HEALTH TECHNOLOGY ASSESSMENT

VOLUME 18 ISSUE 66 OCTOBER 2014
ISSN 1366-5278

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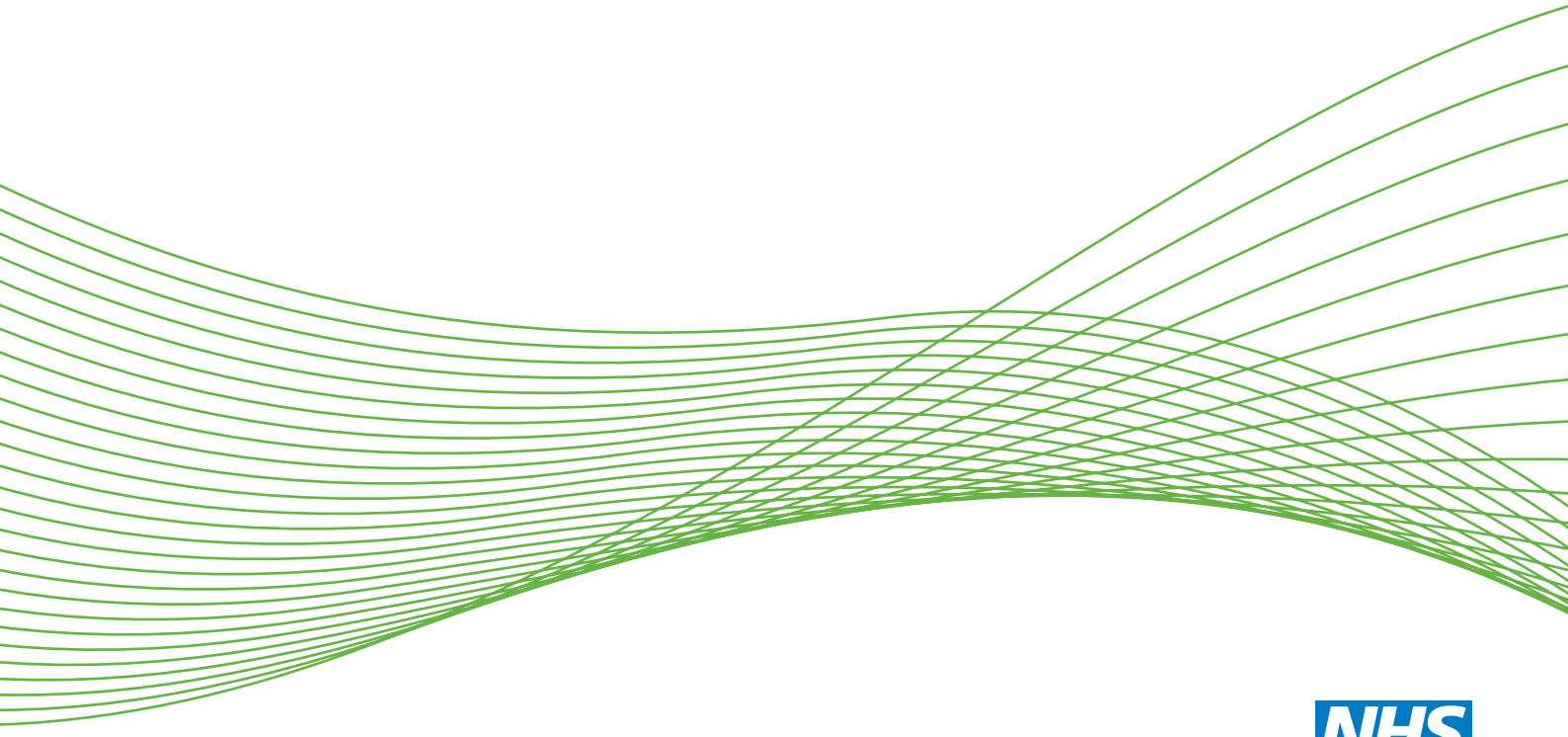

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DOI 10.3310/hta18660

Randomised controlled trial of Tumour necrosis factor inhibitors Against Combination Intensive Therapy with conventional disease-modifying antirheumatic drugs in established rheumatoid arthritis: the TACIT trial and associated systematic reviews

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Declared competing interests of authors: none

Published October 2014
DOI: 10.3310/hta18660

This report should be referenced as follows:

Scott DL, Ibrahim F, Farewell V, O'Keeffe AG, Ma M, Walker D, *et al*. Randomised controlled trial of Tumour necrosis factor inhibitors Against Combination Intensive Therapy with conventional disease-modifying antirheumatic drugs in established rheumatoid arthritis: the TACIT trial and associated systematic reviews. *Health Technol Assess* 2014;**18**(66).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 06/303/84. The contractual start date was in April 2007. The draft report began editorial review in February 2013 and was accepted for publication in September 2013. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

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Abstract

Randomised controlled trial of Tumour necrosis factor inhibitors Against Combination Intensive Therapy with conventional disease-modifying antirheumatic drugs in established rheumatoid arthritis: the TACIT trial and associated systematic reviews

David L Scott,[1]* Fowzia Ibrahim,[1] Vern Farewell,[2] Aidan G O'Keeffe,[2] Margaret Ma,[1] David Walker,[3] Margaret Heslin,[4] Anita Patel[4] and Gabrielle Kingsley[1]

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Background: Rheumatoid arthritis (RA) is initially treated with methotrexate and other disease-modifying antirheumatic drugs (DMARDs). Active RA patients who fail such treatments can receive tumour necrosis factor inhibitors (TNFis), which are effective but expensive.

Objective: We assessed whether or not combination DMARDs (cDMARDs) give equivalent clinical benefits at lower costs in RA patients eligible for TNFis.

Design: An open-label, 12-month, pragmatic, randomised, multicentre, two-arm trial [Tumour necrosis factor inhibitors Against Combination Intensive Therapy (TACIT)] compared these treatment strategies. We then systematically reviewed all comparable published trials.

Setting: The TACIT trial involved 24 English rheumatology clinics.

Participants: Active RA patients eligible for TNFis.

Interventions: The TACIT trial compared cDMARDs with TNFis plus methotrexate or another DMARD; 6-month non-responders received (a) TNFis if in the cDMARD group; and (b) a second TNFi if in the TNFi group.

Main outcome measures: The Heath Assessment Questionnaire (HAQ) was the primary outcome measure. The European Quality of Life-5 Dimensions (EQ-5D), joint damage, Disease Activity Score for 28 Joints (DAS28), withdrawals and adverse effects were secondary outcome measures. Economic evaluation linked costs, HAQ changes and quality-adjusted life-years (QALYs).

Results: In total, 432 patients were screened; 104 started on cDMARDs and 101 started on TNFis. The initial demographic and disease assessments were similar between the groups. In total, 16 patients were lost to follow-up (nine in the cDMARD group, seven in the TNFi group) and 42 discontinued their intervention but were followed up (23 in the cDMARD group and 19 in the TNFi group). Intention-to-treat analysis with multiple imputation methods used for missing data showed greater 12-month HAQ score reductions with initial cDMARDs than with initial TNFis [adjusted linear regression coefficient 0.15,

95% confidence interval (CI) −0.003 to 0.31; $p = 0.046$]. Increases in 12-month EQ-5D scores were greater with initial cDMARDs (adjusted linear regression coefficient −0.11, 95% CI −0.18 to −0.03; $p = 0.009$) whereas 6-month changes in HAQ and EQ-5D scores and 6- and 12-month changes in joint damage were similar between the initial cDMARD group and the initial TNFi group. Longitudinal analyses (adjusted general estimating equations) showed that the DAS28 was lower in the initial TNFi group in the first 6 months (coefficient −0.63, 95% CI −0.93 to −0.34; $p < 0.001$) but there were no differences between the groups in months 6–12. In total, 36 patients in the initial cDMARD group and 44 in the initial TNFi group achieved DAS28 remission. The onset of remission did not differ between groups ($p = 0.085$ on log-rank test). In total, 10 patients in the initial cDMARD group and 18 in the initial TNFi group experienced serious adverse events; stopping therapy because of toxicity occurred in 10 and six patients respectively. Economic evaluation showed that the cDMARD group had similar or better QALY outcomes than TNFi with significantly lower costs at 6 and 12 months. In the systematic reviews we identified 32 trials (including 20–1049 patients) on early RA and 19 trials (including 40–982 patients) on established RA that compared (1) cDMARDs with DMARD monotherapy; (2) TNFis/methotrexate with methotrexate monotherapy; and (3) cDMARDs with TNFis/methotrexate. They showed that cDMARDs and TNFis had similar efficacies and toxicities.

Conclusions: Active RA patients who have failed methotrexate and another DMARD achieve equivalent clinical benefits at a lower cost from starting cDMARDs or from starting TNFis (reserving TNFis for non-responders). Only a minority of patients achieve sustained remission with cDMARDs or TNFis; new strategies are needed to maximise the frequency of remission.

