in GS images of joints and tendon sheaths, and of erosions) can be more useful for predicting the development and/or progression of radiological damage in RA (early or established) than routine clinical evaluation	LE 2a; GR B; LA 93%
12	The finding in MRI of inflammation, synovitis and, above all, BME and erosions could have a greater predictive role in the prognosis of joint damage than other parameters of clinical and biological activity	LE 2a; GR B; LA 93%
13	The US evaluation of subclinical synovitis should be considered in patients in clinical remission (according to the usual indices: [DAS28]; [SDAI]; etc.) due to its predictive role in the development of flares and/or relapses and in the progression of joint damage	LE 2a; GR B; LA 80%
14	MRI could be utilized in patients with RA in clinical remission to check for the presence and grade of subclinical inflammation	LE 2b; GR B; LA 80%
15	The utilization of US to monitor the therapeutic response can be performed with the same periodicity as clinical evaluation (depending on the duration of RA, the presence of factors associated with a good or poor prognosis, therapeutic changes)	LE 5; GR D; LA 80%
16	A specific US count (number and type of joints) cannot be recommended to monitor the therapeutic response in RA; however, US evaluation should include a bilateral assessment of carpi, certain MCP, MTP and a large joint (elbow, knee or ankle)	LE 2a; GR B; LA 93%
17	It seems reasonable to perform US monitoring in RA patients who begin or change a DMARD (synthetic or biological), in those who require an increase in the DMARD dose, or in those in whom DMARD therapy is to be reduced or discontinued	LE 2a-b; GR B; LA 80%
18	The applicability of MRI in monitoring patients in clinical practice is very reduced, although it has been found to be sensitive to change, especially for progression of structural damage and, thus, the panel does not recommend its standardized use in the monitoring of patients	LE 5; GR D; LA 93%
19	The use of MRI (particularly the finding of BME) could be relevant as a prognostic factor associated with severity in RA and, thus, determine the therapeutic approach in early RA	LE 2b; GR B-C; LA 87%
20	In patients with RA, the use of US is recommended for the guidance of injections into sites in which it is difficult to gain access by means of palpation or external anatomical landmarks	LE 2b; GR B-C; LA 100%

BME, bone marrow edema; DAS28, Disease Activity Score of 28 joints; DMARD, disease-modifying antirheumatic drugs; GR, grade of recommendation; GS, gray scale; LA, level of agreement; LE, level of evidence; MCP, metacarpophalangeal; MRI, magnetic resonance imaging; MTP, metatarsophalangeal; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index; US, ultrasound.

obtaining a high LA for synovitis and somewhat less so for BME. Low-field MRI has a high specificity for synovitis and erosions (>90%), but a low-to-moderate sensitivity for BME (39%) compared to high-field scanners (68%).

Recommendation 3. It is recommended that patients with RA and neurological and/or radiological symptoms indicative of cervical instability undergo MRI of the cervical spine (LE 3a; GR B-C; LA 87%).

A number of comparative studies involving different imaging techniques at the level of the cervical spine have been reported in RA patients. However, more than 2 imaging techniques (plain radiography, computed tomography [CT] and MRI) were simultaneously compared in only 1 of them, which showed that the ability of plain radiography and CT for the detection of atlanto-axial and atlanto-occipital lesions is comparable with that of MRI, although the latter is superior because it identifies lesions of the odontoid process, providing good visualization of changes in soft tissue, which makes it possible to assess complications of the spinal cord.⁷² On the other hand, MRI also appears to be the best imaging approach for detecting erosions⁷³ and is the technique of choice for evaluating the status of neural structures at that level.

Value of Ultrasound and Magnetic Resonance Imaging for the Evaluation of Joint Injury

Recommendation 4. Ultrasound can be utilized rather than plain radiography to detect erosions in accessible small joints of hands and feet (LE 2b; GR B; LA 100%).

