Comparison between adalimumab introduction and methotrexate dose escalation in patients with inadequately controlled psoriatic arthritis (CONTROL): a randomised, open-label, two-part, phase 4 study

Laura C Coates, William Tillett, Maria-Antonietta D'Agostino, Proton Rahman, Frank Behrens, Erin L McDearmon-Blondell, Xianwei Bu, Liang Chen, Mudra Kapoor, Philip G Conaghan, Philip Mease**

Lancet Rheumatol 2022; 4: e262–73

Published Online February 25, 2022 https://doi.org/10.1016/S2665-9913(22)00008-X

See Comment page e231

This online publication has been corrected. The corrected version first appeared at thelancet.com on April 13, 2022

*Contributed equally

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK (L C Coates MBChB); Royal National Hospital for Rheumatic Diseases, Pharmacy and Pharmacology, University of Bath, Bath, UK (W Tillett MBChB); Catholic University of Sacred Heart, Agostino Gemelli University Polyclinic Foundation IRCCS, Rome, Italy (Prof M A D'Agostino MD); Memorial University, St John's, NL, Canada (Prof P Rahman MD); Rheumatology and Fraunhofer ITMP, Goethe University, Frankfurt, Germany (Prof F Behrens MD); AbbVie, North Chicago, IL, USA (E L McDearmon-Blondell PhD, X Bu PhD, L Chen PhD, M Kapoor MD); Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, UK (Prof P G Conaghan MD); NIHR Leeds Biomedical Research Centre, Leeds, UK (Prof P G Conaghan); Swedish Medical Center/Providence Health, Seattle, WA, USA (Prof P Mease MD)

Summary

Background Many patients with psoriatic arthritis do not reach minimal disease activity (MDA) on methotrexate alone. This phase 4 open-label study aimed to compare attainment of MDA following introduction of adalimumab with methotrexate escalation in patients with psoriatic arthritis who do not reach MDA after an initial methotrexate course (≤15 mg every week).

Methods CONTROL was a phase 4, randomised, two-part, open-label study conducted in 14 countries and 46 sites. We recruited patients with confirmed active psoriatic arthritis, naive to biologic disease-modifying antirheumatic drugs, with an inadequate response to 15 mg or less of methotrexate. In part 1, patients were randomly assigned (1:1) to receive either methotrexate 15 mg (oral or subcutaneous) every week with the addition of adalimumab 40 mg (subcutaneously) every other week (adalimumab plus methotrexate group) or methotrexate (oral or subcutaneous) escalation up to 25 mg every week (escalated methotrexate group). Randomisation was done using Interactive Response Technology and stratified by the duration of methotrexate treatment (≤3 months and >3 months). In this open-label study there was no masking; participants, people giving the interventions, those assessing outcomes, and those analysing the data were aware of group assignment. The primary endpoint was the proportion of patients who reached MDA at 16 weeks. After 16 weeks (part 2), patients who reached MDA (responders) had their current therapy maintained or modified, wheras patients who did not reach MDA (non-responders) had their therapy escalated until 32 weeks. The primary endpoint in part 2 was the proportion of patients who reached MDA at 32 weeks, analysed in all patients who received one or more doses of study drug. The study is registered with ClinicalTrials.gov, NCT02814175.

Findings Between Aug 5, 2016, and March 19, 2020, 245 of 287 patients initially assessed were enrolled in the study (50% men and 50% women; 92% of patients were White). 123 patients were randomly assigned to receive adalimumab plus methotrexate and 122 patients to receive escalated methotrexate. All 245 patients were included in the primary analysis, and 227 completed part 1 and entered part 2. A significantly higher proportion of patients reached MDA at 16 weeks in the adalimumab plus methotrexate group (51 [41%] patients) compared with the escalated methotrexate group (16 [13%] patients; p<0·0001). Efficacy was generally maintained through 32 weeks for patients who reached MDA at 16 weeks, with 41 (80%) of 51 adalimumab responders and ten (67%) of 15 methotrexate responders maintaining MDA at 32 weeks. Of adalimumab non-responders, 17 (30%) of 57 patients reached MDA at 32 weeks after adalimumab escalation to every week dosing. Among methotrexate non-responders, 50 (55%) of 91 reached MDA after adalimumab introduction. In part 1, two patients in the adalimumab plus methotrexate group reported serious adverse events; and in part 2, one adalimumab responder, three adalimumab non-responders, and three methotrexate non-responders reported serious adverse events. No new safety signals were identified.

Interpretation Results from this novel treatment-strategy trial support the addition of adalimumab over escalating methotrexate in patients with psoriatic arthritis not reaching MDA after an initial methotrexate course. Safety results were consistent with the therapies' known safety profiles.

Funding AbbVie.

Introduction

Psoriatic arthritis is a chronic, systemic inflammatory disease impacting musculoskeletal, dermatological, and extra-articular systems. Early diagnosis and effective treatment are crucial to preventing permanent joint damage and functional impairment that decreases quality of life.[1,2]

International treatment recommendations propose optimising therapy according to treat-to-target strategies to minimise disease progression.[3–6] While there is consensus

Research in context

Evidence before the study

We searched PubMed from inception to Oct 14, 2020 using the search terms ("psoriatic arthritis") AND ("methotrexate") AND ("RCT" OR "Clinical trial" OR "Randomized controlled trial"). Although a consensus regarding an ideal treatment goal in psoriatic arthritis is absent, minimal disease activity (MDA), a validated multidimensional composite measure, has been included as a treat-to-target outcome in several psoriatic arthritis studies including the Tight Control of Psoriatic Arthritis study, and it is recommended as a potential target in the American College of Rheumatology, National Psoriasis Foundation, and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis treatment recommendations. As recommended by the European Alliance of Associations for Rheumatology, standard of care often includes treatment with methotrexate; however, there is a paucity of head-to-head studies underpinning psoriatic arthritis recommendations, and the optimal time to initiate advanced therapy and the effects of escalating methotrexate to reach MDA remain unknown.

Added value of this study

In this phase 4, randomised, open-label trial, a significantly higher proportion of patients reached MDA at 16 weeks after introducing adalimumab (41%) compared with escalating methotrexate (13%; p<0·0001), regardless of previous methotrexate duration. Consistent results were seen across all MDA components and additional secondary endpoints. Withdrawal of methotrexate among adalimumab responders had little effect on MDA, with 80% of patients maintaining MDA at 32 weeks despite the withdrawal of methotrexate. These results present important data on how best to approach therapy within the treat-to-target paradigm.

Implications of all the available evidence

To our knowledge, CONTROL is one of the first treatment-strategy trials to provide evidence that could guide future treatment recommendations. Results from this novel trial support addition of adalimumab over escalating methotrexate in patients with psoriatic arthritis who do not reach MDA after an initial methotrexate course, and could help to inform the duration of initial methotrexate therapy and decision making about modification of therapy. Future studies are required to test the validity of these findings, ideally with greater samples sizes and time periods.

Correspondence to:
Assoc Prof Laura C Coates, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford OX3 7LD, UK
laura.coates@ndorms.ox.ac.uk

on the core outcomes for patients with psoriatic arthritis,[7] consensus regarding an ideal treatment goal is absent. However, minimal disease activity (MDA), a validated multidimensional composite measure that includes patient perspectives, has been included as a treat-to-target outcome in several psoriatic arthritis studies, including the Tight Control of Psoriatic Arthritis study; and it has been recommended as a potential target in American College of Rheumatology (ACR), National Psoriasis Foundation (NPF), and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations.[3,5,8–10] As recommended by the European Alliance of Associations for Rheumatology (EULAR), standard of care in psoriatic arthritis often includes initial treatment with methotrexate (a conventional synthetic disease-modifying antirheumatic drug) before advanced therapy, except in patients with specific disease subtypes (eg, enthesitis or predominantly axial disease).[4] For patients with psoriatic arthritis receiving methotrexate, adherence[11] and gastrointestinal intolerability[12] are important real-world challenges, and clinical trial data regarding efficacy with methotrexate across manifestations are inconsistent.[2] Additionally, data on the appropriate methotrexate dosage necessary for patients with psoriatic arthritis to attain optimal outcomes are scarce.[13–18] The average methotrexate dose used for patients with psoriatic arthritis varies between 7·5 mg and 25 mg every week, with a recommended target of 15–25 mg every week.[3,18,19] In psoriatic arthritis clinical trials, mean baseline methotrexate dose was between 15·8 mg and 7·5 mg every week,[20–22] and in a post-marketing observational study, the mean baseline methotrexate dose was 15·4 mg every week,[23] suggesting that in clinical practice, patients with psoriatic arthritis often receive methotrexate doses at the lower limit or below the recommended target.