Trial registration: Current Control Trials ISRCTN37438295.

Funding: This project was funded by the National Institute for Health Research Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 18, No. 66. See the NIHR Journals Library website for further project information.

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List of abbreviations

ACR	American College of Rheumatology
anti-CCP	anticyclic citrullinated peptide
BeSt	Behandel Strategieen
BSR	British Society for Rheumatology
CARDERA	Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis
cDMARD	combination disease-modifying antirheumatic drug
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRP	C-reactive protein
CSRI	Client Service Receipt Inventory
DAS28	Disease Activity Score for 28 Joints
DAS	Disease Activity Score
DMARD	disease-modifying antirheumatic drug
EDC	electronic data capture
EQ-5D	European Quality of Life-5 Dimensions
ESR	erythrocyte sedimentation rate
GEE	generalised estimating equation
GP	general practitioner
HAQ	Health Assessment Questionnaire
ICER	incremental cost-effectiveness ratio
IL	interleukin
IQR	interquartile range
ITT	intention to treat
MCS	Mental Component summary
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
OR	odds ratio
PCS	Physical Component summary
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RCT	randomised controlled trial
SD	standard deviation
SF-36	Short Form Questionnaire-36 items
Swefot	Swedish Farmacotherapy
TACIT	Tumour necrosis factor inhibitors Against Combination Intensive Therapy
TNFi	tumour necrosis factor inhibitor
VAS	visual analogue scale
WMD	weighted mean difference

Plain English summary

Patients with rheumatoid arthritis (RA) usually take methotrexate or similar conventional drugs to modify the course of their disease. These treatments are called disease-modifying antirheumatic drugs (DMARDs). If conventional DMARDs are insufficient patients try high-cost biological treatments. The main biologics are tumour necrosis factor inhibitors (TNFis).

As conventional DMARDs can be given in combination, it is possible that combination DMARDs (cDMARDs) may be equally as effective as but less expensive than TNFis.

We compared these approaches in a trial [Tumour necrosis factor inhibitors Against Combination Intensive Therapy (TACIT)]. We studied patients at 24 specialist centres to ensure that the findings apply throughout England. The trial lasted 12 months. Patients not helped by cDMARDs switched to TNFis after 6 months.

The trial showed that patients starting cDMARDs and patients starting TNFis do equally well. Disability decreased in both groups and quality of life improved over 1 year. Disease activity also fell in both groups. Joint damage stayed much the same. The chance of having side effects and the severity of side effects were similar in both groups. However, cDMARDs cost much less.

When the TACIT trial was completed we looked at all of the other trials published in the field. We did this systematically to make sure that we did not miss any out. These trials also showed that the two approaches give similar improvements over periods ranging from 6 months to 2 years.

We think that cDMARDs and TNFis are equally good in active RA. However, cDMARDs cost much less. As only a few patients underwent long-term remission neither treatment approach seemed ideal.

Scientific summary

Background

Rheumatoid arthritis (RA) affects nearly 1% of adults in the UK. It causes joint inflammation, joint damage and extra-articular disease, and leads to disability and a reduction in quality of life. Core treatments are methotrexate and other disease-modifying antirheumatic drugs (DMARDs). Treating active RA can involve combination DMARDs (cDMARDs). Active RA patients in the UK who have failed methotrexate and another DMARD can receive tumour necrosis factor inhibitors (TNFis), which are both effective and expensive.

Objectives

Overall

We assessed whether or not RA patients eligible to receive TNFis achieve similar outcomes with cDMARDs in a head-to-head trial that compared both approaches [Tumour necrosis factor inhibitors Against Combination Intensive Therapy (TACIT)]. We also systematically reviewed published trials that assessed the efficacy of cDMARDs, TNFis with methotrexate and both approaches in patients with active RA.

The Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

The TACIT trial tested the hypothesis that patients with active RA meeting UK criteria for receiving TNFis gain equivalent benefit over 12 months at less expense and without increased toxicity if they start cDMARDs.

Systematic reviews

The systematic reviews assessed the efficacy and toxicity of cDMARDs and TNFis with methotrexate. They evaluated published randomised controlled trials that compared (1) cDMARDs with DMARD monotherapy; (2) TNFis plus methotrexate with methotrexate monotherapy; and (3) cDMARDs with TNFis plus methotrexate (head-to-head trials). The trials that enrolled patients with early RA were analysed separately from the trials that enrolled patients with established RA.

Methods

The Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

The TACIT trial was an open-label, 12-month, pragmatic, randomised, multicentre, two-arm trial. It compared cDMARDs with TNFis given with methotrexate or another DMARD in active, established RA. The 6-month non-responders in the cDMARDs arm could start TNFis and the 6-month non-responders in the TNFis arm could have a second TNFi. The Heath Assessment Questionnaire (HAQ), a patient-completed disability assessment, was the primary outcome measure. Secondary outcome measures included quality of life, joint damage, disease activity, withdrawals and adverse effects. An intention-to-treat (ITT) analysis used multiple imputation methods for missing data. The primary outcome was evaluated by linear regression with treatment, sex, ethnicity, age, region and disease duration as explanatory variables. The trial included an economic evaluation from both health and social care, and societal perspectives, linking costs with the HAQ and quality-adjusted life-years (QALYs) based on both the Short Form questionnaire-36 items (SF-36) and European Quality of Life-5 Dimensions (EQ-5D) at 6 and 12 months.

Systematic reviews

Ovid MEDLINE and EMBASE were searched from 1946 to 2012 for trials in English using the search term 'rheumatoid arthritis' with the search term 'DMARDs', 'TNFis' or 'combination therapy'. Treatment arms included cDMARDs or TNFi/methotrexate and control arms included DMARD monotherapy. Early RA trials enrolled patients with a duration of disease of < 3 years. Established RA trials enrolled treatment-resistant patients to at least one DMARD. The results were analysed using Review Manager 5.1.6 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects model estimated pooled effect sizes. Cochran's chi-squared test and I^2-statistics were used to assess heterogeneity.

Results

The Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

The TACIT trial screened 432 patients from 2008 to 2010 at 24 rheumatology clinics. Of these, 218 patients were excluded (196 did not consent) and 214 were randomised. Nine randomised patients withdrew before being treated (six decided not to participate); therefore, 104 patients started cDMARDs and 101 started TNFis. The initial demographic and disease assessments were similar between the groups. Over 12 months, 16 out of 205 were lost to follow-up (nine in the cDMARDs arm and seven in the TNFi arm). In total, 42 out of 205 discontinued their intervention but remained under follow-up (23 in the cDMARDs arm and 19 in the TNFi arm). ITT analysis evaluated all 205 patients. A secondary completer analysis evaluated 147 patients (72 in the cDMARDs arm and 75 in the TNFi arm). After 6 months, 42 out of 104 cDMARDs non-responders switched to TNFis.

Intention-to-treat analysis showed that reductions in HAQ score between baseline and 12 months were greater in the cDMARDs group [mean 0.45; 95% confidence interval (CI) 0.34 to 0.55] than in the TNFi group (mean 0.30, 95% CI 0.19 to 0.42). Adjusted linear regression showed that this was significant (coefficient 0.15, 95% CI −0.003 to 0.31; $p = 0.046$). Increases in EQ-5D score between baseline and 12 months were greater in the cDMARDs group (mean 0.20, 95% CI 0.13 to 0.27) than in the TNFi group (mean 0.14, 95% CI 0.08 to 0.21). Adjusted linear regression analysis showed that this difference was also significant (coefficient −0.11, 95% CI −0.18 to −0.03; $p = 0.009$). Changes between baseline and 6 months in HAQ and EQ-5D scores and between 6 and 12 months in radiological progression were similar between the groups.

Longitudinal analysis showed an overall difference between treatment groups in Disease Activity Score for 28 Joints (DAS28) over the whole 12 months. Patients randomised to the TNFi group had greater overall reductions in DAS28 than those randomised to cDMARDs; the adjusted general estimating equation showed a difference of −0.40 (95% CI −0.69 to −0.10, $p = 0.009$). Comparing the initial and final treatment periods showed different patterns of change. In the first 6 months DAS28 was lower in patients randomised to TNFis (coefficient −0.63, 95% CI −0.93 to −0.34; $p < 0.001$) whereas in the second period there was no difference between the groups (coefficient −0.19, 95% CI −0.55 to 0.18; $p = 0.317$).

In total, 36 out of 104 patients in the cDMARDs group and 44 out of 101 in the TNFi group achieved DAS28 remission. The onset of remission did not differ between groups ($p = 0.085$ on log-rank test). Remissions did not always persist; however, the number of patients in remission gradually increased over time. Fewer than 5% of patients in the cDMARDs group were in remission by 3 months; this rose to 20% by 12 months. In the TNFi group, 16% of patients were in remission by 3 months; this increased to 32% by 11 months.

