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ORIGINAL ARTICLE

Does Combined Clinical and Ultrasound Assessment Allow Selection of Individuals With Rheumatoid Arthritis for Sustained Reduction of Anti–Tumor Necrosis Factor Therapy?

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Objective. **To investigate whether a strategy combining clinical and ultrasound (US) assessment can select individuals with rheumatoid arthritis (RA) for sustained dose reduction of anti–tumor necrosis factor (anti-TNF) therapies.**

Methods. **As part of a real-world approach, patients with RA receiving anti-TNF therapies were reviewed in a dedicated biologic therapy clinic. Patients not taking oral corticosteroids with both Disease Activity Score in 28 joints (DAS28) remission (≤2.6) and absent synovitis on power Doppler US (PDUS 0) for >6 months were invited to reduce their anti-TNF therapy dose by one-third.**

Results. **Between January 2012 and February 2014, a total of 70 patients underwent anti-TNF dose reduction. Combined DAS28 and PDUS remission was maintained by 96% of patients at 3 months followup, 63% at 6 months, 37% at 9 months, and 34% at 18 months followup. However, 88% of patients maintained at least low disease activity (LDA) with DAS28 <3.2 and PDUS ≤1 at 6 months. The addition of PDUS identified 8 patients (25% of those that flared) in DAS28 remission, with subclinically active disease. Those who maintained dose reduction were more likely to be rheumatoid factor (RF) negative (46% versus 17%; $P = 0.03$) and have lower DAS28 scores at biologic therapy initiation (5.58 versus 5.96; $P = 0.038$).**

Conclusion. **Combined clinical and US assessment identifies individuals in remission who may be suitable for anti-TNF dose reduction and enhances safe monitoring for subclinical disease flares. Despite longstanding severe RA, a subset of our cohort sustained prolonged DAS28 and PDUS remission. LDA at biologic therapy initiation and RF status appeared predictive of sustained remission.**

INTRODUCTION

In the treatment of rheumatoid arthritis (RA), biologic therapies, including anti–tumor necrosis factor (anti-TNF) inhibitors, reduce disease activity (1–3), preserve physical function, and prevent joint damage and consequent disability (4–7). Current guidelines for the management of RA propose rapid escalation of drug treatment to control

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Significance & Innovations

- First description of a real-world anti–tumor necrosis factor (anti-TNF) reduction strategy in patients with severe, chronic rheumatoid arthritis.
- It may be possible to use a strategy of combined clinical and ultrasound assessments to identify patients in remission suitable for anti-TNF dose reduction.

disease activity (8,9). This approach encourages the early use of combination disease-modifying antirheumatic drug (DMARD) therapy and the addition of biologic therapies for patients with poor prognostic signs or for those who fail to achieve prompt disease control with conventional DMARDs.

Despite the clinical efficacy of anti-TNF therapies and a generally reassuring safety profile, some concerns remain regarding their long-term use due to the increased incidence of serious infections, tuberculosis (10,11), and potential malignancies (12). The cost of anti-TNF therapy is also an important consideration and leads to restrictions on prescribing in many countries (13). These combined factors have encouraged the investigation of the potential for anti-TNF dose reduction or discontinuation strategies for patients achieving clinical remission or low disease activity (LDA) (14–16).

Evidence to date suggests that while anti-TNF therapy may be discontinued, at least in the short to medium term for some patients treated early in their disease course (17), stopping anti-TNF in established disease leads to high rates of relapse (16). For this reason it has been suggested that in established disease, dose reduction may be a more realistic approach and can be considered for patients in remission or LDA, either by increasing the interval between doses or reducing the dose administered (9,18). Means of accurately assessing disease activity are vital if anti-TNF therapy is going to be reduced. Clinical measures of remission alone, such as the Disease Activity Score in 28 joints (DAS28) assessment, may underestimate the degree of synovitis, with the consequence that joint damage continues to accrue. One way of addressing this concern is by using imaging technology such as ultrasound (US) or magnetic resonance imaging. Previous studies have demonstrated that ongoing synovitis can be detected by US in up to 62% of patients in clinical remission (19–21) and that synovitis demonstrated by power Doppler ultrasound (PDUS) correlates with both progression of structural damage (22) and risk of subsequent RA flare (23). As a result, the use of US assessment for patients in clinical remission has been proposed (24).

To explore this further we implemented a combined clinical and US assessment program as part of real-world care for patients receiving biologic therapies for RA. These combined assessments were then used to define individuals in both clinical and US remission as part of a strategy to select the most appropriate patients for dose reduction.

