Adding ultrasound to treat-to-target shows no benefit in achieving clinical remission nor in slowing radiographic progression in rheumatoid arthritis: results from a multicenter prospective cohort

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ORIGINAL ARTICLE

Adding ultrasound to treat-to-target shows no benefit in achieving clinical remission nor in slowing radiographic progression in rheumatoid arthritis: results from a multicenter prospective cohort

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Abstract

Objective To assess whether using ultrasound (US) in addition to clinical information versus only clinical information in a treat-to-target (T2T) strategy leads to more clinical remission and to less radiographic progression in RA.

Methods Patients with RA from the 2-year prospective BIODAM cohort were included. Clinical and US data (US7-score) were collected every 3 months and hands and feet radiographs every 6 months. At each visit, it was decided whether patients were treated according to the clinical definition of T2T with DAS44 remission as benchmark (T2T-DAS44). T2T-DAS44 was correctly applied if: (i) DAS44 remission had been achieved or (ii) if not, treatment was intensified. A T2T strategy also considering US data (T2T-DAS44-US) was correctly applied if: (i) both DAS44 and US remission (synovitis-score < 2, Doppler-score = 0) were present; or (ii) if not, treatment was intensified. The effect of T2T-DAS44-US on attaining clinical remission and on change in Sharp-van der Heijde score compared to T2T-DAS44 was analysed.

Results A total of 1016 visits of 128 patients were included. T2T-DAS44 was correctly followed in 24% of visits and T2T-DAS44-US in 41%. DAS44 < 1.6 was achieved in 39% of visits. Compared to T2T-DAS44, using the T2T-DAS44-US strategy resulted in a 41% lower likelihood of DAS44 remission [OR (95% CI): 0.59 (0.40;0.87)] and had no effect on radiographic progression [β(95% CI): 0.11 (−0.16;0.39)] assessed at various intervals up to 12 months later.

Conclusion Our results do not suggest a benefit of using the US7-score in addition to clinical information as a T2T benchmark compared to clinical information alone.

Key Points

- *Ultrasound has a valuable role in diagnostic evaluation of rheumatoid arthritis, but it is unclear whether adding ultrasound to the clinical assessment in a treat-to-target (T2T) strategy leads to more patients achieving remission and reduction in radiographic progression.*
- *Our data from a real-world study demonstrated that adding information from ultrasound to the clinical assessment in a T2T strategy led to a lower rather than a higher likelihood of obtaining clinical remission as compared to using only clinical assessment.*
- *Our data demonstrated that adding ultrasound data to a T2T strategy based only on clinical assessment did not offer additional protection against radiographic progression in patients with RA.*
- *Adding US to a T2T strategy based on clinical assessment led to far more treatment intensifications (with consequences for costs and exposure to adverse events) without yielding a meaningful clinical benefit.*

Keywords Rheumatoid arthritis · Treat-to-target · Ultrasound

Extended author information available on the last page of the article

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that typically affects small and medium-sized joints symmetrically. Synovial inflammation (synovitis) constitutes the primary lesion and is the hallmark of the disease. Early diagnosis and intensive treatment strategies targeting synovitis are pillars of the current management of RA [1].

The development of new, highly effective drugs has rendered clinical remission a realistic target in clinical practice [2]. It has been consistently shown that achieving this target results in better long-term outcomes, including halting or minimizing structural damage [3]. This evidence has changed the paradigm in the management of RA to the so-called 'treat to target' (T2T) approach [4]. This new paradigm has also been incorporated in the recommendations for the management of RA [1].

According to the above-mentioned recommendations, clinical remission, as the main target of current T2T strategies, can be assessed using several composite scores, namely, the 44-joint disease activity score (DAS44) [5], the 28-joint disease activity score (DAS28) [6], the Clinical Disease Activity Index (CDAI) [7], the Simplified Disease Activity Index (SDAI) [8] and, more recently, the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) Boolean definition [9].

These composite scores rely mostly on clinical data, and it has been argued that clinical definitions of remission fail to fully capture the presence or absence of synovitis [10]. Physicians may overestimate disease activity in the presence of concomitant painful conditions and, conversely, subtle subclinical synovial inflammation may be missed.

Several studies have shown that patients in clinical remission often have residual synovitis on ultrasound-imaging (US), which may result in silent radiographic progression, functional impairment and clinical flares [11, 12]. US objectively assesses synovitis, its morphology and quantity using grey scale (GS) and synovial vascularity measured by power or color Doppler (hereafter abbreviated PD for both). Therefore, it has been hypothesized that targeting US-detected synovitis may result in 'deeper' remission in clinical practice [10].

The aim of the current study was to assess whether adding ultrasound assessment to the clinical assessment in a T2T strategy leads to more patients meeting the clinical remission target and to a reduction in radiographic progression at their subsequent visit compared to a T2T definition solely based on clinical data in patients with RA in clinical practice.

Methods

Patients and study design

RA BIODAM (acronym that stands for: BIOmarkers of Joint DAMage) is a prospective multicenter (38 centres from 10 countries) cohort in which consecutive adult (≥ 18 years) patients with a clinical diagnosis of RA and also fulfilling the 2010 RA Classification Criteria [13], with ≥ 3 months of symptom duration and DAS44 > 2.4 were included from October 2011 to April 2015. A detailed description of the design of this cohort has been previously published [14]. In brief, patients were eligible in case of: (i) starting or changing (increase dose or add/switch to a different drug) treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); or (ii) starting treatment with their first tumor necrosis factor inhibitor (TNFi). Patients with prior treatment with a biological (bDMARD), an intra-articular steroid injection within 4 weeks before baseline, or any contra-indication to treatment with either csDMARDs or bDMARDs were excluded.