Ten patients in the cDMARDs group had a serious adverse event, compared with 18 in the TNFi group (one died from pneumonia). In total, 10 patients in the cDMARDs group and six in the TNFi group stopped treatment because of toxicity. The cDMARDs group reported 635 different adverse events, compared with 465 in the TNFi group.

The economic evaluation, which was within the trial and did not include an extension to a longer-term disease model, showed that the cDMARDs group had the same or better HAQ, SF-36 QALY and EQ-5D QALY outcomes at 6 and 12 months and significantly lower costs at both time points. From a health-care perspective, focusing on EQ-5D-based QALYs at 12 months using imputed data, the mean adjusted cost difference was –£1937 (95% CI –£2612 to –£1353) and the mean adjusted outcome difference was 0.02 (95% CI –0.00 to 0.05). Combination DMARDs had a higher probability of cost-effectiveness than TNFis at both time points and on all cost–outcome combinations (although based on the HAQ at 6 months, the probability of cost-effectiveness decreased with increased willingness-to-pay thresholds). These conclusions apply from both a health and social care perspective and a societal perspective.

Systematic reviews

The early RA review identified 32 trials (including 20–1049 patients), which enrolled over 8400 patients; 19 trials compared cDMARDs with DMARD monotherapy, 10 trials compared TNFi/methotrexate with methotrexate and three were head-to-head trials. Indirect comparisons showed that (1) more patients achieved American College of Rheumatology (ACR)20–ACR70 responses [odds ratio (OR) 1.76–2.81) with cDMARDs than with DMARD monotherapy and fewer withdrew for lack of effect (OR 0.47) and (2) more patients achieved ACR20–ACR70 responses (OR 1.88–2.22) with TNFi/methotrexate than with methotrexate and fewer withdrew for lack of effect (OR 1.42, 95% CI 0.87 to 2.34). Head-to-head trials showed no differences in ACR20 responses or inefficacy withdrawals but fewer ACR50 and ACR70 responses with cDMARDs (ORs 0.53 and 0.54 respectively). Indirect comparisons showed greater HAQ improvements with both combination regimens.

The established RA review identified 19 trials (including 40–982 patients), which enrolled over 5500 patients: 10 trials compared cDMARDs with monotherapy (six involving methotrexate), eight trials compared TNFi/methotrexate with methotrexate and there was also a single head-to-head trial. Indirect comparisons showed that (1) more patients achieved ACR20–ACR70 responses with cDMARDs than with monotherapy (OR 2.75–5.07) and fewer withdrew for inefficacy (OR 0.38) and (2) more patients achieved ACR20–ACR70 responses with TNFi/methotrexate than with methotrexate (OR 5.32–8.13) and fewer withdrew for inefficacy (OR 0.12). The head-to-head trial showed no difference in ACR20–70 responses between the two treatment arms. Indirect comparisons showed greater HAQ improvements with both combination regimens.

Conclusions

The TACIT trial showed that RA patients who have failed to respond to methotrexate and another DMARD show clinically important improvements over 12 months if initially treated with cDMARDs, reserving TNFis for non-responders to these combinations. These improvements were equivalent to those achieved by starting all patients on TNFis in line with current National Institute for Health and Care Excellence (NICE) guidance. The equivalence of cDMARDs with TNFis was confirmed in systematic reviews of published trials in both early RA and established RA.

Implications for health care

In patients with active RA who have failed to respond to initial DMARDs:

1. This study indicates that giving all patients intensive cDMARD therapy and reserving TNFis for 6-month non-responders may be effective and cost-effective.
2. Only a minority of patients achieve sustained remission with cDMARDs or TNFis, indicating that neither represents an ideal long-term treatment for all RA patients.

Recommendations for research

1. Identifying predictors of response to cDMARDs and TNFis will enable a move towards individualised treatment. This is of crucial importance as some patients respond well to cDMARDs whereas others respond well to TNFis, and prospectively identifying potential good responders should optimise treatment outcomes.
2. We need to define the most effective ways of using current treatments in strategy trials to examine novel ways of using high-cost treatments. Examples include identifying the benefits of short courses of biologics in early RA, in which the rapid effects of biologics may be very beneficial, and redefining the optimal duration of TNFi treatment in established RA.
3. There should be a greater emphasis on head-to-head trials of cDMARDs and TNFis compared with effective low-cost comparators when defining the overall benefits of high-cost treatments in RA. Placing excessive reliance on short-term placebo-controlled trials in conjunction with modelling of future benefits based on data from historical observational studies has limitations when defining optimal treatment pathways.

Trial registration

This trial is registered as ISRCTN37438295.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Rheumatoid arthritis

Key impacts

Rheumatoid arthritis (RA), one of the commonest disabling diseases in the UK, remains a major health-care problem.[1–3] It affects almost 1% of UK adults and is more common in women. There are two peak ages of onset, early adulthood (mainly women) and later life (equal sex distribution). There are internationally accepted classification criteria for RA; from time to time these been revised and modernised.[3–6]

Its main impacts are increasing disability and reduced quality of life.[7] Both are substantial and persistent and reflect the combined effects of persisting joint inflammation, progressive joint damage and extra-articular features of RA.[8] Another significant impact of RA is reduced life expectancy, which is mainly due to associated comorbidities such as coronary artery disease.[9] The final major impact of RA is the substantial costs in terms of medical and social care and lost employment.[10]

Disease course and outcomes

The primary clinical feature of RA is chronic, usually persistent, inflammatory synovitis, initially mainly affecting the small joints of the hands and feet but subsequently spreading to involve multiple other joints.[7] Without adequate treatment many patients will develop joint damage, classically erosions, but also joint space loss and secondary osteoarthritis.[11] In addition, RA may be associated with extra-articular features, such as nodules and interstitial lung disease,[8] and with comorbidities, such as the increased risk of cardiovascular disease and infection.[12]

Diagnosis combines clinical features with laboratory tests such as acute phase markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)],[13] rheumatoid factor, anticyclic citrullinated peptide (anti-CCP) antibodies[14–16] and imaging [ultrasound, magnetic resonance imaging (MRI) and/or radiography].[17–19] Definitive differentiation from other forms of inflammatory arthritis is difficult in early arthritis but usually uncontroversial in established disease.

The outcome of RA is highly variable, ranging from mild disease with limited impact on a patient's life to severe unremitting disease unresponsive to treatment. Some features are known genetically and epidemiologically to be associated with a poorer outcome, including specific human leucocyte antigen genotypes, smoking and the presence of anti-CCP antibodies.[20–22] However, it has proved difficult to develop an outcome predictor at the level of the individual patient, which would be required to develop tailor-made individual treatment regimens.

Disease costs

Rheumatoid arthritis results in high medical and social costs,[23] with drug costs a significant part of the economic cost. Conventional drugs are relatively inexpensive whereas newer biological agents are very expensive; over time, drug costs have risen substantially. A second cost component is other medical care. These costs are modest in the short term but rise substantially when surgical treatment or supportive long-term medical treatment is needed for disabling severe RA or for comorbid disease. The final costs are societal costs. These include loss of work, support from family and carers and costs of care within the community. These societal costs usually exceed medical expenses and rise with disease duration and severity.

Historically, in the period before biological treatments were available, the direct and indirect costs were estimated to be in the region of £55–70M per million of the population,[24] with a total disease cost of £4B for the UK as a whole.[25] Since the introduction of biological treatments, drug costs have increased substantially. A report by the National Audit Office in 2009 estimated that RA costs the NHS around

£560M a year in health-care costs, with the majority of this in the acute sector.[26] This report estimated that the costs to the NHS of biologics for treating RA were around £160M annually. As biologics prescribing for RA has continued to increase, the current costs are likely to be substantially higher but may be balanced by reductions in other medical costs, such as orthopaedic interventions for RA, if high-cost drug treatments improve medical outcomes. The National Audit Office report also estimated that the additional cost to the UK economy of sick leave and work-related disability for RA is £1.8B a year.

Assessments

Assessments in RA mainly look at joint inflammation. Clinical-based assessments include swollen and tender joint counts and global assessment, which estimates overall disease activity and health status. Standard joint counts focus on 28 joints in the hands, upper limbs, and knees. Some experts prefer extended 66 and 68 joint counts; these include the feet. Laboratory measures include the ESR, CRP or both. Patient-based measures span pain, global assessment and disability.[27–29] The Health Assessment Questionnaire (HAQ) measures disability.[30] Other areas, such as fatigue and depression,[31,32] are very relevant to patients but are not always formally assessed. Patient-based measures are especially important because they measure an individual's perspective of the burden of their RA.

