Title: Targeting ultrasound remission in early rheumatoid arthritis – the results of the TaSER Study, a randomised clinical trial

Authors: James Dale[1,2], Anne Stirling[3], Ruiqi Zhang[4], David Purves[5], Jonathan Foley[6], Martin Sambrook[7], Philip G Conaghan[8,9], Désirée van der Heijde[10], Alex McConnachie[4], Iain B. McInnes[1], Duncan Porter[1,3]

1. Institute of Infection, Immunity and Inflammation, University of Glasgow
2. Wishaw General Hospital
3. Gartnavel General Hospital, Glasgow
4. Robertson Centre for Biostatistics, University of Glasgow
5. Department of Management Science, Strathclyde University
6. Edinburgh Royal Infirmary
7. East Sussex Hospitals Trust
8. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds
9. NIHR Leeds Musculoskeletal Biomedical Research Unit
10. Leiden University Medical Centre

Corresponding Author
Dr James Dale
Consultant Rheumatologist
Wishaw General Hospital
50 Netherton Street
Wishaw, North Lanarkshire
ML2 0DP

jamesdale1@nhs.net
+44 1698 361100

Keywords
Early rheumatoid arthritis, DAS28, ultrasonography

Abstract

Objective

To investigate whether an intensive early rheumatoid arthritis (RA) treat-to-target (T2T) strategy could be improved through the use of musculoskeletal ultrasound (MSUS) assessment of disease activity

Methods

111 newly diagnosed RA or undifferentiated arthritis patients (symptom duration<1year) were randomised to strategies that aimed to attain either DAS28- erythrocyte sedimentation rate (ESR)<3.2 (control) or a total Power Doppler (PD) joint count ≤1 during a combined DAS28-ESR/MSUS assessment (intervention). MSUS examination was indicated if: DAS28- (ESR)<3.2 or DAS28-ESR≥3.2 with 2 swollen joints. Step-up DMARD escalation was standardized: methotrexate monotherapy, triple therapy, and then etanercept/triple therapy. American College of Rheumatology (ACR) core-set variables were assessed 3 monthly by a metrologist blinded to group allocation. MRI of dominant hand and wrist, and plain radiographs of hands and feet were undertaken at baseline and 18 months for grading by 2 readers using the OMERACT RAMRIS and van der Heijde modified-Sharp scores respectively. The co-primary outcomes were mean change from baseline of DAS44 and RAMRIS erosion score

Results

Groups were matched for baseline clinical, demographic and radiographic features. The intervention group received more intensive DMARD therapy. Both groups demonstrated significant improvements in DAS44 (mean change: Control -2.58, Intervention -2.69; 95%CI difference between groups -0.70, to 0.48; p=0.72). There were no significant between group differences for any ACR-core set variables, except DAS44 remission after 18 months (Control 43%, Intervention 66%; p=0.03). There was minimal progression of MRI and radiographic erosions and no difference in imaging outcomes or serious adverse event rates.

Conclusions

In early RA, a MSUS-driven T2T strategy led to more intensive treatment but was not associated with significantly better clinical or imaging outcomes than a DAS28-driven strategy.

Introduction

Early, intensive treatment of rheumatoid arthritis (RA) produces significant improvements in short-to-medium term clinical, functional and imaging outcomes (1-6). Current treatment guidelines (7,8) advocate the early use of disease modifying anti-rheumatic drugs (DMARDs), singly or in combination, as part of 'treat-to-target' (T2T) strategies that aim to achieve low disease activity (LDAS) or remission in all patients. T2T strategies utilise composite disease activity scores (e.g. DAS44, DAS28, SDAI), that incorporate tender and swollen joint counts, patient and physician assessments of disease activity and an acute phase reactant. However, these scores have limitations: patients with painful comorbidities can exhibit high scores that do not reflect active synovitis (9-11); conversely, many patients in remission exhibit subclinical synovitis that is associated with adverse outcomes. For example, during musculoskeletal ultrasound (MSUS) examination, the presence of intra-articular power Doppler (PD) signal predicts clinical flare (12-14), and progressive radiographic damage (15).