It has been observed that US detects a larger number of bone erosions than plain radiography in accessible joints (2nd and 5th MCP, 5th metatarsophalangeal [MTP], proximal interphalangeal and cubital styloid process), both in early and established RA.^{17,26,28,30,32,74–87} In comparison with CT and MRI, US has been found to be more sensitive than plain radiography for the detection of erosions and its specificity is high.^{76–78}

On the other hand, the authors of one study observed good sensitivity for the detection of erosions with US and a good relationship between their severity when compared with micro-CT of the hands, although the results of that report showed that the specificity of US was lower than that of micro-CT.⁸⁸ We should point out, however, that its availability is limited both in Europe and America.

All of the evaluated studies demonstrated that US detects a higher number of patients with “erosive disease” than plain

radiography, regardless of the duration of the disease.^{74,77,80,82–84,88–90} Finally, it has been shown that US and MRI are capable of detecting a similar number of patients with “erosive disease”, irrespective of the joints being examined (MCP and MTP).³⁴

Recommendation 5. Magnetic resonance imaging can be utilized to detect erosions in patients with normal radiological findings, especially in early RA (LE 2a–b; GR B; LA 93%).

Magnetic resonance imaging has been found to detect a higher number of bone erosions than plain radiography, both in early and established RA.^{26,28,30–32,74,76,77,90–94} Moreover, it has been observed that 78% of new erosions can be visualized by MRI between 1 and 5 years earlier than by plain radiography.⁹⁵

Recommendation 6. Magnetic resonance imaging can be utilized, if necessary, to detect structural damage of cartilage and tendons in RA patients (LE 2b; GR B–C; LA 93%).

It has been established that the volume of cartilage according to MRI corresponds to the histological cartilage volume.⁹⁴ On the other hand, evidence of the value of MRI for visualizing tendon damage in RA is limited. The authors of one study observed that MRI had a rate of detection of tendon ruptures in the carpus of 69% and US of 75%, in comparison with surgical findings.⁹⁶ In another article, the LA between MRI and US was 85% for the evaluation of complete tendon rupture in the shoulder.²³

Diagnostic Value

Recommendation 7. Ultrasound (presence and grade of synovitis in GS and Doppler mode, like the presence of erosions) is, together with the clinical, analytical and radiological evaluation, a useful aid in the diagnosis of RA (LE 2a; GR B; LA 100%).

Recommendation 8. Ultrasound examination for diagnostic purposes should include at least the wrists and MCP and MTP joints, especially the 5th (target of early erosions) (LE 2a; GR B; LA 100%).

Recommendation 9. Ultrasound can be useful in RA for the differential diagnosis with regard to other inflammatory arthritides, such as psoriatic arthritis or crystal arthropathy (LE 5; GR D; LA 87%).

The presence of synovitis and erosions in US is a valuable finding for the diagnosis of RA (to differentiate healthy individuals), as is tenosynovitis, although, in the latter case, the number of studies is much smaller.^{97–99} On the other hand, the utility of US for the diagnosis of early undifferentiated arthritis has also been demonstrated.⁹⁸ However, the results concerning the ability to discriminate between RA and other inflammatory arthritides are insubstantial.^{89,100,101} Nevertheless, on the basis of their experience, the members of the panel consider that US may be useful in establishing the differential diagnosis with respect to other arthritides.

Examination with US makes it possible to improve the classification of RA according to different clinical criteria (1987 American College of Rheumatology [ACR] and 2010 ACR/EULAR), as it enhances the sensitivity (0.97 vs 0.59) and has a high specificity.^{83,102}

For the moment, there are few data on the minimum number of joints that should be examined for diagnostic purposes, although the best results have been obtained with the MCP joints.¹⁰³

The sensitivity and specificity of US for the diagnosis of RA vary depending on the US criteria employed: sensitivity is greater for synovitis utilizing GS images, whereas the highest specificity is found with Doppler synovitis.^{102,104} We should also point out that the specificity of GS examination has been reported to increase when utilizing the criteria of synovitis of a higher grade.¹⁰⁵ On the other hand, erosion detected by US has been seen to have a moderate sensitivity (although higher than that of plain radiography), with an excellent specificity for the diagnosis of RA.^{103,105}

The results of multivariate analysis carried out in 2 studies confirmed the role of US (synovitis in the hands) as an independent predictor of the diagnosis of RA.^{106,107}

At the present time, although we have no clear data on the value of US in the differential diagnosis in the different types of arthritides, on the basis of their experience, the members of the panel consider that it could be useful in that respect.