For the current ancillary post hoc BIODAM sub-study, a subset of patients from centres with expertise in US (11 BIODAM centres from 6 countries) were included. Patients were followed every 3 months up to 2 years. In each visit, both clinical and US data were collected and patients' treating rheumatologists had full access to all information (i.e., clinical and US) to decide whether the patient was treated according to the protocol, using the clinical definition of T2T with DAS44 remission (< 1.6) as benchmark (T2T-DAS44). US data could also be used for this purpose, but this was not mandatory. In addition, hands and feet radiographs were obtained every 6 months. The database used for this analysis was locked in April 2017. Guidelines for Good Clinical Practice were followed, and the study has been approved by the local ethics committees. All patients provided written informed consent before inclusion.

Ultrasound protocol

Consecutive US assessments were performed by one US expert in nine of the eleven centres (details on the US machines and settings are provided in Supplementary Table S1). The assessor was not blinded to clinical data. The previously validated 7-Joint US Score (US-7 score) was used [15]. It includes seven joints [wrist, second and third metacarpophalangeal (MCP2 and MCP3), second and third proximal interphalangeal (PIP2 and PIP3) and

second and fifth metatarsophalangeal (MTP2 and MTP5) joints] of the clinically dominant hand and foot (for tenderness and/or swelling) both dorsal and palmar/plantar. Synovitis was assessed semi-quantitatively (range: 0–3) by GSUS (range: 0–27) and PDUS (range: 0–39). Tenosynovitis was qualitatively scored as absent or present in GSUS (range: 0–7) and graded on a scale of 0–3 in PD (range: 0–21). Bone erosions were scored qualitatively in two perpendicular planes from the dorsal and palmar/plantar and medial/lateral (only MCP2, MTP5) aspects of the respective finger and toe joints (range: 0–14).

Ultrasonographers from all centres ($n = 11$) underwent a 1-day calibrating exercise with 6 RA patients in 2 rounds using an online eCRF in order to enhance the reliability of ultrasound scoring before the start of the study [16]. The inter-reader intraclass correlation coefficient (ICC) for synovitis (sum of the GSUS and PDUS scores) was 0.65 (95% CI: 0.30; 0.89) and 0.85 (95% CI: 0.59; 0.96) in the first and second rounds, respectively. The intra-reader ICC was 0.75 (95% CI: 0.42; 0.92).

Outcomes

The main outcome was DAS44 calculated with the erythrocyte sedimentation rate (DAS44-ESR) (range: 0–10) remission (< 1.6) [17]. In addition, the following outcomes were also assessed: DAS28-ESR (range: 0–9.3) remission (< 2.6) [18], ACR/EULAR Boolean remission (yes/no) [9], CDAI (range: 0–76) remission (≤ 2.8) [19], and SDAI (range: 0–86) remission (≤ 3.3) [20]. US remission was also defined a posteriori as GS for synovitis < 2 at the joint level and absence of PD signal in all joints included in the US-7 score [21, 22].

Radiographic damage was scored with the Sharp-van der Heijde method (SvdH) by two readers blinded for clinical data and who were aware of the known chronological order [23, 24]. The average score of the two readers was used in the analyses. SvdH measures erosions and joint space narrowing in 44 different joints and provides an aggregated sum score (range: 0 to 448). Radiographic progression was defined as the 6-month and 12-month change in SvdH score.

Treat-to-target definitions

Two definitions of T2T were compared: (i) Clinical definition of T2T (T2T-DAS44), for which only clinical data were considered; (ii) Combined definition of T2T (T2T-DAS44-US) where both clinical and US data were taken into consideration when deciding about whether or not the target had been reached.

Figure 1 describes the different, and mutually exclusive, scenarios where T2T-DAS44 or T2T-DAS44-US were considered.

T2T-DAS44 was considered correctly applied if:

- Scenario 1: a patient already had a disease activity score below the remission target (i.e., DAS44 < 1.6) and treatment was not intensified,
- Scenario 2: a patient had a DAS44 > 1.6 and treatment was intensified (increasing dosage and/or adding drugs including csDMARDs, bDMARD and/or GC).

T2T-DAS44-US was considered correctly applied if:

- Scenario 3: a patient was already in remission for both DAS44 and US remission and treatment was not intensified,
- Scenario 4: a patient had a DAS44 > 1.6 and inflammation on US and treatment was intensified.

T2T-DAS44 or T2T-DAS44-US was considered incorrectly applied in the main analysis but as following T2T-DAS44-US in sensitivity analyses:

- Scenario 5: a patient was in clinical but not US remission and treatment was intensified,
- Scenario 6: a patient was in US, but not clinical remission, and treatment was not intensified,

Finally, T2T was also considered incorrectly applied in visits where both DAS44 and US remission had not been achieved but treatment was not intensified (scenario 7), or if both clinical and US remission were already met, and treatment was still intensified (scenario 8).

Additional clinical data

At baseline, age, gender, smoking status (smoker/non-smoker), rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) status (positive/negative), and symptom duration were collected.

Statistical analysis

The effect of adding US to T2T (T2T-DAS44-US) on clinical remission 3 months later, over a period of 2 years of follow-up, compared to a clinical benchmark alone (T2T-DAS44), was analysed in time-lagged generalized estimating equations (GEE) models in patients with ≥ 2 consecutive visits with both clinical and US data available (a schematic representation of the analysis is provided in Supplementary Fig. S1). An 'exchangeable' working correlation structure was used to account for the within-patient correlation of the repeated measurements. The effect of T2T-DAS44-US on radiographic progression measured 3 months later was tested in a similar model but with the SvdH 6-month change-score as outcome (Supplementary Fig. S2).