MSUS provides an attractive additional method for assessing RA disease activity since it avoids the use of ionizing radiation, is more convenient than serial MRI assessments and allows multiple joint regions to be examined during a single consultation. We have previously reported that regular assessment by a limited MSUS joint set alters approximately 25% of all DAS28-based DMARD decisions (16). This could allow therapy to be more accurately tailored to patients' needs: those with sub-clinical synovitis could receive more intensive DMARD therapy to achieve 'tighter' overall disease control and potentially better outcomes. Conversely, symptomatic patients with elevated DAS28 assessments, but no MSUS evidence of synovitis, could avoid unnecessary treatment escalation. The Targeting Synovitis in Early Rheumatoid Arthritis (TaSER) study was designed to test the hypothesis that incorporating MSUS disease activity assessment into a T2T strategy would produce superior clinical and imaging outcomes compared to a strategy driven by a composite disease activity score.

Methods

The TaSER study was conducted within the Rheumatology Departments of three Scottish teaching hospitals between September 2009 and April 2013. The study protocol was approved by the NHS West of Scotland Research Ethics Committee and registered with ClinicalTrials.Gov (NCT00920478). All participants provided written informed consent.

Patients

Patients were eligible if: they were aged over 18; had a new clinical diagnosis of RA or UA (defined as positive anti-CCP antibodies and ≥3 clinically swollen joints); had a symptom duration <12 months and active disease (DAS44>2.4). Patients were excluded if: they had received more than 6 weeks DMARD therapy; had significant liver (transaminases >twice upper limit of normal) or renal (serum creatinine >200umol/l, eGFR<30ml/min) dysfunction; significant cytopenias (white cell count <4x109/l, hemoglobin <10g/dl, platelets <150x109/l); were pregnant or planning pregnancy or had a contraindication to aggressive DMARD escalation.

Design

The study was an open label, randomized controlled trial with assessment of outcomes by investigators who were blind to group allocation and treatment. Patients were randomized 1:1 to a control group, in whom DMARD escalation decisions were based upon the DAS28-ESR score, or an intervention group, in whom DMARD escalation decisions were based upon a combined DAS28-ESR and MSUS assessment. Randomization used a telephone administered Interactive Voice Response System and was minimized using the patient's baseline DAS28 (<5.1/≥5.1), rheumatoid factor (positive/negative) and erosion (Yes/No) status.

Treatment

Patients attended monthly review appointments for 18 months and were treated by the same rheumatologist (JD). Both groups followed the same step-up DMARD escalation sequence. DMARD doses were optimised to a target (or highest tolerated) dose. Treatment was escalated if the patient's disease activity target had not been reached, and ≥3 months had elapsed since the previous escalation

Step1: methotrexate (MTX) 20mg/week (or sulfasalazine (SSZ) 40mg/kg/day if MTX was contraindicated);
Step2: MTX, SSZ and hydroxychloroquine (HCQ, <6.5mg/kg/day up to maximum 400mg/day)
Step3: subcutaneous MTX (up to 25mg/week), SSZ and HCQ;
Step4: sc MTX, SSZ, HCQ and etanercept 50mg/week

Patients could receive up to 120mg of triamcinolone acetonide during any consultation. Clinically swollen joints were actively injected if they had not been injected within the preceding 3 months, and/or bridging intra-muscular steroid was administered if disease activity remained elevated within 3 months of DMARD escalation. MSUS was not used to guide intra-articular steroid injections. The use of other concomitant medications (including NSAIDs and analgesics) was not restricted. Oral corticosteroids were limited to patients with either persistently active disease despite multiple triamcinolone injections or those with significant extra-articular disease.

Target

In the control group, the target was LDAS (DAS28-ESR<3.2)
In the intervention group, the target was total PD joint count ≤1. In patients with high disease activity (DAS28-ESR>5.1), or moderate disease activity (3.2<DAS28-ESR≤ 5.1) with ≥2 swollen joints, treatment was escalated without MSUS assessment. Treatment was not escalated in patients with moderate disease activity if the clinical swollen joint count and total MSUS PD joint count were both ≤1. Intervention group patients were informed whether treatment escalation decisions were based on DAS28 or MSUS findings.

MSUS assessments

Only patients allocated to the intervention group underwent MSUS assessment. MSUS assessment was undertaken when i) DAS28>3.2 and <2 swollen joints or ii) DAS28<3.2. All MSUS assessments were conducted by the same operator (JD) using a portable Voluson I, GE Healthcare machine, a 10-16MHz linear probe (SP10-16RS) and standardized PD settings: frequency high (machine preset), pulse repetition frequency (PRF) 0.9kHz, wall filter low (machine preset) and gain adjusted to just below the level at which Doppler artifact appeared beneath bone. The dorsal recesses of the index and middle proximal interphalangeal and metacarpophalangeal, radiocarpal, 2nd and 5th metatarsophalangeal joints were examined bilaterally. Intra-articular PD activity was graded using a semi-quantitative scale of 0-3 (17). Active disease was defined as the presence of any PD in 2 joints.

