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Tightening Up? Impact of Musculoskeletal Ultrasound Disease Activity Assessment on Early Rheumatoid Arthritis Patients Treated Using a Treat to Target Strategy

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Objective. **To determine the level of agreement and potential impact on disease-modifying antirheumatic drug (DMARD) escalation decisions and of adding musculoskeletal ultrasound (MSUS) assessment of disease activity to the Disease Activity Score in 28 joints (DAS28) in early rheumatoid arthritis (RA).**

Methods. **Data were gathered from 53 early RA patients randomized to the MSUS assessment group of the Targeting Synovitis in Early Rheumatoid Arthritis study. DAS28 scores were calculated every month. MSUS was performed on patients with low disease activity (DAS28 <3.2) and on those with moderate disease activity (3.2 ≤ DAS28 <5.1) without clinically swollen joints (swollen joint count [SJC] ≤1). Fourteen joints (bilateral proximal interphalangeal joints 2 and 3, metacarpophalangeal [MCP] joints 2 and 3, the radiocarpal, and metatarsophalangeal joints 2 and 5) were examined. Active disease was defined as ≥2 joints demonstrating any power Doppler (PD) signal. Data from 414 paired DAS28 and MSUS assessments were pooled to determine the level of agreement between each method.**

Results. **A total of 369 MSUS assessments were conducted on patients with DAS28 <3.2; 92 (25%) of these assessments identified active disease. A total of 271 MSUS assessments were performed on those with DAS28 <2.6; 66 (24%) of these identified active disease. Forty-five MSUS assessments were conducted on patients with 3.2 ≤ DAS28 <5.1 and SJC ≤1; 15 (33%) of these assessments confirmed active disease. On 120 occasions (29%), MSUS findings contradicted the DAS28 and led to modified treatment decisions. The joints that most frequently exhibited PD signal were radiocarpal and index and middle MCP joints.**

Conclusion. **Compared to the DAS28, global RA disease activity assessment using a limited MSUS joint set provided additional disease activity information and led to altered treatment decisions in a significant minority of occasions. This may allow further tailoring of DMARD therapy by supporting DMARD escalation in patients with continuing subclinical synovitis and preventing escalation in symptomatic patients with minimal clinical and/or ultrasonographic synovitis.**

INTRODUCTION

The Tight Control of Rheumatoid Arthritis study demonstrated that intensive management of early rheumatoid arthritis (RA) results in improved outcomes (1,2). The findings have been replicated in other studies (3,4) and "treating to target" management strategies are now routinely recommended by national and international guidelines (5–7). The strategy relies on 3 key components: frequent review of the patient after initial diagnosis, careful systematic assessment of disease activity, and escalation of therapy in patients with persistent disease activity until stable low disease activity or remission is attained.

The majority of studies have utilized composite measures of disease activity, such as the Disease Activity Score (DAS) (8), the DAS in 28 joints (DAS28) (9), or the Sim-

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Significance & Innovations

- Musculoskeletal ultrasound (MSUS) assessment of a limited joint set provided additional information, which led to modified treatment decisions during 29% of assessments of global disease activity.
- MSUS assessment identified active disease and supported additional disease-modifying antirheumatic drug (DMARD) escalation in 25% of occasions of low disease activity (Disease Activity Score in 28 joints [DAS28] <3.2) and 24% of occasions of clinical remission (DAS28 <2.6).
- MSUS assessment did not identify active disease and therefore prevented further DMARD escalation in 67% of assessments of moderate disease activity ($3.2 \leq$DAS28 <5.1) but minimal clinical synovitis (swollen joint count ≤ 1).

plified Disease Activity Index (SDAI) (10). While routine use of composite scores has undoubtedly improved treatment efficacy, the scores have also demonstrated limitations. First, the DAS28 score includes no direct assessment of disease activity in the feet. Second, it has been shown that patients with low DAS/DAS28 scores may continue to exhibit subclinical synovitis that is associated with progressive joint damage (11,12). Third, some patients may exhibit elevated disease activity scores in the absence of measurable synovitis (e.g., fibromyalgia RA [13]). In essence, DAS/DAS28 have less than perfect sensitivity and specificity for the assessment of overall disease activity and may either under- or overestimate the true inflammatory disease burden. Clearly, this may have implications for disease-modifying antirheumatic drug (DMARD) escalation decisions that are solely based upon composite disease activity scores, since it may lead to under- or overtreatment.