PATIENTS AND METHODS

Ethical approval to report anonymized routine clinical data for the study was not required by the National Health Research Authority. However, our local Biologic Therapy Steering Group assessed progress and ensured the study was carried out to international standards of good clinical practice.

As a pragmatic approach to achieving the best clinical outcomes, we developed a dedicated clinic for patients with inflammatory arthritis receiving biologic therapy who were identified from within the existing departmental cohort and channeled into the new service. Hospital records were examined from diagnosis onward and relevant characteristics entered into a biologic agent database. Patients all received standard care within the UK National Health Service. This agency provides comprehensive health care to all UK citizens free at the point of delivery and is funded from general taxation. In the UK, to be eligible for anti-TNF therapy, patients must meet National Institute for Health and Care Excellence criteria, i.e., DAS28 score >5.1 on 2 occasions at least 1 month apart despite treatment with at least 2 DMARDs, one of which must be methotrexate (13).

All patients attending the clinic underwent regular clinical examination (including DAS28 assessment) by the same consultant (CRH) or specialist nurse. In addition, patients underwent standardized PDUS imaging of their hands and wrists (Esoate Mylab 70). Musculoskeletal US was performed using an Esaote linear probe (LA 435; 40 mm, frequency setting 18 MHz for wrist, metacarpophalangeal [MCP] joints and proximal interphalangeal [PIP] joints; mechanical index: 0.65; pulse repetition frequency [PRF] settings: usual PRF set at 750 Hz [possible range 125 Hz–21.9 kHz]) by either a consultant rheumatologist (CRH) or trained musculoskeletal ultrasonographer. A total of 18 joints were scanned, consisting of MCP joints 2–5, PIP joints 2–5 (dorsal midline longitudinal view) and wrists (3 dorsal longitudinal views: midline [radio-lunate-capitate], medial [radiocarpal], and lateral [distal ulnar-carpal]) bilaterally. PDUS findings were graded on a 0–3 semiquantitative scale, where 0 indicated no vascularity and 3 indicated marked hyperemia in line with previously proposed scales (25,26) (Figure 1). Analysis of interoperator variability (IOV) demonstrated substantial agreement (kappa statistic = 0.7545, SE 0.088 [95% confidence interval (95% CI)] 0.58–0.93) between ultrasonographers.

From January 2012, all patients receiving biologic therapy were routinely reviewed 12 weeks after initiating therapy and then every 24 weeks in the biologic therapy clinic. Dose reduction of anti-TNF was discussed with patients if they had been receiving anti-TNF therapy for more than a year, were not taking oral corticosteroids, and were in DAS28 remission (<2.6) for more than 6 months with no evidence of synovitis on PDUS. A one-third reduction was proposed (adalimumab 40 mg every

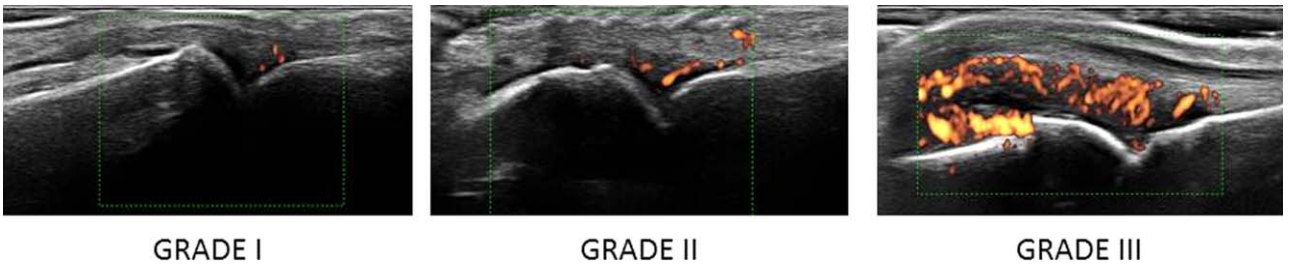

Figure 1. Power Doppler ultrasonography findings graded on a 0–3 semiquantitative scale, where 0 indicates no vascularity and 3 indicates marked hyperemia.