Data Collection

Clinical outcome measures were collected every 3 months by the same metrologist (AS) who was blinded to each patient's treatment strategy. The treating rheumatologist (JD) was unaware of these findings and they were not used to inform treatment decisions. The ACR core-set variables were collected (18): 44 swollen joint count, Ritchie Articular Index, erythrocyte sedimentation rate, C-reactive protein, patient global health 10cm visual analogue score (VAS), pain 10cm VAS, physician global disease activity Likert scale (0-5) and Health Assessment Questionnaire (HAQ). The EuroQoL5D-3L was also collected and converted to a single health utility index using standard UK

value sets (19). The DAS28-ESR, commonly used in clinical practice, was used to inform treatment escalation decisions, whereas the original DAS44 (which includes clinical assessment of a larger joint set) was used as the outcome measure..

MRI scans of the dominant wrist and metacarpophalangeal joints and plain radiographs of hands and feet were undertaken at baseline and 18 months. All MRI scans were performed on a single machine (1.5T Siemans Avanto) using the following sequences: coronal T2-weighted fat-saturated and axial and coronal T1-weighted pre-and post-intravenous gadolinium. MRI images were graded using the OMERACT RAMRIS atlas (20,21) and plain radiographs were graded using the modified Van der Heijde/Sharp Score (vdHSS) (22). Both sets of images were graded independently, in chronological order, by two experienced readers who were blinded to the patient's treatment strategy. The mean of the reader's scores for each component of the scoring system were used in the statistical analysis. Plain radiographs were scored by a commercial company (Imaging Rheumatology International).

Statistical Analysis

The co-primary clinical and imaging outcomes were the mean change in DAS44 and RAMRIS erosions score between baseline and 18 months. All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute). Between group comparisons of normally distributed continuous variables were conducted using Student's T test and, for non-normally distributed variables, the Mann-Whitney U test. Paired continuous variables were compared using the Wilcoxon rank sum test and proportions within categorical groupings were compared using Fisher's exact test. Inter-observer agreement for each component of the RAMRIS score and vdHSS was assessed using the intraclass correlation coefficient and the mean of the difference between each reader's findings. Each reader re-graded 30 randomly selected sets of images and intra-reader variability was estimated using the intra-class correlation coefficient. The smallest detectable change of RAMRIS and vdHSS erosion scores was calculated to differentiate true progression from measurement error (23).

With co-primary outcomes, the Type I and II error rates were effectively doubled. So, to obtain 90% power at 5% significance level, sample size calculations were based on 95% power and 2.5% significance level. Assuming a standard deviation of the change in DAS44 of 0.7 (24), 50 patients needed to be recruited to each group to have sufficient power to detect a between group difference in the mean change in DAS44 of 0.55, approximately half of a clinically significant change (25). Further, assuming a standard deviation of the change in RAMRIS wrist erosions of 1.64 (26), this sample size was powered to detect a between group difference in the mean change of 1.29.

Results

Study Cohort

170 patients with clinical diagnoses of UA or RA were screened for recruitment and 111 consented to participate (Figure1). The randomization process assigned 57 patients to the control group and 54 patients to the intervention group. The control group contained a higher proportion of females (75vs61%), but no other differences in baseline characteristics were observed between the groups (Table1). Fifty-one control group and 50 intervention group patients completed the follow-up period and were included in the analysis of the primary outcomes. In total, 5 patients were lost to follow-up, 4 withdrew consent to participate and 1 was withdrawn after he developed an overlap syndrome with dermatomyositis that required aggressive immunosuppression. In the MSUS group, the median number of MSUS assessments performed per patient was XXXXX (IQR XX-XX) and all patients in this group underwent at least one MSUS assessment

Treatment Exposure

Patients in the intervention group received more intensive DMARD treatment than the control group (Table2). After 6 months, a higher proportion of intervention group were prescribed combination therapy (67vs38%,p=0.003), and after 18 months a higher proportion had received etanercept (22vs10%,p=0.11). There were no significant differences in the mean doses of individual DMARDs at any time point, except at 18 months when oral MTX dose was higher in the control group (Control 18mg/week, Intervention 15mg/week,p=0.016). Both groups received similar total doses of triamcinolone acetonide (mean: Control 288mg (SD207), Intervention 247mg(SD171),p=0.25). Three control group and two intervention group patients received oral prednisolone. By study completion, three control group (mean dose 10mg/day) and one intervention group patient (6.5mg/day) remained on oral prednisolone.