In contrast to EULAR, the ACR and NPF[5] recommend the use of a tumour necrosis factor (TNF) inhibitor as the first-line treatment for most patients with psoriatic arthritis; GRAPPA[3] also includes biologics (eg, TNF inhibitor) as a first-line treatment option. In support of this, the TNF inhibitor etanercept, when used as monotherapy or combined with methotrexate in methotrexate-naive patients, has shown higher rates of MDA after 24 weeks than methotrexate 20 mg every week alone, although methotrexate alone did result in improvements across various disease activity measures from baseline.[24,25] Disease activity, prognostic factors, and access to therapies could determine treatment decisions for individual patients. In addition, comorbidities should be considered when selecting the most appropriate treatment.[26,27]

There is a paucity of treatment-strategy trials underpinning psoriatic arthritis recommendations, with few head-to-head studies[28,29] conducted; therefore, the optimal time to initiate advanced therapy, and the effects of escalating methotrexate to reach MDA remain unknown. Here, we present results of the Comparing the Effectiveness of Adalimumab Introduction and Methotrexate Dose Escalation in Subjects with Psoriatic Arthritis (CONTROL) study, which aimed to compare

attainment of MDA following introduction of adalimumab with escalation of methotrexate in patients with psoriatic arthritis who did not reach MDA following initial methotrexate treatment. CONTROL is one of the first treatment-strategy trials to provide evidence that could guide future recommendations.

Methods

Study design and participants

CONTROL was a phase 4, randomised, open-label study conducted in 14 countries and 46 hospitals, clinical research centres, or outpatient clinics in North America, South America, Europe, Asia, and Africa between Aug 5, 2016, and March 19, 2020. Patients were recruited by identification by the study investigators, referral to a study site by a local physician, or recruited via advertisement materials approved by the ethics committees. Eligible patients were adult patients with active psoriatic arthritis who were naive to biological disease-modifying antirheumatic drugs (DMARD), and who had three or more tender or swollen joints at baseline on the 66-68 swollen-tender joint count (66-68 STJC), a psoriatic arthritis diagnosis confirmed by Classification of Psoriatic Arthritis (CASPAR) criteria[30] at screening, and an inadequate response (ie, not in MDA at screening) to methotrexate (≤15 mg every week) for 4 weeks or more. Exclusion criteria included a history of methotrexate intolerance or toxicity, medical conditions precluding methotrexate more than 15 mg every week (as per the investigator's judgement), and previous exposure to any TNF inhibitor or biological DMARD with a different mechanism of action or a systemic biologic agent in general (appendix pp 2–6).

See Online for appendix

The study was conducted according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations and guidelines governing clinical study conduct, and the Declaration of Helsinki. Study-related documents were reviewed and approved by independent ethics committees and institutional review boards in each of the study sites. All patients provided written informed consent before participation in the study.

Randomisation and masking

The study was conducted in two parts, each of 16 weeks duration (figure 1). In part 1, patients were randomly assigned (1:1) to receive either adalimumab (formulation containing citrate) 40 mg every other week by subcutaneous injection combined with oral or subcutaneous methotrexate 15 mg every week (adalimumab plus methotrexate group), or oral or subcutaneous methotrexate escalated to 20–25 mg or less every week (based on previously suggested dosing[3,18,31]) or highest tolerable dose (escalated methotrexate group). Using Interactive Response Technology (IRT), patients were first stratified by the duration of methotrexate treatment at 15 mg every week (≤3 months and >3 months). Within each stratum, IRT assigned a randomisation number that encoded the patient's treatment group assignment according to the randomisation schedule generated by the study sponsor. This was an open-label study with no masking; study participants, people giving the interventions, those assessing outcomes, and those analysing the data were aware of group assignment. During part 2, therapy was adjusted on the basis of the patient's MDA status at 16 weeks.

Procedures

During part 1, patients remained on their regular methotrexate administration schedule. In the escalated

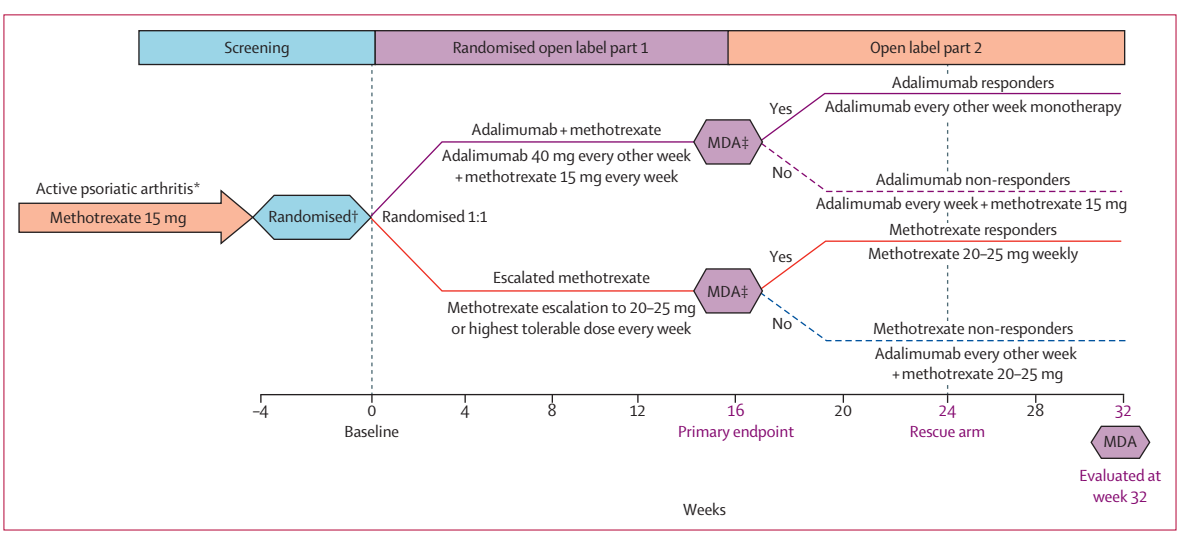

Figure 1: **Study design**

MDA=minimal disease activity. *Defined as not in MDA at screening, three or more tender joints, and three or more swollen joints after methotrexate treatment (15 mg every week) for 4 weeks or more. †Patients were stratified by duration of previous methotrexate (15 mg every week for ≤3 months or >3 months). ‡In part 2, patients were assigned to treatment groups on the basis of their MDA status.

methotrexate group, methotrexate was escalated in increments of 5 mg every other week. In cases of suspected methotrexate intolerance or toxicity in the escalated methotrexate group, the dosage was reduced by 5 mg and patients remained on the highest tolerable dose. Disease activity measures (ACR response, Psoriasis Area and Severity Index [PASI], Disease Activity Index for Psoriatic Arthritis [DAPSA], Psoriatic Arthritis Disease Activity Score [PASDAS], 28-joint Disease Activity Score with C-reactive protein [DAS28(CRP)], Leeds Enthesitis Index [LEI], dactylitic digit count, tender joint count [TJC68], and swollen joint count [SJC66]) were evaluated by the investigator at 2 weeks, 4 weeks, and then monthly until week 16, with patient-reported outcomes (Health Assessment Questionnaire-Disability Index [HAQ-DI], 36-Item Short Form Health Survey Physical Component Summary and Mental Component Summary [SF-36 PCS and MCS], Dermatology Life Quality Index [DLQI], and Psoriatic Arthritis Impact of Disease questionnaire [PSAID]) assessed at the same timepoints.

During part 2, patients initially randomly assigned to adalimumab plus methotrexate who reached MDA at 16 weeks (adalimumab responders) discontinued methotrexate and continued adalimumab monotherapy 40 mg every other week. Patients initially randomly assigned to adalimumab plus methotrexate who did not reach MDA at 16 weeks (adalimumab non-responders) had their adalimumab dose escalated to 40 mg every week and continued methotrexate 15 mg every week. Among patients originally randomly assigned to escalated methotrexate, those reaching MDA at 16 weeks (methotrexate responders) continued escalated methotrexate therapy. Patients who did not reach MDA (methotrexate non-responders) initiated adalimumab 40 mg every other week and continued escalated methotrexate (20–25 mg every week or highest tolerable dose). Rescue treatment was available from 24 weeks for patients who did not reach MDA. The rescue regimen was at the investigators' discretion, but it had to include adalimumab or methotrexate and no prohibited medications (ie, any biological DMARD [except adalimumab] or other systemic biologic agent with a potential therapeutic impact on psoriatic arthritis; appendix p 7). Monthly study visits were conducted during part 2, assessing the same disease activity measures and patient-reported outcomes as in part 1.