A number of combined indices amalgamate individual assessments. A widely used combined index is the Disease Activity Score for 28 Joints (DAS28), which combines the numbers of swollen and tender joints (hands, arms and knees) out of a total of 28, a patient's global assessment and the ESR to indicate a patient's current status.[33] As calculating the DAS28 involves a complex mathematical formula, simplified variants have been devised.[34] The Simplified Disease Activity Index uses the number of tender and swollen joints (out of a total of 28), doctors' and patients' global assessments and CRP level. The Clinical Disease Activity Index is similar but omits CRP level. The American College of Rheumatology (ACR) improvement criteria, which gauge change in status in clinical trials, include falls in joint counts and several other measures (patients' and doctors' global assessments, ESR, pain and HAQ). They record 20% (ACR20), 50% (ACR50) and 70% (ACR70) improvements in five of the seven measures.[35]

Juxta-articular erosions characterise progressive, established RA and are usually irreversible. They can be readily identified on radiographic images of the hands and feet. Two typical erosions are sufficient for diagnosis.[36] Extensive damage seen on radiographs suggests that RA is inadequately controlled. Rapid progression of joint damage needs intensive treatment.[37] Several scoring systems are used to quantify damage seen on radiographs in research studies. Although new imaging modalities such as ultrasound and MRI can assess structural changes, they are not yet widely used except in research.[38]

Treatment goals

The overall treatment goal is making patients feel better and minimising the impact of RA on their lives.[39] The main immediate treatment goal over the last two decades has been to reduce disease activity. Reducing joint and systemic inflammation is beneficial in itself. Crucially, it is also associated with other benefits including decreased disability, improved quality of life and reduced progression of joint damage. A dominant theme has been to treat patients with active RA; in the main, current treatments mean that few patients now have persisting active disease.

More recently there has been a shift towards making remission the main goal. An ideal treatment would result in the majority of patients achieving remission with no active joint inflammation and no functional deterioration or erosive progression.[40] Although 10–50% of patients with early RA can achieve remission,[41] only a small minority of established RA patients achieve sustained remission. An associated difficulty in determining the frequency of remission depends on how it is defined and the intensity of treatment.[42]

Relatively cheap, readily available disease-modifying antirheumatic drugs (DMARDs) such as methotrexate have made major inroads into managing active RA. DMARDs were initially given as monotherapies but in recent years there has been greater emphasis on using combinations of two or more DMARDs as this has been shown to be more effective in disease control.[43]

Since the mid-1990s a new treatment approach has been developed – the use of targeted biological treatments. They are usually given in combination with methotrexate or other DMARDs. Biologics have revolutionised the treatment of severe RA, for which they appear highly effective. A major limiting factor is their high cost.[44]

Reducing disease activity appears a clear-cut well-defined goal. However, the degree of reduction required for a good ultimate outcome is not yet known. Intensive treatment aimed at inducing remission[45] appears an inevitable next step. However, it is not clear whether or not this is appropriate for every patient. Furthermore, there remains uncertainty about the appropriate definition of remission in RA.[46]

Synopsis of specific drug treatment

Conventional disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs are a diverse range of drugs.[47] They form a single group because they both improve symptoms and also, to a greater or lesser extent, modify the course of the disease. This means that they reduce the progression of erosive joint damage and decrease disability.[48,49]

Many drugs have some features of DMARDs but only a few have been accepted into clinical practice. The use of DMARDs varies, with a small number being particularly favoured. The current situation is summarised in *Table 1*. At present, methotrexate is the dominant DMARD because of its greater efficacy and retention compared with other DMARDs.[50] As the most widely used DMARD, methotrexate is now considered by regulatory agencies as a benchmark against which new agents must be tested. The majority of RA patients treated with DMARDs in most UK specialist units either are currently taking or have previously received methotrexate. Sulfasalazine, leflunomide and hydroxychloroquine (the last largely as part of a combination regime) are the only other DMARDs used to any appreciable extent in the UK.[51]

TABLE 1 Disease-modifying antirheumatic drugs

Theme	DMARDs
Range of DMARDs	
Commonly used	Methotrexate, leflunomide, sulfasalazine
Infrequently used	Hydroxychloroquine/chloroquine, injectable gold, azathioprine
Rarely used	Ciclosporin, auranofin, cyclophosphamide
Combinations of DMARDs	
Methotrexate-based	Methotrexate, sulfasalazine, hydroxychloroquine
	Methotrexate, leflunomide
	Methotrexate, ciclosporin
	Methotrexate, gold
	Methotrexate, sulfasalazine
	Methotrexate, azathioprine
Other DMARDs	Leflunomide, sulfasalazine
	Gold, hydroxychloroquine
Steroid based	Steroids, methotrexate, sulfasalazine
	Steroids, methotrexate, ciclosporin
	Steroids, methotrexate

The efficacy of DMARDs involves reduced features of joint inflammation, such as fewer swollen joints and a lower ESR, a reduction in the progression of joint damage, particularly erosive damage, decreased levels of disability and improved quality of life. The harms, or adverse events, related to DMARDs include common problems seen with most DMARDs such as low white cell or platelet counts and unique toxicities with specific DMARDs. There is a reasonable evidence base for their use as monotherapies.[52–58]

Steroids

The commonest use of steroids in RA is as adjunctive agents to control disease flares; they may be given intra-articularly, intramuscularly or orally. Because in early disease it has been suggested that steroids exert a disease-modifying effect, they form an initial but temporary component of several early arthritis combination regimens. They are also widely used as part of intensive DMARD combination therapy regimes in patients with uncontrolled established disease. There is a reasonably strong evidence base for their use.[59–61]

Disease-modifying antirheumatic drug combinations with and without steroids

Disease-modifying antirheumatic drugs can be used in combination (see *Table 1*). This approach, initially advocated by McCarty,[62] has been examined in many clinical trials. Initial studies evaluated combinations that turned out to have excessive toxicity (gold–hydroxychloroquine)[63] or limited efficacy (methotrexate–azathioprine).[64] This toxicity led early reviews to suggest that risk/benefit ratios were unfavourable compared with monotherapy.[65]

However, the situation changed when randomised controlled trials (RCTs) of methotrexate–ciclosporin,[66] methotrexate–sulfasalazine–hydroxychloroquine[67] and methotrexate–sulfasalazine–steroids[68] reported improved disease control in active RA with mild or no excess toxicity; similar results were obtained in subsequent combination therapy studies. Combination DMARDs (cDMARDs) may not be required for all RA patients. In the only RCT of mild, early RA patients on stable DMARD monotherapy, they did not add benefit.[69]

Overall, from our 2005 systematic review,[70] and as suggested by a gradual expansion of its use in routine practice,[71] the benefits of combination therapy are now thought to outweigh the risks in patients with active disease not controlled by monotherapy. They are recommended in UK national guidelines[72] for early RA patients with active disease to avoid delay in bringing the disease under control, which is known to be associated with a poor outcome.

The RCT evidence for using DMARD combinations is of crucial importance to the Tumour necrosis factor inhibitors Against Combination Intensive Therapy (TACIT) trial. It is summarised in detail for both early and established RA in two systematic reviews (see *Chapter 3*).

Tumour necrosis factor inhibitors

These agents were developed in the late 1980s to target tumour necrosis factor (TNF)-α, a cytokine of central importance in the pathogenesis of RA, which exerts its effects by binding to type 1 and 2 receptors on immune, inflammatory and endothelial cells in the lymphoid system and joints and in less well-studied systems such as the central nervous system.[73]

The proof of principle for inhibiting this cytokine came from an open-label clinical study in which patients with RA received a single infusion of a tumour necrosis factor inhibitor (TNFi). Patients showed a rapid response, including an early fall in CRP level. However, the anti-inflammatory effect lasted only 6–12 weeks and was followed by a return of active disease.[74] As a result, patients were retreated with further infusions; these showed responses of similar magnitude and duration.[75] The scene was set for a major clinical development programme.

There are currently five TNFis available to treat inflammatory arthropathies, summarised in *Table 2*. All have been shown to be effective in large clinical trials, which have been collated in systematic reviews.[76–80] These TNFis can be subdivided into first-generation agents (comprising etanercept, infliximab and adalimumab) and second-generation agents (comprising certolizumab and golimumab). In RA, all of these agents are licensed for use in routine clinical care; they are also approved by National Institute for Health and Care Excellence (NICE) for use in the NHS although in some cases this has required a financial risk-sharing agreement.[81–83]

There is no clear-cut evidence that any one of these agents is superior to any other, and practical issues, including cost, determine which is chosen. There have been network meta-analyses of the efficacy and toxicity of different TNFis and these suggest potential minor differences in efficacy and adverse event risks.[84–86]

Infliximab must be given concurrently with methotrexate (or another DMARD in methotrexate-intolerant patients) to prevent the formation of human antichimeric antibodies.[87] The licence for adalimumab also requires concomitant methotrexate unless the patient is intolerant. Although concomitant treatment is not required for etanercept, substantial data suggest that combination treatment is more effective, especially in terms of the effect on bone erosion. Therefore, all three drugs are almost always given with methotrexate or another DMARD.[88]

The RCT evidence for using TNFis in combination with methotrexate and other DMARDs is also of crucial importance to the TACIT trial. This evidence is also summarised in detail in the systematic reviews in *Chapter 3*.