Clinical Outcomes

Both groups exhibited the greatest improvement in disease activity during the first three months of treatment. After 18 months, there was no significant between group difference in the mean change in DAS44 (Figure2: Control -2.58 (95% CI -3.02, -2.14), Intervention -2.69 (-3.09, -2.29), p=0.72). nor the mean area under the curve DAS44 (Control 40.9 (SD19.3), Intervention 37.9 (SD17.7), p=0.42). Both groups exhibited significant improvements in all ACR core set variables with no significant between-group differences for any variable (Table 2).

There were no significant differences in the proportion of patients achieving ACR-Boolean remission (27), EULAR good, ACR20, ACR50 or ACR70 responses (Figure3). After 18 months, a higher proportion of intervention group patients had achieved DAS44 remission (DAS44<1.6: Control 43%,

Intervention 66%,p=0.03); but there were no differences in DAS44 remission rates at any other time point.

After 15 and 18 months, the intervention group exhibited numerically lower HAQ scores (Figure4: median HAQ: 0.38 vs 0.06,p=0.31 at 15 months; 0.5 vs 0.0,p=0.06 at 18 months). Health utility index values improved significantly in both groups, with no significant between group differences at any time point, nor the number of Quality Adjusted Life Years gained over the follow-up period (Mean [95%CI]: Control 0.97 [0.84,1.10], Intervention 1.02 [0.90,1.14], p=0.57).

Imaging Outcomes

There was good-excellent intra-reader and inter-reader agreement for each component of the RAMRIS Score and vdHSS (Supplementary Tables 1 and 2). Baseline values for individual components of the RAMRIS and vdHSS were similar (Table1). Both groups showed small increases in the RAMRIS erosion score and significant decreases in the synovitis and osteitis scores. Similarly, on plain radiographs, both groups showed very small increases in erosion, joint space narrowing and total vdHSS (Table 2). However, for each RAMRIS and vdHSS component, there was no significant between group differences in either the change from baseline (Table2) nor the value at each time point (Supplementary Table 3 and 4). Numerically fewer patients in the intervention group had changes in RAMRIS erosion (16 vs 24%,p=0.39) and vdHSS erosion (11 vs 23%,p=0.17) scores that exceeded the smallest detectable change (RAMRIS erosions SDC=2.5, vdHSS erosion SDC=1.3).

Adverse Events

Forty eight control group patients (89%) and 46 intervention group patients (81%) reported at least one adverse event. Both groups reported similar numbers of adverse events (Control 109, Intervention 100) and mean number of events per patient (2.3 vs 2.2,p=0.72). The most commonly reported adverse events were abnormal liver function tests (Control 19, Intervention 15), nausea (18 vs14), lower respiratory tract infection (15 vs 18), urinary tract infection (6 vs 3), rash (3 vs 3) and leucopenia (2 vs 6). One control group patient was diagnosed with small lymphocytic lymphoma and one intervention group patient developed Waldenstrom's macroglobulinemia. Neither diagnosis was thought related to participation in the study.

A higher number of serious adverse events (including elective admissions) was observed in the intervention group (8 vs 19). There were no deaths in either group and one serious infective episode (pneumonia) in the intervention group required emergency admission for intravenous antibiotics. Two control group patients and four intervention group patients underwent elective orthopaedic admissions. One intervention group patient underwent 3 hospital admissions with abdominal pain and nausea (chronic symptoms that preceded participation in the study) and another intervention group patient underwent 4 admissions for treatment of a pre-existing cardiac condition. All of these episodes

were classified as serious adverse events but were not thought related to participation in the study. One control group patient underwent emergency admission for assessment of an exudative pleural effusion that was considered to be an extra-articular manifestation of RA.