The presence of synovitis detected by musculoskeletal ultrasound (MSUS) is useful in the diagnosis of undifferentiated arthritis (UA) (14) and in inflammatory arthritides is predictive of persistent disease (15), joint damage (16), and acute disease flare (17). In RA, MSUS is more sensitive than clinical examination for detecting synovitis (11,18) and the presence of MSUS synovitis correlates with future radiographic progression (19). Consequently, it has been suggested that MSUS should be included in the definition of remission (20) and that MSUS assessment of disease activity could be utilized to inform therapeutic decisions as part of a treating to target strategy (21).

However, MSUS also has its limitations. The technique is operator dependent, not every rheumatologist is skilled in its use, and assessments are time consuming if a large number of joints are examined. Furthermore, while MSUS is more sensitive than clinical examination, it may also overdiagnose the presence of synovitis. Observational studies have demonstrated that a significant proportion of normal subjects show some evidence of gray-scale synovitis (22) or power Doppler (PD) signal (23). As yet there is no consensus about which joints should be assessed by MSUS. Several MSUS "joint sets" have been proposed, assessing between 6 and 60 joints per assessment. Assessing more joints may improve diagnostic accuracy at the expense of a more prolonged assessment. However, recent evidence suggests that the findings of smaller "limited" joint sets correlate very highly with those from larger, "extensive" joint sets (24,25).

It has not yet been established how often the use of MSUS would change treatment decisions within a treating to target management strategy, or whether it would lead to significant improvements in outcome. The Targeting Synovitis in Early Rheumatoid Arthritis (TASER) study is a randomized controlled trial investigating the hypothesis that the use of MSUS will improve the accuracy of disease activity assessments and that consequently basing treatment decisions on DAS28 plus MSUS assessment will result in superior clinical and radiographic outcomes. The protocol was designed to both minimize the undertreatment of subclinical synovitis and prevent unnecessary overtreatment of fibromyalgic RA. The work described herein compared simultaneous DAS28 and MSUS disease activity assessment findings for patients randomized to the MSUS group in order to explore the potential impact of systematic MSUS assessment on treatment escalation decisions.

PATIENTS AND METHODS

Ethical approval for the study was granted by the local research ethics committee. A total of 111 patients with a clinical diagnosis of early RA or anti–citrullinated protein antibody–positive UA were recruited between September 2009 and April 2012. Fifty-three patients were randomized to receive therapy directed by MSUS assessment in addition to DAS28 scores. All clinical and MSUS assessments have been made by the same clinician (JD) at 3 Glasgow teaching hospital sites. All examinations were conducted using the same portable ultrasound machine (Voluson I, GE Healthcare) and a 10–16 MHz linear array probe (SP 10–16RS, GE Healthcare). PD examination was standardized using the following settings: frequency high (machine preset), pulse repetition frequency 0.9 kHz, wall filter low, and gain adjusted to below the level at which Doppler artifact appeared beneath bone. The dorsal recesses of 14 joints were assessed (the second and third proximal interphalangeal [PIP] joints, the second and third metacarpophalangeal [MCP] joints, wrist, and second and fifth metatarsophalangeal [MTP] joints bilaterally) for the presence of gray-scale and PD synovitis positivity and graded on a Likert scale of 0–3 (26). Active disease on MSUS was defined as the presence of grade 1 or higher intraarticular PD signal in at least 2 joints. PD signal has also been identified in the joints of healthy individuals (22,23). Therefore, the presence of PD signal in ≥ 2 joints was chosen as a pragmatic threshold for DMARD escalation since it was felt to reduce the risk of false-positive identification of synovitis.

Treatment decisions were standardized by following a predefined treating to target management strategy with monthly assessments and aggressive step-up therapy comprising conventional and biologic DMARDs (methotrexate → methotrexate, sulfasalazine, and hydroxychloroquine → triple DMARD therapy that included subcutaneous methotrexate → triple DMARD therapy and etanercept) and liberal use of intramuscular/intraarticular corticosteroid injections. DMARD doses were escalated rapidly to either the maximum or highest tolerated dose. The following thresholds for performing MSUS assessment and escalating DMARD therapy were used: 1) DAS28 ≥5.1, escalate DMARD therapy, no MSUS required; 2) 3.2 ≤ DAS28 <5.1 and swollen joint count (SJC) ≥2, escalate DMARD therapy, no MSUS required; 3) 3.2 ≤ DAS28 <5.1 and SJC <2, perform MSUS assessment, escalate DMARD therapy if MSUS identifies active disease; and 4) DAS28 <3.2, perform MSUS assessment, escalate DMARD therapy if MSUS identifies active disease (even if the patient is in DAS28 remission).