Safety evaluations included adverse event monitoring, vital signs, physical examination, and laboratory tests. Adverse events were monitored from the time of study drug administration until 70 days following discontinuation. Investigators could assign causality to adalimumab, methotrexate, or both (if both were part of the regimen). There was no data-monitoring committee for the study, but safety reports from the study were routinely reviewed by the sponsor's product safety team. Blood samples for measurement of serum adalimumab and anti-adalimumab antibody concentrations were collected before dosing, and concentrations were determined using validated ligand-binding methods under the supervision of the sponsor's Drug Analysis Department.

Outcomes

The primary endpoint was the proportion of patients who attained MDA at 16 weeks[7] (defined as five of seven of: TJC68 ≤1 and SJC66 ≤1, PASI ≤1 or body surface area [BSA] ≤3%, Patient Assessment of Pain Visual Analogue Scale [VAS] ≤15, Patient Global Assessment of Disease Activity-VAS ≤20, HAQ-DI ≤0·5, and tender entheseal points ≤1).

Secondary efficacy endpoints included the proportion of patients achieving more than or equal to 20%, 50%, and 70% improvement in ACR response criteria (ACR20, ACR50, and ACR70, respectively) at 16 weeks; a more than or equal to 75%, 90%, and 100% reduction in PASI score (PASI75, PASI90, and PASI100 for patients with BSA ≥3% at baseline) at 16 weeks; the MDA response at 32 weeks; and the change from baseline to 16 weeks in LEI for patients with enthesitis at baseline, HAQ-DI, PADAS, DAPSA, PSAID, SF-36 PCS and MCS, DLQI, and dactylitic digit count (for patients with baseline dactylitis at baseline). The proportion of patients attaining a minimum clinically important improvement in HAQ-DI (ie, reduction in HAQ-DI from baseline ≥0·35) at 16 weeks was evaluated as an exploratory endpoint.

A prespecified exploratory ultrasound substudy evaluated inflammation detected in joints, entheses, and tendons in a subset of patients (appendix pp 8–9); and a prespecified substudy evaluated the presence of anti-adalimumab antibodies at the end of the study.

Statistical analysis

The study was powered to detect a 20% difference in MDA response rates at 16 weeks between the adalimumab plus methotrexate and escalated methotrexate groups. Assuming an MDA response rate of 40% in the adalimumab plus methotrexate group and 20% in the escalated methotrexate group, a total sample size of 240 patients, 120 per group, was planned to provide 90% or more statistical power to detect the difference between the two treatment groups with a significance level of 0·05, allowing for an approximate dropout rate of 10%.

Primary and secondary efficacy endpoints in part 1 were analysed in all randomised patients who received one or more doses of study drug (modified intent-to-treat population). Comparisons of response rates between treatment groups, including for the primary endpoint and secondary binary endpoints, were analysed using the Cochran–Mantel–Haenszel test, adjusted for previous methotrexate duration (≤3 months *vs* >3 months), with a significance level of 0·05. Non-responder imputation was used to impute missing data for binary variables (ie, patients who had missing data at a specific visit were

treated as a non-responder for that visit; patients who prematurely discontinued or received rescue therapy were considered a non-responder for all subsequent visits). A prespecified sensitivity analysis based on observed case and subgroup analyses for the primary endpoint was also conducted. Changes from baseline in secondary continuous endpoints (baseline to 16 weeks [part 1]) were analysed using mixed model repeated measures (MMRM) with treatment, the stratification factor of previous methotrexate duration (≤3 months *vs* >3 months), visit and treatment-by-visit interaction as fixed effects, and baseline measurement as a covariate. MMRM analysis was based on observed case data and missing data were handled by means of MMRM, with the assumption of missing data at random. In addition, the evaluation of MDA across several subgroups was prespecified, including age (<40 years, 40 to <65 years, or ≥65 years), sex (male or female), body-mass index (<25 kg/m² or ≥25 kg/m²), race (White or non-White), and region (USA; western Europe or Canada; eastern Europe, Middle East or Africa; Latin America; Asia or Pacific). To account for the potential imbalance in disease severity between men and women, post-hoc analyses, in which sex and sex by treatment interaction were added to the model as fixed effects, were conducted for the primary and secondary endpoints at 16 weeks. Binary endpoints were analysed using a logistic regression model adjusting for duration of previous methotrexate use, sex, and interaction of sex with treatment. Missing data were handled by non-responder imputation. Continuous endpoints were analysed using the MMRM model, adjusting for duration of previous methotrexate use, sex, and interaction of sex with treatment. Long-term efficacy analyses from baseline to 32 weeks were performed on the basis of the intent-to-treat long-term population (ie, all randomised patients who received at least one dose of study drug), with descriptive statistics summarised for the four treatment regimens. For binary endpoints, patients who received rescue therapy after 24 weeks were considered non-responders for all subsequent visits after initiating rescue medication. For continuous efficacy endpoints, data occurring after initiating rescue medication were overwritten by the last observation carried forward for subsequent visits. Data were analysed

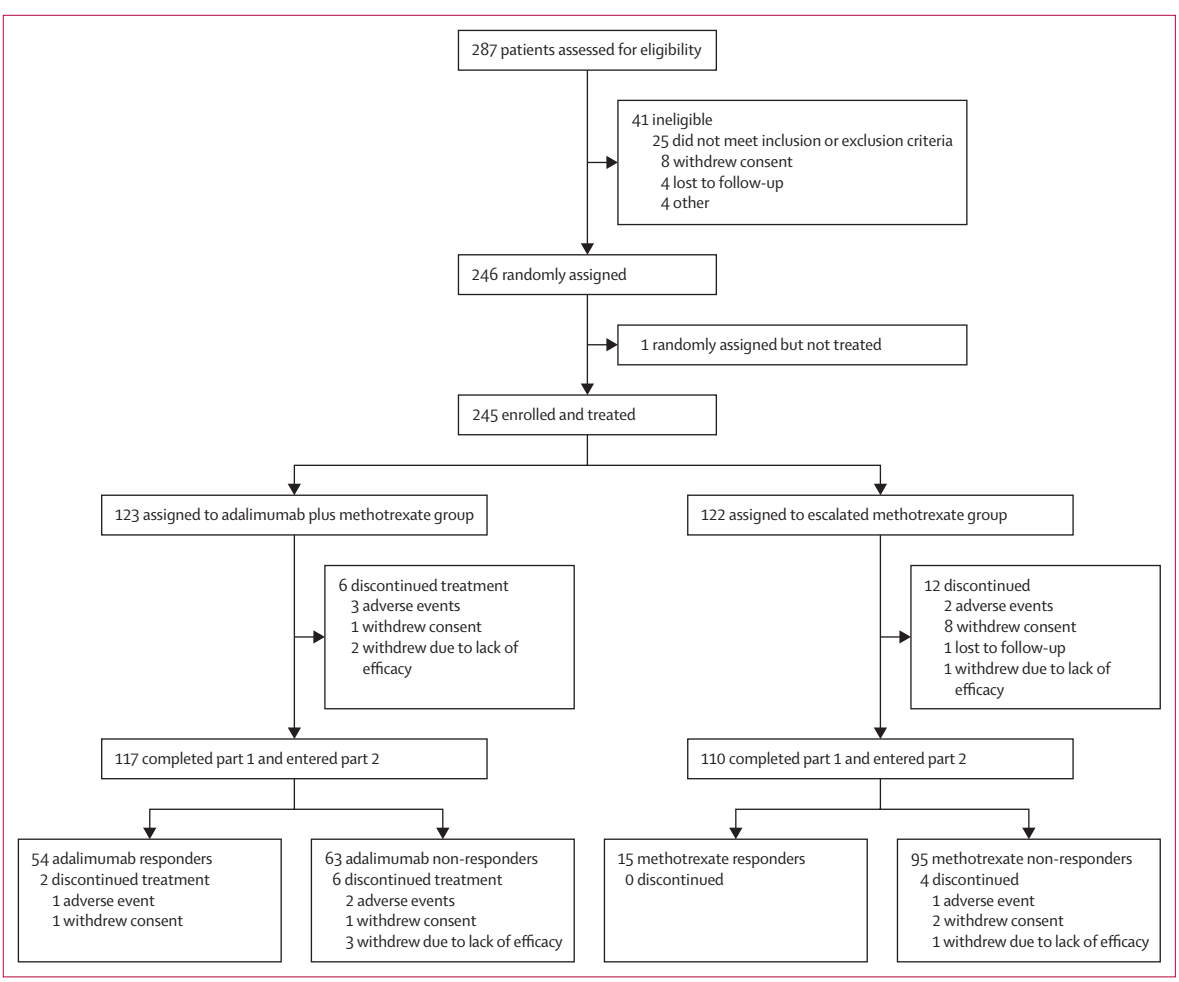

Figure 2: **Trial profile**

using SAS, version 9.4. The study is registered with ClinicalTrials.gov, NCT02814175.