Discussion

This is the first randomized control trial to evaluate the impact of integrating MSUS assessments into a T2T strategy of newly diagnosed RA/UA. The presence of MSUS synovitis, and intra-articular PD signal in particular, is associated with active RA and radiographic progression; consequently, sonographic remission has been proposed as a potential disease activity target (28). Similarly, composite disease activity scores are known to have limited sensitivity and specificity and may not wholly represent the true disease activity state. This study demonstrates that regular assessment of RA disease activity by MSUS, aiming for MSUS remission leads to a greater intensity of DMARD therapy. However, whilst this was not associated with a higher rate of adverse events, it was also not associated with superior clinical, functional, health related quality of life or imaging outcomes.

Both groups experienced an excellent overall response to treatment that may have limited the power of the study to detect significant between group differences. However the 95% confidence intervals for the difference in the primary clinical outcome (95%CI mean improvement in DAS44: -0.70,0.48) indicate that clinically significant differences in outcome are unlikely. Over the first 12 months of the study there were no differences in any of the clinical outcomes. After 15 months, HAQ scores were numerically lower in the intervention group, and after 18 months, a significantly higher proportion of patients had attained DAS44 (but not ACR/EULAR Boolean) remission. These differences should not be over-interpreted. Given the large number of comparisons, a small number of statistically significant results might be expected by chance. However, it is also possible that improved outcomes might only become apparent in the intervention group over a longer follow-up period, perhaps as the rate of etanercept use rises.

It is notable that the rate of damage progression in this study was considerably lower than observed in the TICORA study: (median change total vdHSS: 4.5 [IQR 1-9.9]) compared to either group in this study (Control 0.5 [IQR 0-1.5], Intervention 0 [IQR 0-1.0]). Patients in the TICORA study presented with higher DAS44 scores (mean 4.76 [SD 0.94]), higher rates of smoking (46%) and longer symptom durations (mean 20 months [SD16]) all of which could contribute to a higher overall risk of radiographic progression. Whilst there was no significant difference observed in the primary imaging outcome there were numerically fewer intervention group patients that exhibited progression in RAMRIS and vdHSS erosion scores that exceeded the SDC. It is possible that with a larger cohort and with longer follow up that these observations might become statistically significant.. However, it has previously been shown that there is very little radiographic progression in patients who attain stringent remission criteria (27,29,30, 31,32) suggesting that any differences that might be observed between those in clinical and sonographic remission are unlikely to be clinically relevant. The excess of reported SAEs in the intervention group was not statistically significant, and is unlikely to be of clinical significance either – the majority of SAEs were not thought to be adverse reactions to treatment.

The routine, systematic use of MSUS assessment in all patients with DAS28-LDAS resulted in a large number of negative assessments that did not influence management (16). This is time consuming and may not be practical in busy clinics. Several recent studies have proposed limited MSUS joint sets (33,34) that require shorter examination times, perform as well as extended joint sets (34-37) and are responsive to changes in disease activity (34,38). Even now, there is no consensus about which is the most appropriate set of joints to examine, nor is there an accepted definition of what level of MSUS findings constitutes 'active' RA. The MSUS joint set used by this study was designed pragmatically by combining the common peripheral joints of two previously proposed sets (33,34). Any benefit from using a more extensive joint set, or more detailed examination (e.g to include tendons) would need to offset against the additional time and expertise required. The observation that the joints of healthy volunteers may also display PD signal (39,40) argued against a very stringent MSUS treatment target. Requiring at least two joints to exhibit PD signal was thus a pragmatic decision aimed at avoiding potentially unnecessary treatment escalation, cognizant that it might have excluded some patients from reaching true MSUS remission. Specifically, PRF was set at 0.9 kHz for all assessments; using a lower PRF settings would have increased the sensitivity for the detection of PD signal at the risk of increased artefact, but this would be unlikely to affect the conclusions of the study.

Since the study was undertaken, there have been significant advances in ultrasound technology leading to increased sensitivity for the detection of gray scale and PD abnormalities. The significance of these abnormalities is not certain - recent studies have suggested that modern machines may detect identify grey scale synovitis in healthy individuals (41) although this is not usually associated with PD signal (43), and PD abnormalities of grade $\geq$2 are rare (42). Given the favourable outcomes achieved in the control group, it is arguable whether the use of improved technology would alter any of the study's conclusions.

