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Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial

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ABSTRACT OBJECTIVE

To determine whether intensive combinations of synthetic disease modifying drugs can achieve similar clinical benefits at lower costs to high cost biologics such as tumour necrosis factor inhibitors in patients with active rheumatoid arthritis resistant to initial methotrexate and other synthetic disease modifying drugs.

DESIGN

Open label pragmatic randomised multicentre two arm non-inferiority trial over 12 months.

SETTING

24 rheumatology clinics in England.

PARTICIPANTS

Patients with rheumatoid arthritis who were eligible for treatment with tumour necrosis factor inhibitors according to current English guidance were randomised to either the tumour necrosis factor inhibitor strategy or the combined disease modifying drug strategy.

INTERVENTIONS

Biologic strategy: start tumour necrosis factor inhibitor; second biologic in six month for non-responders. Alternative strategy: start combination of disease modifying drugs; start tumour necrosis factor inhibitors after six months in non-responders.

MAIN OUTCOME MEASURE

Primary outcome: reduction in disability at 12 months measured with patient recorded health assessment questionnaire (range 0.00–3.00) with a 0.22

non-inferiority margin for combination treatment versus the biologic strategy. Secondary outcomes: quality of life, joint damage, disease activity, adverse events, and costs. Intention to treat analysis used multiple imputation methods for missing data.

RESULTS

432 patients were screened: 107 were randomised to tumour necrosis factor inhibitors and 101 started taking; 107 were randomised to the combined drug strategy and 104 started taking the drugs. Initial assessments were similar; 16 patients were lost to follow-up (seven with the tumour necrosis factor inhibitor strategy, nine with the combined drug strategy); 42 discontinued the intervention but were followed-up (19 and 23, respectively). The primary outcome showed mean falls in scores on the health assessment questionnaire of -0.30 with the tumour necrosis factor inhibitor strategy and -0.45 with the alternative combined drug strategy. The difference between groups in unadjusted linear regression analysis favoured the alternative strategy of combined drugs. The mean difference was -0.14 , and the 95% confidence interval (-0.29 to 0.01) was below the prespecified non-inferiority boundary of 0.22 . Improvements at 12 months in secondary outcomes, including quality of life and erosive progression, were similar with both strategies. Initial reductions in disease activity were greater with the biologic strategy, but these differences did not persist beyond six months. Remission was seen in 72 patients (44 with biologic strategy; 36 with alternative strategy); 28 patients had serious adverse events (18 and 10, respectively); six and 10 patients, respectively, stopped treatment because of toxicity. The alternative strategy reduced health and social care costs per patient by £3615 (€4930, \$5585) for months 0–6 and £1930 for months 6–12.

CONCLUSIONS

In patients with active rheumatoid arthritis who meet English criteria for biologics an alternative strategy with combinations of intensive synthetic disease modifying drugs gives non-inferior outcomes to treatment with tumour necrosis factor inhibitors. Costs are reduced substantially.

TRIAL REGISTRATION

ISRCTN 37438295.

Introduction

Tumour necrosis factor inhibitors, the first biologics for rheumatoid arthritis, have changed specialist

WHAT IS ALREADY KNOWN ON THIS TOPIC

Placebo controlled trials have shown that tumour necrosis factor inhibitors are effective in patients with active rheumatoid arthritis, and some economic models justify use when methotrexate does not work. Despite their high costs, their use has continually grown, and by 2012 international spending exceeded £15bn (€20.5bn, \$23bn) a year

A combination of synthetic disease modifying drugs is an alternative cheaper and effective strategy in active rheumatoid arthritis

WHAT THIS STUDY ADDS

Patients with active rheumatoid arthritis eligible for biologic treatments according to current English guidance achieve non-inferior benefits in disability, with no demonstrable difference in quality of life or prevention of joint damage, with combined synthetic disease modifying drugs or tumour necrosis factor inhibitors

As combinations of synthetic disease modifying drugs cost less they should be considered when monotherapy with disease modifying drugs is not successful

management.¹ Placebo controlled trials in patients with active rheumatoid arthritis defined their efficacy.² Long term observational studies confirmed their relative safety.³ Economic modelling used placebo controlled trials to justify their use in patients with active rheumatoid arthritis who were resistant to methotrexate.⁴ European and North American expert groups provided international guidance on their use in rheumatoid arthritis.^{5,6} English guidance from the National Institute for Health and Care Excellence (NICE) recommends starting them in patients with persistent active rheumatoid arthritis that is resistant to methotrexate and one other synthetic disease modifying drug⁷ and continuing them as long as the patients maintain good responses.

Tumour necrosis factor inhibitors are expensive. By 2012 international spending exceeded £15bn (€20.5bn, \$23bn) a year. Guidance for their use is driven by results of placebo controlled trials in rheumatoid arthritis sponsored by manufacturers. Few trials have compared them with active non-biological treatments,^{8,9} even though lower cost strategies, such as combinations of synthetic disease modifying drugs, are effective.¹⁰⁻¹³ England spends over £600 m (€820 m, \$926 m) a year on tumour necrosis factor inhibitors, which has a substantial impact on the National Health Service's budget. Healthcare commissioners would prefer lower cost alternatives provided patients were not disadvantaged.

