Review

One year in review 2018: ultrasonography in rheumatoid arthritis and psoriatic arthritis

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ABSTRACT

Ultrasound is playing an increasingly important role in the differential diagnosis and monitoring of rheumatoid arthritis (RA) and psoriatic arthritis (PsA). This technique is more sensitive and specific than clinical examination to detect active synovitis, and the identification of specific synovitis patterns enable differentiation of PsA from RA and other entities. Ultrasound verified inflammation changes along with clinical improvement during therapy, and ultrasound was shown to predict future clinical and structural outcomes thus complementing the clinical risk assessment of patients. In the present review, we summarised the scientific evidence published in 2017 focussing on the use of ultrasonography for clinically relevant and pragmatic aspects of diagnosis and management of RA and PsA.

Introduction

Ultrasonography (US) has shown to be of particular help in the management of chronic arthritis (1, 2), from its preclinical phases to established disease, from early diagnosis to evaluation of damage progression. US integrated into clinical examination could improve the outcome of patient with arthritis. However, this requires the pragmatic use of US in clinical practice (3). For this purpose, this review focuses on the use of US for clinically relevant aspects of the management of the two most common inflammatory arthritides, namely rheumatoid arthritis (RA) and psoriatic arthritis (PsA). We performed a Medline search of English language articles published in the PubMed database from January 2017 to April 2018. All the articles were critically analysed in order to select the most relevant contributions with regard to diagnosis, prognosis and monitoring of disease activity and damage in RA and peripheral PsA.

Ultrasonographic imaging of rheumatoid arthritis

Role of US in predicting progression to RA from clinically suspected arthralgia or undifferentiated arthritis

Early treatment is the cornerstone of the management of early arthritis, favouring a higher rate of remission and a lower disability. Currently, the preclinical phases of RA include two possible clinical entities: clinically suspected arthralgia (CSA) and undifferentiated arthritis (UA); predictive algorithms for RA progression have been recently implemented with the aim to stratify patients and improve outcome (*e.g.* even prevent RA development) (4). Data on the role of US in the earlier phases of RA in patients with CSA without clinical synovitis are emerging and of high interest. Nam *et al.* found that in anti-CCP-positive patients without clinical synovitis, the detection of US synovitis, particularly the presence of power Doppler (PD) could predict progression to inflammatory arthritis (IA) (5). The importance of synovial PD signal, as a risk factor to develop IA was confirmed one year later in another cohort of CSA patients (6). Furthermore, given the high negative predictive value of US, the same authors suggested that US has added value to identify which patients (*i.e.* patients without US synovitis) would not develop into IA. In patients with UA (*i.e.* clinical synovitis without fulfilment of classification criteria for RA or other chronic arthritis), US could be useful not only for differential diagnosis, but also to predict RA development or reclassify UA as RA, detecting subclinical synovitis or bone erosions (7). Recently, Horton *et al.* showed

that the degree of grey-scale (GS) synovitis appeared to be a sensitive indicator of disease progression to RA in early UA patients: the presence of at least two joints with GS synovitis ≥2 was clinically relevant to the starting of methotrexate while five joints with GS synovitis ≥2 discriminated between low and high risk to develop RA (8). Furthermore, Sahbudin *et al*. suggested that alongside synovitis also tenosynovitis of the flexor tendon of the digits provided additional predictive data for the development of RA (9).

Role of US in making a diagnosis of RA

A multicentre study, which aimed to map the way US is used in RA in a real-life setting, revealed that formulating a diagnosis was the second most common indication (after monitoring disease activity) for performing an US scan (10), which confirms findings of a recent study (11). Indeed the 2013 EULAR recommendations for the use of imaging in RA suggest the use of US to improve the certainty of a diagnosis above clinical criteria alone as a number of observational studies used US to confirm the diagnosis of RA when the diagnosis could not be confirmed using conventional methods (12). PD assessment of hand joints, especially wrists, was shown to be an independent predictor with improved AUC values from 0.738 to 0.872 when combined with the 2010 ACR/EULAR classification criteria in RA patients who were negative for anti-CCP antibodies (13). In a systematic literature review on the value of US in the early diagnosis of RA when added to the clinical examination, 13/15 studies concluded that US had an added value compared to clinical examination and laboratory evaluation alone for diagnosing RA, especially in seronegative arthritis. Importantly, the review points out that there has been no study so far demonstrated any effect of subclinical (sonographic) arthritis on patient outcomes alone. (14). A systematic literature search, that evaluated the diagnostic accuracy of US for synovitis detected by MRI as the reference standard for wrist, MCP, PIP and knee, found that US is a valid and reproducible technique for detecting synovitis in the wrist and finger joints and may be considered for routine use as part of the standard diagnostic armamentarium in RA (15).