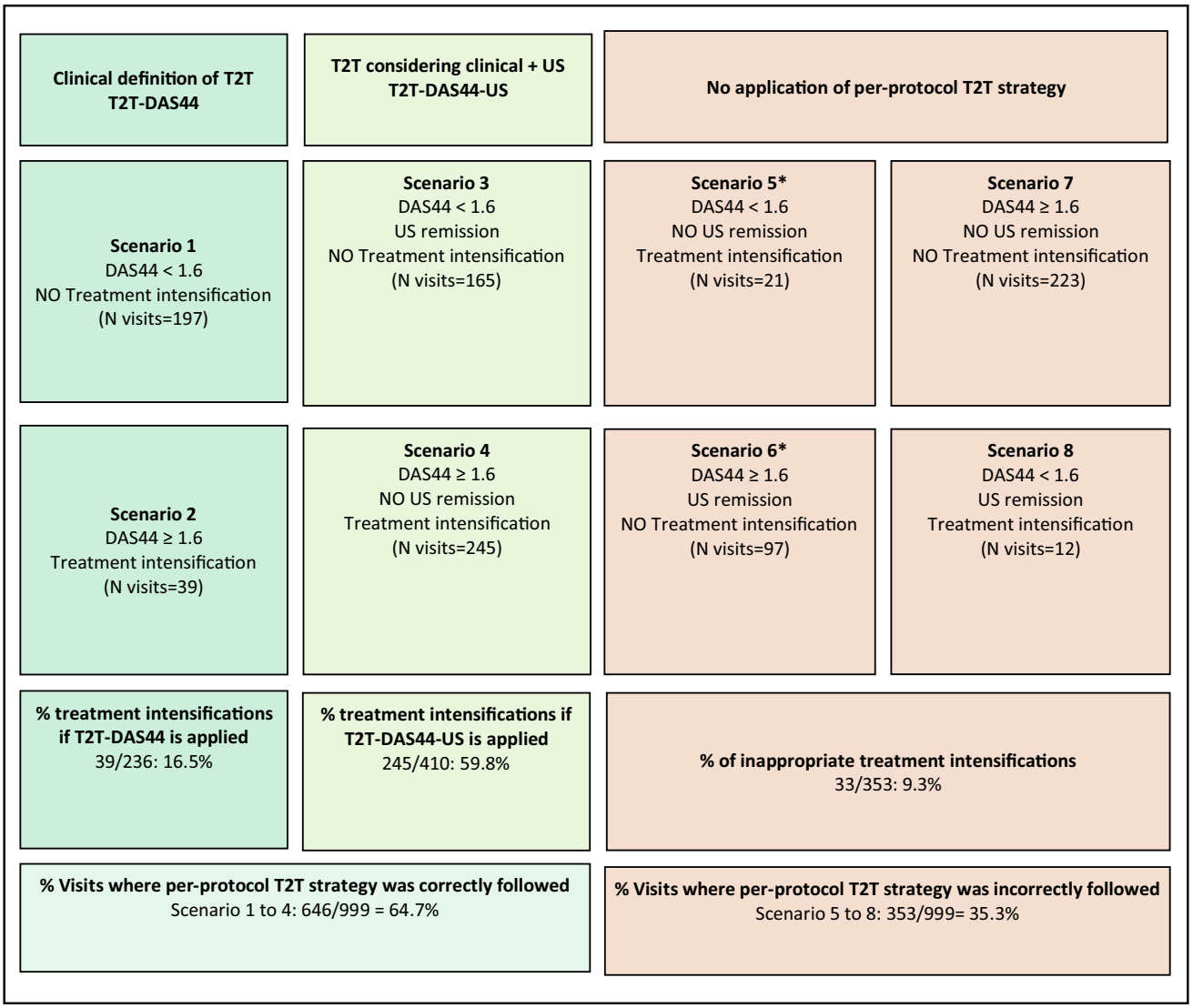

Fig. 1 Application of per-protocol T2T strategy in BIODAM (999 visits over 2 years; in 17 visits per-protocol T2T was not possible to be assessed due to missing data). US remission: GSUS for synovitis < 2 and PDUS = 0 for all joints in the US-7 score. * Also considered as part of the combined T2T-DAS44-US strategy in a sensitivity analysis (Table 4)

For each model interactions between the T2T variable and age, gender, disease duration and RF/ACPA positivity were tested and if significant ($p < 0.15$), the model was fitted in each subgroup. Each final multivariable GEE model was adjusted for potential confounders selected a priori on clinical grounds, including age, gender, disease duration (if proved not to be effect modifiers) and country of residence.

Sensitivity analyses

In two centres, US results were not made available to the treating rheumatologists. Thus, a sensitivity analysis was performed excluding patients from these centres. In two additional sensitivity analyses, we considered less strict definitions of the combined T2T-DAS44-US strategy by additionally considering T2T-DAS44-US strategy as being followed if patients were in clinical, but not US, remission and treatment was intensified (scenario 5); and if patients were in US, but not clinical remission, and treatment was not intensified (scenario 6).

Three additional analyses were performed to evaluate the effect of T2T-DAS44-US on 6-month radiographic progression measured 6 months, 9 months and 12 months later (Supplementary Figs S3, S4 and S5 respectively). Finally, the effect of T2T-DAS-44-US on 12-month radiographic progression measured 12 months later was also assessed (Supplementary Fig. S6).

Data analysis was performed using Stata V.15.0.

Results

In total, 128 patients (with 1016 visits) were included and, out of these, the majority (101; 78.9%) completed the 2-year follow-up. Baseline patient- and disease-characteristics are described in Table 1. Compared to patients lost to follow-up, those with complete follow-up had shorter disease duration [(mean (standard deviation)) 5.5 (6.5) vs 8.4 (8.6) years] and were less likely to be RF (59% vs 79%) or ACPA (69% vs 89%) positive at baseline.

Effect of adding US to T2T-DAS44 on clinical remission

As shown in Fig. 1, T2T (by protocol) was correctly applied in the majority of the visits (total: 65%; T2T-DAS44: 24% and T2T-DAS44-US: 41%), while an incorrect T2T strategy was followed in 35% of the visits. The likelihood of treatment intensification in visits in which the combined T2T-DAS44-US strategy was followed was higher as compared to visits in which only the clinical definition of T2T was applied (59.8% vs 16.5%). Treatment intensifications were uncommon in visits in which patients were in clinical but not US remission (scenario 1 and 5) (21/218; 10%). Similarly, treatment was not intensified in the majority of visits in which patients were in US but not clinical remission (scenario 2 and 6) (97/136; 71%).