We evaluated this possibility by testing the hypothesis that a lower cost strategy of combinations of synthetic disease modifying drugs achieves outcomes that are not inferior and costs substantially less.

Methods

Design

The TACIT (tumour necrosis factor inhibitors against combination intensive therapy) trial was an open label pragmatic randomised two arm non-inferiority trial carried out over 12 months in multiple centres.

Participants

Patients were recruited from 24 rheumatology clinics in England. We included men and women aged over 18 with disease durations over 12 months who met the 1987 criteria for classification of rheumatoid arthritis and NICE criteria for starting biologics in England. The NICE criteria comprise disease activity score for 28 joints >5.1 twice over one month apart after treatment with methotrexate and one other disease modifying drug.⁷ We excluded patients who unable or unwilling to give informed consent, had not had successful results with or had contraindications to all combinations of disease modifying drugs (including possible pregnancy), had contraindications to tumour necrosis factor inhibitors, had serious inter-current illness, or were taking high dose corticosteroids (>10 mg prednisolone).

Interventions

The trial compared two treatment strategies in patients who completed local screening procedures for treatment with tumour necrosis factor inhibitors, including tuberculosis screening. Safety monitoring followed national guidance. Treatment was guided by monthly changes in disease activity scores for 28 joints. The box outlines the tumour necrosis factor inhibitor strategy, which replicated NICE guidance when the trial started, and the combined disease modifying drug strategy. Treatments used as required at standard doses included non-opiate analgesics, non-steroidal anti-inflammatory drugs, folic acid (5 mg/week) with methotrexate, bone protection (such as alendronate and calcium/vitamin D) with glucocorticoids, and intra-articular steroids.

Primary outcome

The primary outcome was the score on the health assessment questionnaire at 12 months.¹⁴ Scores were measured initially at baseline and at six and 12 months. Trials of disease modifying drugs¹⁵ and biologics¹⁶ have shown that this patient assessed outcome is sensitive to change. Its performance is equal to disease activity measures like joint counts. Changes in health assessment questionnaire scores influenced NICE's decisions on biologics. It involves questions across eight domains: dressing and grooming, getting up, eating, walking, hygiene, reach, grip, and chores or activities. There are four possible answers: 0=without any difficulty; 1=with some difficulty; 2=with much difficulty; and 3=unable to do. The sum of the highest score per domain is divided by eight. The total score ranges from 0 to 3 (0=best; 3=worst) in 0.125 increments.

Secondary outcomes

Every six months we assessed quality of life, erosive damage, and economics. Assessments comprised the EuroQol 5-dimension scale (EQ5D-3L), medical outcomes study short form 36 (SF-36), and radiographs of the hands (including wrists) and feet. An experienced observer (DLS) who was blinded to treatment read the digitised radiographs using modified Larsen scores¹⁷ after the trial ended. Use of resources was recorded with a modified client service receipt inventory¹⁸

TREATMENT STRATEGIES

Tumour necrosis factor inhibitor strategy

This had two steps:

- Start one tumour necrosis factor inhibitor from adalimumab, etanercept, and infliximab. The choice depended on current local practice
- Switch to another tumour necrosis factor inhibitor after six months if fall in disease activity score for 28 joints was <1.2.

All patients also received methotrexate or another disease modifying drug. Patients taking more than one disease modifying drug before randomisation had this tapered to monotherapy. Patients taking oral prednisolone at entry continued as needed.

Disease modifying drug strategy

This had four steps:

- Maximise initial disease modifying drug treatment(s)
- Add second/third disease modifying drug
- Start fourth/fifth disease modifying drug
- Offer tumour necrosis factor inhibitors after six months if fall in disease activity score for 28 joints was <1.2.

Disease modifying drugs were given in combination and sequentially. Patients taking oral prednisolone at entry continued as needed; short term oral or intramuscular steroids were an option with this strategy.

administered as self completed questionnaires retrospectively for the previous three month period. Costs (for 2010–11 in £) were assessed from a health and social care perspective and were multiplied by two to represent the six month period before each assessment.

We assessed disease activity monthly by recording tender and swollen joint counts (28 joints), erythrocyte sedimentation rates, patients' global assessments of disease activity (100 mm visual analogue scale), and the disease activity scores for 28 joints. Withdrawals from treatment or the trial were also recorded monthly together with details of drugs and adverse events.

An anonymised electronic data capture system collected clinical data except radiographs (www.medscinet.net).

Sample size calculation

Published data on 12 month changes in scores on the health assessment questionnaire in rheumatoid arthritis trials of tumour necrosis factor inhibitors (mean baseline score 1.7; reduction after treatment of 25%; standard deviation of change 0.4)¹⁹ and combination therapy with disease modifying drugs (mean baseline score 1.6; reduction after treatment of 31%; standard deviation of change 0.6)²⁰ gave an average standard deviation for changes in health assessment questionnaire scores of 0.5.