Role of US in predicting outcome in RA

Subclinical disease activity detected by imaging methods such as US or MRI were shown to be predictive for both structural damage as well as flares in RA patients in remission by a number of studies (15, 16). In a recent remission study on patients with longstanding low disease activity (LDA), the added value of US was assessed in two ways: first, by the extent to which individual predictions for flare at 52 weeks with and without US differed; and second, by comparing how US information improved the prediction to classify patients according to risk of flare. US was found to be a predictor of flare at the group level, but at the patient level it had limited added value when common clinical parameters were used already, however the predictive value of clinical predictors was modest as well (17). However, Bellis *et al*. found that tenosynovitis, a frequent finding in RA patients in clinical remission, was associated with unstable remission (18). Bone erosions on US were shown to be a relapse risk factor after the discontinuation of bDMARDs therapy in patients with RA whose PD synovitis activity and clinical disease activity were well controlled (19). Given the risk of flare in patients in clinical but not sonographic remission, surprisingly few studies have investigated the association of sonographic findings and patient reported outcomes. A study examining general health, functional ability, fatigue, depression and anxiety, pain or morning stiffness in patients in clinical *vs*. sonographic remission, however found no association between the outcomes and the status of US remission (20). Recently Zavada *et al*. found that in an US 7-joint inflammation score, PD and GS synovitis sum-scores alone were positively associated with current functional status reflected by the HAQ in patients with RA, and this relationship was stronger in patients with early disease. When combined with the DAS28 or HAQ, reduced sonographic scores (*i.e*. the US 7-joint inflammation PD and GS synovitis sum-scores) were predictive of the change in HAQ score over one year (21). Regarding treatment response, poor improvement of GS and PD scores at three months had good predictive value for non-responders at six months ($p<0.05$) in RA patients treated with bDMARDs, suggesting that responsiveness of US disease activity may eventually be considered as a predictor of clinical response (22).

Role of US in detecting disease activity

US may complement clinical examination when assessing disease activity in patients with RA. Several studies have demonstrated that it is more sensitive than clinical examination to detect inflammation and vice versa, patients with high clinical scores, mainly those with several tender joints and pain, may not reveal active inflammation on US (10, 23, 24). In a prospective study on 209 RA patients who started a new treatment with DMARDs, pain catastrophising, which is conceptualised as a negative cognitive-affective response to anticipated or actual pain, strongly correlated with patient reported outcomes and clinical composite scores but not with swollen joints, CRP-levels and US scores of inflammation. US results also correlate well with quality of life and functionality as high levels of inflammation were associated with reduced patient mobility, self-care and usual activities as well as increased HAQ scores, respectively (21, 25). US results, particularly PD also correlate with histological scores of inflammation (26). PD negative patients for example yield lower levels of synovial infiltration with inflammatory cells and vessels as compared to patients with PD positive RA (27, 28). When conducting US evaluation to assess disease activity, several variables need to be considered that might influence results, particularly PD, such as smoking, skin temperature, previous use of NSAIDs (29), joint position (30) and time of day (31). In obese patients