The question of what to do when a TNFi failed was a crucial question, particularly in the early 2000s when other biologics were not available. There is only limited information about the relative merits of switching from one TNFi to another. The only RCT studied golimumab in patients who had failed another TNFi; this showed some benefit from the switch.[89] The relative benefits of switching TNFis in patients who, for one reason or another, have not responded to their first biologic has also been addressed using observational data from registries and similar studies. Again, these studies provided some evidence that switching TNFis can give clinically useful improvements although response rates for second and subsequent TNFis are lower than for first-time use.[90]

More recently, several trials evaluating non-TNF-targeted biologics, including abatacept, rituximab and tocilizumab, have provided convincing evidence that non-TNF-targeted biologics are effective in patients who have failed with TNFis, and this is increasingly the preferred approach.[91,92]

TABLE 2 Tumour necrosis factor inhibitors

TNFi	Site of action	Dosing	Methotrexate
Infliximab	Binds soluble/transmembrane TNF-α and inhibits binding of TNF-α to receptors	Intravenous administration every 4–8 weeks	Essential to co-prescribe
Etanercept	Binds TNF-α and lymphotoxin and competitive inhibitor of TNF receptor	Subcutaneous twice weekly	Optional to co-prescribe
Adalimumab	Binds soluble/transmembrane TNF-α and inhibits binding of TNF-α to receptors	Subcutaneous fortnightly	Optional to co-prescribe
Certolizumab	Binds soluble/transmembrane TNF-α and inhibits binding of TNF-α to receptors	Subcutaneous fortnightly	Optional to co-prescribe
Golimumab	Binds soluble/transmembrane TNF-α and inhibits binding of TNF-α to receptors	Subcutaneously monthly	Optional to co-prescribe

Other new agents

A number of other biological treatments have been licensed, and in some cases approved by NICE, for treating RA. An early agent, anakinra, which is an interleukin-1 (IL1) receptor protein, is relatively ineffective[93] and is not often used for treating RA. It is, however, highly effective in a range of other disorders including acute gout, some forms of juvenile arthritis and some familial periodic fevers. Further anti-IL1 agents are in late-stage development, currently for these indications.

Rituximab targets B cells and is highly effective in active RA.[94] Its mechanism of action is controversial as the presence of rheumatoid factor is not essential for its efficacy. Tocilizumab targets IL-6 and is also highly effective in active RA.[95] The third effective biological treatment, abatacept, targets costimulatory molecules on T lymphocytes.[96] Although some of these other biological treatments are licensed to be used as first-line treatment in methotrexate incomplete responders with RA, network meta-analysis and similar comparative studies[84,85] show that these different biologics have comparable efficacy. TNFis are the most widely used treatment in methotrexate incomplete responders. Therefore, comparing cDMARDs with TNFis will provide results of general interest.

Several new non-biological agents such as kinase inhibitors[97,98] are being developed. One of these agents, tofacitinib, has been licensed in the USA[99] but is not yet approved for use in Europe. Depending on their cost, and relative efficacy and toxicity, such orally active agents may also change the treatment pathways for RA. However, for the present their roles are uncertain.

Non-TNFi biologics and new oral DMARDs are not part of the TACIT trial. Most of their actual or projected use is for patients who have failed to respond to both conventional DMARDs and TNFis. This late-stage treatment pathway for RA, which is complex and less well defined than the earlier management stages for RA, is not the key focus of the TACIT trial. We have therefore not reviewed it in detail.

Treatment strategies

Supportive and symptomatic treatment

As with all long-term disorders the management of RA requires multiple inputs from a range of health-care professionals from primary and secondary care. Patients need to be fully informed about their condition and be able to access advice; this is one of the key roles of the specialist nurses. Patients need effective treatment for pain, using analgesics and non-steroidal anti-inflammatory drugs,[100,101] and their comorbidities, notably ischaemic heart disease, need to be appropriately managed.[102] Finally, they need access to physiotherapists and in some cases occupational therapists and need to be encouraged to take regular exercise.[103,104] The appropriate use of all of these treatments is crucial to ensure a good outcome. However, they are outside the focus of the TACIT trial and so have not been considered in detail.

Treat to target

There is evidence that intensive treatment is important in early RA both to suppress disease activity[105–109] and to maintain low disease activity when it has been reduced. Welsing *et al.*[110] investigated the longitudinal relationship between disease activity and radiological progression in two independent follow-up cohorts. Both showed significant relationships between disease activity and radiological progression, but only in patients seropositive for rheumatoid factor. The results support systematic monitoring to achieve persistent low disease activity. This approach, termed ‘tight control’ or ‘treat to target’, includes several standard procedures such as:

- a predefined treatment protocol to which the treatment of individual patients is adjusted
- being able to assess whether or not the treatment chosen is necessary and effective
- incorporating measures to ensure that patients are not overtreated.

Many groups have reported on aspects of tight control.[111–114] Most used the Disease Activity Score (DAS) or DAS28 to guide treatment or as the primary end point. Overall clinical and radiological outcomes were more favourable in patients receiving tight-control regimens; in particular, remission rates were generally higher with tight control than with conventional therapy. These improved clinical and radiological outcomes did not appear to be at the cost of increased drug toxicity.

Access to high-cost treatments

Different countries have taken divergent approaches to the use of high-cost treatments such as biologics. A range of international groups, specialist societies and regulatory bodies recommends TNFis for patients with active RA who have failed to respond to conventional DMARDs.[115–118] The current UK consensus recommends that TNFis are started only in patients who have a DAS28 of > 5.1[115] and who have failed to respond to adequate therapeutic trials of two standard DMARDs including methotrexate.[119] Some UK experts believe that the threshold for active RA should be reduced to a DAS28 of > 3.2 with at least three or more tender joints and three or more swollen joints.[120] There are major national differences in the guidelines followed by rheumatologists for starting biological treatments and considerable diversity in biological treatment use across Europe.[121–124]

Economic modelling and biological treatments

Economic modelling conventionally extends beyond conventional RCTs,[125,126] bringing together cost and outcome evidence from a range of sources. Several modelling methods are used including simple decision trees, Markov models and individual sampling models. Most economic studies evaluate the impact of biological treatments on quality-adjusted life-years (QALYs). In the absence of direct QALY measures, values may be inferred from other available outcomes.[127] Recent systematic reviews of health economic studies in RA highlight the different conclusions reached based on assessments of the much the same set of published evidence. Schoels *et al.*[128] identified 21 relevant studies of biological treatments and, based on willingness-to-pay thresholds of US$50,000–100,000 per QALY, they concluded that combinations of TNFis with methotrexate were cost-effective after conventional DMARD failure. The sequential use of TNFis has been a difficult problem to resolve; however, Brennan *et al.*[129] reported favourable incremental cost-effectiveness ratios (ICERs) for using a second TNFi compared with DMARD treatment. A different perspective was taken in a systematic review by van der Velde *et al.*[130] They concluded that the economic evidence suggests that biological treatments are not cost-effective compared with DMARDs for RA in adults at a cost-effectiveness threshold of C$50,000 per QALY and that there is mixed evidence of cost-effectiveness in selected populations at a willingness-to-pay threshold of C$100,000 per QALY.

Rationale for the Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

Alternative approaches for accessing high-cost biological treatments in rheumatoid arthritis

Different groups of experts have reached widely differing views on when biological treatments in general and TNFis in particular should be started in RA. Almost all experts recommend usually using them in combination with methotrexate or other DMARDs. There is also universal agreement that they should be reserved for active RA, although there is uncertainty about what constitutes active disease.

Most experts recommend that they are used in patients who have failed to respond fully to methotrexate and who continue to have active RA. Many trials have been undertaken in such patients with positive findings. Most countries in continental Europe and North America have adopted this approach. The UK is more conservative and TNFis are generally used after patients have failed two DMARDs and still have active disease.

There are many alternative ways in which TNFis could be used in RA. One approach, which might be the most effective and cost-effective, is to reserve them until RA patients have tried and failed to respond to intensive DMARD combination treatments. Such an approach would place TNFis slightly lower down the therapeutic cascade; however, this might be of greater overall benefit to the health service by optimising the use of resources without causing patients any problems. This option is specifically explored in the TACIT trial.