In both groups, DAS44 improved most quickly between the baseline and month 3 visits. Therefore, the intervention that had the greatest impact on disease activity was commencement of treatment and not the method used to monitor disease activity. This study used a standardized DMARD escalation protocol that was similar to other early RA strategy studies (1,5,44-47). There are some conflicting data about the relative merits of initial combination and step-up strategies: some studies suggest they are equally effective (45,46), whereas others suggest modest advantages associated with combination therapy (5,48). The SWEFOT study suggested that a substantial minority (approximately 30%) will achieve LDAS with methotrexate monotherapy (47) and the RACAT study demonstrated that, after methotrexate monotherapy failure, the sequence of progression from triple to biologic therapy does not significantly affect clinical or radiographic outcomes (45). The results of the TaSER study are in line with these findings; very intensive MSUS-driven DMARD escalation did not produce significantly better clinical or imaging outcomes than an intensive DAS28ESR driven strategy.

Previous studies have suggested that MSUS evidence of subclinical disease (especially PD signal) is not benign, being predictive of acute flare (12-14), radiographic damage progression (15) and failure

to successfully taper biologic therapy (49). It is possible, that treating to eradicate imaging evidence of subclinical disease will achieve a more stable disease state, that eventually becomes associated with more favourable long term outcomes, than treating to attain LDAS. However, given that both groups exhibited an excellent treatment response, it may not be possible (or feasible) to use current disease activity measures to demonstrate subtle between group differences in response without powering studies to examine markedly smaller effect sizes over much longer follow-up periods.

This study confirms that newly diagnosed early RA/UA patients treated according to an intensive T2T strategy have excellent short-term clinical, functional, health-related quality of life and imaging outcomes. There will undoubtedly continue to be a major role for the use of MSUS in the management of patients with RA, including assessment of disease activity, and informing treatment decisions when disease activity status is not clinically apparent. However, the results of this study do not currently support the routine use of MSUS assessment as part of an enhanced T2T strategy in newly diagnosed inflammatory arthritis.

Funding

This study was jointly funded by a Clinical Academic Fellowship from the Chief Scientist's Office, Scottish Executive and an Investigator Initiated project grant from Pfizer UK. Neither funder had any role in the design, performance, analysis, interpretation or reporting of the study.

Acknowledgements

The authors sincerely thank the staff and patients from the Departments of Rheumatology at Gartnavel General Hospital, Glasgow Royal Infirmary, Inverclyde Royal Hospital and Stobhill Hospital, Glasgow for their contribution to this study

Contributors Statement

JD, IMcI and DP conceived the study. JD, PC, AMcC and DP designed the study. AS, JF, MS and DvdH were responsible for the collection of outcome variables. JD, RZ, DP and AMcC conducted the statistical analysis. JD drafted the manuscript and all authors helped to finalise the manuscript

Competing Interests

Dr. Dale reports grants from Chief Scientist's Office, Scottish Government, grants from Pfizer, during the conduct of the study; personal fees and non-financial support from Abbvie, personal fees from Janssen, personal fees from Pfizer, outside the submitted work; Sr. Stirling reports grants from Chief Scientist's Office, Scottish Government, grants from Pfizer, during the conduct of the study; Ms. Zhang has nothing to disclose; Mr. Purves reports grants from Pfizer and Chief Scientists Office, Scottish Government, during the conduct of the study; Dr. Foley has nothing to disclose; Dr. Sambrook reports that he is an Executive Member of the British Society of Radiologists; Dr. Conaghan reports grants and personal fees from BMS, personal fees from Abbvie, personal fees from Janssen, personal fees from Pfizer, personal fees from Roche, personal fees from Novartis, personal fees from Merck, outside the submitted work; Dr. van der Heijde reports other from University of Glasgow, during the conduct of the study; personal fees from AbbVie, personal fees from Amgen, personal fees from Astellas, personal fees from AstraZeneca, personal fees from BMS, personal fees from Celgene, personal fees from Daiichi, personal fees from Eli-Lilly, personal fees from Galapagos, personal fees from Merck, personal fees from Novartis, personal fees from Pfizer,personal fees from Roche, personal fees from Sanofi-Aventis, personal fees from UCB, other from Imaging Rheumatology BV, outside the submitted work; Dr. McConnachie reports grants from Chief Scientists Office, Scottish Government, grants from Pfizer, during the conduct of the study; Dr. McInnes reports grants and personal fees from Pfizer, during the conduct of the study; grants and personal fees from UCB, grants and personal fees from AbbVie , grants and personal fees from BMS, grants and personal fees from MSD, grants and personal fees from Roche , outside the submitted work; Dr. Porter reports grants from Pfizer, grants from Chief Scientists Office, Scottish Government, during the conduct of the study; grants and personal fees from Pfizer, outside the submitted work.