as well as in patients with prominent subcutaneous swelling, sensitivity of PD might be limited, yet US may still be more objective to assess synovitis than clinical examination (32). US results may improve along with clinical amelioration after the implementation of effective therapy (7). A rapid reduction of joint synovitis and tenosynovitis has been observed in a prospective study on 157 RA patients undergoing biological treatment (33). In patients treated with adalimumab and tocilizumab, a similar reduction of US scores of inflammation has been observed while clinical composite indices (containing acute phase reactants) were lower in the tocilizumab as compared to the adalimumab group (34). The authors suggested that US might be more precise for the objective evaluation of inflammation in patients treated with tocilizumab than CRP, given the direct effect of this drug on acute phase reactants. The best combination of joints for an US synovitis score remains unclear. Several reduced US scores have been proposed in the last years, usually combining semi-quantitative evaluations of GS and PD (*e.g.* 7-, 12-, 28- and 44-joint scores are available) (35). A EULAR-OMERACT US taskforce provided a new semi-quantitative scoring system for synovitis by combining GS and PD findings into a single score ranging from 0 (= absence of inflammation) to 3 (worst score) (36). This new OMERACT synovitis score (also termed GLOESS) was validated in a patient exercise as well as using stored images and videos (36, 37). The UltraSound-CLinical ARthritis Activity (US-CLARA) index is another proposal combining clinical data (from the Recent-Onset Arthritis Disability questionnaire plus self-evaluated tender joint count) and results from US assessment of 6 joints (bilateral MCP 2, 3, wrist) into a single measure of disease activity (ranging from 0–10). It has been validated in RA patients starting treatment with abatacept, and cut-offs for remission (<2) and low disease activity (<3) have been proposed (38). In a Japanese study on 406 RA patients, routine US assessment of eight joints (bilateral MCP 2, 3, wrist and knee) was supplemented with the most symptomatic joint outside this set, resulting in a higher sensitivity to detect active synovitis (39). Tan *et al*. suggested to even replace traditional 7- and 12-joint scores with the selection of the 7 and 12 most affected joints either by US or based on a combined US and clinical assessment. The individualised scores performed better than the traditional scores, however, they might be limited by feasibility in clinical practice and by the open question, whether results obtained with these scores are comparable across different patients and studies (40). A study on 100 RA patients in clinical remission reported that a six-joint score (bilateral MCP 2, 3, wrist) had moderate sensitivity (75%) to detect subclinical activity (that had been found in 60% of cases using a 38-joint US joint count). The authors concluded that the six-joint score might be an efficient tool to screen for smouldering disease activity in clinical practice (41) . Similar results were reported from a study in Norway, in which the authors demonstrated that US of the hands was sensitive to detect subclinical inflammation in RA patients in clinical remission as compared to a score involving also large joints and feet (42).

US for therapeutic management strategies of RA

Two strategic studies from 2016 comparing US with clinical examination to guide treatment decisions in RA, the ARTIC and the TASER study, were intensively debated among advocates of sonography and clinical scoring. The ARCTIC study included 238 patients with early RA and randomised them either to a conventional or an US tight control strategy with a predefined treatment protocol (43). Treatment was modified as long as the clinical (DAS44 <1.6) or US target (PD=0) had not been reached, respectively and as long as clinical (change of the DAS44 of ≥0.6 or ≥1.2, depending on the previous DAS result) or US response (reduction of PD by ≥10% or ≥20%, accordingly) was insufficient, respectively. The US group was not superior in regard to the primary outcome which was DAS44-based clinical remission, no swollen joints, and non-progression of radiographic joint damage at 16, 20 and 24 months whereas use of biological agents was higher in the US group. The study, however, had some limitations such as the absence of blinding or the fact that the outcome (DAS44 remission) was part of the intervention in the conventional group. Besides, there was a trend toward a better radiological outcome in the US group. A *post-hoc* analysis of the ARCTIC trial revealed that intra-articular infiltration was most effective in joints with moderate PD activity regardless of clinical swelling and irrespective of whether an US -guided or palpation-guided injection procedure was used (44). In TASER, 111 patients with early RA or undifferentiated arthritis were randomised. In the intervention group, US was conducted in patients with DAS28 <3.2 and in those with DAS28 ≥3.2 and <2 swollen joints, and treatment was increased in case PD was positive in at least 2 joints. In patients with high clinical disease activity, treatment was changed without considering US. In the conventional group, treatment decisions were based on clinical scoring only. The results demonstrated no difference in mean DAS44 change after 18 months, however, there was a higher DAS remission rate and a trend for a better HAQ result in the s compared to the conventional group (45). Other studies have been conducted to investigate whether US can be used to guide discontinuation of biological agents with discordant results (46, 47). In a recent study, biological therapy was stopped in 40 patients with clinical remission/low disease activity and US remission (PD-score ≤1 in each of the 22 joints investigated). Nineteen (47.5%) patients flared during the 12 months after discontinuation of therapy and the presence of US-verified bone erosion at baseline was the only predictor of a subsequent relapse (19). A study from clinical practice on 78 RA patients, in which the influence of US results to change clinical decisions was investigated, revealed that sonography overruled clinical decisions toward an intensification or reduction of treatment in 32% of patients (48).