MSUS assessment was not performed if new DMARD therapy had been added (i.e., treatment escalation) within the preceding 3 months; therefore, no MSUS assessments were conducted during months 1 and 2 of followup.

To determine the frequency with which patients' treatment plans were modified by the MSUS findings, the percentage agreement between DAS28 and MSUS findings was calculated. Agreement was defined as DAS28 and MSUS findings that supported the same treatment decision. Disagreement occurred when the MSUS examination provided disease activity information that contradicted the information suggested by the DAS28. In instances of disagreement, the MSUS findings took precedence over the DAS28 and led to a modified treatment decision. Total PD scores were calculated by summing together all the PD scores from a single assessment. Total PD joint counts represent the number of joints exhibiting any positive PD signal during a single assessment.

RESULTS

The baseline characteristics of the MSUS assessment group are described in Table 1. Up until February 2013, patients in the MSUS assessment group had been reviewed on 753 occasions and MSUS assessment had been performed on 414 occasions (55% of the total number of reviews). All patients required at least 1 MSUS assessment and the mean number of MSUS assessments performed for each patient, so far, was 8 (range 1–15) (Figure 1). Most patients (n = 34) underwent between 4 and 10 assessments; in these patients, active disease was frequently identified (27.8–70% for positive assessments). A subset of patients (n = 13) underwent repeated MSUS assessment (between 11 and 15 assessments) that identified relatively low rates of active disease (2.2–14.5% for positive assessments).

Of the 414 MSUS assessments, 244 (59%) identified PD signal in ≥1 joint, 107 (26%) identified PD signal in ≥2 joints, and 39 (9%) identified PD signal in ≥3 joints. Forty-seven patients (89%) had at least 1 DMARD escalation decision changed because of the MSUS findings.

Table 1. Baseline characteristics*

Characteristic	Statistic
Subjects, no.	53
Female sex, no. (%)	30 (59)
Symptom duration, months	5.1 ± 2.8
Rheumatoid factor positive, %	66
Anti–citrullinated protein antibody positive, %	66
Health Assessment Questionnaire	1.6 ± 0.7
Disease Activity Score in 28 joints	5.0 ± 1.1
Erythrocyte sedimentation rate	35.9 ± 25.0
C-reactive protein	37 ± 41
Swollen joint count	5.8 ± 3.2
Tender joint count	6.1 ± 4.3
Patient global assessment of disease activity	51.5 ± 20.4

* Values are the mean ± SD unless indicated otherwise.

Agreement between DAS28 and MSUS assessments of disease activity. A total of 369 MSUS assessments were conducted when scores were DAS28 <3.2 (Table 2). Of these assessments, 277 (75%) showed no evidence of active disease, thereby supporting the disease activity assessment provided by the DAS28. However, 92 (25%) of these assessments did identify PD signal in ≥2 joints, which led to further DMARD escalation. A total of 271 MSUS assessments were conducted in patients who fulfilled DAS28 remission criteria (DAS28 <2.6); 66 (24%) of these assessments identified active disease and supported further DMARD escalation. Forty-five MSUS assessments were performed when scores were 3.2 ≤ DAS28 <5.1 and SJC <2. Thirty (67%) of these assessments showed no evidence of active disease, thereby contradicting the clinical impression of moderate disease activity and preventing DMARD escalation at that time point. A subgroup of patients (n = 13) underwent repeatedly negative MSUS assessments (Figure 1) for both MSUS indications, and therefore an element of repeated testing bias may have been

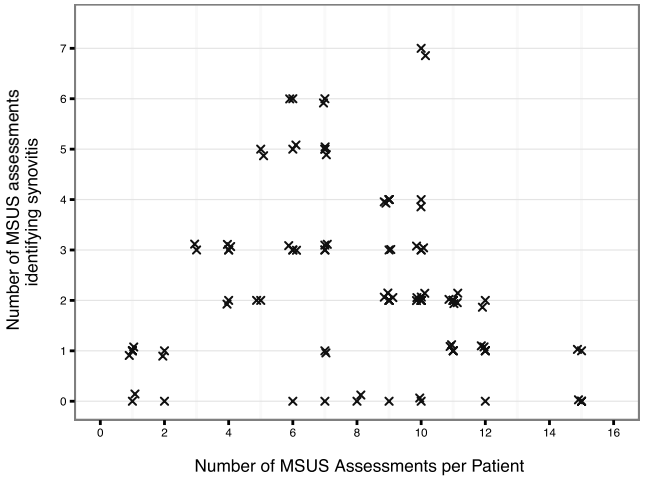

Figure 1. Relationship between the number of musculoskeletal ultrasound (MSUS) assessments performed per patient and the number of positive MSUS assessments that identified active synovitis.