3 weeks; etanercept 50 mg every 10 days; infliximab 2 mg/kg per infusion; certolizumab 200 mg every 3 weeks; and golimumab 50 mg every 6 weeks) with followup at 12 weeks and then every 24 weeks thereafter. Patients who did not meet these criteria, or elected not to undergo dose reduction, continued with routine 24-week followup (Figure 2). All patients were advised to telephone a dedicated specialist nurse helpline if they felt their disease control deteriorated prior to the next planned consultation. All patients who telephoned the helpline were reviewed within 2 working days. Following dose reduction, treatment failure was defined as either loss of DAS28 remission (DAS28 $\geq$2.6), evidence of synovitis on PDUS (score $\geq$1) in any joint, or disease recurrence as defined by the patient. Patients who flared were re-escalated to full treatment dose.

All continuous variables were checked for normality of the distributions. Differences in the baseline characteristics between patients undergoing dose reduction and those continuing on standard dose anti-TNF were assessed for statistical significance using the chi-square test, Fisher's exact test, *t*-test, or Mann-Whitney test as appropriate, with a *P* value less than or equal to 0.05 considered as being statistically significant. In the patients who underwent anti-TNF dose reduction, univariate and multivariate regression analyses were performed to investigate factors influencing sustained remission. Multivariate analysis included adjustment for age, sex, ethnicity, rheumatoid factor (RF) and anti–citrullinated peptide antibody status, duration of disease prior to anti-TNF therapy, and duration of treatment with anti-TNF prior to achieving remission. All analyses were performed with SPSS statistical software, version 2.1 (IBM).

RESULTS

Between January 1, 2012 and February 4, 2014, a total of 321 patients with RA (American College of Rheumatology/European League Against Rheumatism [EULAR] 2010 criteria) (27) were treated with a biologic agent, of whom 219 were receiving anti-TNF therapies. Patients had longstanding (mean 10.54 years) severe RA (mean DAS28 score 5.75 on initiation of anti-TNF) and had generally failed multiple DMARDs prior to biologic agent initiation (mean 3.6 DMARDs) (Table 1).

A total of 115 patients (36%) met eligibility criteria for anti-TNF dose reduction, of whom 70 patients agreed to undergo dose reduction. One patient was excluded from our analysis due to missing data. Older patients were

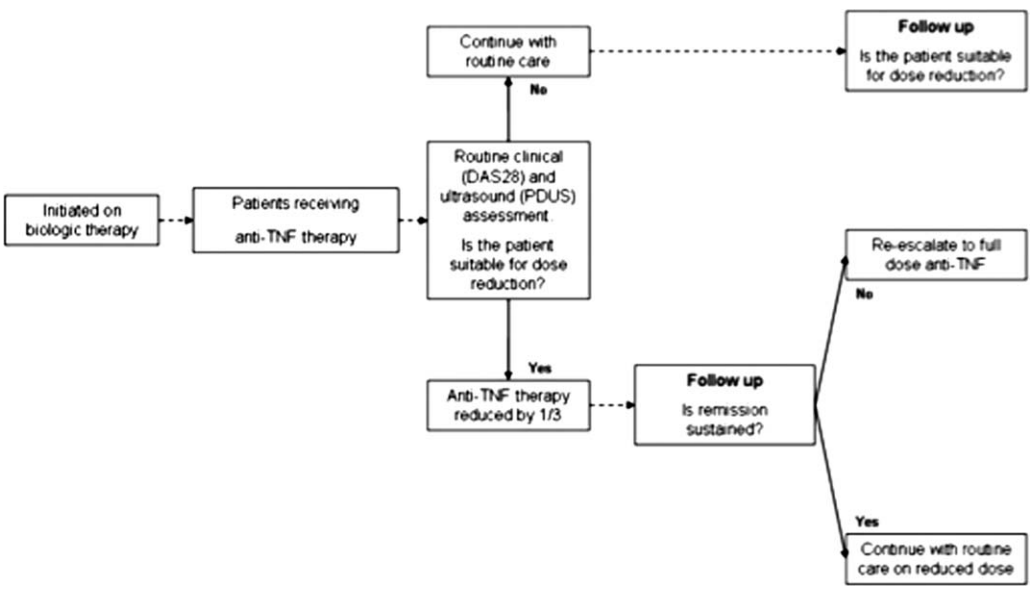

Figure 2. Schematic for patient pathway.