Ultrasonographic imaging of psoriatic arthritis

Role of US in predicting progression to PsA in patients with psoriasis

Imaging studies have found that a significant proportion of patients with psoriasis (Pso) without musculoskeletal symptoms have subclinical signs of synovitis and enthesitis, supporting the concept of psoriatic disease with various degrees of activity in various domains and different clinical expressiveness. Currently, the majority of US studies in psoriatic patients without musculoskeletal complaints have a cross-sectional design, with the aim to identify subclinical articular inflammatory involvement compared to healthy controls: lower limbs enthesis were frequently evaluated showing an increase of subclinical enthesitis (49). At present, only one US study focalised on extra-entheseal structures showing a significant increase in subclinical synovitis (50). Up to now, little information exists about preclinical phases of PsA and, considering that in many cases the psoriatic skin lesions precede the onset of arthritis by several years, psoriasis gives us a unique opportunity to study a defined pool of patients at risk of developing arthritis (51). Recently, Eder *et al*. demonstrated that prior to the diagnosis of PsA, a preclinical phase exists, and it is characterised by nonspecific musculoskeletal symptoms (*i.e*. joint pain, fatigue and stiffness) (52). In this scenario, imaging could be useful not only to identify subclinical inflammatory lesions but also to identify, if any, a possible imaging biomarker for the prediction of PsA. For this purpose, imaging studies, focusing not only on enthesis but also on synovial and soft tissue abnormalities and with a prospective design, are needed. Recently, Faustini *et al*. in a MRI prospective study, showed that subclinical inflammation appears to substantially influence the risk of patients with psoriasis to progress to PsA, but the small sample size and high proportion of arthritis development at one year of follow up, due to the inclusion also of patients with arthralgia, could influence the results of the study (53). Among US studies, only one had a longitudinal design and it showed that GUESS scores of patients with Pso who developed PsA, compared with those who did not develop PsA, did not statistically differ but in the logistic regression analysis, baseline thickness of the quadriceps tendon was found to be an independent predictor of the development of PsA (54). These data strongly suggest that US is a useful tool to detect subclinical involvement, but prospective studies are needed to consider it as a biomarker of arthritis development.

Role of US in making a diagnosis of PsA

The 2016 EULAR recommendations for the management of early arthritis recognise US as a supportive tool for the detection of synovitis (2), as several controlled studies suggested a greater sensitivity of US than clinical examination. Furthermore, enthesitis has been identified as an important clinical entity in diagnosing and classifying PsA in accordance with the CASPAR criteria (55). Currently, no study evaluated the overall performance of US in addition to clinical findings to diagnose PsA (49). Nevertheless, the ability of US to detect elementary lesions, which may support the diagnosis of PsA has been demonstrated in a number of studies, particularly those focusing on entheses of the lower limbs. The use of high frequency probes gives us the opportunity not only to detect the presence of joint inflammation, but also to describe the type of involvement (*e.g*. prominent synovial *vs*. prominent extra-synovial) (56, 57). In this regard, the involvement of the synovio-entheseal complex (SEC) and enthesis-related inflammation have a pivotal role: functional or classical enthesitis with or without associated synovitis could support and assist in the differential diagnosis of early PsA or peripheral spondylarthritis (SpA), especially in case of clinically undifferentiated forms (58, 59). For example, the sonographic detection of functional enthesitis (namely peritenonitis of the extensor digitorum tendons at the level of the MCP joints as well as thickening of the pulleys and soft tissue oedema) has been demonstrated to be specific for PsA, which may be used to differentiate PsA with prevalent hands involvement from RA (56, 60). Furthermore, US could be useful to support the diagnosis of inflammatory and non-inflammatory disease (*e.g*. fibromyalgia). Recently, it has been proposed that there is a PsA subgroup suffering mostly from enthesitis, without association of evident clinically swollen joints and increase of acute phase reactants. In this scenario, pain could be localised at one or a few entheseal sites, but could involve the whole body, resulting in chronic widespread syndrome, mimicking fibromyalgia (61). In this case, the sonographic detection of entheseal inflammatory changes, particularly PD signal, could be useful to discriminate between PsA and fibromyalgia (62, 63).

Role of US in detecting disease activity and damage

US could be useful to monitor disease activity (both for synovial and entheseal involvement) and therefore to support clinical assessment of PsA patients and for this purpose the use of high-sensitivity PD signal is essential. Recently, in patients with chronic arthritis (including PsA), Najm *et al*. demonstrated that US examination of the knee with both B-mode and PD, reflected accurately histological inflammation and vascularisation (26); previously, in the unique US study in PsA patients using histopathology as gold standard, the amount of PD was not significantly associated with the histopathological inflammatory score (64). Further studies on correlations between US activity and histology are needed to clarify the role of US as an imaging biomarker for activity. Furthermore, US provides the clinician a more accurate picture of inflamed joints demonstrating US synovitis in clinically silent areas, in certain cases leading to the reclassification of PsA patients from oligoarthritis to polyarthritis, which may therefore improve their follow up. Interestingly, US enthesitis seems to have no correlation with clinical examination in PsA patients (65). Recently, Michelsen *et al*. reported that Achilles enthesitis, detected by US, was not significantly associated with clinical enthesitis in their PsA population and that the percentage

of patients with inflammation and/or structural damage was similar for the groups with and without entheseal palpatory tenderness, suggesting a limited value of clinical examination compared with US evaluation (66). As a damage biomarker, US can easily depict structural lesions of bones (*e.g.* erosions, bony spurs and enthesophytes) and tendon (*e.g.* thickening of the tendon and tendinous lesions). These damage lesions are useful not only to evaluate reversible *versus* irreversible features, but they could improve the differential diagnosis since a large component of the structural changes is driven by entheseal inflammation which is a hallmark of SpA (67).