Recommendation 10. Magnetic resonance imaging can contribute to the diagnosis of RA in patients with undifferentiated arthritis in whom the differential diagnosis is of special relevance, for example, in cases of negative autoantibodies and possible nonautoimmune/inflammatory arthritis (LE 2b; GR B–C; LA 80%).

Magnetic resonance imaging has an adequate sensitivity, specificity and ability to discriminate a diagnosis of RA (versus healthy individuals),^{17,108} but the results were not consistent enough to differentiate RA from other inflammatory arthritides.^{109–112} However, on the basis of their experience and data reported in the medical literature, the members of the panel considered that the pattern of inflammation detected with MRI may be characteristic and, thus, help to differentiate between RA and other inflammatory arthritides.^{110–112}

Like US, MRI enhances the discriminative ability of the clinical classification criteria for RA (1987 ACR and 2010 ACR/EULAR).^{104,113}

Finally, we wish to point out that symmetrical synovitis of the hands is the most important MRI parameter for the diagnosis of RA, followed by BME and the erosions.¹⁰⁹

Prognostic Value

Recommendation 11. Ultrasound data (especially the presence of a synovial Doppler signal, but synovial proliferation as well, in GS images of joints and tendon sheaths, and of erosions) can be more useful for predicting the development and/or progression of radiological damage in RA (early or established) than routine clinical evaluation (LE 2a; GR B; LA 93%).

The value of US synovitis, particularly that detected by Doppler, in predicting the development and/or progression of structural damage (radiographic of up to at least 3 years) is greater than that of clinical synovitis and comparable with that of MRI.^{114–119}

It has specifically been demonstrated that US synovitis (in GS images and Doppler study) predicts structural damage, in both early and established RA, in patients being treated with disease-modifying antirheumatic drugs (DMARD) or biological agents, and in joints in which US activity is maintained or in which subclinical US synovitis is detected. At this moment, we have insufficient data to establish a cutoff point for the grade of US synovitis that would enable us to predict structural damage, although, generically, the presence of baseline erosions detected by US may predict structural damage.¹¹⁴

On the other hand, at the present time, we can offer little evidence related to the ability to predict structural damage in tenosynovitis identified by US in RA patients.^{120,121}

Recommendation 12. The finding in MRI of inflammation, synovitis and, above all, BME and erosions could have a greater predictive role in the prognosis of joint damage than other parameters of clinical and biological activity (LE 2a; GR B; LA 93%).

It has been shown that the finding in MRI of BME predicts the progression of structural damage (radiographic, evaluated by CT or MRI) in RA.^{122–131}

A number of studies have demonstrated that the predictive ability of synovitis and baseline erosions in MRI, in terms of the progression of short-term and long-term structural damage, in early and established RA, is superior to that of other clinical and laboratory parameters.^{71,116,126,130,132–137}

Evidence of tenosynovitis of the hands in MRI as a predictor of structural damage is less conclusive.^{66,116,125,127,128} Nevertheless,

there are findings that suggest a certain predictive role of tendon rupture seen in MRI over the medium term (1 year) (126) and long term (6 years).¹³⁸

The presence and size of the erosions in MRI predict the development of new erosions and progression of existing erosions, detected by plain radiography or by MRI, in both early and established RA.^{14,116,117,122–124,131–133}

It has also been observed that the lower values corresponding to inflammation scores in MRI (synovitis, BME and tenosynovitis) and the absence of BME, erosions and synovitis in MRI, have a high negative predictive value (>0.90) in terms of the structural damage detected by radiography or by MRI.^{129,130,137}

There are preliminary data¹³⁹ that indicate that BME and baseline synovitis may predict progression of cartilage damage in MRI observed in carpus at 3 years. Thus, they could be useful in predicting long-term functional status.^{140,141} Further studies must be carried out to define this point more precisely.