Role of the funding source

AbbVie participated in the study design, research, analysis, data collection, interpretation of data, review, and approval of the publication.

Results

Between Aug 5, 2016, and March 19, 2020, we screened 287 patients from 14 countries for eligibility, 41 were ineligible and were not randomly assigned to treatment (figure 2). One additional patient was randomised but did not receive study treatment, and was excluded from all efficacy and safety analyses. Of the 245 patients who received treatment (50% men and 50% women), 123 patients were randomly assigned to the adalimumab plus methotrexate group and 122 to the escalated methotrexate group, and were included in the primary and secondary analysis. In total, 117 (95%) patients in the adalimumab plus methotrexate group and 110 (90%) patients in the escalated methotrexate group completed part 1 (figure 2). Baseline demographics and disease characteristics were similar between the treatment groups, and they were indicative of high disease activity (mean TJC68 22·1 [SD 14·1]; mean SJC66 10·8 [7·1]; mean BSA 13·3% [18·2%]) despite methotrexate treatment (table 1). More than 80% of patients had active enthesitis (n=206 based on LEI and plantar fascia count, and n=198 based on LEI only) and 57% (n=139) had active dactylitis at baseline. In the adalimumab plus methotrexate group, 64 (52%) patients had been receiving methotrexate 15 mg every week for 3 months or less, versus 59 (48%) patients for more than 3 months; whereas 61 (50%) patients in the escalated methotrexate group had been receiving methotrexate 15 mg every week for 3 months or less versus 61 (50%) patients for more than 3 months. During part 1, the mean methotrexate dose in the escalated methotrexate group was 21·8 mg (SD 2·8) every week. Of the 122 patients, 104 (85%) received 20 mg or more every week, 67 (55%) received oral methotrexate, 44 (36%) received subcutaneous methotrexate, and 11 (9%) received both oral and subcutaneous methotrexate.

The proportion of patients who reached MDA at 16 weeks was higher in the adalimumab plus methotrexate group (51 [41%] of 123 patients) than in the escalated methotrexate group (16 [13%] of 122 patients; p<0·0001) regardless of previous methotrexate duration (≤3 months *vs* >3 months, figure 3). Results were consistent in the observed case analysis, in which 51 (44%) of 117 patients reached MDA on adalimumab plus methotrexate compared with 16 (15%) of 110 patients on escalated methotrexate. Results were also similar when sex and interaction of sex with treatment were included in the statistical model (odds ratio [OR] 4·6 [95% CI 2·4–8·9]).

Consistent numerical improvement across all MDA components was observed at 16 weeks for patients receiving adalimumab plus methotrexate and escalated methotrexate (appendix p 10). Adalimumab plus methotrexate resulted in numerically higher MDA rates compared with escalated methotrexate in all prespecified subgroups, consistent with results seen in the overall population (appendix p 11). A lower response rate for adalimumab plus methotrexate versus escalated

	Adalimumab plus methotrexate group (n=123)	Escalated methotrexate group (n=122)	Total (n=245)
Sex			
Male	59 (48%)	63 (52%)	122 (50%)
Female	64 (52%)	59 (48%)	123 (50%)
Race			
White	115 (93%)	111 (91%)	226 (92%)
Asian	1 (1%)	7 (6%)	8 (3%)
Black or African American	2 (2%)	2 (2%)	4 (2%)
Native Hawaiian or Pacific Islander	1 (1%)	0	1 (<1%)
Multiple	4 (3%)	2 (2%)	6 (2%)
Age, years	51·4 (12·2)	48·8 (12·7)	50·1 (12·5)
Region			
USA	28 (23%)	28 (23%)	56 (23%)
Western Europe or Canada	40 (33%)	31 (25%)	71 (29%)
Eastern Europe, Middle East, or Africa	39 (32%)	45 (37%)	84 (34%)
Latin America	7 (6%)	7 (6%)	14 (6%)
Asia or Pacific	9 (7%)	11 (9%)	20 (8%)
BMI, kg/m²	31·1 (7·0)*	30·0 (6·2)	30·5 (6·6)†
BSA	14·2% (20·0)‡	12·3% (16·2)‡	13·3% (18·2)§
Median (IQR)	6·0 (2·0–15·0)	6·0 (3·0–13·0)	6·0 (2·0–14·0)
BSA >3%	74 (60%)	78 (64%)	152 (62%)
PASI among patients with ≥3% BSA	9·6 (8·8)¶	7·9 (6·7)‖	8·7 (7·8)**
Median (IQR)	7·6 (3·7–12·2)	5·9 (3·6–9·5)	6·7 (3·6–10·6)
Previous methotrexate duration, days	188·0 (519·9)	135·2 (138·2)	161·7 (381·2)
Median (IQR)	84·0 (56·0–160·0)	90·0 (55·0–168·0)	86·0 (56·0–166·0)
TJC68	22·0 (13·1)	22·2 (15·0)	22·1 (14·1)
SJC66	10·1 (6·4)	11·5 (7·7)	10·8 (7·1)
Patient's Global Assessment of Pain (VAS, 0–100)	63·7 (19·5)	62·3 (20·9)	63·0 (20·2)
Patient's Global Assessment of Disease Activity (VAS, 0–100)	65·0 (19·9)	62·9 (21·0)	64·0 (20·4)
HAQ-DI	1·2 (0·6)	1·2 (0·7)	1·2 (0·6)
Presence of enthesitis based on LEI plus plantar fascia count	102 (83%)	104 (85%)	206 (84%)
LEI plus plantar count††	3·5 (2·1)	3·5 (2·1)	3·5 (2·1)
Presence of enthesitis based on LEI only	97 (79%)	101 (83%)	198 (81%)
LEI††	2·9 (1·5)	2·9 (1·6)	2·9 (1·6
Presence of dactylitis	65 (53%)	74 (61%)	139 (57%)
Tender dactylitis count‡‡	3·5 (2·7)	3·9 (3·2)	3·7 (3·0)

Data are n (%) or mean (SD) unless otherwise stated. BMI=body-mass index. BSA=body surface area. HAQ-DI=Health Assessment Questionnaire-Disability Index. LEI=Leeds Enthesitis Index. PASI=Psoriasis Area and Severity Index. SJC66=swollen joint count based on 66 joints. TJC68=tender joint count based on 68 joints. VAS=visual analogue scale. *n=122. †n=244. ‡n=111. §n=222. ¶n=78. ‖n=87. **n=165. ††For patients with presence of enthesitis at baseline. ‡‡For patients with presence of dactylitis at baseline.