The minimal clinically important change in scores on the health assessment questionnaire is 0.22.²¹ We based our sample size on testing the null hypothesis of a difference of >0.22 between the two treatments. With a (one sided) testing level of 5%, we needed a sample size of 176 to achieve 90% power. We recruited 214 patients to allow for patients not receiving treatment or dropping out when treatment had started.

Randomisation

Potentially eligible patients were screened and reasons for non-entry recorded. Consenting patients were randomised in blocks of four with allocation stratified by region. MedSciNet generated the allocation sequence; trial staff had no prior knowledge of the allocation sequence. There were variable delays between randomisation and baseline assessments because patients received combination disease modifying drugs and tumour necrosis factor inhibitors through routine NHS systems.

Blinding

The trial was unblinded because it used treatment specific algorithms with the adjustment of multiple drug doses. Patients assessed their own disability and quality of life. Radiographs were read blinded.

Statistical methods

Baseline characteristics were summarised by randomisation group as means and standard deviations (continuous normally distributed variables), medians and interquartile ranges (non-normally distributed variables), and frequencies and percentages (categorical variables).

Randomised patients who received treatment were assessed on an intention to treat basis. All participants had complete observations at baseline. Missing data at follow-up was imputed regardless of the reason(s) they was missing. For participants with missing outcomes, we used the baseline outcomes and other explanatory covariates (treatment group, sex, age, ethnicity, region, and disease duration) to impute the missing data, assuming unobserved measurements were missing at random (see appendix table A).

Linear regression evaluated 12 month outcomes. Univariate analyses were adjusted for region (design variable). Multivariable analyses were adjusted for sex, ethnicity, age, region, and duration of disease and baseline scores, which all influence disability. Generalised estimating equations with working correlations (auto-regressive with lag one) evaluated disease activity score for 28 joints and its components measured monthly. Treatment withdrawals and toxicities were compared with Fisher's exact tests. These analyses compared treatment strategies ignoring subsequent treatment switches. In all analyses patients in the tumour necrosis factor inhibitor strategy were the reference group. Only the primary outcome was tested for non-inferiority. Other outcomes were compared for evidence of superiority of one or other treatment strategy.

Exploratory analyses examined good responders according to the European League Against Rheumatism (EULAR)²² with odds ratios and the development of remission based on disease activity scores for 28 joints²³ with log rank tests on all observed data. No imputations were performed for these data. These analyses also examined differences between patients in the disease modifying drug strategy who stayed taking these drugs or switched to tumour necrosis factor inhibitors. Finally complete case analyses evaluated patients who followed the protocol and received 12 months' treatment.

We also undertook a full economic evaluation, which will be reported separately.

Results

Patients and treatments

Participant flow and recruitment

Between September 2008 and December 2010, we screened 432 patients, randomised 214, and treated 205 (fig 1). Of these 205 treated patients, 147 (72%) completed 12 months of treatment; 16 (8%) were lost to follow-up; 42 (20%) discontinued the intervention and were followed-up; 16 (8%) stopped treatment because of toxicity (10 in combined drug strategy; six in tumour necrosis inhibitor factor strategy); five stopped (2%) because of disease progression (one and four, respectively); and 37 (18%) stopped for other reasons including patients' decisions to stop treatment (21 and 16, respectively).

Baseline data and numbers analysed

Demographic and disease assessments were similar in both groups of treated patients (Table 1). All treated patients were analysed.

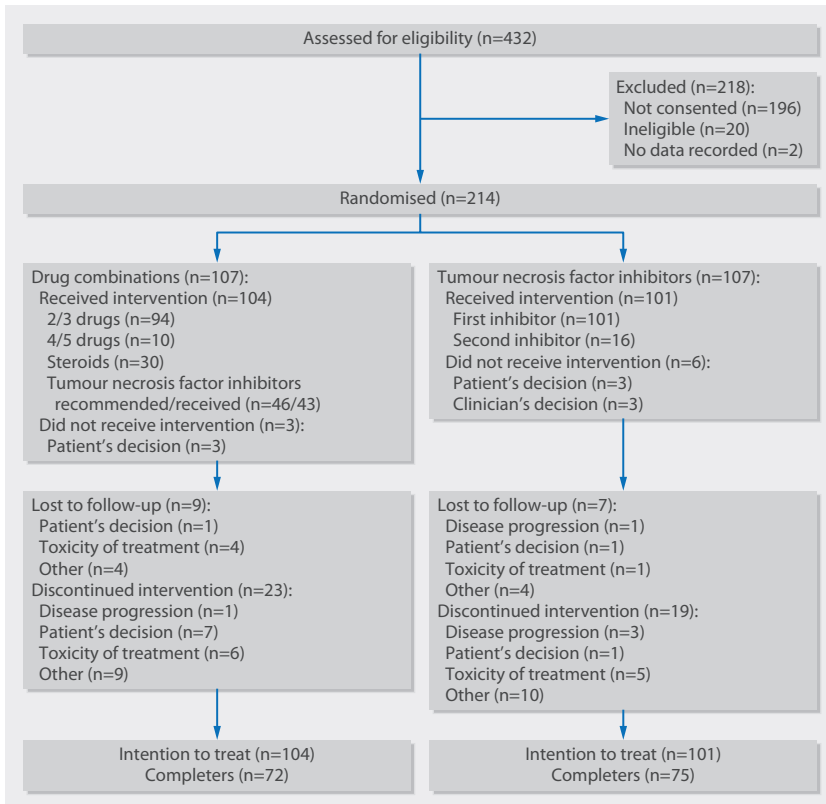


Fig 1 | Consort flowchart of study in patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors

Treatments

Before randomisation all patients had received two disease modifying drugs (Table 1): 62 had received three; 77 were taking combinations of two or more disease modifying drugs; 24 were taking prednisone (mean dose 4 mg/day; range 1–7 mg). The treatments used are given in detail in appendix table B. In the disease modifying drug strategy the main initial combination was methotrexate and leflunomide (62 patients). Most patients received two or three disease modifying drugs; 10 received four or five drugs, though not concurrently. At six months, 46 patients were offered tumour necrosis factor inhibitors; 43 received them starting treatment at a mean of nine months. Steroids were given to 27 patients. Non-trial drugs were used by 88 patients in the first six months and by 90 in the second six months.

In the tumour necrosis factor inhibitor strategy the dominant initial biologic was adalimumab (58 patients). After six months, 16 patients received another tumour necrosis factor inhibitor. Steroids were given to 19 patients. Non-trial drugs were used by 94 patients in the first six months and by 91 in the second six months.

Outcomes

Primary outcome

Both groups had less disability, shown by falls in their scores on the health assessment questionnaire. Mean reductions were -0.30 (95% confidence interval -0.42 to -0.19) with the tumour necrosis factor strategy and -0.45 (-0.55 to -0.34) with the disease modifying drug strategy. Figure 2 shows that the difference between

groups favoured the disease modifying drug strategy. The figure follows the recommendations of Piaggio and colleagues.²⁴ It shows unadjusted regression coefficients with 95% confidence intervals. The non-inferiority margin is shown for the scores on the primary outcome health assessment questionnaire. The mean difference was -0.14 and the 95% confidence interval (-0.29 to 0.01) was below the prespecified non-inferiority boundary of 0.22 . There were no pre-defined non-inferiority margins for the secondary outcome measures. Adjustment for baseline and demographic variables did not change this conclusion (appendix table C).

Secondary outcomes

Both groups had improved quality of life, shown by increases in EQ5D-3L utility scores and SF-36 summary scores, and some erosive progression, shown by increases in Larsen scores. Difference between groups favoured the disease modifying drug strategy with EQ5D-3L scores, SF-36 physical component summary scores, and Larsen scores and the tumour necrosis factor inhibitor strategy with SF-36 mental component summary scores (fig 2). With all four outcomes, 95% confidence intervals of the differences between groups included zero. Adjustment for baseline and demographic variables did not change these conclusions (appendix table D). Fifty eight patients withdrew from study treatments; there was no difference between strategies (32 in disease modifying drug strategy v 26 in tumour necrosis factor strategy; Fisher's exact test $P=0.44$).

Baseline health and social care costs were similar in both groups. Compared with the tumour necrosis factor strategy, the disease modifying drug strategy reduced costs for months 0–6 by a mean of $-\pounds3615$ (95% confidence interval $-\pounds4104$ to $-\pounds3182$) and for months 6–12 by $-\pounds1930$ ($-\pounds2599$ to $-\pounds1301$).

Disease activity fell in both groups (fig 3). Initial falls were greater with the tumour necrosis factor inhibitor strategy, but with time the differences equalised. Over the whole 12 months the unadjusted difference between groups was 0.48 (95% confidence interval 0.17 to 0.79), favouring the tumour necrosis factor inhibitor strategy. The difference was predominantly because of changes in the erythrocyte sedimentation rate (appendix table E).

Ancillary analyses

Switching treatments

Patients in the disease modifying drug strategy who remaining taking disease modifying drugs ($n=58$) or switched to tumour necrosis factor inhibitors ($n=46$) had similar 12 month outcomes in all analyses. At six months the “switchers” had higher mean scores on the health assessment questionnaire (1.64 v 1.42) and disease activity scale for 28 joints (5.76 v 4.01).