Remission

Recommendation 13. The US evaluation of subclinical synovitis should be considered in patients in clinical remission (according to the usual indices: Disease Activity Score of 28 joints [DAS28]; Simple Disease Activity Index [SDAI]; etc.) due to its predictive role in the development of flares and/or relapses and in the progression of joint damage (LE 2a; GR B; LA 80%).

Ultrasound can provide added value to physical examination in patients with RA in remission. The identification of synovial hypertrophy in the US study (GS [35%–98.4%] and Doppler activity [17%–93.3%]) in RA patients in clinical remission occurs more frequently in established disease than in early disease, even in clinically silent joints.^{142–152} Subclinical synovitis detected in Doppler mode may predict the development of relapses or new flares over the short-to-medium term,^{144,148} as well as progression of the structural damage.^{146,148,153}

There is a good correlation between different models of US evaluation, comprehensive and reduced, in patients with RA in clinical remission.¹⁴²

Recommendation 14. Magnetic resonance imaging could be utilized in patients with RA in clinical remission to check for the presence and grade of subclinical inflammation (LE 2b; GR B; LA 80%).

Magnetic resonance imaging detects subclinical inflammation (synovitis and/or BME) in carpi and MCP in patients with RA in remission (defined according to distinct criteria), in an elevated percentage of evaluated patients and joints (synovitis between 87% and 96.2%, BME between 23% and 53% and tenosynovitis between 20.8% and 46.8%).^{71,146–148,154–158}

Preliminary data indicate that synovitis, possibly BME and tenosynovitis identified by MRI may predict the progression of structural damage (radiographic damage in hands and feet or of the hands) in RA patients in clinical remission.^{146,148,154} In fact, cutoff points have been established in MRI scoring to differentiate levels of risk of radiographic progression in patients with RA in remission with subclinical inflammation.¹⁵⁵ On the other hand, however, there is presently limited evidence on the value of MRI for predicting relapses.¹⁴⁸

Evaluation/monitoring of the Therapeutic Response

Recommendation 15. The utilization of US to monitor the therapeutic response can be performed with the same periodicity as clinical evaluation (depending on the duration of RA, the presence of factors associated with a good or poor prognosis, therapeutic changes) (LE 5; GR D; LA 80%).

Recommendation 16. A specific US count (number and type of joints) cannot be recommended to monitor the therapeutic response in RA; however, US evaluation should include a bilateral assessment of carpi, certain MCP, MTP and a large joint (elbow, knee or ankle) (LE 2a; GR B; LA 93%).

Recommendation 17. It seems reasonable to perform US monitoring in RA patients who begin or change a DMARD (synthetic or biological), in those who require an increase in the DMARD dose, or in those in whom DMARD therapy is to be reduced or discontinued (LE 2a-b; GR B; LA 80%).

Ultrasound synovitis (in GS images or Doppler mode) is sensitive to change that is at least similar to that produced by clinical examination and to that induced by other laboratory parameters related to inflammation.^{37,117,121,159–165} On the other hand, it has been observed that sensitivity to change of US synovitis is the same in RA patients with different treatment modalities (synthetic or biological DMARD, biological therapies, as first-line approach, with treatment switches, etc.), regardless of the disease activity and disease duration.¹²¹

At the present time, we have little data on the utility of US for monitoring erosions because of a lack of consistent evidence, although some authors indicate that it could be as sensitive to change as plain radiography, which would mean that it could be a useful tool for patient monitoring.^{71,166}

Different systems have been utilized for US joint evaluation for monitoring RA patients: comprehensive, reduced and composite clinical-laboratory US indices.^{119,161,167–170} However, to date, there is insufficient evidence to specifically recommend one or another.