The proportion of patients in clinical remission increased over time for all outcomes (Fig. 2), but, the total number of visits in clinical remission was highest for DAS44 ($N=399$; 39%) and DAS28 ($N=399$; 40%) and lowest for SDAI ($N=230$; 23%), Boolean definition ($N=210$; 21%) and CDAI ($N=190$; 19%). The number of visits in which patients were in remission according to DAS44 across the various scenarios described in Fig. 1 is shown in Table 2.

None of the pre-specified interactions was significant. Thus, the final multivariable models were fit in the entire population without stratification.

Failure to implement the clinical T2T-DAS44 strategy led to a 35% lower likelihood of DAS 44 remission 3 months later [OR (95% CI): 0.65 (0.44; 0.97) (Table 3). However, using a combined clinical and US benchmark for T2T led to a 41% lower likelihood of DAS44 remission 3 months later when compared to the clinical T2T-DAS44 strategy [OR (95% CI): 0.59 (0.40; 0.87)]. Similar results were found regardless of the remission definition used (Table 3).

Table 1 Baseline patient- and disease- characteristics

	RA patients ($N=120$*)
Age (years), mean (SD)	54.8 (12.5)
Gender (female), *n* (%)	95 (79.2%)
Disease duration (years), mean (SD)	5.9 (6.9)
Education (years), mean (SD) ($N=117$)	13.3 (3.7)
Number of comorbidities, mean (SD)	1.0 (1.1)
RF positivity, *n* (%) ($N=117$)	73 (62.4%)
ACPA positivity, *n* (%) ($N=118$)	85 (72.0%)
RF and/or ACPA positivity, *n* (%) ($N=116$)	91 (78.4%)
DAS44 ESR (0–10), mean (SD)	3.8 (1.0)
DAS28 ESR (0–9.3), mean (SD)	5.1 (1.1)
SDAI (0–86), mean (SD)	27.8 (11.3)
CDAI (0–76), mean (SD)	26.3 (10.4)
Patient global assessment (0–10), mean (SD)	5.5 (2.2)
Swollen joint count (0–44), mean (SD)	1.0 (0.7)
Tender joint count (0–53), mean (SD)	8.3 (5.9)
ESR (mm/h), mean (SD)	13.2 (8.8)
CRP (mg/L), mean (SD)	29.2 (22.0)
Total SvdH score, mean (SD) ($n=101$) (0–448)	17.7 (29.4)
Therapy, *n* (%) ($N=114$)	
Change csDMARD	17 (14.9%)
Start csDMARD	54 (47.4%)
Start bDMARD	43 (37.7%)

*8 out of the 128 patients missed the baseline visit. *RA*, rheumatoid arthritis; *RF*, rheumatoid factor; *ACPA*, anti-citrullinated protein antibodies; *DAS*, disease activity score; *SDAI*, Simplified Disease Activity Index; *CDAI*, Clinical Disease Activity Index; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *csDMARD*, conventional synthetic disease-modifying antirheumatic drugs; *bDMARD*, biological DMARD

Effect of adding US to T2T-DAS44 on radiographic progression

The mean SvdH score at baseline was 17.7 (29.4) and increased to 19.7 (26.9) in 2 years. Taking all intervals into account, there was an average increase of 0.6 (1.6) units in the SvdH score per each 6-month interval. Compared to the clinical T2T-DAS44 strategy using a combined clinical and US benchmark for T2T did not result in a significant change in the SvdH score [β (95% CI): 0.11 (−0.16; 0.39); Table 3].

Sensitivity analyses

Effect of adding US to T2T-DAS44 on clinical remission

Sensitivity analysis 1 performed after excluding the 13 patients from the 2 centres where the protocol was violated yielded the same results as the main analysis (Supplementary Table S2). Scenario 5 (visits in which patients achieved DAS44-clinical but not US-remission and in which treatment was intensified), and scenario 6 (visits in which patients were in US-remission but not in DAS44-remission and treatment was not intensified) occurred in 21 and 97 visits, respectively (Fig. 1). Patients had ≥ 1 swollen joint in 43/97 (44%) of visits from scenario 6. A lower likelihood

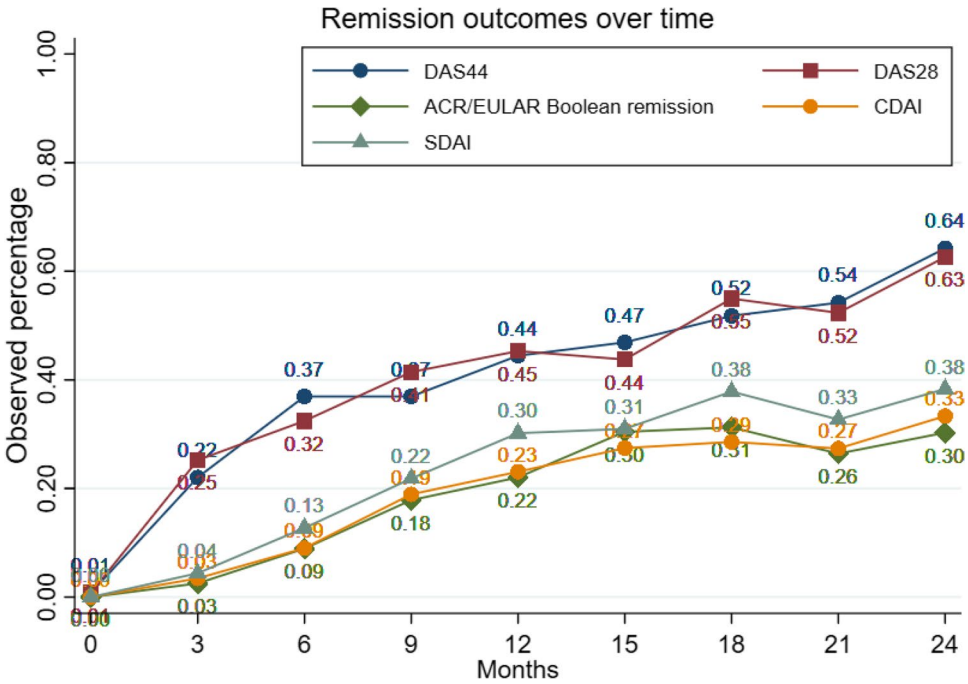

Fig. 2 Proportion of patients in clinical remission according to the different outcomes, over the 2-year follow-up. DAS, disease activity score; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism

Table 2 Number of subsequent visits in which patients were in remission according to DAS44 across the various scenarios and in the groups compared in the multivariable model

	All patients N visits DAS44 rem/all visits in each scenario (%)	Patients with ≥ 2 consecutive visits N visits DAS44 rem/all visits in each scenario (%)	Groups compared in the model* N visits DAS44 rem/all visits in each scenario (%)
Scenario 1	126/197 (64%)	126/163 (77%)	137/200 (69%)
Scenario 2	11/39 (28%)	11/37 (30%)	
Scenario 3	106/165 (64%)	106/126 (84%)	149/344 (43%)
Scenario 4	43/245 (17%)	43/218 (20%)	
Scenario 5	11/21 (52%)	11/19 (58%)	95/300 (32%)
Scenario 6	25/97 (26%)	25/77 (32%)	
Scenario 7	52/223 (23%)	52/194 (27%)	
Scenario 8	7/12 (58%)	7/10 (70%)	

*Clinical definition of T2T (T2T-DAS44): Scenarios 1 and 2; Combined definition of T2T (T2T-DAS44-US): scenario 3 and 4; no T2T: scenarios 5 to 8. *N*, number; *rem*, remission; *T2T*, treat to target; *DAS*, disease activity score; *US*, ultrasound

of clinical remission was still found for the combined T2T-DAS44-US strategy compared to the clinical T2T-DAS44 strategy when only scenario 5 (sensitivity analysis 2) or when both scenarios 5 and 6 (sensitivity analysis 3) were considered part of the T2T-DAS44-US strategy (Table 4).

Effect of adding US to T2T-DAS44 on radiographic progression

The effect of the combined T2T-DAS44-US strategy on the 6-month radiographic progression did not differ from that of the clinical T2T-DAS44 strategy when considering intervals larger than 3 months between the application of T2T and the measurement of radiographic progression nor when the outcome was the 12-month change in the SvdH score (Supplementary Table S3).

Discussion

In this observational multicenter prospective cohort study, we have tested the added value of using US data as well as clinical data in a T2T-strategy in comparison to a T2T-strategy solely based on clinical data. To our surprise, adding information obtained by the US-7 Score to clinical information and use of this as a T2T-benchmark, led to a lower rather than a higher likelihood of obtaining clinical remission later on, when compared to using clinical information

Table 3 Main analysis: Effect of following the T2T-DAS44-US (new combined approach) as compared to the conventional (T2T-DAS44; reference level) in meeting the clinical targets and on radiographic progression

	DAS44 remission [OR (95% CI)]	DAS28 remission [OR (95% CI)]	Boolean remission [OR (95% CI)]	CDAI remission [OR (95% CI)]	SDAI remission [OR (95% CI)]	6-month Δ in SvdH [β (95% CI)]
No T2T *vs* T2T-DAS44	**0.65 (0.44; 0.97)**	0.72 (0.48; 1.07)	0.69 (0.44; 1.07)	**0.64 (0.43; 0.97)**	**0.59 (0.40; 0.88)**	0.27 (-0.05; 0.59)
T2T-DAS44-US *vs* T2T-DAS44	**0.59 (0.40; 0.87)**	**0.55 (0.38; 0.81)**	**0.56 (0.37; 0.84)**	0.64 (0.41; 1.00)	**0.52 (0.33; 0.80)**	0.11 (-0.16; 0.39)

T2T-DAS44 (clinical definition of T2T): is correctly applied if: either (i) a patient is already in DAS44 remission and treatment is not intensified, or (ii) if not in DAS44 remission, treatment was intensified; T2T-DAS44-US (T2T taking also US data into account): is correctly applied if: either (i) both DAS44 remission and US remission are present and treatment is not intensified; or (ii) if not in remission for both DAS44 and US, the treatment is intensified. All models adjusted for age, gender, disease duration and country. *DAS*, disease activity score; *SDAI*, Simplified Disease Activity Index; *CDAI*, Clinical Disease Activity Index; *T2T*, treat-to-target; *SvdH*, Sharp van der Heijde score

Table 4 Effect of following the T2T-DAS44-US (new combined approach) as compared to the conventional (T2T-DAS44; reference level) in meeting the clinical targets and on radiographic progression: Sensitivity analyses

	DAS44 remission [OR (95% CI)]	DAS28 remission [OR (95% CI)]	Boolean remission [OR (95% CI)]	CDAI remission [OR (95% CI)]	SDAI remission [OR (95% CI)]	6-month Δ in SvdH [β (95% CI)]
Sensitivity analysis 2: Considering scenario 5 as following T2T-DAS44-US						
No T2T *vs* T2T-DAS44	**0.66 (0.44; 0.99)**	0.74 (0.49; 1.11)	**0.60 (0.38; 0.97)**	**0.59 (0.38; 0.90)**	**0.54 (0.36; 0.84)**	0.31 (−0.05; 0.68)
T2T-DAS44-US *vs* T2T-DAS44	**0.59 (0.40; 0.87)**	**0.56 (0.39; 0.80)**	**0.62 (0.42; 0.91)**	0.68 (0.44; 1.05)	**0.55 (0.36; 0.84)**	0.17 (−0.11; 0.46)
Sensitivity analysis 3: Considering both scenario 5 and scenario 6 as following T2T-DAS44-US						
No T2T *vs* T2T-DAS44	**0.64 (0.42; 0.98)**	0.71 (0.45; 1.11)	0.63 (0.38; 1.06)	**0.54 (0.32; 0.90)**	**0.51 (0.32; 0.82)**	−0.13 (−0.38; 0.13)
T2T-DAS44-US *vs* T2T-DAS44	**0.61 (0.42; 0.87)**	**0.59 (0.41; 0.84)**	**0.61 (0.41; 0.90)**	0.69 (0.45; 1.04)	**0.56 (0.37; 0.85)**	0.15 (−0.19; 0.49)