Exploratory analyses using all observed data

Eighty patients had remissions (36 in disease modifying drug strategy, 44 in tumour necrosis factor inhibitor strategy) at any point in the trial. Only 30 patients (11 and 19, respectively) had sustained remissions. Time to first remission did not differ significantly between

Table 1 | Baseline demographic and clinical characteristics of patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors. Figures are means (SD) unless stated otherwise

	Combination disease modifying drugs strategy (n=104)	Tumour necrosis factor inhibitor strategy (n=101)
Demographic variables		
Age (years)	58 (13)	57 (11)
No (%) of women/men	73/31 (70/30)	79/22 (78/22)
No (%) by ethnic group:		
White	89 (86)	92 (91)
Black (African, Caribbean, other)	6 (6)	2 (2)
Other	9 (9)	7 (7)
Median (IQR) duration of disease (years)	4.4 (1.6–9.9)	5.9 (2.2–13.4)
Height (m)	1.64 (0.11)	1.66 (0.09)
Weight (kg)	78 (20)	81 (17)
Median (IQR) BMI	29 (24–33)	29 (25–32)
Clinical variables		
Disease activity score for 28 joints	6.2 (0.9)	6.3 (0.8)
Tender joint count	16 (7)	18 (7)
Swollen joint count	11 (6)	11 (7)
ESR (mm in first hour)	33 (26)	30 (23)
Patient global visual analogue score (mm)	68 (20)	68 (21)
Health assessment questionnaire score	1.8 (0.6)	1.9 (0.7)
Larsen score	45 (42)	38 (39)
EQ5D score	0.39 (0.31)	0.35 (0.31)
SF-36 physical component summary score	28 (7)	27 (7)
SF-36 mental component summary score	43 (12)	41 (12)
Previous disease modifying drug treatments (No of patients)		
Methotrexate	98	97
Sulfasalazine	68	56
Leflunomide	27	29
Other	48	49
Three previous treatments	33	29
Combination drugs at screening	38	39
Prednisolone at screening (mean daily dose)	16 (4 mg)	8 (4 mg)

BMI=body mass index; IQR=interquartile range; ESR=erythrocyte sedimentation rate.

groups (log rank test $P=0.09$). More patients in the tumour necrosis factor inhibitor strategy, however, achieved early remission; after three months 16 patients were in remission compared with five in the disease modifying drug strategy.

Sixty six patients had good responses according to the European League Against Rheumatism at 12 months (37/94 in the tumour necrosis factor inhibitor strategy, 29/92 in the disease modifying drug strategy). The odds ratio of achieving a good response with the disease modifying strategy was 0.71 (95% confidence intervals 0.39 to 1.30) compared with the tumour necrosis factor inhibitor strategy.

Completer analysis

The results comparing treatments in the 147 complete cases (72 in disease modifying drug strategy, 75 in tumour necrosis factor inhibitor strategy) were similar to those seen in the intention to treat analysis (appendix table A).

Harms

Adverse events (Table 2) were common: 28 patients had serious adverse events (18 with the tumour necrosis factor inhibitor strategy; 10 with the disease modifying

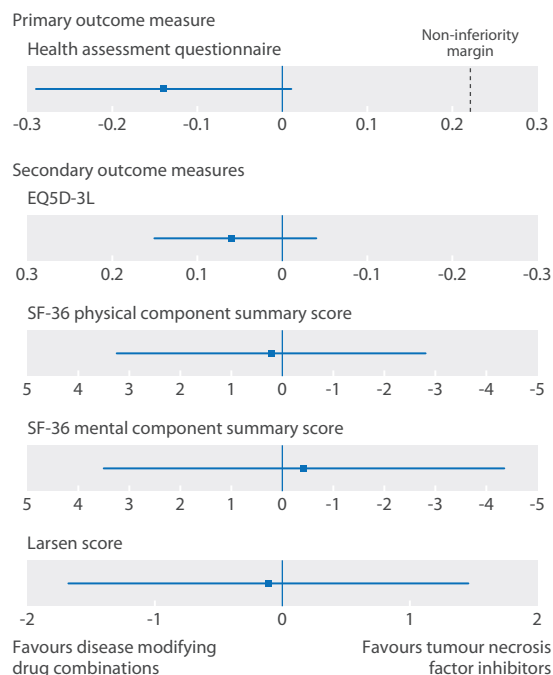


Fig 2 | Observed treatment differences for primary and secondary outcome measures in study in patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors. Scales and direction of change for different outcome measures vary: health assessment questionnaire ranges from 0–3, higher scores are worse, and positive differences favour tumour necrosis factor strategy; EQ5D-3L ranges from 0–1, higher scores are better, and negative differences favour tumour necrosis factor strategy; SF-36 physical component score and mental component score range from 0–100, higher scores are better, and negative differences favours tumour necrosis factor strategy; Larsen score ranges from 0–200, higher scores are worse, and positive differences favours tumour necrosis factor strategy; Fisher’s exact test $P=0.11$). One patient in the tumour necrosis factor strategy died from pneumonia and multiple organ failure. Sixteen patients (six and 10, respectively) stopped treatment because of toxicity (Fisher’s exact test $P=0.44$). Overall there were 1100 adverse events; more occurred with the disease modifying drug strategy (635 v 465). Infections that involved several body systems occurred in 54 patients in the tumour necrosis factor strategy and 30 patients in the disease modifying drug strategy.