Table 2. Agreement between DAS28 and MSUS assessments of disease activity*

	MSUS assessments	
	PD in 0 or 1 joint	PD in ≥2 joints
DAS28 assessment (n = 414)		
DAS28 <2.6 (n = 271)	205 (76)	66 (24)
2.6 ≤ DAS28 <3.2 (n = 98)	72 (73)	92 (27)
3.2 ≤ DAS28 <5.1 and SJC <2 (n = 45)	30 (67)	15 (33)

* Values are the number (percentage). DAS28 = Disease Activity Score in 28 joints; MSUS = musculoskeletal ultrasound; PD = power Doppler; SJC = swollen joint count.

introduced. Altogether, 71% of treatment decisions based on the DAS28 assessments were unaltered by the addition of MSUS disease activity assessment, but in 29% the MSUS examination altered the treatment decision taken.

C-reactive protein levels were measured at 3-month intervals and, therefore, the SDAI was also calculated every 3 months. There were 166 occasions with paired SDAI and MSUS data available. SDAI low disease activity (3.3 > SDAI ≤11) corresponded to a higher incidence of MSUS synovitis (44% of assessments) than DAS28 <3.2. However, compared to DAS28, rates of agreement between SDAI and MSUS disease activity assessment were virtually identical for SDAI remission (SDAI ≤3.3) and SDAI moderate disease activity (11 > SDAI ≤26). Overall agreement between SDAI and MSUS was 62%. Supplementary Table 1 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22218/abstract) shows the degree of agreement between SDAI disease activity and MSUS assessment.

Joint involvement findings during MSUS disease activity assessment. Of the 14 joints examined by MSUS, PD signal ≥1 was identified most frequently in one or both radiocarpal joints, index MCP joints, and middle MCP joints (54%, 21%, and 12% of assessments, respectively). By comparison, the index and middle PIP joints and second and fifth MTP joints exhibited PD signal relatively infrequently (5%, 1%, 2%, and 5%, respectively).

Changes in MSUS findings over followup. The most frequent indication for performing MSUS assessment was consistently DAS28 <3.2 (Figure 2). Typically, applying the protocol to the care of 53 patients required 20–30 scans each month, which gives an indication of the potential workload involved if regular MSUS assessment were to be included in the routine management of early RA. Overall, there was a gradual downward trend in the number of MSUS assessments identifying active disease (Figure 2). Mean PD score (sum of positive findings) and PD joint count (number of joints with positive findings) fell significantly between the first and last MSUS assessment. Mean PD score decreased from 2.70 to 1.34, a reduction of 1.36 (95% confidence interval [95% CI] 0.63–2.09, $P < 0.001$) from first subject US to last, and PD index decreased from

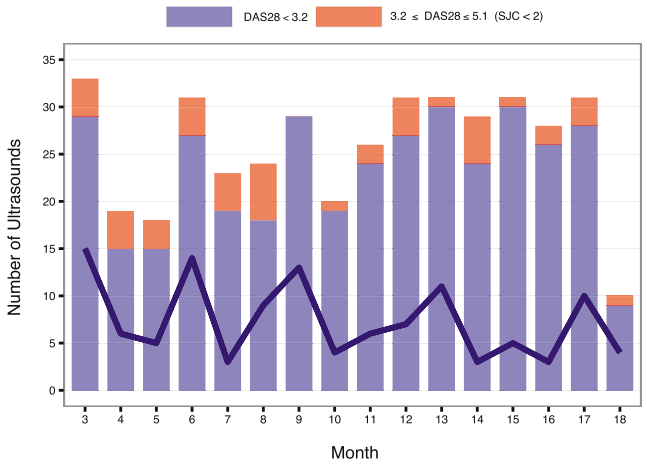

Figure 2. Frequency of each indication for musculoskeletal ultrasound (MSUS) (bars) and frequency that MSUS assessment identified active disease (line). DAS28 = Disease Activity Score in 28 joints; SJC = swollen joint count.