Ethics Approval

West of Scotland Research Ethics Service. All patients provided written, informed consent to Participate

References

1. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. The Lancet. 2004 Jul;364(9430):263–9.

2. Verstappen SMM, Jacobs JWG, van der Veen MJ, Heurkens AHM, Schenk Y, Borg ter EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Annals of the Rheumatic Diseases. 2007 Nov 1;66(11):1443–9.

3. Bakker MF, Jacobs JWG, Welsing PMJ, Vreugdenhil SA, van Booma-Frankfort C, Linn-Rasker SP, et al. Early clinical response to treatment predicts 5-year outcome in RA patients: follow-up results from the CAMERA study. Annals of the Rheumatic Diseases. 2011 May 2;70(6):1099–103.

4. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet. 1999 May 8;353(9164):1568–73.

5. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007 Mar 20;146(6):406–15.

6. Schoels M, Knevel R, ALETAHA D, Bijlsma JWJ, Breedveld FC, Boumpas DT, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Annals of the Rheumatic Diseases. 2010 Mar 17;69(4):638–43.

7. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res. 2012 Apr 2;64(5):625–39.

8. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Annals of the Rheumatic Diseases. 2014 Feb 4;73(3):492–509.

9. Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize ra patients with fibromyalgia. The Journal of Rheumatology. 2004 Apr 1;31(4):695–700.

10. Leeb BF. The DAS28 in rheumatoid arthritis and fibromyalgia patients. Rheumatology. 2004 Jul 13;43(12):1504–7.

11. Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology. 2010 Apr 13;49(5):924–8.

12. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology. 2009 Aug 17;48(9):1092–7.

13. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010 Dec 15;70(1):172–5.

14. Saleem B, Brown AK, Quinn M, Karim Z, Hensor EMA, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Annals of the Rheumatic Diseases. 2012 Jul 14;71(8):1316–21.

15. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008 Oct;58(10):2958–67.

16. Dale J, Purves D, McConnachie A, McInnes I, Porter D. Tightening Up? Impact of Musculoskeletal Ultrasound Disease Activity Assessment on Early Rheumatoid Arthritis Patients Treated Using a Treat to Target Strategy. Arthritis Care Res. 2013 Dec 24;66(1):19–26.

17. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, ØStergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003 Apr;48(4):955–62.

18. Felson DT, Anderson JJ, BOERS M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum. Wiley Online Library; 1993;36(6):729–40.

19. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997 Nov;35(11):1095–108.

20. Conaghan P. The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the metacarpophalangeal joints. Annals of the Rheumatic Diseases. 2005 Feb 1;64(suppl_1):i11–i21.

21. Ejbjerg B. The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the wrist joint. Annals of the Rheumatic Diseases. 2005 Feb 1;64(suppl_1):i23–i47.

22. van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, vad de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. The Lancet. 1989 May 13;1(8646):1036–8.

23. Bruynesteyn K. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Annals of the Rheumatic Diseases. 2005 Feb 1;64(2):179–82.

24. Haagsma CJ, van Riel PLCM, DE ROOIJ DJRAM, VREE TB, RUSSEL FJM, van't Hof MA, et al. COMBINATION OF METHOTREXATE AND SULPHASALAZINE VS METHOTREXATE ALONE: A RANDOMIZED OPEN CLINICAL TRIAL IN RHEUMATOID ARTHRITIS PATIENTS RESISTANT TO SULPHASALAZINE THERAPY. Rheumatology. 1994;33(11):1049–55.

25. van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. 1990.

26. Haavardsholm E, OSTERGAARD M. Reliability and sensitivity to change of the OMERACT rheumatoid arthritis magnetic resonance imaging score in a multireader, longitudinal setting - Haavardsholm - 2005 - Arthritis & Rheumatism - Wiley Online Library. Arthritis & …. 2005.

27. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LHD, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011 Feb 3;63(3):573–86.

28. Wakefield RJ, d'Agostino MA, Naredo E, Buch MH, Iagnocco A, Terslev L, et al. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? Annals of the Rheumatic Diseases. 2012 May 7;71(6):799–803.

29. Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology. 2010 Mar 15;49(4):683–90.

30. Sakellariou G, Scirè CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Annals of the Rheumatic Diseases. BMJ Publishing Group Ltd and European League Against Rheumatism; 2013;72(2):245–9.