Table 1: **Baseline characteristics**

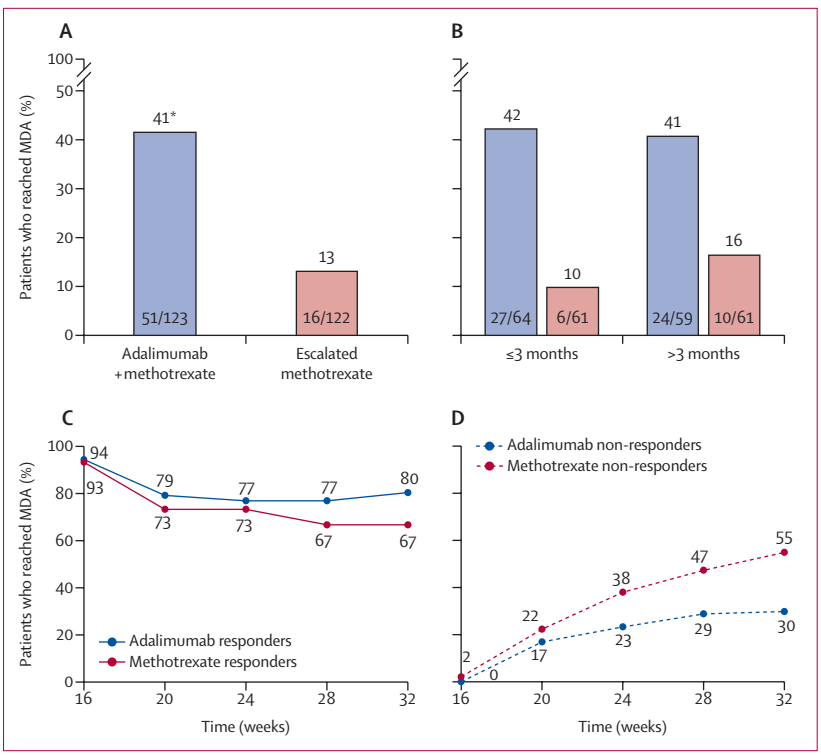

***Figure 3*: Attainment of MDA**
MDA=minimal disease activity. *p<0·0001 versus escalated methotrexate. (A) shows the percentage of patients who reached MDA at 16 weeks overall. (B) shows the percentage of patients who reached MDA stratified by previous methotrexate duration. (C) shows the percentage of part 1 responders who reached MDA at each timepoint from 16 weeks to 32 weeks. (D) shows the percentage of part 1 non-responders who reached MDA at each timepoint from 16 weeks to 32 weeks. Full data shown in appendix p 17.

methotrexate was observed for women (11·4 [95% CI –2·3 to 25·2]) versus men (46·6 [31·6–61·6]) and for White patients (24·7 [13·7–35·8]) versus non-White patients (75·0 [45–100]). There was no apparent difference in response rate in patients from the USA (14·3 [–6·9 to 35·5]) or from western Europe or Canada (11·4, [–7·6 to 30·3) versus other regions, or in patients aged 65 years or older (22·5 [–3·9 to 48·9]) versus younger patients (appendix p 11). Women in both groups generally had higher disease activity at baseline than men (appendix p 13).

At 16 weeks the proportion of patients who reached ACR20, ACR50, ACR70, PASI75, PASI90, and PASI100 was higher in the adalimumab plus methotrexate group than in the escalated methotrexate group (p<0·0001 for all endpoints except PASI100 [p=0·0009]; table 2). Greater improvements from baseline were seen across various clinical and patient-reported functional and quality of life outcomes for patients receiving adalimumab plus methotrexate. 48 (74%) of 65 patients and 58 (60%) of 97 of patients receiving adalimumab plus methotrexate had resolution of dactylitis and enthesitis, respectively, compared with 27 (36%) of 74 patients and 36 (36%) of 101 patients, respectively, on escalated methotrexate (table 2). Results were similar when sex and interaction of sex with treatment were included in the model (appendix p 14).

MDA was generally maintained through 32 weeks for patients who reached MDA at 16 weeks (adalimumab or methotrexate responders, figure 3C; appendix p 17). Among adalimumab responders, 41 (80%) of 51 patients maintained MDA despite withdrawal of methotrexate at 16 weeks. In comparison, among methotrexate responders, ten (67%) of 15 patients maintained MDA through 32 weeks with continued escalated methotrexate therapy. Modifying therapy in patients who did not reach MDA at 16 weeks resulted in increased proportions of patients reaching MDA by 32 weeks (figure 3D; appendix p 17). Among adalimumab non-responders, 17 (30%) of 57 patients reached MDA after adalimumab escalation to every week dosing. Among methotrexate non-responders, 50 (55%) of 91 patients reached MDA after the introduction of adalimumab every other week in addition to continued escalated methotrexate. A similar pattern was observed for additional efficacy endpoints, including disease activity, functional outcomes, and quality of life at 32 weeks (table 2). Of note, baseline characteristics at randomisation for the four groups in part 2 of the study varied as anticipated, with slightly higher baseline disease activity observed in the non-responder groups for endpoints such as TJC68 and pain (appendix p 15).

Overall, more patients received rescue therapy at 28 weeks in the non-responder groups than the responder groups (15 [16%] of 95 methotrexate non-responders and 16 [25%] of 63 adalimumab non-responders *vs* two [13%] of 15 methotrexate responders and five [9%] of 54 adalimumab responders). Additional patients in all groups reached MDA following rescue therapy, although the percentage was numerically higher in responder groups (appendix p 16).

In part 1, the median duration of adalimumab exposure was 112 days (IQR 112–112) in the adalimumab plus methotrexate group, whereas the median duration of methotrexate exposure was 112 days (106–112) in the adalimumab plus methotrexate group and 112 days (112–113) in the escalated methotrexate group. Mean adalimumab concentrations were similar in patients in the adalimumab plus methotrexate group at 16 weeks, regardless of MDA attainment (7·0 µg/mL [SD 3·3] in responders *vs* 7·3 µg/mL [4·0] in non-responders), appendix p 20). In part 1, two serious adverse events were reported (pneumonia and sciatica; table 3) in the adalimumab plus methotrexate group. The most common adverse events were injection-site reaction (adalimumab plus methotrexate, 13 [11%] of 123 patients; escalated methotrexate, 3 [2%] of 122 patients) and upper respiratory tract infection (10 [8%] of 123 patients and 11 [9%] of 122 patients, respectively). Infections occurred in 41 (33%) of 123 patients in the adalimumab plus methotrexate group and in 25 (20%) of 122 patients in the escalated methotrexate group. There were minimal grade 3 or 4 changes in alanine aminotransferase,