1.78 to 1.12, a reduction of 0.66 (95% CI 0.22–1.10, $P = 0.004$). However, some patients did still exhibit MSUS synovitis in multiple joints after 12–18 months of followup, suggesting that the integration of MSUS into the treatment paradigm should not be limited to the early months of treatment (Figure 3).

Comparison of DAS28 components between different disease activity states. For each disease activity state the mean values of the individual components of the DAS28 were calculated to determine whether the proposed indications identified groups of patients that were likely to benefit from MSUS assessment (Table 3). As the DAS28 score increased there was a stepwise increase in all the DAS28 components. Patients with low disease activity (DAS28 <3.2) and clinical remission (DAS28 <2.6) exhibited essentially normal DAS28 components. Conversely, patients with high disease activity (DAS28 >5.1) had clear clinical evidence of active disease (high SJC and elevated erythrocyte sedimentation rate [ESR]). Patients with mod-

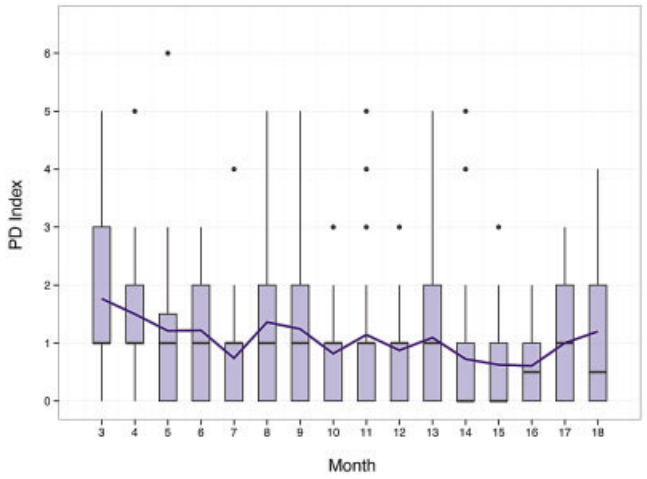

Figure 3. Box and whisker plot of power Doppler (PD) index findings by month. Boxes represent interquartile range, whiskers represent ranges of values, and line represents mean PD index.

Table 3. DAS28 components assessed between 3 and 18 months followup*

Clinical disease activity assessment	DAS28	28TJC	28SJC	ESR	Global VAS	Pain VAS
DAS28 <2.6 (n = 432)	1.7 ± 0.5	0.1 ± 0.4	0.5 ± 0.9	9.5 ± 6.2	7.6 ± 12.4	7.9 ± 13.4
DAS28 <3.2 (n = 580)	2.0 ± 0.7	0.4 ± 0.9	0.7 ± 1.3	12.5 ± 10.3	11.3 ± 16.0	11.8 ± 17.3
3.2 ≤ DAS28 <5.1 and SJC <2 (n = 78)	3.8 ± 0.5	3.6 ± 3.0	0.4 ± 0.5	21.8 ± 14.5	48.8 ± 23.1	47.1 ± 22.2
3.2 ≤ DAS28 <5.1 and SJC ≥2 (n = 83)	4.0 ± 0.5	3.1 ± 2.8	3.3 ± 1.6	30.2 ± 23.8	35.3 ± 25.9	34.1 ± 26.6
DAS28 ≥5.1 (n = 12)	5.7 ± 0.6	8.3 ± 5.0	6.6 ± 4.1	42.5 ± 25.5	72.3 ± 17.4	65.2 ± 20.2

* Values are the mean ± SD. DAS28 = Disease Activity Score in 28 joints; TJC = tender joint count; SJC = swollen joint count; ESR = erythrocyte sedimentation rate; VAS = visual analog scale.

erate disease activity (3.2 ≤ DAS28 <5.1) but minimal clinical synovitis (SJC <2) exhibited higher global health and pain visual analog scale (VAS) scores than those patients with moderate disease activity and clinical synovitis (SJC ≥2). This pattern has been previously associated with fibromyalgic RA (27), although it may also have been skewed by deliberately restricting the number of swollen joints for the 3.2 ≤ DAS28 <5.1 and SJC <2 group.