Limiting the use of high-cost treatments has always been a component of Western health care. No country allows universal access to all high-cost treatments for all patients who would like to have them. It is equally important to ensure that patients are not denied effective treatments. If intensive cDMARDs are effective in some patients and the use of biological treatments can be changed so that they are given to patients most likely to show substantial benefits, the needs of both patients and health-care funders can be met. TNFis are not universally effective in RA; they have a response failure rate in the region of 20–30% of patients.[131–134] Some patients who would fail TNFis may respond to intensive cDMARD regimens. As the number of treatment options is limited in RA, and as patients rarely move from biological to non-biological treatment, there is a sound logic in exhausting treatment options in an organised sequence. If TNFis were curative such an argument would be misplaced; however, the balance of evidence indicates that DMARDs and biological treatments are both suppressive therapies that do not appear to alter the long-term clinical phenotype.

Systematic reviews of intensive treatments

The two treatment strategies used in the TACIT trial – cDMARDs and TNFis given in combination with methotrexate or another DMARD – have both been studied in RCTs in RA. Systematically reviewing these previous trials is crucial for both designing the TACIT trial and interpreting its findings.

We have previously published three systematic reviews of combination therapy trials: one looked at all combinations at all time points;[70] the second compared DMARD combinations and TNFi/methotrexate combinations in early RA;[135] and the third specifically examined the toxicity of combination therapies.[136] A number of other groups have also published systematic reviews of both cDMARDs and TNFis.[65,85,137–144] These systematic reviews all show that both DMARD combinations and TNFi/methotrexate combinations are effective in both active early and established RA. Their effectiveness in clinical trials is broadly comparable, although there are insufficient head-to-head clinical trials of these two treatment strategies. Overall, these published systematic reviews provide strong clinical support for undertaking a head-to-head trial such as the TACIT trial.

In early RA the relative clinical effectiveness and cost-effectiveness of conventional DMARD combinations have been considered in detail in guidance from NICE.[72] This guidance recommends cDMARDs, including methotrexate, as first-line treatment for early active RA. Biological treatments were excluded as first-line therapy by NICE because they were not considered cost-effective in these patients. Not all guidance accepts this conclusion; for example, the ACR advises the use of biological treatments (TNFis) combined with methotrexate as one initial therapy for active early RA patients with a poor prognosis[118] as an alternative to cDMARDs.

In patients with established RA disease the overall value of intensive DMARD combination regimens compared with TNFi/methotrexate combinations is less certain, particularly as these patients will usually have failed one or more previous DMARDs. The TACIT trial is aimed at these patients because there is genuine uncertainty about the relative merits of cDMARDs in such cases.

Aims and trial design

The TACIT trial focuses on the treatment of patients with active RA who have failed two DMARDs and who meet the current NICE criteria for starting TNFis. These NICE criteria are based partly on evidence from RCTs, partly on economic modelling and partly on expert opinion. Our alternative view is that many of these patients will do equally well on intensive combination therapy with conventional DMARDs.

Agreeing the research hypothesis and designing a RCT to test the hypothesis required considering the following three crucial issues:

- the key outcome
- the duration of the trial
- minimising the risk that patients randomised to receive cDMARDs are disadvantaged.

Our previous research has shown that the HAQ is a sensitive patient-assessed outcome measure in active RA trials of DMARDs.[145,146] It also has a crucial role in the economic modelling that is used to justify prescribing biological treatments. The HAQ was also the primary outcome measure in the Behandel Strategieen (BeSt) trial;[147] the only previous trial involving comparisons between cDMARDs and biological treatments published before the start of the TACIT trial, albeit in early RA. We therefore decided that changes in HAQ score should be the primary outcome measure.

The trial duration was more straightforward. Six months is probably too short a period of time to judge both clinical effectiveness and cost-effectiveness. A duration longer than 12 months appeared to be impractical and had no obvious advantage. As a consequence we decided that 12 months was the optimal time. This was also the time point at which the BeSt trial was first analysed.[147]

The final issue, about minimising risks to patients randomised to cDMARDs, was more complex. There were two potential risks. The first was that cDMARDs may have excessive toxicity. This risk would be minimised by independent oversight of the trial by the Data Monitoring and Ethics Committee. The other risk was inefficacy. We considered that if patients showed no response to cDMARDs after 6 months of treatment they should then be offered TNFis. We also considered that a response should adopt the same criterion that NICE recommends for maintaining patients on TNFis – a change in DAS28 of ≥ 1.20.

The final issue for the TACIT trial was whether it could be a placebo-controlled trial or an open-label strategy trial. As cDMARDs need to be individualised it would be impractical to deliver a placebo-controlled trial; instead, we considered that the trial had to be open label.

Hypothesis

The TACIT trial was designed to test the hypothesis that patients with active RA who meet the NICE criteria for treatment with TNFis will gain equivalent benefit over 12 months at substantially less expense and without increased toxicity from starting treatment with intensive combination therapy with DMARDs.

Primary and secondary outcomes

As a result of these various considerations the TACIT trial used the following outcome measures:

- primary outcome measure: HAQ, the key patient-completed disability measure in RA
- secondary outcome measures: joint damage, quality of life, disease activity, withdrawal rates, adverse effects, costs, QALYs, cost-effectiveness and cost–utility.

Testing the hypothesis

The TACIT hypothesis would be rejected if the primary outcome measure – the HAQ – showed substantial clinically important improvements at 12 months in patients randomised to receive TNFis. The TACIT trial was designed to confirm or refute the equivalence of treatment with TNFis and cDMARDs in improving HAQ scores over 12 months.

The TACIT hypothesis would also be either rejected or substantially weakened if economic evaluations at 12 months – including health and social care costs, societal costs, cost-effectiveness and cost–utility – showed disadvantages in patients randomised to receive cDMARDs or if the adverse event profile was substantially worse with cDMARDs.

The TACIT trial also collected a range of secondary outcomes to help evaluate the clinical usefulness of cDMARDs in these patients. These included assessing joint damage, quality of life, disease activity using the DAS28 and retention rates on such DMARD treatment. We considered also collecting other outcomes such as ACR response rates and responses on other indexes such as the Simplified Disease Activity Index. However, we concluded that measuring the same outcome in multiple ways, particularly using methods not followed in the UK where the trial is based to inform routine practice, would be counterproductive.

Systematic reviews

In the last few years more trials have been published about DMARD combinations and TNFi/methotrexate combinations. To ensure that the results of the TACIT trial can be placed into an appropriate context it is essential to provide an updated systematic review.

As there are different issues in early RA and established RA we have undertaken two reviews of these different aspects of RA treatment. As it is crucial to define whether or not there are differences in these two clinical settings in the relative efficacy of cDMARDs and TNFis, we used similar methods in both reviews. Our analytical approach is also comparable.

Consequently, the two systematic reviews assess the efficacy and toxicity of combination treatment with both cDMARDs and TNFis with methotrexate in the two groups of RA patients. The first group was patients with early disease, which is disease of < 3 years' duration. The second group was patients with established disease who have failed one or more DMARDs. The reviews evaluate treatments in trials that compared (1) cDMARDs with DMARD monotherapy; (2) TNFis plus methotrexate with methotrexate monotherapy; and (3) cDMARDs with TNFis plus methotrexate. The trials that enrolled patients with early RA were analysed separately from the trials that enrolled patients with established RA.

Chapter 2 Methods

Trial design

The TACIT trial was an open-label, pragmatic, randomised, multicentre, two-arm trial. Patients were allocated to each arm in equal numbers. The duration of the TACIT trial was 12 months.

The trial compared intensive cDMARDs with TNFis given together with methotrexate or another DMARD in active established RA. Patients who failed to respond to cDMARDs were eligible to receive TNFis after 6 months; this period was considered optimal to judge responsiveness to DMARDs. Patients in the TNFi arm were assessed for response to their first TNFi at 6 months, reflecting NICE guidance. Those who did not respond tried another TNFi. If they failed they were offered alternative treatment such as cDMARDs.

The trial was unblinded because individually optimised intensive cDMARD therapy cannot be given blind. Many previous RCTs in RA using such treatments have been unblinded. This approach provided the closest possible approximation to routine clinical care. The disadvantage of unblinded studies – that clinicians have excessive influence on the results – was ameliorated because the primary outcome measure, the HAQ, was a patient self-completed questionnaire. In addition, another key outcome, radiographic changes, was measured without knowledge of treatment group.

The TACIT trial raised a number of ethical issues related to whether or not patients were being potentially denied access to highly effective treatments. These are considered in detail in the discussion.

Eligibility criteria

The trial was aimed at patients with RA attending outpatient rheumatology clinics in England who met the current NICE criteria for receiving TNFis.[81]

Inclusion criteria

- Men and women aged > 18 years.
- Established RA according to the 1987 criteria of the ACR.[5]
- Disease duration of at least 12 months.
- Meet NICE criteria for being prescribed TNFis:[81] DAS28 > 5.1; failure to respond to two DMARDs including methotrexate; no contraindications to TNFis (including possibility of pregnancy).

Exclusion criteria

- Unable or unwilling to give informed consent.
- Failure of, or contraindications to, all proposed DMARD combinations (including possibility of pregnancy).
- Serious intercurrent illness.
- On high-dose steroids (in excess of 10 mg prednisolone or equivalent per day at trial entry).