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Discussion Interpretation

In patients with rheumatoid arthritis, our strategy of treatment with synthetic disease modifying drugs achieved non-inferior outcomes to the NICE approved strategy of treatment with tumour necrosis factor inhibitor over 12 months. It also cost substantially less. Our primary outcome—the score on the health assessment questionnaire—fell in both groups, indicating reduced disability at the trial endpoint. The difference between groups favoured the disease modifying drug strategy, with 95% confidence intervals

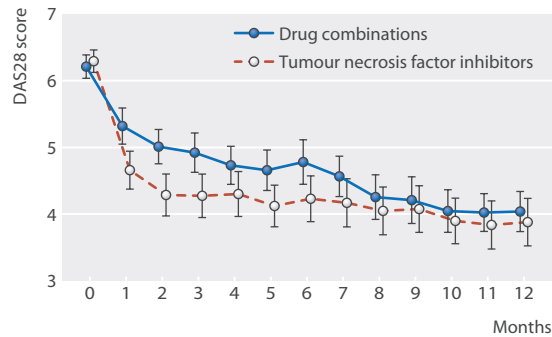


Fig 3 | Changes in mean (SE) DAS28 scores (intention to treat analysis) in patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors

Table 2 | Adverse events by body system in patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors

Body system*	Combination disease modifying drugs strategy (n=104)		Tumour necrosis factor inhibitor strategy (n=101)	
	Serious	All	Serious	All
Cardiovascular	2	22	2	17
Digestive	0	148	4	60
Ear, nose, throat	0	88	1	76
Endocrine/metabolic	0	7	1	7
Genitourinary	3	28	1	27
Haematological	1	25	1	10
Mental	0	24	0	15
Musculoskeletal	0	104	1	94
Nervous system	1	61	2	41
Ophthalmological	0	12	0	5
Respiratory	3	59	3	66
Skin	0	57	2	47
Total		635		465

*As infections involved several different body systems, they could not be incorporated within table. In combination disease modifying drugs strategy, five serious adverse events involved an infection and 30 patients had infection. In tumour necrosis factor inhibitor strategy, seven serious adverse events involved an infection and 54 patients had infection.

within the prespecified boundary of non-inferiority. Both strategies improved quality of life similarly and resulted in minimal erosive progression. The tumour necrosis factor inhibitor strategy cost an additional average £5545 (€7570, \$8586) per patient. Its main benefit was rapid falls in disease activity and more early remissions. As synthetic disease modifying drugs are “slow acting” agents,²⁵ this difference is not surprising. Patients who did not respond to six months of treatment with disease modifying drugs and who switched to tumour necrosis factor inhibitors were not disadvantaged.

Over 12 months, health and social care costs were £5545 less in patients who were treated with the combined drug strategy. These reduced costs were associated with reduced scores on the health assessment questionnaire, which have immediate economic benefits.^{26 27} Our results support using the combined drug strategy for 12 months. Longer term observational and detailed

economic modelling studies are needed to show whether this approach has any enduring benefits.^{28 29}

Tumour necrosis factor inhibitors have many advantages. Their innovative nature, rapid effects, and ease of use attract patients and clinicians. Their defined mechanism of action contrasts with the uncertainties about the molecular effects of drugs like methotrexate. Combinations of lower cost synthetic disease modifying drugs, however, are relevant for advanced health economies and might be even more relevant in health economies where biologics are unaffordable.

Generalisability

The patients in our trial had diverse ethnicities and deprivation levels and were seen in routine practice settings in geographically dispersed centres in England. We focused on patient centred outcomes, which are crucial for people with arthritis. Levels of disease activity replicated levels in national and international registers^{30 31} before and during treatment.

Limitations

Our trial had several limitations. Firstly, many eligible patients did not participate, mainly because they did not consent. Although non-consenting patients could have responded differently to participants,³² participation levels replicated other English grant funded trials in rheumatoid arthritis²⁰ and recent tumour necrosis factor inhibitors trials.³³ Non-participation is likely to reflect patients’ concerns about all intensive treatments³⁴ and our cautiously worded patient information sheet.³⁵

Secondly, disease modifying drugs regimens varied because standardisation was impossible in this context. Thirdly, few trials in rheumatoid arthritis use the health assessment questionnaire as their primary outcome measure. It was relevant in our trial because it measures changes important to patients, is sensitive to improvements with all tested treatments,^{15 16} and helps NICE to determine treatment benefits. Scores on the health assessment questionnaire change less in those with late rheumatoid arthritis,³⁶ but both groups had clinically important improvements, and the durations of disease in our patients were comparable with those in pivotal biologic trials.^{19 37 38} Although minimally important differences in scores might be less than 0.22 in routine practice,³⁹ this lower difference would not change our conclusions.

Fourthly, our trial was un-blinded because blinding is impractical when many different treatments are used. The primary outcome, however, was self completed by patients and not directly influenced by clinicians. Fifthly, our trial lasted only 12 months because when it was designed longer delays in assessing biologic treatments raised ethical concerns.