T2T scenario 5: clinical remission but no US remission and treatment intensification. T2T-DAS44 (clinical definition of T2T) is correctly applied if either: (i) a patient is already in DAS44 remission or (ii) if not in DAS44 remission, treatment was intensified; T2T-DAS44-US (T2T taking also US data into account) is correctly applied if either: (i) both DAS44 remission and US remission are present; or (ii) if not in remission for both DAS44 and US, the treatment is intensified. All models adjusted for age, gender, disease duration and country. *DAS*, disease activity score; *SDAI*, Simplified Disease Activity Index; *CDAI*, Clinical Disease Activity Index; *T2T*, treat-to-target; *SvdH*, Sharp van der Heijde score

only. In addition, adding US data to a clinical T2T strategy did not offer additional protection against radiographic progression in patients with RA.

The use of US information in T2T strategies has been previously suggested [10]. Up to now, none of the studies performed has been supportive of this approach. Two recent randomized clinical trials (RCT) have failed to show a benefit of adding US to a T2T strategy (the ARCTIC and TaSER trials) [25, 26]. Important methodological differences between these trials and the current study render comparisons difficult (e.g. the studied population; T2T strategy allocation; US- and clinical-target definitions; treatment escalation protocol; and the US protocol) [27]. Still, keeping these differences in mind, all studies reached the same conclusion: no clinical benefit of routinely adding US to a clinical T2T strategy.

Adherence of patients and physicians to a standardized treatment strategy, such as T2T, is challenging. Rheumatologists may be reluctant to make treatment decisions solely based on a (clinical) algorithm rather than integrating all available information. In fact, we have previously shown that patient- and disease-characteristics do affect adherence to T2T in the BIODAM cohort [28]. As expected for an RCT-context, the ARCTIC trial had very high adherence to the T2T protocol (81%). Information about protocol adherence was not available for the TaSER trial. In the current study, that likely better reflects normal clinical practice, adherence to protocol was somewhat lower (65%). Moreover, the

T2T-strategy combining US-remission and DAS44 remission as targets was followed more often than the T2T-strategy taking only clinical data into account (41% vs 24%).

The combined T2T definition used in the main analysis implies concordance between US and clinical data. As shown in Fig. 1, in visits in which clinical remission and US remission were discordant, rheumatologists could either follow the protocol and apply the T2T strategy based on clinical data only or could decide to tailor treatment according to US data and ignore clinical information. Although not considered in the predefined combined T2T strategy, it may be considered reasonable to include in this strategy visits in which treatment was intensified when patients were in clinical but not in US remission (scenario 5). When we tested this in a sensitivity analysis, the results did not change. Importantly, of the 218 visits in which patients were in clinical but not US remission, treatment intensifications were uncommon (scenario 5: 21/218; 10%), while in most of the visits (scenario 1: 197/218; 90%), clinical data prevailed and no intensification was prescribed. This suggests that, in case of inflammation detected only on US, most rheumatologists still prioritized clinical data.

Of note, adding US data to a clinical T2T strategy also did not reduce radiographic progression compared with using clinical information alone. This finding adds to the results of a previous study (also from the BIODAM cohort) in which strictly following the clinical-only approach to T2T was not superior to having a more permissive attitude towards T2T [29], by showing that the addition of US information (US-7 score) carries no additional benefit for preventing structural progression.

There is neither consensus on the number of joints that should be assessed by US, nor on which joints should be assessed, to best monitor disease and inform treatment decisions. The ARCTIC and TaSER trials assessed 32 and 14 joints, respectively. In a clinical practice setting, it is reasonable to image fewer joints, and the US7 score, used in this study, has proven its validity, discriminative ability and feasibility [15]. Still, it is arguable whether too much focus on a few US-assessed joints may lead clinicians to overlook clinically manifest synovitis in other non-measured sites. In fact, when patients were not in clinical remission, but US was negative for inflammation (scenarios 2 and 6; 136 visits), rheumatologists opted for no intensification in the majority of the visits (scenario 6: 97/136; 71%) including 44% in which patients had at least one swollen joint. This may, at least partially, explain the lower likelihood of attaining clinical remission by following the combined definition of T2T-US as compared to the T2T strategy based only on clinical data.

Our study has several limitations. First, patients were not randomly allocated to the T2T strategies. Thus, the possibility that both patient characteristics and rheumatologists' expectations affect how US data were used to inform treatment decisions cannot be ruled out (confounding by indication). However, unlike RCTs this setting allows us to assess how T2T performs in clinical practice and has far higher generalizability to the entire RA population. Second, different US devices were used across centres, with different Doppler sensitivities, and this may introduce 'noise'/variability into the estimates of the effect of T2T on the outcomes [30, 31]. Even though ultrasonographers participated in a calibration exercise before the study start, residual between device- and between reader-heterogeneity cannot be excluded. But variability is expected in clinical practice which, as mentioned above, is the very scope of our study. Third, DAS44 remission was part of both the T2T strategy and the outcome, whereas US was not. It is arguable whether using a combined US-clinical outcome could have led to different results. However, similar to clinical trials and other cohort studies, in the current study, we used only validated clinical measures of remission as outcomes. Moreover, the results of the analysis with an outcome not included in the T2T definition (radiographic progression) did not differ from the one focusing on clinical remission. Fourth, we used a previously validated US remission definition that considers only the absence of synovitis [21, 22]. Whether tenosynovitis could be relevant in a US-based T2T strategy should be clarified in future studies. Fifth, the current study includes patients with relatively short disease duration, thus the lack of benefit of adding US into T2T on radiographic progression does not necessarily translate to patients with more established longstanding disease. More damage at baseline might result in a higher likelihood of progression and thus in detecting differences across groups. Finally, it should be noted that not all patients completed the 2-year follow-up of the study which might have introduced bias. However, we used a statistical technique (GEE) that addresses, to some extent, right censoring bias by allowing the inclusion of patients with at least 2 follow-up visits in the analyses (even if not completing the 2-year follow-up). Ultrasound has proved to be a major resource to rheumatologists for different purposes, such as for diagnosis [32, 33]. However, results from this study in 'real-world' RA patients, corroborate the results of two pivotal trials in telling us that adding US to a clinical T2T strategy leads to far more treatment intensifications (with consequences for costs and exposure to risks) without yielding a meaningful clinical benefit. In conclusion, current evidence convincingly tells us that when practicing a T2T-strategy, rheumatologists should focus on clinical data to inform subsequent treatment decisions.