Table 1. Anti-TNF population characteristics*

Characteristic	Nonreducers	Dose reducers	*P*
Subjects, no.	149	69	
Female sex	162 (74.0)	52 (74.3)	0.942
Age, mean ± SD years	57.74 ± 14.06	61.86 ± 12.81	0.039
White	139 (93.3)	65 (92.9)	0.906
Current smoker	24 (18.5)	7 (10.1)	0.305
RF positive	97 (70.3)	45 (69.2)	0.878
ACPA positive	57 (71.3)	24 (68.6)	0.772
Disease duration until first biologic agent, mean ± SD months	125.5 ± 100.7	129.5 ± 119.0	0.092
DMARDs prior to biologic therapy, mean ± SD no.	3.60 ± 2.05	3.57 ± 1.85	0.212
DAS28 score prior to biologic initiation, mean ± SD	5.66 ± 0.99	5.75 ± 0.83	0.287
DMARD co-prescribed with anti-TNF	122 (81.88)	59 (84.29)	0.069

* Values are number (percentage) unless indicated otherwise. Anti-TNF = anti–tumor necrosis factor; RF = rheumatoid factor; ACPA = anti–citrullinated peptide antibody; DMARD = disease-modifying antirheumatic drug; DAS28 = Disease Activity Score in 28 joints.

more likely to agree to undertake anti-TNF reduction (mean ± SD age 61.86 ± 12.81 years versus 57.74 ± 14.06 years; $P = 0.039$).

To understand what factors might predict sustained dose reduction, we first performed a cross-sectional analysis of our cohort. This demonstrated that 37 patients (54%) who underwent anti-TNF dose reduction had remained in sustained DAS28 and PDUS remission at mean ± SD 10.2 ± 6.52 months followup. Thirty-two patients (46%) had flared, with this occurring typically between months 3 and 9 (mean ± SD time to flare 7.65 ± 5.17 months).

Sustained remission was more likely in patients with a lower DAS28 score at anti-TNF initiation (mean ± SD 5.58 ± 0.72 versus 5.96 ± 0.85; $P = 0.04$) and also in patients who were RF negative (44.1% versus 16.7%; $P = 0.03$) (Table 2). There were no other significant differences in measured baseline characteristics between the 2 groups and no differences in the component parts of the DAS28 score (tender joint count, swollen joint count, visual analog scale score, or erythrocyte sedimentation rate). Using logistic regression modeling, lower DAS28 score at anti-TNF initiation was associated with a significantly greater probability of sustained dose reduction (odds ratio 2.04, 95% CI 1.006–4.133, $P = 0.048$). No other statistically significant associations were identified.

To further analyze how and when patients flared, we then examined individual case data. This demonstrated that following dose reduction, 96% of patients maintained combined DAS28 (<2.6) and PDUS remission (PDUS 0) at 3 months followup, 63% at 6 months, 37% at 9 months, and 34% after 18 months followup. However, 88% of patients maintained at least LDA with

Table 2. Characteristics of sustained and nonsustained anti-TNF reducers*

Characteristic	Sustained	Nonsustained	*P*
Subjects, no.	37	32	
Female sex	24 (64.9)	27 (84.4)	0.066
Age, mean ± SD years	60.57 ± 12.37	64.5 ± 11.72	0.065
White	35 (94.6)	29 (90.6)	0.526
Current smoker	4 (10.8)	3 (9.7)	0.988
RF positive	19 (55.9)	25 (83.3)	0.030
ACPA positive	12 (60)	12 (80.0)	0.281
Disease duration until first biologic agent, mean ± SD months	123.1 ± 111.7	141.7 ± 123.1	0.313
DMARDs prior to biologic therapy, mean ± SD no.	3.64 ± 1.79	3.39 ± 1.66	0.693
DAS28 score prior to biologic initiation, mean ± SD	5.58 ± 0.72	5.96 ± 0.85	0.040
DMARD co-prescribed with anti-TNF	33 (89.2)	25 (78.1)	0.452

* Values are number (percentage) unless indicated otherwise. Anti-TNF = anti–tumor necrosis factor; RF = rheumatoid factor; ACPA = anti–citrullinated peptide antibody; DMARD = disease-modifying antirheumatic drug; DAS28 = Disease Activity Score in 28 joints.