31. ALETAHA D, Funovits J, Breedveld FC, Sharp J, Segurado O, Smolen JS. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. Arthritis Rheum. 2009 May;60(5):1242–9.

32. Lillegraven S, Prince FHM, Shadick NA, Bykerk VP, Lu B, Frits ML, et al. Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. Annals of the Rheumatic Diseases. 2012 May;71(5):681–6.

33. Backhaus M, Ohrndorf S, Kellner H, Strunk J, Backhaus TM, Hartung W, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum. 2009 Sep 15;61(9):1194–201.

34. Naredo E, Rodríguez M, Campos C, Rodríguez-heredia JM, Medina JA, Giner E, et al. Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. Arthritis Rheum. 2008;59(4):515–22.

35. Hammer HB, Kvien TK. Comparisons of 7- to 78-joint ultrasonography scores: all different joint combinations show equal response to adalimumab treatment in patients with rheumatoid arthritis. Arthritis Res Ther. 2011;13(3):R78.

36. Mandl P, Balint PV, Brault Y, Backhaus M, d'Agostino MA, Grassi W, et al. Metrologic properties of ultrasound versus clinical evaluation of synovitis in rheumatoid arthritis: Results of a multicenter, randomized study. Arthritis Rheum. 2012 Mar 27;64(4):1272–82.

37. Dougados M, Jousse-Joulin S, Mistretta F, d'Agostino MA, Backhaus M, Bentin J, et al. Evaluation of several ultrasonography scoring systems for synovitis and comparison to clinical examination: results from a prospective multicentre study of rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010 Apr 22;69(5):828–33.

38. Backhaus TM, Ohrndorf S, Kellner H, Strunk J, Hartung W, Sattler H, et al. The US7 score is sensitive to change in a large cohort of patients with rheumatoid arthritis over 12 months of therapy. Annals of the Rheumatic Diseases. 2012 Sep 6.

39. Terslev L, Torp-Pedersen S, Qvistgaard E, Recke von der P, Bliddal H. Doppler ultrasound findings in healthy wrists and finger joints. Annals of the Rheumatic Diseases. 2004 Jun;63(6):644–8.

40. Ellegaard K, Torp-Pedersen S, Holm CC, Danneskiold-Samsoe B, Bliddal H. Ultrasound in finger joints: Findings in normal subjects and pitfalls in the diagnosis of synovial disease. ULTRASCHALL IN DER MEDIZIN. RUDIGERSTR 14, D-70469 STUTTGART, GERMANY: GEORG THIEME VERLAG KG; 2007 Aug;{28}({4}):{401–408}.

41. Padovano I, Costantino F, Breban M, d'Agostino M-A. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. Annals of the Rheumatic Diseases. 2015 Nov 27;:annrheumdis–2015–208103.

42. Kitchen J, Kane D. Greyscale and power Doppler ultrasonographic evaluation of normal synovial joints: correlation with pro- and anti-inflammatory cytokines and angiogenic factors. Rheumatology. 2015 Feb 19;54(3):458–62.

43. Witt M, Mueller F, Nigg A, Reindl C, Leipe J, Proft F, et al. Relevance of Grade 1 Gray-Scale Ultrasound Findings in Wrists and Small Joints to the Assessment of Subclinical Synovitis in Rheumatoid Arthritis. Arthritis Rheum. 2013 Jul 2;65(7):1694–701.

44. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: The Treatment of Early Aggressive Rheumatoid Arthritis trial. Arthritis Rheum [Internet]. Wiley Subscription Services, Inc., A Wiley Company; 2012;64(9):2824–35. Available from: http://dx.doi.org/10.1002/art.34498

45. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for Active Rheumatoid Arthritis after Methotrexate Failure. N Engl J Med. 2013 Jun 11;:130611150115007.

46. Saunders SA, Capell HA, Stirling A, Vallance R, Kincaid W, McMahon AD, et al. Triple therapy in early active rheumatoid arthritis: A randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. Arthritis Rheum. 2008;58(5):1310–7.

47. van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012 Mar 28.

48. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. Annals of the Rheumatic Diseases. 2014 Jun 6;73(7):1331–9.

49. Naredo E, Valor L, la Torre De I, Montoro M, Bello N, Martinez-Barrio J, et al. Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis. Rheumatology. 2015 Mar 1.