DISCUSSION

Many RA patients who are regarded as having clinically inactive disease still exhibit evidence of persistent synovitis on magnetic resonance imaging or MSUS scanning (11) that appears predictive of worse outcomes (16). This has led to the hypothesis that clinical assessment alone is insufficiently accurate to guide therapeutic decisions and that radiologic remission may be a more appropriate target for optimizing outcomes. However, other studies suggest that radiographic progression in patients in DAS28 remission is largely restricted to those patients who continue to exhibit clinical evidence of joint inflammation (SJC ≥2), since patients with an SJC ≤1 had minimal disease progression (28). Similarly, patients in sustained DAS28 remission exhibit very little disease progression (29). Taken together, these studies suggest that the challenge lies not only with clinical assessment but also with the durability and extent of clinical response.

The TASER study was designed to explore the hypothesis that the routine incorporation of MSUS examination into disease activity assessment in early RA facilitates superior outcomes through more accurate measurement of disease activity and better informed treatment decisions. First, it would establish how often MSUS examination would lead to a change in the assessment of the disease activity state; second, how often MSUS assessment would result in either an intensification or reduction in treatment that had not been suggested by DAS28; and third and most important, whether this influence on therapeutic strategy would result in meaningful improvements in outcome.

Herein we report, in the context of a treating to target strategy in early RA, that MSUS examination provides additional disease activity information that leads to modified therapeutic decisions in 29% of assessments. In patients with low disease activity (DAS28 <3.2) or clinical remission (DAS28 <2.6), MSUS assessment identified evidence of persistent disease activity in 25% and 24% of assessments, respectively, resulting in treatment escalation. In due course, the results of the TASER clinical trial will help clarify whether this treatment intensification led to improved clinical and/or radiographic outcomes. Conversely, 67% of MSUS assessment conducted on patients with moderate disease activity (3.2 ≤ DAS28 <5.1) but minimal clinical synovitis (SJC <2) did not identify active disease and therefore treatment escalation was avoided. This subgroup did exhibit an elevated mean ESR, indicating that some patients still had persistent disease activity (for example, in the feet). However, this subgroup also exhibited elevated mean tender joint counts, global health VAS scores, and pain VAS scores (data not shown), suggesting that noninflammatory processes such as degenerative disease or fibromyalgia were contributing to the overall DAS28. In both cases MSUS assessment is still indicated to differentiate between the active and inactive disease state for each patient individually. Those patients with persistently active disease will be highlighted for consideration of further DMARD escalation, whereas those symptomatic patients who do not exhibit active disease can be considered for alternative therapeutic approaches that are more likely to be beneficial.

The adoption of MSUS examination into the routine assessment of RA global disease activity will require careful consideration of what is required for a reliable assessment and what is achievable during daily practice. A number of studies have shown that examining a limited set of joints is a reliable and reproducible way of assessing global disease activity without having to conduct time consuming examinations of numerous joints (25,30,31). However, at present there remains no universally agreed upon limited joint set or MSUS definition of active disease. The joint set used by the TASER study was a pragmatic combination of 2 previously published limited joint sets (25,30) and is similar to a number of proposed sets that are currently being validated (32). Likewise, the indications for MSUS assessment were devised to represent clinical scenarios when MSUS assessment was likely to contribute useful additional disease activity information. Furthermore, the MSUS definition of active disease was pragmatically chosen as a level that represented sufficient evidence of systemic disease (i.e., involvement of more than 1 joint) to justify the potential risks of further DMARD intensification. Examination was focused on the identifica-

tion of intraarticular PD signal since this has previously been associated with several independent markers of active disease, including histologic evidence of synovial inflammation (33), risk of acute flare (17), and risk of progressive joint destruction (12,34). Of the joints examined, the radiocarpal and the second and third MCP joints were most likely to exhibit positive PD signal and therefore contributed most frequently to DMARD decision making. To improve the efficiency of the MSUS examination, it may be possible to exclude assessment of the PIP and MTP joints without unduly compromising its sensitivity. For this research, MSUS examination was limited to the easily accessible dorsal recesses of hand and foot joints. However, it has previously been demonstrated that synovial hypertrophy is more frequently identified on the flexor side of PIP joints (31) and also on the radial and extensor sides of MCP joints (35,36). A more detailed MSUS examination incorporating every joint recess may have increased the sensitivity of the overall disease activity assessment, but at the expense of additional examination time. Furthermore, the MSUS findings reported by this study were obtained by a single ultrasonographer (JD) and require confirmation by other practitioners.