	Part 1 (up to 16 weeks)			Part 2 (up to 32 weeks)			
	Adalimumab plus methotrexate group	Escalated methotrexate group	p value	Adalimumab responders	Adalimumab non-responders	Methotrexate responders	Methotrexate non-responders
ACR response							
ACR20	83/123 (67·5%, 59·2–75·8)	40/122 (32·8%, 24·5–41·1)	<0·0001	43/46 (93·5%, 86·3–100·0)	24/39 (61·5%, 46·3–76·8)	12/13 (92·3%, 77·8–100·0)	65/74 (87·8%, 80·4–95·3)
ACR50	56/123 (45·5%, 36·7–54·3)	20/122 (16·4%, 9·8–23·0)	<0·0001	38/46 (82·6%, 71·7–93·6)	21/39 (53·8%, 38·2–69·5)	11/13 (84·6%, 65·0–100·0)	54/74 (73·0%, 62·9–83·1)
ACR70	38/123 (30·9%, 22·7–39·1)	10/122 (8·2%, 3·3–13·1)	<0·0001	36/45 (80·0%, 68·3–91·7)	17/39 (43·6%, 28·0–59·2)	8/13 (61·5%, 35·1–88·0)	46/73 (63·0%, 51·9–74·1)
PASI response*							
PASI75	57/78 (73·1%, 63·2–82·9)	27/87 (31·0%, 21·3–40·8)	<0·0001	30/38 (78·9%, 66·0–91·9)	19/30 (63·3%, 46·1–80·6)	10/12 (83·3%, 62·2–100·0)	46/61 (75·4%, 64·6–86·2)
PASI90	45/78 (57·7%, 46·7–68·7)	16/87 (18·4%, 10·3–26·5)	<0·0001	29/38 (76·3%, 62·8–89·8)	18/30 (60·0%, 42·5–77·5)	8/12 (66·7%, 40·0–93·3)	41/61 (67·2%, 55·4–79·0)
PASI100	23/78 (29·5%, 19·4–39·6)	8/87 (9·2%, 3·1–15·3)	0·0009	21/38 (55·3%, 39·5–71·1)	10/30 (33·3%, 16·5–50·2)	5/12 (41·7%, 13·8–69·6)	29/61 (47·5%, 35·0–60·1)
DAPSA remission (≤4)	27/114 (23·7%, 15·9–31·5)	3/108 (2·8%, 0·0–5·9)	<0·0001	34/51 (66·7%, 53·7–79·6)	13/57 (22·8%, 11·9–33·7)	7/15 (46·7%, 21·4–71·9)	32/89 (36·0%, 26·0–45·9)
PASDAS remission (≤1·9)	19/114 (16.7%, 9·8–23·5)	3/105 (2·9%, 0·0–6·0)	<0·00081	35/51 (68·6%, 55·9–81·4)	8/57 (14·0, 5·0–23·1)	5/15 (33·3%, 9·5–57·2)	32/89 (36·0%, 26·0–45·9)
Change from baseline in HAQ-DI	–0·5 (–0·6 to –0·4; n=116)	–0·3 (–0·4 to –0·2; n=110)	0·0021	–0·9 (–1·1 to –0·7; n=51)	–0·4 (–0·6 to –0·3; n=57)	–0·8 (–1·1 to –0·5; n=15)	–0·7 (–0·8 to –0·5; n=91)
Change from baseline in SF-36 PCS	8·9 (7·6–10·2; n=117)	4·4 (3·1–5·7; n=107)	<0·0001	14·2 (11·5–16·8; n=52)	8·5 (6·6–10·4; n=58)	9·3 (5·5–13·1; n=15)	10·2 (8·4–12·0; n=92)
Change from baseline in SF-36 MCS	4·4 (2·9–6·1; n=117)	1·3 (–0·4 to 3·0; n=107)	0·0079	7·0 (4·2–9·9; n=52)	3·6 (0·8–6·3; n=58)	7·2 (2·1–12·3; n=15)	4·9 (2·7–7·1; n=92)
Change from baseline in DLQI	–5·9 (–6·7 to –5·2; n=117)	–3·1 (–3·9 to –2·3; n=109)	<0·0001	–7·9 (–9·7 to –6·1; n=52)	–6·0 (–8·0 to –4·1; n=58)	–6·1 (–8·9 to –3·4; n=15)	–6·0 (–7·5 to –4·5; n=91)
Change from baseline in PASDAS	–2·8 (–3·1 to –2·5; n=114)	–1·2 (–1·5 to –0·9; n=105)	<0·0001	–4·4 (–4·9 to –4·0; n=50)	–2·9 (–3·3 to–2·4; n=57)	–3·4 (–4·3 to –2·5; n=14)	–3·4 (–3·7 to –3·0; n=88)
Change from baseline in DAPSA	–28·2 (–31·6 to –24·9; n=114)	–12·1 (–15·6 to –8·7; n=108)	<0·0001	–37·6 (–42·6 to –32·6; n=50)	–27·4 (–33·8 to –21·1; n=57)	–31·5 (–41·7 to –21·4; n=14)	–29·6 (–34·1 to –25·2; n=88)
Change from baseline in PsAID	–3·3 (–3·7 to –3·0; n=117)	–1·7 (–2·1 to –1·3; n=107)	<0·0001	–4·5 (–5·2 to –3·9; n=51)	–3·5 (–4·1 to –2·8; n=57)	–4·2 (–5·6 to –2·8; n=14)	–3·5 (–4·0 to –3·0; n=90)
Change from baseline in DAS28(CRP)	–2·0 (–2·2 to –1·8; n=114)	–0·9 (–1·1 to –0·7; n=108)	<0·0001	–2·9 (–3·2 to –2·6; n=50)	–1·8 (–2·2 to –1·5; n=57)	–2·3 (–3·0 to –1·6; n=14)	–2·2 (–2·5 to –1·9; n=88)
Change from baseline in LEI†	–1·9 (–2·2 to –1·5; n=92)	–1·1 (–1·4 to –0·8; n=89)	0·0015	–2·3 (–2·8 to –1·9; n=37)	–2·0 (–2·5 to –1·4; n=49)	–2·4 (–3·2 to –1·6; n=13)	–1·9 (–2·3 to –1·4; n=73)
Resolution of enthesitis—ie, LEI=0	58/97 (59·8%, 50·0–69·6)	36/101 (35·6%, 26·3–45·0)	<0·00078	31/37 (83·8%, 71·9–95·7)	28/49 (57·1%, 43·3–71·0)	11/13 (84·6%, 65·0–100·0)	52/73 (71·2%, 60·8–81·6)
Change from baseline in dactylitic count‡	–2·8 (–3·4 to –2·2; n=62)	–0·9 (–1·5 to –0·4; n=66)	<0·0001	–3·6 (–4·5 to –2·7; n=29)	–2·6 (–3·7 to –1·5; n=30)	–2·6 (–4·2 to –1·1; n=8)	–3·1 (–3·9 to –2·2; n=55)
Resolution of dactylitis—ie, dactylitis=0	48/65 (73·8%, 63·2–84·5)	27/74 (36·5%, 25·5–47·5)	<0·0001	29/29 (100%, 100–100)	22/30 (73·3%, 57·5–89·2)	7/8 (87·5%, 64·6–100)	44/55 (80·0, 69·4–90·6)
Achievement of MCID for HAQ-DI	62/112 (55·4%, 46·2–64·6)	48/108 (44·4%, 35·1–53·8)	0·11	42/46 (91·3%, 83·2–99·4)	34/54 (63·0%, 50·1–75·8)	11/13 (84·6%, 65·0–100·0)	61/80 (76·3%, 66·9–85·6)

Data are n/N (%, 95% CI) or presented as a point estimate (95% CI) unless otherwise stated. ACR=American College of Rheumatology. CRP=C-reactive protein. DAPSA=Disease Activity Index for Psoriatic Arthritis. DAS28=Disease Activity Score-28. DLQI=Dermatology Life Quality Index. HAQ-DI=Health Assessment Questionnaire-Disability Index. LEI=Leeds Enthesitis Index. MCID=minimal clinically important difference. PASDAS=Psoriatic Arthritis Disease Activity Score. PASI=Psoriasis Area and Severity Index. PsAID=Psoriatic Arthritis Impact of Disease. SF-36 PCS=36-Item Short Form Health Survey mental component summary. SF-36 MCS=36-Item Short Form Health Survey Physical Component Summary. *For patients with baseline body surface area ≥3%. †For patients with presence of enthesitis at baseline. ‡For patients with presence of dactylitis at baseline.

Table 2: **Additional efficacy endpoints at week 16 and week 32**

aspartate aminotransferase, or glucose in the adalimumab plus methotrexate group; however, numerically higher changes were seen in the escalated methotrexate group (appendix p 19).

In part 2, the median duration of adalimumab exposure was 112 days (IQR 112–113) in adalimumab responders, 119 days (117–119) in adalimumab non-responders, and 112 days (112–118) in methotrexate non-responders. The median duration of methotrexate exposure was 106 days (IQR 106–106) in adalimumab non-responders, 106 days (105–106) in methotrexate non-responders, and 106 days (106–106) in methotrexate

	Part 1 (0–16 weeks)			Part 2 (16–32 weeks)			
	Adalimumab plus methotrexate group (n=123)	Escalated methotrexate group (n=122)	Percentage difference (95% CI)	Adalimumab responders (n=54)	Methotrexate responders (n=15)	Adalimumab non-responders (n=63)	Methotrexate non-responders (n=95)
Any adverse event	76 (62%)	70 (57%)	4·4 (–7·9 to 16·7)	24 (44%)	5 (33%)	42 (67%)	54 (57%)
Serious adverse events	2 (2%)*	0	1·6 (–0·6 to 3·9)	1 (2%)†	0	3 (5%)‡	3 (3%)§
Severe adverse events	4 (3%)	4 (3%)	–0·0 (–4·5 to 4·4)	2 (4%)	1 (7%)	5 (8%)	6 (6%)
Adverse events with reasonable possibility of being adalimumab related	39 (32%)	..	..	11 (20%)	0	19 (30%)	17 (18%)
Adverse events with reasonable possibility of being methotrexate related	37 (30%)	50 (41%)	–10·9 (–22·8 to 1·0)	2 (4%)	4 (27%)	18 (29%)	28 (29%)
Adverse events leading to discontinuation of study drug	3 (2%)	2 (2%)	0·8 (–2·7 to 4·3)	2 (4%)	0	2 (3%)	1 (1%)
Death	0	0	0	0	0	0	0
Herpes zoster	2 (2%)	0	1·6 (–0·6 to 3·9)	1 (2%)	0	1 (2%)	0
ALT increased	5 (4%)	6 (5%)	–0·9 (–6·0 to 4·3)	1 (2%)	1 (7%)	3 (5%)	3 (3%)
AST increased	5 (4%)	3 (2%)	1·6 (–2·8 to 6·0)	0	0	1 (2%)	2 (2%)
Adverse events of special interest							
Infection	41 (33%)	25 (20%)	12·8 (1·9–23·8)	15 (28%)	1 (7%)	23 (37%)	30 (32%)
Serious infection	1 (1%)¶	0	0·8 (–0·8 to 2·4)	0	0	0	2 (2%)‖
Injection-site reaction	13 (11%)	3 (2%)	8·1 (2·0–14·2)	0	0	3 (5%)	1 (1%)
Allergic reaction, including angioedema or anaphylaxis	4 (3%)	3 (2%)	0·8 (–3·4 to 5·0)	2 (4%)	0	2 (3%)	2 (2%)
Other adverse events							
Headache	10 (8%)	2 (2%)	6·5 (1·2–11·8)	0	0	0	0
Upper respiratory tract infection	10 (8%)	11 (9%)	–0·9 (–7·9 to 6·1)	2 (4%)	0	9 (14%)	13 (14%)
Cough	7 (6%)	1 (1%)	4·9 (0·5–9·3)	0	0	0	0
Nausea	5 (4%)	11 (9%)	–5·0 (–11·1 to 1·2)	0	1 (7%)	1 (2%)	4 (4%)
Drug intolerance	0	8 (7%)	–6·6 (–10·9 to –2·2)	0	0	0	0
Bronchitis	0	0	0	0	1 (7%)	0	0
Pneumonia	0	0	0	0	1 (7%)	1 (2%)	0
Transaminases increased	0	0	0	0	1 (7%)	1 (2%)	0
Hepatitis	0	0	0	0	1 (7%)	0	0
Nasopharyngitis	0	0	0	1 (2%)	0	2 (3%)	6 (6%)
Back pain	0	0	0	1 (2%)	0	4 (6%)	1 (1%)
Psoriatic arthropathy	0	0	0	0	1 (7%)	4 (6%)	0