Finally, the effects of withdrawal and switching treatments need careful consideration. Only a few patients (16/205, 8%) were lost to follow-up and required the imputation of missing data. As the complete case analysis gave similar findings to the intention to treat analysis, it seems unlikely that withdrawals influenced our conclusions. Comparable numbers of patients withdrew from both trial arms, suggesting withdrawals were unlikely to be

influenced by the treatment strategies. Overall withdrawal rates were similar to those in comparable rheumatoid arthritis strategy trials involving biologics and disease modifying drugs.^{40–43} The frequencies with which patients discontinued tumour necrosis factor inhibitors were comparable with UK national registry data of routine practice results.⁴⁴ The evidence suggests withdrawals in our trial were unlikely to have influenced our main conclusions.

Overall evidence

In early rheumatoid arthritis three head-to-head trials have shown that combinations of disease modifying drugs achieve similar benefits to tumour necrosis factor inhibitors.^{40–42} RACAT, the only other trial in established active rheumatoid arthritis,⁴³ showed that triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) achieved similar benefits to etanercept plus methotrexate in incomplete methotrexate responders treated for 12 months. Our trial and RACAT had comparable results, despite differences in patients and trial design. They highlight the role of head-to-head trials against effective conventional comparators to evaluate expensive treatments.⁴⁵ Although toxicity remains a potential concern with combined disease modifying drugs because single trials like ours cannot fully assess risks, such combinations have been used for many years without evidence of major toxicity.^{10 11}

The current trial questions the status quo of use of biologics in patients with active rheumatoid arthritis in whom methotrexate does not achieve the required response. In these patients the clinical and economic evidence from our trial supports preferentially starting combinations of synthetic disease modifying drugs. We also believe that modernising biologic treatment regimens for rheumatoid arthritis requires more strategy trials. Increasing efficacy is important, and optimising cost effectiveness is crucial. Options include giving biologics to patients with rheumatoid arthritis who are likely to respond to specific agents,^{46 47} discontinuing biologics when patients do not fully respond, and tapering treatment when patients achieve sustained remissions.⁴⁸

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Contributions: DLS was chief investigator and grant holder and designed the study, developed the protocol, led the trial, searched literature, produced figures, interpreted data, and was responsible for writing paper and associated reports. FI wrote the statistical analysis plan, undertook the main data analysis, produced tables for publication, and wrote the statistical section. VF was senior trial statistician and co-applicant on the grant, advised on the statistical analysis plan, reviewed all the data produced for the trial, and critically revised all statistical analyses. AGO'K was additional trial statistician and independently imputed trial data for intention to treat analysis and checked all trial outcome analyses. DW was co-applicant on the grant and helped design study, was a major recruiter to the trial, and provided a critical review of the results and final paper. CK was a major recruiter to the trial and served on the trial steering committee and provided a critical review of the results and final paper. FB was a major recruiter to the trial and provided a critical review of the results and final paper. KC was a major recruiter to the trial and provided a critical review of the results and final paper. PM was independent chair of the trial steering committee and was responsible for oversight of the trial, provided substantial ongoing independent advice to the grant holders and funders, and provided a critical review of the results and the final paper. MH analysed all the economic data for the trial. AP was a grant-holder, devised the economic aspects of the trial, oversaw the economic analysis, wrote the economic report of the trial, and contributed to the economic aspects of the final paper. GHK was deputy chief investigator and grant-holder and supported the chief investigator in the design of the study, the ongoing conduct of the trial, data interpretation, and the content of the final paper and associated reports. DLS is guarantor.

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Transparency declaration: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: Anonymised patient level data and a technical and statistical appendix will be available from the corresponding author for inclusion in meta-analyses and other relevant similar academic endeavours.