The disease activity target that should be pursued by treating to target DMARD escalation strategies continues to be debated. Most clinical studies have targeted low disease activity (2,37–39) but consensus guidelines recommend the pursuit of clinical remission (6). Either way, these targets are usually based around a fixed composite disease activity score threshold. However, while the routine use of disease activity scores has undoubtedly improved outcomes, they have also demonstrated consistent weaknesses. At low numerical values composite scores may be insufficiently sensitive to highlight ongoing subclinical disease (11,40); furthermore, in the presence of overlapping causes of musculoskeletal pain, composite scores may lack sufficient specificity to differentiate RA-related features from other causes (13,27). The results of this study support the emerging argument (21) that MSUS assessment may contribute to treating to target strategies of care and allow further individualization of treatment regimens to each patient's specific needs. Patients who continue to exhibit active clinical and/or ultrasonographic disease can be considered for aggressive DMARD escalation until ultrasonographic remission is achieved, while the subgroup of symptomatic patients who no longer exhibit MSUS evidence of synovitis can be offered alternative treatments without needing to face the risks of potentially unnecessary DMARD escalation.

It may be possible to identify more stringent indications for MSUS that limit the resource impact; for instance, there appeared to be a subgroup of patients who underwent multiple MSUS examinations that repeatedly failed to identify active disease (Figure 1). It is likely that this subgroup represents patients in persistent ultrasonographic remission and/or those with persistently elevated DAS28 without clinical or ultrasonographic synovitis, who may not require such close monitoring if their MSUS findings have remained stable for several consecutive assessments.

Taken altogether, these results suggest that systematic MSUS examination could become a useful adjunct to clinical examination in a carefully selected subset of patients. While synovitis remains clinically evident, early RA patients may continue to have their DMARD therapy guided by clinical assessment and composite disease activity measures. Once clinical synovitis has receded, or if there is doubt relating to the clinical findings, MSUS assessment and monitoring could then be used to determine if there is any residual subclinical synovitis or whether ultrasonographic remission has been achieved.

Patients frequently underwent MSUS assessments (n = 140; data not shown) that identified positive PD signal in a single joint but were not offered treatment escalation since this was not felt sufficient evidence to justify the risks of DMARD intensification (Figure 3). Clearly, patients may have had evidence of active synovitis in other joints that were not part of the proposed set; however, in order to limit variability a standardized joint set was preferred. Due to the number of potential confounders it will be extremely difficult to determine whether omitting DMARD escalation in these circumstances had any detrimental, short-term impact on clinical and radiologic outcomes. Equally, requiring positive PD signal in at least 2 separate joints does reduce the risk of inappropriate treatment decisions being made on the basis of misinterpretation of MSUS PD artifact (41).

Care must be taken before accepting the conclusion that this will lead to improved outcomes, and the results of the clinical trial are still awaited. First, patients in the study continue to have their treatment escalated, including the addition of biologic therapy, even if they are in clinical remission, if they have MSUS evidence of subclinical synovitis. It will be important to make a careful assessment of the risk–benefit of such an approach. Second, it is possible that the incremental improvement in clinical outcomes that accrue from improving patients from a state of clinical remission to imaging remission are not clinically important from a patient perspective. It is also possible that meaningful improvement in outcomes will be achieved, but only at the expense of drug-related toxicity; for example, in another biologic system, the use of high-dose statin therapy, when compared to low-dose therapy, results in a greater reduction in the risk of subsequent cardiovascular events, but at the expense of an increased risk of incident diabetes mellitus (42). Third, the cost of the implementation of routine MSUS assessments into routine care will need to be assessed in terms of hardware acquisition, operator training and reliability, physician time, and increased drug costs. Equally, financial and morbidity savings may occur if complex DMARD combinations and biologic therapies are avoided in patients with elevated DAS28 assessments but no ultrasonographic evidence of active synovitis. A robust cost-effectiveness analysis may be required before MSUS assessments will be routinely applied in clinical practice to direct treatment decisions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors ap-

proved the final version to be submitted for publication. Dr. Dale had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Dale, McConnachie, McInnes, Porter.

Acquisition of data. Dale.

Analysis and interpretation of data. Dale, Purves, McConnachie, McInnes, Porter.

ROLE OF THE STUDY SPONSOR

Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

ADDITIONAL DISCLOSURE

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