Data are n (%) unless otherwise indicated. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Pneumonia and sciatica. †Lumbar vertebral fracture and ureterolithiasis. ‡Gastric mucosa erythema, gastritis, and basal cell carcinoma; uterine polyp; and asthma. §Diverticulitis; subcutaneous abscess; and ankle fracture, ligament sprain, ALT increased, and AST increased. ¶Pneumonia. ‖Diverticulitis; and subcutaneous abscess.

Table 3: **Treatment-emergent adverse events in part 1 (0–16 weeks) and part 2 (16–32 weeks)**

responders. Adalimumab mean concentrations remained similar in adalimumab responders who continued treatment with adalimumab between 16 weeks and 32 weeks (6·4 µg/mL [SD 4·2] at 32 weeks; appendix p 20). Mean concentrations were also similar in methotrexate non-responders who switched to adalimumab plus methotrexate in part 2 (9·0 µg/mL [SD 5·9] at 32 weeks). Seven patients reported serious adverse events, one in the adalimumab responder group, three in the adalimumab non-responder group, and three in the methotrexate non-responder group, table 3). No serious adverse events were reported in methotrexate responders. The most common adverse events were upper respiratory tract infections (adalimumab responders, 2 [4%] of 54 patients; methotrexate responders, 0 [0%] of 15 patients; adalimumab non-responders, 9 [14%] of 63 patients; methotrexate non-responders, 13 [14%] of 95 patients); and four patients experienced injection-site reactions in part 2 of the study (n=3 [5%] adalimumab non-responders and n=1 [1%] methotrexate non-responders).

In the ultrasound substudy (n=21 in the adalimumab plus methotrexate group, and n=31 in the escalated

methotrexate group), numerically greater improvements were observed for enthesitis, synovitis, and tenosynovitis in patients receiving adalimumab plus methotrexate than in those receiving escalated methotrexate, although statistical comparisons are not provided due to the small sample size (appendix p 15). At 16 weeks, the least squares mean improvements in the adalimumab plus methotrexate group were –0·3 (95% CI –0·8 to 0·2) in enthesitis, –5·7 (–9·1 to –2·3) in synovitis, and –2·5 (–4·1 to –0·9) in tenosynovitis, compared with –0·1 (–0·5 to 0·3) in enthesitis, –1·7 (–4·6 to 1·1) in synovitis, and –1·3 (–2·6 to –0·1) in tenosynovitis in the escalated methotrexate group.

Overall, 12 (5%) of 219 of patients were positive for anti-adalimumab antibodies at the end of the study, of whom four were antibody positive by 16 weeks. In antibody-positive patients, mean adalimumab concentrations were lower than in antibody-negative patients. The number of antibody-positive patients at 16 weeks was too small to evaluate the impact of anti-adalimumab antibodies on efficacy. Immunogenicity did not appear to affect the safety of adalimumab in antibody-positive patients compared with antibody-negative patients (data not shown).

Discussion

In the CONTROL trial, a significantly higher proportion of patients with an inadequate response to methotrexate reached MDA at 16 weeks after introducing adalimumab compared with escalating methotrexate, regardless of previous methotrexate duration. Furthermore, higher response rates were seen with adalimumab plus methotrexate across musculoskeletal, skin, and quality of life secondary endpoints. Patients who reached an MDA response at 16 weeks generally maintained that response through 32 weeks. Safety results were consistent with the known profiles of adalimumab and methotrexate, with a numerically higher incidence of infections in the adalimumab plus methotrexate group.

At 32 weeks, 41 (80%) of 51 adalimumab responders maintained MDA on adalimumab monotherapy following discontinuation of methotrexate, demonstrating limited value of adalimumab combination therapy with methotrexate in psoriatic arthritis, in contrast to rheumatoid arthritis.[32] This finding is in line with previous reports of adalimumab with or without methotrexate in psoriatic arthritis routine care,[23] and it could inform practitioner decisions surrounding reducing polypharmacy in controlled disease. Similarly, ten (67%) of 15 methotrexate responders maintained MDA without further therapy adjustment, although interpretation of these results is limited by the small sample size. Among patients who did not reach MDA at 16 weeks, therapy modification enabled more patients to reach MDA at 32 weeks. 50 (55%) of 91 methotrexate non-responders reached MDA by 32 weeks after introducing adalimumab every other week, whereas 17 (30%) of 57 adalimumab non-responders, who potentially represent a biological DMARD refractory and harder-to-treat population, reached MDA by 32 weeks after adalimumab escalation to every week. Although this has not yet been assessed in patients with psoriatic arthritis, studies investigating the safety of adalimumab 40 mg every week versus every other week in patients with various conditions, including rheumatoid arthritis, have identified no new safety risks with every week dosing, making this a potential option to explore in harder-to-treat patients.[33]

Patients in the escalated methotrexate group were permitted to reach a maximum methotrexate dose of 25 mg every week, with the average dose being 22 mg every week, suggesting that patients were receiving adequate methotrexate doses. Additionally, CONTROL included the six standard LEI sites plus plantar fascia, for a total of eight sites. This gave a robust assessment of MDA using a stringent enthesitis measure. Despite this, 58 (60%) of 97 patients receiving adalimumab plus methotrexate had resolution of enthesitis (ie, LEI=0) compared with 36 (36%) of 101 patients on escalated methotrexate.

The results seen in CONTROL are consistent with data from the SEAM-PsA trial,[24,25] which reported that 36% of patients reached MDA on etanercept plus methotrexate at 24 weeks compared with 23% of patients receiving methotrexate 20 mg monotherapy (p=0·005). Although a higher proportion of patients in SEAM-PsA versus CONTROL reached MDA in the methotrexate groups (23% *vs* 13%, respectively), it should be noted that patients in CONTROL were already partial non-responders to methotrexate, whereas SEAM-PsA patients were methotrexate-naive; and the evaluation of MDA occurred at 24 weeks in SEAM-PsA compared with 16 weeks in CONTROL. Other important distinctions between the trials include the study design (open-label in CONTROL *vs* blinded in SEAM-PsA) and the dose of methotrexate (maximum of 25 mg every week in CONTROL *vs* 20 mg every week in SEAM-PsA). Despite these differences, results from both trials support improved outcomes by advancing therapy to a TNF inhibitor over continued, escalated methotrexate.