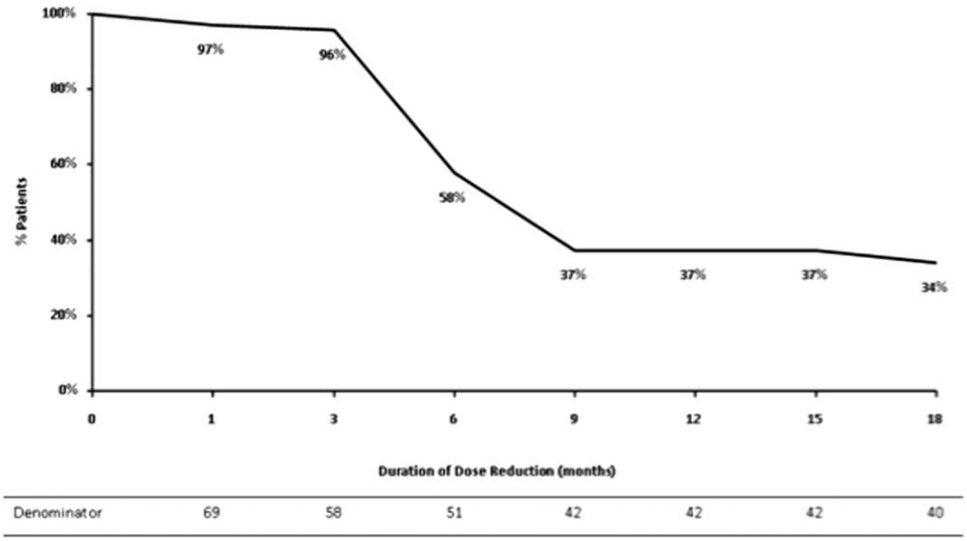

Figure 3. Percentage of individuals maintaining sustained Disease Activity Score in 28 joints and power Doppler ultrasonography remission following dose reduction by time.

DAS28 <3.2 and PDUS ≤1 at 6 months. In patients who maintained remission beyond 9 months, this appeared to be largely sustained with only 2 further dropouts due to disease flare by 18 months followup **(**Figure 3).

Of the patients who failed to maintain remission on a reduced dose of anti-TNF, 41% demonstrated an increase in DAS28 score only, 25% demonstrated development of synovitis using PDUS only, and 25% demonstrated both an increased DAS28 and PDUS activity. The mean ± SD change in DAS28 was an increase of 1.14 ± 1.02 for those patients demonstrating increased clinical disease activity. Using an increase in DAS28 of >1.2 to define a flare of RA, only 34% of patients in our cohort would have been classified as flaring following dose reduction, although half of these patients also demonstrated PDUS at the time of re-escalation. Three patients (9%) felt as if they had flared following dose reduction despite maintaining DAS28- and PDUS-defined measures of remission.

Following disease flare and treatment re-escalation, 6 patients (19%) returned to combined DAS28 and PDUS remission, 6 patients (19%) were in DAS28 remission (with active synovitis on PDUS assessment), and 15 patients (47%) demonstrated LDA (DAS28 ≥2.6 to <3.2). Five patients (15%) had moderate disease activity (DAS28 ≥3.2 to <5.1) despite re-escalation of treatment after an average 15 months of further followup. No patients had severe disease activity (DAS28 ≥5.1) or required a change of biologic treatment following anti-TNF dose reduction.

DISCUSSION

Using clinical and US criteria to define remission in a group of patients with severe longstanding RA, we have shown that at 6 months following dose reduction 63% remained in a stringent remission criteria of DAS28 <2.6 and PDUS 0. It is also worth pointing out that 88% of patients maintained at least LDA with DAS28 <3.2 and PDUS ≤1 at 6 months. However, longer-term followup suggests that by 18 months, approximately two-thirds of patients had flared. Interestingly, flares appeared to occur predominantly between months 3 and 9 after dose reduction. Further flare was rare after this time point, suggesting that patients declare their "flare phenotype" early. In addition, certain characteristics, such as being RF negative and having a lower DAS28 score at anti-TNF initiation, seemed to reduce the likelihood of flare, although the difference in mean DAS28 score between the 2 groups was small (0.38) and less than measurement error for DAS28 (0.6) (28). Our results suggest that it may be possible to identify individuals who are most appropriate for dose reduction using a combination of biomarkers (including PDUS assessment) and clinical scoring systems.

This study has several advantages. It is the first to report the outcomes of anti-TNF dose reduction as part of real-world clinical practice. While other studies have demonstrated the value of US assessment when making decisions about escalating treatment (29,30), this study is unique in including the US assessment of synovitis as part of the clinical decision-making algorithm when tapering biologic therapy. Because of the uncertainties that still exist when integrating US into clinical decision making, and because our patients had severe longstanding disease, we adopted a cautious approach defining US remission as PDUS 0 in all joints, even though the significance of grade 1 change is uncertain and can occur in patients with osteoarthritis (31) and a proportion of healthy volunteers (32). We elected to make treatment decisions on the basis of PDUS only and ignored gray-scale changes because their significance in later RA remains uncertain (33). Following anti-TNF dose reduction, 8 patients were identified as having subclinical synovitis despite DAS28 remission using US at routine

followup appointments. In 4 of these patients PDUS was only grade 1 (in at least 2 joints), and in the remaining 4 PDUS was >1 (in at least 2 joints).