Settings, locations and patient identification

Patients were recruited from rheumatology clinics in England and Wales, divided into three sectors: London/south, the Midlands and the north. The trial was undertaken in a routine outpatient setting with patient management shared between rheumatology specialist nurses and consultant rheumatologists. The supervising consultant was responsible for all aspects of patient care within the trial.

Before starting recruitment the primary care trusts (health-care commissioners) associated with each collaborating centre were contacted to ensure that they were informed about the nature and purpose of the trial and understood its clinical and economic implications. Collaborating rheumatologists and their specialist nurses were fully briefed to ensure that they had a good understanding of the rationale behind the study and of the principles and practice of using combinations of DMARDs in an intensive regimen. These processes were designed to allowed unhindered recruitment into the study.

Patients likely to be eligible to receive TNFis were managed in the following way (in line with NICE guidance):

- ensure that they have failed adequate treatment with two DMARDs and have a DAS28 > 5.1.
- negative screen for tuberculosis including chest radiography (and other local measures such as Mantoux testing where applicable)
- repeat the DAS28 assessment 4 weeks after the initial DAS28 assessment to ensure that it remains > 5.1.

Patients were eligible to enter the trial only at this stage, when they received full information about the trial and informed consent was obtained. Patients had adequate time and information to decide whether or not they wished to participate.

Patients were pre-screened and the following data were collected:

- number of patients who were potentially eligible to receive TNFis
- reasons why patients chose not to enter the trial (insufficient disease activity, consent not obtained and other reasons).
- numbers of patients randomised.

Trial interventions

The TACIT trial compared two treatment algorithms, one for TNFis and one for cDMARDs. Treatments were individualised and depended on patients' responses.

Tumour necrosis factor inhibitors

The three licensed agents available when the trial started – adalimumab, etanercept and infliximab – were allowed at standard doses (*British National Formulary*[148]). The choice of TNFi reflected patient preference and local circumstances. Methotrexate was also given to maximise efficacy and (in the case of infliximab) reduce the formation of antichimeric antibodies. Patients intolerant to methotrexate took another DMARD. DAS28 at 3 and 6 months defined responses to therapy.

Patients had their TNFi stopped for one or more of three reasons:

- lack of effect as defined by the NICE criterion,[81] that is, a change in DAS28 of < 1.2 at 3 or 6 months
- an adverse event that, in the opinion of the supervising specialist, necessitated treatment withdrawal
- patients could stop therapy for any reason should they wish (reasons to be specified if patient willing).

Patients in whom one TNFi was stopped were able to start another. This option represented current UK practice when the trial started. Patients who failed two TNFis for whatever reason were not able to start a third agent and required alternative treatment such as cDMARDs.

The principles of the treatment algorithm were as follows:

(a) start a TNFi of choice on the basis of local circumstances and patient preference
(b) assess at 3 months: no change if good response (change in DAS28 $\geq$ 1.2); change to second TNFi if change in DAS28 is < 1.2
(c) assess at 6 months: no change if good response (change in DAS28 $\geq$ 1.2); change to second TNFi if change in DAS28 is < 1.2; if two biologics already given and DAS28 change is < 1.2, TNFi stopped and patient offered DMARD combination or other therapy.

Combination disease-modifying antirheumatic drugs

Those cDMARDs with proven efficacy over DMARD monotherapy in RCTs were used, including:

- triple therapy with methotrexate (methotrexate–sulfasalazine–hydroxychloroquine)
- other methotrexate combinations (methotrexate–ciclosporin, methotrexate–leflunomide and methotrexate–gold)
- a sulfasalazine combination (sulfasalazine–leflunomide)
- additional monthly steroids [intramuscular Depo-Medrone (120 mg stat) or equivalent] were used if needed.

The DMARD combinations were stopped for three reasons: adverse events, patient-initiated withdrawals (which are identical to those reasons for stopping a TNFi) and lack of effect (change in DAS28 < 1.2), which is similar to that for TNFis but was implemented only at 6 months.

The principles of the treatment algorithm were:

- initially: maximise initial DMARD/optimise administration (e.g. parenteral methotrexate); start second/third DMARD; give intramuscular Depo-Medrone® (methylprednisolone, Pfizer) (whenever possible)
- second step: maximise dose of second/third DMARD
- third step: change combination (repeated if needed)
- additional option: continue with intramuscular Depo-Medrone monthly short term if RA remains active
- assess monthly and change treatment if change in DAS28 is < 1.2 or DAS28 is > 3.2
- at 6 months start a TNFi if change in DAS28 is < 1.2.

The target doses of different DMARDs used in combinations were as follows:

- methotrexate: 25 mg weekly – preferably by intramuscular injections although could be oral (achieved by 5-mg increments)
- sulfasalazine: 3 g daily (starting at 500 mg daily and increasing by 500-mg increments)
- hydroxychloroquine: 400 mg daily (starting at 200 mg and increasing as one increment)
- ciclosporin: 3.5 mg/kg (starting at 2 mg/kg and increasing incrementally depending on creatinine levels)
- leflunomide: 20 mg/day (staring at 10 mg/day and not increasing if used in combination with methotrexate)
- gold: 50 mg/month (starting with test dose, then 50 mg/week for 20 weeks, then 50 mg/month)
- intramuscular Depo-Medrone: 120 mg/month for 3 months; further courses were given if the RA was still active.

Dose adjustments to all drugs depended on both disease activity and evidence of adverse events. Decisions about changes in treatment were made by the supervising rheumatologist but were reviewed by the principal investigator (DS) or deputy to ensure that the algorithm was followed.

Concomitant therapy

Non-opiate analgesics and non-steroidal anti-inflammatory drugs were used as needed at standard doses. Patients taking methotrexate also received folic acid (5 mg/week) to limit adverse events. Patients taking steroids received bone protection (e.g. alendronate and calcium/vitamin D). Other drugs (e.g. antihypertensives) were used as needed. Patients taking oral prednisolone up to 10 mg at entry stayed on treatment. Intra-articular steroids were used as required.

Safety monitoring

Safety monitoring followed national guidelines with monthly blood counts and liver function tests plus measurement of renal function (creatinine), urinalysis and blood pressure recording for some DMARDs.[149–151] Patients were screened for tuberculosis.

Trial outcomes

Primary clinical outcome

Patient self-assessed outcomes were used in the TACIT trial.[152] The HAQ was the primary clinical outcome measure.[153] Although it is sometimes termed the HAQ Disability Index, most reports refer to it simply as the HAQ. The HAQ is a self-assessed questionnaire that is completed by patients. It primarily measures disability and is the dominant disability assessment in RA.[154] Scores range from 0 to 3, with higher scores indicating greater disability. It has established reliability and validity and has been used in many published RCTs in RA. HAQ scores were measured initially and at 6 and 12 months.

Secondary clinical outcomes

The European Quality of Life-5 Dimensions (EQ-5D)[155] and the Short Form questionnaire-36 items (SF-36)[156] were measured initially and at 6 and 12 months. These are also self-assessed questionnaires completed by patients. They measure health-related quality of life and can be used to estimate health utility and have been extensively studied in RA.[157–160]

Plain radiographs of the hands (including the wrists) and the feet were taken initially and at 6 and 12 months. These are widely used outcome measures.[161] Digital images of the radiographs were read at the end of the trial by a single observer (DS) experienced in reading radiographs using the Larsen score,[162] modified for minor changes.[163] The radiographs were assessed in known date order without knowledge of the treatments that patients had received.

Disease activity scores for 28 joint counts were measured initially and every month throughout the trial.[164] Scores are calculated using tender joint counts and swollen joint counts for 28 joints assessed by trained specialist nurses, the ESR and patients' global assessments of their disease activity recorded on a 100-mm visual analogue scale (VAS). DAS28 was used to guide treatment based on the predefined treatment targets and to assess responses to treatment.

Adverse effects were recorded each month by patient reporting. Specific events such as hospital admission were also recorded following international guidance.[165]

International recommendations

These outcome measures have all been recommended by international bodies including the European Medicines Agency[166] and the US Food and Drug Administration.[167]

Health economic assessments

An adapted version of the Client Service Receipt Inventory (CSRI) was used[168] to measure individual-level resource use. It covered sociodemographics, the use of (all-cause) secondary and community-based health and social care services, time off work because of illness, receipt of social security benefits and medication prescribed in addition to the study treatments. The CSRI has been previously used successfully in trials in

arthritis.[169] We also measured take-up rates (without intention to attribute costs) for NHS/social services contributions towards more exceptional resources, such as special mobility equipment, adaptations to the home or transport to health care. The CSRI was administered as a self-complete questionnaire retrospectively for the previous 3-month period at three assessment points: baseline, 6 months after randomisation and 12 months after randomisation. Use of trial medications was recorded separately and prospectively by the clinical/research teams over the entire study period in the form of medication name, dose, frequency and duration of use.