Role of US in predicting outcome in PsA

Establishing the prognosis of a patient with PsA is important to define the treatment strategy. Currently, observational and prospective cohort studies have identified some prognostic factors correlating with the achievement of therapeutic response. Recently, Eder *et al*. demonstrated that overweight and obesity, female gender, old age and a longer duration of the disease were associated with a lower probability of achieving sustained Minimal Disease Activity (MDA) (68). Furthermore, in accordance with the criterion of "the sooner the better" in the Swedish Early PsA register, a shorter delay between the onset of symptoms and diagnosis was a predictor for MDA (69). To date, in PsA, US predictors of poorer outcome have not been clearly identified and many studies had an inappropriate design for evaluating prognostic measures (49). For this purpose, the US study group of the Italian Society of Rheumatology developed the *Ultrasound in PSoriatic Arthritis TREAtMent (UPSTREAM)*" study (registered at ClinicalTrial. gov, NCT03330769). UPSTREAM is a multicentre, observational, prospective cohort study, which represents the first example of integration between clinical examination and US with the aim to identify predictors of achieving MDA in patients with PsA starting a new course of therapy. In early PsA the detection of clinically enthesitis was associated with a lower chance to achieve MDA, supporting the superiority of US. Polacheck *et al*. found that a higher MAdrid Sonographic Enthesitis Index (MASEI) score was associated with severity of peripheral radiographic joint damage (*e.g.* erosions, ankylosis) (70). However, these clinical and US results need to be validated in a larger cohort. Moving to clinical remission, active synovitis, defined as PD grade ≥1, was found to be a strong predictor of flare during short-term follow up in PsA patients, and similar findings were recently confirmed also in juvenile idiopathic arthritis (71).

Table I. Research agenda on ultrasonography in rheumatoid arthritis: items that need to be prioritised.

1. To conduct clinical studies using US-based parameters as outcomes
2. To investigate how US can guide management decisions in clinical practice
3. To study the role of US in predicting patient reported outcomes
4. To investigate the prognostic role of US in identifying CSA or UA patient at risk to develop RA

CSA: clinically suspect arthralgia; RA: rheumatoid arthritis; UA: undifferentiated arthritis; US: ultrasound.

Table II. Research agenda on ultrasonography in psoriatic arthritis: items that need to be prioritised.

1. To investigate the integration of US in clinical practice in order to improve the clinical diagnosis
2. To investigate which US elementary lesions could be highly specific for PsA
3. To investigate the prognostic role of US in identifying Pso patient at risk to develop PsA
4. To identify US predictors of treatment response in order to stratify treatment regimen (*i.e.* better selection of patients with poorer outcome)

Pso: psoriasis; PsA: psoriatic arthritis; US: ultrasound.

Conclusion

In 2017, significant progress was made in the development of US for diagnosis, monitoring and outcome prediction of RA and PsA. While the role of US in the diagnosis of synovitis has been well recognised, recent data indicate that it may be of value in the pre-disease phases to identify those patients who eventually develop full-blown RA and PsA. Specific sonographic patterns of inflammation at finger joints enable differentiation of PsA from mimicking diseases, including RA. Different proposals have been made for selecting the most relevant sites for monitoring of US changes during treatment, a consensus on which method being used in clinical practice, however, is still lacking. In RA, US has been demonstrated to predict clinical and structural outcomes, whereas in PsA, such data are still needed. Whether US should be part of management strategies has in part been answered by ARCTIC and TASER studies in RA. US plus clinical remission seems not to be superior to strict clinical remission concerning clinical disease activity as the primary outcome. In clinical practice, however, US is probably more relevant for the assessment of patients with high clinical composite scores due to accompanying osteoarthritis or fibromyalgia. In these patients, US might enable a more objective evaluation of disease activity and exclude active inflammation despite high levels of pain. Whether an US-based management strategy in these patients might result in better outcomes and a more adequate use of resources are questions that only future research will clarify.

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