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- 1 Scott DL. Biologics-based therapy for the treatment of rheumatoid arthritis. *Clin Pharmacol Ther* 2012;91:30–43.
- 2 Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ* 2009;181:787–96.
- 3 Ruderman EM. Overview of safety of non-biologic and biologic DMARDs. *Rheumatology* 2012;51(suppl 6):37–43.
- 4 Doan QV, Chiou CF, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. *J Manag Care Pharm* 2006;12:555–69.
- 5 Smolen JS, Landewé 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. *Ann Rheum Dis* 2014;73:492–509.
- 6 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;64:625–39.
- 7 Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130). National Institute for Health and Care Excellence, 2007
- 8 Estellat C, Ravaud P. Lack of head-to-head trials and fair control arms: randomized controlled trials of biologic treatment for rheumatoid arthritis. *Arch Intern Med* 2012;172:237–44.
- 9 Ioannidis JP, Karassa FB, Druyts E, Thorlund K, Mills EJ. Biologic agents in rheumatology: unmet issues after 200 trials and \$200 billion sales. *Nat Rev Rheumatol* 2013;9:665–73
- 10 Choy EH, Smith C, Dore CJ, Scott DL. A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal. *Rheumatology* 2005;44:1414–21.
- 11 Ma MH, Kingsley GH, Scott DL. A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. *Rheumatology* 2010;49:91–8.
- 12 Graudal N, Jürgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. *Arthritis Rheum* 2010;62:2852–63.
- 13 Graudal N, Jürgens G. The level of the indication of biologic agents in the 2012 ACR recommendations on the treatment of Rheumatoid Arthritis. *Arthritis Care Res* 2013;65:832.
- 14 Klarenbeek NB, Kerstens PJ, Huizinga TW, Dijkmans BA, Allaart CF. Recent advances in the management of rheumatoid arthritis. *BMJ* 2010;341:c6942.
- 15 Scott DL, Strand V. The effects of disease-modifying anti-rheumatic drugs on the Health Assessment Questionnaire score. Lessons from the leflunomide clinical trials database. *Rheumatology* 2002;41:899–909.
- 16 Her M, Kavanaugh A. Patient-reported outcomes in rheumatoid arthritis. *Curr Opin Rheumatol* 2012;24:327–34.
- 17 Scott DL, Houssien DA, Laasonen L. Proposed modification to Larsen's scoring methods for hand and wrist radiographs. *Br J Rheumatol* 1995;34:56.
- 18 Beecham J, Knapp M. Costing psychiatric interventions. In: Thornicroft G, ed. *Measuring mental health needs*, 2nd ed. Gaskell, 2001.
- 19 Lipsky PE, van der Heijde D, St Clair E, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343:1594–602.
- 20 Choy EH, Smith CM, Farewell V, Walker D, Hassell A, Chau L, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann Rheum Dis* 2008;67:656–63.
- 21 Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. *J Rheumatol* 1993;20:557–60.
- 22 Van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996;39:34–40.
- 23 Thiele K, Huscher D, Bischoff S, Späthling-Mestekemper S, Backhaus M, Aringer M, et al. Performance of the 2011 ACR/EULAR preliminary remission criteria compared with DAS28 remission in unselected patients with rheumatoid arthritis. *Ann Rheum Dis* 2013;72:1194–9.
- 24 Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308:2594–604.
- 25 Van Gestel AM, Haagsma CJ, Furst DE, van Riel PL. Treatment of early rheumatoid arthritis patients with slow-acting anti-rheumatic drugs (SAARDs). *Baillieres Clin Rheumatol* 1997;11:65–82.
- 26 Fautrel B. Economic benefits of optimizing anchor therapy for rheumatoid arthritis. *Rheumatology* 2012;51(suppl 4):iv21–6.
- 27 Kobelt G, Jönsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. *Arthritis Rheum* 2002;46:2310–9.
- 28 Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. *J Health Serv Res Policy* 2004;9:110–118.
- 29 Marra CA, Bansback N, Anis AH, Shojania K. Introduction to economic modelling for clinical rheumatologists: application to biologic agents in rheumatoid arthritis. *Clin Rheumatol* 2011;30(suppl 1):S9–18.
- 30 Hyrich KL, Watson KD, Lunt M, Symmons DP. Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. *Rheumatology* 2011;50:117–23.
- 31 Greenberg JD, Reed G, Decktor D, Harrold L, Furst D, Gibofsky A, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Ann Rheum Dis* 2012;71:1134–42.
- 32 Marcus SM. Assessing non-consent bias with parallel randomized and nonrandomized clinical trials. *J Clin Epidemiol* 1997;50:823–8.
- 33 Weinblatt ME, Bingham CO, Mendelsohn AM, Kim L, Mack M, Lu J, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. *Ann Rheum Dis* 2013;72:381–9.
- 34 Lempp H, Hofmann D, Hatch SL, Scott DL. Patients' views about treatment with combination therapy for rheumatoid arthritis: a comparative qualitative study. *BMC Musculoskelet Disord* 2012;13:200.
- 35 Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ* 2002;325:766–70.
- 36 Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improvement in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. *Ann Rheum Dis* 2008;67:238–43.
- 37 Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340:253–9.
- 38 Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48:35–45.
- 39 Pope JE, Khanna D, Norrie D, Ouimet JM. The minimally important difference for the health assessment questionnaire in rheumatoid arthritis clinical practice is smaller than in randomized controlled trials. *J Rheumatol* 2009;36:254–9.
- 40 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;20;146:406–15.
- 41 Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. TEAR Investigators. 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* 2012;64:2824–35.
- 42 Van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, et al. Swefot study group. 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;379:1712–20.
- 43 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;369:307–18.

- 44 Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL; British Society for Rheumatology Biologics Register. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011;70:583–9.
- 45 Stafford RS, Wagner TH, Lavori PW. New, but not improved? Incorporating comparative-effectiveness information into FDA labeling. *N Engl J Med* 2009;361:1230–3.
- 46 Saevarsdottir S, Wedrén S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S, et al. Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. *Arthritis Rheum* 2011;63:26–36.
- 47 Canhão H, Rodrigues AM, Mourão AF, Martins F, Santos MJ, Canas-Silva J, et al. Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis. *Rheumatology* 2012;51:2020–6.
- 48 Van der Maas A, Kievit W, van den Bemt BJ, van den Hoogen FH, van Riel PL, den Broeder AA. Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis* 2012;71:1849–54.

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Appendix: Supplementary tables A-E