Recommendation 18. The applicability of MRI in monitoring patients in clinical practice is very reduced, although it has been found to be sensitive to change, especially for progression of structural damage and, thus, the panel does not recommend its standardized use in the monitoring of patients (LE 5; GR D; LA 93%).

According to some authors, MRI is sensitive to changes in patients with RA and different treatment modalities.^{162,171,172} The results of another study have shown that low baseline scores and early reduction (at 12 and 24 weeks) of synovitis and BME in MRI of the hand after treatment with a biological DMARD is associated with less marked radiographic progression at 1 and 2 years.¹³¹

Recommendation 19. The use of MRI (particularly the finding of BME) could be relevant as a prognostic factor associated with severity in RA and, thus, determine the therapeutic approach in early RA (LE 2b; GR B-C; LA 87%).

In some studies, baseline BME was the only independent predictor of progression of radiographic structural damage after 2 and 5 years of follow-up in multivariate analyses.^{122,123} Another article also demonstrated that BME (defined as a score >2 in the Rheumatoid Arthritis Magnetic Resonance Imaging Score [RAMRIS]) is an independent predictor of damage progression (radiographic and in MRI),¹²⁸ a finding also observed in another report in which BME was a predictor of progression of structural damage in MRI.¹²⁹ In this case, it was also shown that the development of radiological erosions at 1 year was not very probable in the absence of baseline inflammation in MRI (negative predictive value of 0.92).

Prediction of Response to Treatment

There is insufficient data on the predictive role of US and MRI in the response to therapy of RA patients.¹⁷³

Guided Injection

Recommendation 20. In patients with RA, the use of US is recommended for the guidance of injections into sites in which it is difficult to gain access by means of palpation or external anatomical landmarks (LE 2b; GR B-C; LA 100%).

It has been demonstrated that US-guided injection is more precise for achieving the objective (making it easier to reach the intended site) than that oriented exclusively by palpation or external anatomical landmarks (verified in shoulder, elbow carpus, knee and ankle). However, to date, we have little evidence concerning the efficacy (in terms of outcome variables like pain or inflammation) of US-guided injection in RA patients as compared to the other approach.^{174–179} In this respect, the members of the panel consider that its use be recommended, as it facilitates the work of the physician and, if it is easier to gain access to the injection site with US guidance, the results should be better, at least, theoretically, than if the injection is performed without guidance.

Discussion

These are the first recommendations with the participation of the SER on the use of US and MRI in RA in clinical practice. Its support is based on the best evidence currently available.

Ultrasound and MRI were introduced into clinical practice and clinical trials as ancillary tests, together with the clinical parameters of RA; this affirmation is especially evident in the case of US, since its performance is mostly in the hands of the clinicians themselves. The most important added value provided by these techniques is their higher sensitivity for the detection of synovitis and structural damage as compared to standard clinical evaluation and plain radiography. On the other hand, although, in recent years, publications on the metric properties of the two techniques (validity, reliability and sensitivity to change) and on their diagnostic and predictive value have proliferated, at the present time, they will need to be defined and a consensus reached on their use in rheumatology clinical practice.

Therefore, for the purpose of improving clinical practice, we must establish explicit recommendations that encompass aspects as important as the diagnosis or monitoring of treatment. Although it is certain that the evidence is insufficient in certain areas, this document provides a series of highly relevant recommendations that can be especially useful for clinicians.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflicts of Interest

Esperanza Naredo has received fees for presentations from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, UCB and Novartis.

Estibaliz Loza has received fees for research projects from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, MSD, UCB, Sanofi-Aventis and Novartis.

Paz Collado has received fees for presentations from Abbvie and Pfizer.

Enrique Batlle has received fees for presentations, courses, projects and/or has worked as a consultant for Abbvie, BMS, Lilly, Menarini, MSD, Pfizer, Roche, UCB, Menarini and the Spanish Foundation of Rheumatology (FER).

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