We ensured that patients were involved in a shared decision-making process when considering their dose reduction. We chose a dose reduction of one-third primarily because of concerns regarding disease flare following reduction in a cohort of patients with such longstanding severe disease. In addition, this was a real-world clinical situation, and our policy of shared-care decision making meant that we felt patients were unlikely to agree to a voluntary 50% reduction outside of a more formal clinical trial. Even with this cautious approach, it is interesting to note that of patients who appeared clinically eligible for anti-TNF reduction, a significant proportion (40%) elected not to take part. This group was younger (mean ± SD 55.75 ± 16.04 years versus 61.86 ± 12.81 years; $P = 0.01$) but were otherwise well matched with those that underwent dose reduction. The age differential may reflect younger patients' concerns regarding the loss of remission state and its impact on quality of life and work participation.

Other recent studies have explored the possibility of dose reduction. Compared to our results, the PRESERVE (Prospective, Randomized Etanercept Study to Evaluate Reduced Dose Etanercept Combined with MTX Versus Full Dose Etanercept Combined with MTX Versus MTX Alone) Trial (16), reported that 60.2% of patients maintained DAS28 remission (<2.6) following a 50% reduction in the dose of etanercept at 9 months followup. However, our population had significantly longer disease duration (mean 10.5 years versus 6.3 years) and higher disease activity (mean baseline DAS28 5.75 versus 4.4) compared to the PRESERVE participants.

Our data suggest that lower DAS28 at biologic initiation and being RF negative may be predictive of the likely success of anti-TNF dose reduction. The results of ongoing trials such as PRIZE (Productivity and Remission in a Randomized Controlled Trial of Etanercept Versus Standard of Care in Early Rheumatoid Arthritis) (34) and DOSERA (Discontinuing Etanercept in Subjects With Rheumatoid Arthritis) (35) should provide further clarity regarding the suitability of dose reduction for patients with either very early, or very late RA, respectively.

There is uncertainty regarding the long-term prospects for maintaining remission on reduced dose biologic agents. Our results suggest that in longstanding RA, the majority of patients will experience disease flare; although it is reassuring that 85% of those who flare will re-attain LDA or remission following return to standard dose anti-TNF therapy. Real-world studies such as this can provide important long-term followup data to inform future decision making. While dose reduction may be possible within the context of time-limited clinical trials, the practicality of translating such clinical trial data to everyday practice over the longer term remains to be established.

There are a number of limitations to our study. First, US is well recognized as being subject to user variability. We used either a single-trained consultant rheumatologist or a single-trained musculoskeletal ultrasonographer, who both perform scans routinely in the clinic with good IOV. While our US room is temperature controlled, we did not control for other factors that may influence the detection of synovitis by PDUS, such as concomitant nonsteroidal antiinflammatory drug use, joint position, alcohol or caffeine consumption, or recent physical exertion (36). For pragmatic reasons we did not use a validated US scoring system such as the 12-joint count (37) or 7-joint count (38), nor did we assess foot synovitis (39). Therefore, we may have underestimated the overall likelihood of disease remission, although we would have expected patients with active arthritis in nonassessed joints to decline dose reduction. Finally, because the criteria that we applied to define successful dose reduction are stricter than current EULAR targets of LDA or remission (9), this introduces the possibility that we over-identified disease flare. Consequently, our data may well underestimate the true value of dose reduction.

In conclusion, anti-TNF dose reduction by one-third is possible for some patients with severe longstanding RA and can be undertaken safely within the confines of routine clinical practice. The use of semiquantitative PDUS scoring in addition to clinical assessment and disease characteristics may enable clinicians to identify and safely monitor individuals in whom this can be considered.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Edwards 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. Marks, Holroyd, Armstrong, Cooper, Davidson, Dennison, Harvey.

Acquisition of data. Marks, Holroyd, Armstrong, Calogeras, Cooper, Davidson, Dennison, Harvey.

Analysis and interpretation of data. Marks, Holroyd, Dimitrov, Cooper, Davidson, Dennison, Harvey.

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