One potential limitation of this study was the requirement for patients to have received only a minimum of 4 weeks of previous methotrexate therapy, which might not be long enough to confidently determine if a patient is having an inadequate response. Regardless of the duration of previous methotrexate exposure, there was a small numerical difference in the MDA response rate between patients with 3 months or less versus more than 3 months previous methotrexate exposure in the escalated methotrexate group (9·8% *vs* 16·4%, respectively). However, 59 (48%) of 123 enrolled patients had a previous methotrexate therapy duration of more than 3 months, and prespecified stratification of results on the basis of

previous methotrexate duration was consistent with the overall analysis. It should also be noted that the open-label nature of the study and the absence of placebo injections could have influenced patient perceptions of adalimumab injections as being more effective than oral methotrexate. Moreover, 67 (55%) of patients in the methotrexate escalation group received oral methotrexate only; and it has previously been shown that systemic methotrexate exposure can plateau with increased oral administration, although not with subcutaneous injection.[34] In many countries, subcutaneous methotrexate is not available, potentially reducing the impact of methotrexate escalation regimens.

Another limitation of this study is that the results might not be generalisable to patients with oligoarthritis, as patients enrolled in CONTROL had a high burden of joint disease as reflected in the mean LEI plus plantar count, dactylitic count, swollen joint count, and tender joint count. In addition, CONTROL only measured response rates up to 32 weeks. Overall, the numbers of patients in each group in part 2 were relatively small and real-world evidence of longer duration is needed in larger patient populations to determine whether these results are generalisable to a broader population. Although, higher baseline disease activity was noted in women than in men, the study results were significant even after adjusting for sex and interaction of sex with treatment. Thus, although some baseline differences between sexes were observed, adalimumab was effective for both men and women. In future, it might be beneficial for studies to be prospectively stratified by sex to explore sex-related differences further.

CONTROL contributes meaningful data regarding therapy modification for patients with psoriatic arthritis who do not adequately respond to methotrexate alone. Results suggest that prolonged therapy with methotrexate, even at an escalated dose, is effective at attaining MDA in patients who are not in MDA after a shorter course of low-dose methotrexate. However, initiation of adalimumab led to a significantly higher proportion of patients reaching MDA compared with escalated methotrexate in the context of this study, with clinical results supported by improvements in objective measures of inflammation in the ultrasound substudy. Overall, these results provide important data on how to best approach therapy within the treat-to-target paradigm.

Contributors

WT, M-AD, PR, FB, PM, ELM-B, MK, XB, and LC participated in data acquisition. LCC, PGC, PM, WT, and M-AD participated in study design. XB and LC participated in statistical analyses. PM and XB assessed and verified the data. All authors participated in data interpretation, critically reviewed the manuscript, and provided final approval for publication. All authors had full access to all data in the study and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

LCC reports funding from a National Institute for Health Research (NIHR) clinician scientist award; support from the NIHR Oxford Biomedical Research Centre; and reports serving on advisory boards, or consultancy, or speaker fees from AbbVie, Amgen, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, Medac, Novartis, Pfizer, Serac, and UCB. WT reports research grants from AbbVie, Celgene, Janssen, and Lilly; and consultancy or speaker fees from AbbVie, Amgen, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, and UCB. M-AD reports serving on advisory boards, or consultancy, or speaker fees from AbbVie, BMS, Janssen, and Novartis. PR reports consulting fees from Abbott, AbbVie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, and Pfizer; speakers bureau fees from Abbott, AbbVie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, and Pfizer; and research grants from Janssen and Novartis. FB reports research grants from Celgene, Chugai, Janssen, Pfizer, and Roche; and personal fees from AbbVie, Boehringer, Celgene, Chugai, Genzyme, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, and Sanofi. ELM-B, XB, LC, and MK are full-time employees of AbbVie and might own stock or stock options. PGC reports serving as a consultant or on speaker bureaus for AbbVie, BMS, Eli Lilly, EMD Serono, Flexion Therapeutics, Galapagos, Gilead, GlaxoSmithKline, Novartis, and Pfizer. PM reports research grants and consultation or speaker honoraria from AbbVie, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Sun Pharma, and UCB.

Data sharing

The clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal, statistical analysis plan, and execution of a data-sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following website: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Acknowledgments

The study was funded by AbbVie. Medical writing support was provided by Jamie Urbanik, PharmD, Nancy Dudek (both of AbbVie), and Laura Chalmers, PhD (2 the Nth, Cheshire, UK), funded by AbbVie. PGC is supported in part through the NIHR Leeds Biomedical Research Centre; the views expressed in this manuscript are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. AbbVie and the authors thank Maja Hojnik, a former employee of AbbVie, Erica Cummings, and Aurore Diamand, from the AbbVie Clinical Operations Group, for contributions to the study conception and design. The authors also thank Jenny M Chan, Nael Mostafa, and Christine M Lee, all of AbbVie, for their support with the pharmacokinetic analyses.

References

1 Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann Rheum Dis* 2015; **74:** 1045–50.
2 Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med* 2017; **376:** 2095–96.
3 Coates LC, Kavanaugh A, Mease PJ, et al. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheumatol* 2016; **68:** 1060–71.
4 Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020; **79:** 700–12.
5 Singh JA, Guyatt G, Ogdie A, et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Rheumatol* 2019; **71:** 5–32.
6 Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2018; **77:** 3–17.
7 Orbai A-M, de Wit M, Mease P, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. *Ann Rheum Dis* 2017; **76:** 673–80.
8 Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010; **69:** 48–53.

9 Coates LC, Navarro-Coy N, Brown SR, et al. The TICOPA protocol (tight control of psoriatic arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis. *BMC Musculoskelet Disord* 2013; **14:** 101.

10 Wells GA, Boers M, Shea B, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. *J Rheumatol* 2005; **32:** 2016–24.

11 Lie E, van der Heijde D, Uhlig T, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2010; **69:** 671–76.

12 Nikiphorou E, Negoescu A, Fitzpatrick JD, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. *Clin Rheumatol* 2014; **33:** 609–14.

13 Kingsley GH, Kowalczyk A, Taylor H, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology (Oxford)* 2012; **51:** 1368–77.

14 Baranauskaite A, Raffayová H, Kungurov NV, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. *Ann Rheum Dis* 2012; **71:** 541–48.

15 Coates LC, Helliwell PS. Methotrexate efficacy in the tight control in psoriatic arthritis study. *J Rheumatol* 2016; **43:** 356–61.

16 Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2012; **71:** 319–26.

17 Acosta Felquer ML, Coates LC, Soriano ER, et al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. *J Rheumatol* 2014; **41:** 2277–85.

18 Soriano ER, Acosta-Felquer ML, Luong P, Caplan L. Pharmacologic treatment of psoriatic arthritis and axial spondyloarthritis with traditional biologic and non-biologic DMARDs. *Best Pract Res Clin Rheumatol* 2014; **28:** 793–806.

19 Gossec L, Smolen JS, Ramiro S, et al. European league against rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016; **75:** 499–510.

20 Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014; **73:** 1020–26.

21 McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013; **382:** 780–89.

22 Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014; **73:** 990–99.

23 Behrens F, Koehm M, Arndt U, et al. Does concomitant methotrexate with adalimumab influence treatment outcomes in patients with psoriatic arthritis? Data from a large observational study. *J Rheumatol* 2016; **43:** 632–39.

24 Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. *Arthritis Rheumatol* 2019; **71:** 1112–24.

25 Mease PJ, Gladman DD, Samad AS, et al. Design and rationale of the study of etanercept and methotrexate in combination or as monotherapy in subjects with psoriatic arthritis (SEAM-PsA). *RMD Open* 2018; **4:** e000606.

26 Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: psoriasis comorbidities and preferred systemic agents. *J Am Acad Dermatol* 2019; **80:** 27–40.

27 Kaushik SB, Lebwohl MG. Psoriasis: which therapy for which patient: focus on special populations and chronic infections. *J Am Acad Dermatol* 2019; **80:** 43–53.

28 McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. *Lancet* 2020; **395:** 1496–505.

29 Mease PJ, Smolen JS, Behrens F, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. *Ann Rheum Dis* 2020; **79:** 123–31.

30 Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; **54:** 2665–73.

31 Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; **79:** 685–99.

32 Behrens F, Koehm M, Schwaneck EC, et al. Addition or removal of concomitant methotrexate alters adalimumab effectiveness in rheumatoid arthritis but not psoriatic arthritis. *Scand J Rheumatol* 2019; **48:** 375–82.

33 Ryan C, Sobell JM, Leonardi CL, et al. Safety of adalimumab dosed every week and every other week: focus on patients with hidradenitis suppurativa or psoriasis. *Am J Clin Dermatol* 2018; **19:** 437–47.

34 Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. *Ann Rheum Dis* 2014; **73:** 1549–51.