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Data availability All data pertaining to this study are available in the article and supplementary material.

Declarations

Conflict of interest Alexandre Sepriano: speaking and/or consulting fees from Novartis, Abbvie, UCB and Lilly.
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References

1. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D, Aringer M, Boers M, Buckley CD, Buttgereit F, Bykerk V, Cardiel M, Combe B, Cutolo M, van Eijk-Hustings Y, Emery P, Finckh A, Gabay C, Gomez-Reino J, Gossec L, Gottenberg JE, Hazes JMW, Huizinga T, Jani M, Karateev D, Kouloumas M, Kvien T, Li Z, Mariette X, McInnes I, Mysler E, Nash P, Pavelka K, Poor G, Richez C, van Riel P, Rubbert-Roth A, Saag K, da Silva J, Stamm T, Takeuchi T, Westhovens R, de Wit M, van der Heijde D (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 76(6):960–977. https://doi.org/10.1136/annrheumdis-2016-210715
2. Aga AB, Lie E, Uhlig T, Olsen IC, Wierod A, Kalstad S, Rodevand E, Mikkelsen K, Kvien TK, Haavardsholm EA (2015) Time trends in disease activity, response and remission rates in rheumatoid arthritis during the past decade: results from the NOR-DMARD study 2000–2010. Ann Rheum Dis 74(2):381–388. https://doi.org/10.1136/annrheumdis-2013-204020
3. Smolen JS, Han C, van der Heijde DM, Emery P, Bathon JM, Keystone E, Maini RN, Kalden JR, Aletaha D, Baker D, Han J, Bala M, St Clair EW, Active-controlled study of patients receiving infliximab for the treatment of rheumatoid arthritis of early onset study G (2009) Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 68(6):823–827. https://doi.org/10.1136/ard.2008.090019
4. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, Kvien TK, Navarro-Compan MV, Oliver S, Schoels M, Scholte-Voshaar M, Stamm T, Stoffer M, Takeuchi T, Aletaha D, Andreu JL, Aringer M, Bergman M, Betteridge N, Bijlsma H, Burkhardt H, Cardiel M, Combe B, Durez P, Fonseca JE, Gibofsky A, Gomez-Reino JJ, Graninger W, Hannonen P, Haraoui B, Kouloumas M, Landewe R, Martin-Mola E, Nash P, Ostergaard M, Ostor A, Richards P, Sokka-Isler T, Thorne C, Tzioufas AG, van Vollenhoven R, de Wit M, van der Heijde D (2016) Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 75(1):3–15. https://doi.org/10.1136/annrheumdis-2015-207524
5. van der Heijde DM, van't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, van Rijswijk MH, van de Putte LB (1990) Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 49(11):916–920
6. van Gestel AM, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL (1996) Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 39(1):34–40
7. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, Smolen JS (2005) Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 7(4):R796-806. https://doi.org/10.1186/ar1740
8. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, van Riel PL, Tugwell P (2003) A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 42(2):244–257

9. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, Aletaha D, Allaart CF, Bathon J, Bombardieri S, Brooks P, Brown A, Matucci-Cerinic M, Choi H, Combe B, de Wit M, Dougados M, Emery P, Furst D, Gomez-Reino J, Hawker G, Keystone E, Khanna D, Kirwan J, Kvien TK, Landewe R, Listing J, Michaud K, Martin-Mola E, Montie P, Pincus T, Richards P, Siegel JN, Simon LS, Sokka T, Strand V, Tugwell P, Tyndall A, van der Heijde D, Verstappen S, White B, Wolfe F, Zink A, Boers M (2011) American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 70(3):404–413. https://doi.org/10.1136/ard.2011.149765
10. Wakefield RJ, D'Agostino MA, Naredo E, Buch MH, Iagnocco A, Terslev L, Ostergaard M, Backhaus M, Grassi W, Dougados M, Burmester GR, Saleem B, de Miguel E, Estrach C, Ikeda K, Gutierrez M, Thompson R, Balint P, Emery P (2012) After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? Ann Rheum Dis 71(6):799–803. https://doi.org/10.1136/annrheumdis-2011-201048
11. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P (2008) An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 58(10):2958–2967. https://doi.org/10.1002/art.23945
12. Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, Peterfy C, Wakefield RJ, Emery P (2012) Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis 71(8):1316–1321. https://doi.org/10.1136/annrheumdis-2011-200548
13. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Menard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovsky J, Wolfe F, Hawker G (2010) 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 69(9):1580–1588. https://doi.org/10.1136/ard.2010.138461
14. Maksymowych WP, FitzGerald O, Ostergaard M, Homik J, van der Heijde D, Lambert RG, Elkayam O, Ramiro S, Thorne JC, Larche MJ, Ferraccioli G, Backhaus M, Burmester GR, Boire G, Combe B, Schaeverbeke T, Saraux A, Dougados M, Rossini M, Govoni M, Sinigaglia L, Cantagrel A, Barnabe C, Bingham CO, 3rd, Tak PP, van Schaardenburg D, Hammer HB, Paschke J, Dadashova R, Hutchings E, Sepriano A, Landewe R (2020) Outcomes and findings of the international rheumatoid arthritis (RA) BIODAM cohort for validation of soluble biomarkers in RA. J Rheumatol 47(6):796–808. https://doi.org/10.3899/jrheum.190302
15. Backhaus M, Ohrndorf S, Kellner H, Strunk J, Backhaus TM, Hartung W, Sattler H, Albrecht K, Kaufmann J, Becker K, Sorensen H, Meier L, Burmester GR, Schmidt WA (2009) Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum 61(9):1194–1201. https://doi.org/10.1002/art.24646
16. www.carearthritis.com/service/ultrasound/
17. Prevoo ML, van Gestel AM, van THMA, van Rijswijk MH, van de Putte LB, van Riel PL (1996) Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 35(11):1101-1105
18. Fransen J, Creemers MC, Van Riel PL (2004) Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology (Oxford) 43(10):1252–1255. https://doi.org/10.1093/rheumatology/keh297
19. Aletaha D, Smolen J (2005) The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 23(5 Suppl 39):S100-108
20. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS (2005) Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 52(9):2625–2636. https://doi.org/10.1002/art.21235
21. Nakagomi D, Ikeda K, Okubo A, Iwamoto T, Sanayama Y, Takahashi K, Yamagata M, Takatori H, Suzuki K, Takabayashi K, Nakajima H (2013) Ultrasound can improve the accuracy of the 2010 American College of Rheumatology/European League against rheumatism classification criteria for rheumatoid arthritis to predict the requirement for methotrexate treatment. Arthritis Rheum 65(4):890–898. https://doi.org/10.1002/art.37848
22. Glimm AM, Ohrndorf S, Fischer I, Strunk J, Schmidt W, Hartung W, Sattler H, Kellner H, Schmittat G, Burmester GR, Backhaus M (2016) Imaging remission by musculoskeletal ultrasound leads to a better functional outcome – results of the US impera study – US 7-Score implementation study in early rheumatoid arthritis [abstract]. Arthritis Rheumatol 68 (suppl 10)
23. van der Heijde D (2000) How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 27(1):261–263
24. van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB (1989) Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1(8646):1036–1038. https://doi.org/10.1016/s0140-6736(89)92442-2
25. Dale J, Stirling A, Zhang R, Purves D, Foley J, Sambrook M, Conaghan PG, van der Heijde D, McConnachie A, McInnes IB, Porter D (2016) Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. Ann Rheum Dis 75(6):1043–1050. https://doi.org/10.1136/annrheumdis-2015-208941
26. Haavardsholm EA, Aga AB, Olsen IC, Lillegraven S, Hammer HB, Uhlig T, Fremstad H, Madland TM, Lexberg AS, Haukeland H, Rodevand E, Hoili C, Stray H, Noraas A, Hansen IJ, Bakland G, Nordberg LB, van der Heijde D, Kvien TK (2016) Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ 354:i4205. https://doi.org/10.1136/bmj.i4205
27. D'Agostino MA, Boers M, Wakefield RJ, Emery P, Conaghan PG (2017) Is it time to revisit the role of ultrasound in rheumatoid arthritis management? Ann Rheum Dis 76(1):7–8. https://doi.org/10.1136/annrheumdis-2016-210453
28. Sepriano A, Ramiro S, FitzGerald O, Ostergaard M, Homik J, van der Heijde D, Elkayam O, Thorne JC, Larche MJ, Ferraccioli G, Backhaus M, Burmester GR, Boire G, Combe B, Schaeverbeke T, Saraux A, Dougados M, Rossini M, Govoni M, Sinigaglia L, Cantagrel A, Barnabe C, Bingham CO 3rd, Tak PP, van Schaardenburg D, Hammer HB, Paschke J, Dadashova R, Hutchings E, Landewe R, Maksymowych WP (2020) Adherence to treat-to-target management in rheumatoid arthritis and associated factors: data from the international RA BIODAM cohort. J Rheumatol 47(6):809–819. https://doi.org/10.3899/jrheum.190303
29. Ramiro S, Landewe R, van der Heijde D, Sepriano A, FitzGerald O, Ostergaard M, Homik J, Elkayam O, Thorne JC, Larche MJ, Ferraccioli G, Backhaus M, Boire G, Combe B, Schaeverbeke T, Saraux A, Dougados M, Rossini M, Govoni M, Sinigaglia L, Cantagrel AG, Allaart CF, Barnabe C, Bingham CO, van Schaardenburg D, Hammer HB, Dadashova R, Hutchings E, Paschke J, Maksymowych WP (2023) Stricter treat-to-target in RA does not result in less radiographic progression: a longitudinal analysis in

RA BIODAM. Rheumatology (Oxford) 62(9):2989–2997. https://doi.org/10.1093/rheumatology/kead021
30. Brulhart L, Ziswiler HR, Tamborrini G, Zufferey P, programmes SS (2015) The importance of sonographer experience and machine quality with regards to the role of musculoskeletal ultrasound in routine care of rheumatoid arthritis patients. Clin Exp Rheumatol 33(1):98–101
31. Torp-Pedersen S, Christensen R, Szkudlarek M, Ellegaard K, D'Agostino MA, Iagnocco A, Naredo E, Balint P, Wakefield RJ, Torp-Pedersen A, Terslev L (2015) Power and color Doppler ultrasound settings for inflammatory flow: impact on scoring of disease activity in patients with rheumatoid arthritis. Arthritis Rheumatol 67(2):386–395. https://doi.org/10.1002/art.38940
32. Wakefield RJ, Kong KO, Conaghan PG, Brown AK, O'Connor PJ, Emery P (2003) The role of ultrasonography and magnetic resonance imaging in early rheumatoid arthritis. Clin Exp Rheumatol 21(5 Suppl 31):S42-49
33. Caporali R, Smolen JS (2018) Back to the future: forget ultrasound and focus on clinical assessment in rheumatoid arthritis management. Ann Rheum Dis 77(1):18–20. https://doi.org/10.1136/annrheumdis-2017-211458

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