As discussed earlier, health-related quality of life was assessed by self-report questionnaires at baseline, and 6 and 12 months using the EQ-5D and SF-36 for the purpose of estimating QALY gains.

Data collection

Patient details and outcomes, with the exception of radiographic outcomes, were collected using an academic online database system with direct entry of data into the electronic case record form (see www.medscinet.net/tacit). This electronic data capture (EDC) system collected information anonymously using patients' initials and date of birth as identifiers.

Sample size

The TACIT trial sought to show equivalence between treatment strategies; in this setting the calculation of sample size is more complex than in conventional trials intended to show that one treatment is superior. One specific issue is that high-cost treatments such as TNFis can be justified only if they show substantial benefits over conventional inexpensive treatments. Key issues in this respect are the extent to which a difference in HAQ score (the primary outcome) between groups is clinically relevant, the degree of certainty in avoiding a type II error and the degree of conservatism in the statistical approach taken. The final sample size calculation has taken into account these various considerations.

This sample size was defined by the trial hypothesis that treating active RA patients who have failed to respond to two DMARDs with intensive conventional treatment using cDMARDs and steroids gives equivalent results to treatment with TNFis.

The sample size calculation was based on changes in HAQ scores in:

- the ATTRACT (Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy) trial (infliximab versus placebo in RA patients receiving concomitant methotrexate), in which the mean HAQ score at baseline was 1.7, which was reduced after treatment by 25%; the standard deviation (SD) of the change in HAQ score was 0.4[170]
- the CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) trial, an Medical Research Council-funded UK trial of 464 patients in which the mean HAQ score at baseline was 1.6, which was reduced after treatment by 31%; the SD of the change in HAQ score was 0.6.[171]

We used the average SD for change in HAQ score in these two trials, estimated at 0.5.

Most experts consider that the minimal clinically important change in HAQ score in RA is considered to be ≥ 0.22.[48,172–175] The trial was therefore designed under the assumption that cDMARDs and TNFis produce equivalent reductions in HAQ score and that a difference of < 0.22 would be regarded as equivalence.

Formally, the trial was designed to test the null hypothesis of a difference > 0.22. With a (one-sided) testing level of 5%, a sample size of 176 was required to achieve 90% power. To allow for a dropout rate of 5–7%, we planned to recruit 190 patients.

Recruitment method, randomisation and baseline assessments

Recruitment

Patients were recruited from rheumatology clinics in England, which were divided into three sectors: London and the south of England, the Midlands and the north of England.

Potentially eligible patients were identified by rheumatologists and clinic nurses at the participating centres. Rheumatologists approached potentially eligible patients and outlined the trial to them. Patients interested in participating were given the patient information sheet and were then contacted by telephone at least 24 hours after receiving the patient information sheet to see whether or not they were interested in participating. If they were, a screening assessment was arranged.

Screening involved making the following checks against NICE guidance to ensure that patients were eligible to receive TNFis:

- ensure that patient has failed adequate treatment with two DMARDs and has a DAS28 > 5.1
- negative screen for tuberculosis including chest radiography (and other local measures such as Mantoux testing where applicable)
- repeat DAS28 assessment 4 weeks after the initial DAS28 assessment to ensure that it remains > 5.1.

The screening assessment pages were collected anonymously using the EDC system. Once complete and eligible, the EDC system automatically assigned consecutive patient numbers to patients in chronological order.

Randomisation

Randomisation numbers were formed of four numbers and prefixed by the region identifier (i.e. 1 for London and the south, 2 for the Midlands and 3 for the north). The allocation sequence for randomisation was generated by the EDC system. Block randomisation was used in blocks of four with allocation balancing. Randomisation was stratified by region. Formally, the trial was designed to test the null hypothesis of a difference of > 0.22. With a (one-sided) testing level of 5%, a sample size of 176 was required to achieve 90% power. To allow for a dropout rate of 5–7%, we planned to recruit 190 patients. The clinicians at each of the trial centres and the trial co-ordinator were unaware of the allocation sequence.

Once a randomisation number was allocated, the EDC system automatically informed the researcher at the individual centre and the trial co-ordinator by e-mail. The trial co-ordinator informed the pharmacy at site of the randomisation. The patient was then informed that they had been recruited to the trial and the baseline assessment was arranged.

Data collected during screening

As part of screening data were collected on:

- number of patients who were potentially eligible to receive TNFis
- reasons why patients chose not to enter the clinical trial (insufficient disease activity, consent not given and other reasons)
- numbers of patients randomised.

Baseline assessment

Delays between screening and baseline were anticipated because of the pragmatic nature of the trial and local practices relating to the supply and delivery of TNFis. It was recognised that patients may therefore require additional treatment between the screening assessment and the baseline assessment, which would usually be an intramuscular steroid injection. The following rules were therefore applied:

- patients were given an appropriate dose of intramuscular steroid if needed
- the baseline assessment was delayed for 1 month after the date of injection.

Eligibility based on a DAS28 of > 5.1 at screening was not required to be maintained at the baseline assessment as this is not a requirement for receiving TNFis in routine practice.

Blinding

The TACIT trial was not blinded and both clinicians and patients knew to which treatment strategy patients had been allocated.

Statistical methods

Recruitment and follow-up patterns

Recruitment was recorded by year and region. The numbers of patients enrolled – excluding patients who had been withdrawn from therapy and who were unwilling to continue follow-up – were reported by treatment arm. The numbers of patients who withdrew from therapy, who were lost to follow-up or who died while taking part in the study were also reported by treatment arm.

Baseline comparability

Baseline characteristics were summarised by randomised group. Summary measures for the baseline characteristics of each group have been presented as means and SDs for continuous (approximate) normally distributed variables, medians and interquartile ranges (IQRs) for non-normally distributed variables, and frequencies and percentages for categorical variables.

Intention-to-treat population

Except for enrolled patients who withdrew consent or who were found to be ineligible at the baseline visit and so never received any treatment and for whom no data were therefore available, analyses on an intention-to-treat (ITT) basis reflect the randomisation process. We also carried out two additional analyses on the following populations:

1. a complete-case population: these were observations that subjects completed without missing data or violation of the protocol; this analysis is therefore referred to as a 'complete-case analysis' throughout this report
2. a per-protocol population: these were observations that excluded those patients who were found to deviate from the protocol.

The allowed variations to the protocol are shown in *Appendix 1*. The results of the per-protocol analysis were similar to those of the ITT analysis. Therefore, the results of the ITT and complete-case analyses have been presented in this report.

Imputing missing data

All participants had observations at baseline. However, some subjects had missing data on the outcome variables at 6 months, 12 months or both. The outcome variables that were measured at baseline and 6 and 12 months (HAQ, SF-36, EQ-5D and Larsen score) were imputed under different assumptions from those used for the DAS28 and its components, because DAS28 was measured monthly.

All missing data were imputed regardless of the reasons why it was missing. For the subjects who had missing outcomes, the baseline outcomes and other explanatory covariates (treatment group, sex, age, ethnicity, region and disease duration) were used to impute the missing data, assuming that unobserved measurements were missing at random.

For the subjects who had missing outcomes at 6 months, under the monotone assumption, baseline outcomes and explanatory covariates were used to impute these missing values. Then, for those patients who had missing outcomes at 12 months, baseline and 6-month outcomes with explanatory covariates were used to impute the missing values at 12 months. If the outcome variables were missing

at 6 and 12 months then the outcome variables at 6 months were imputed first followed by the outcome variables at 12 months.

The DAS28 and its component were imputed using multivariate sequential imputation using chained equations. First, all missing values were filled in by simple random sampling with replacement from the observed values. The first variable with missing values, say DAS28 at month 1, was regressed on all other variables, DAS28–0, DAS28–2 through to DAS28–12, restricted to individuals with the observed DAS28–1. Missing values for DAS28–1 were replaced by simulated data points drawn from the corresponding posterior predictive distribution of DAS28–1. Then, the next variable with missing values was replaced using the same cycle.[176]

The imputation was 20 cycles; at the end of the first cycle one imputed data set was created and the process was then repeated to create 20 imputed data sets. The 20 data sets were combined using Rubin's rules;[177–179] therefore, the estimates and standard errors presented here are the combined ones. As an additional check of the robustness of the analyses performed to the missing at random assumption, we further analysed the individual HAQ scores, EQ-5D scores, Larsen scores and DAS28 and its components) using the linear increments method of Diggle *et al.*[180] to handle the missingness. As the results obtained using this approach were qualitatively the same as those of the multiple imputation approach adopted, we report only the findings from the standard multiple imputation analyses.

Adjustment for design factors

Randomisation was stratified by region and therefore analyses of outcomes in the univariate or multivariable analyses were adjusted for region.

Outcomes assessed every 6 months

The primary outcome (HAQ score) and three of the secondary outcomes (EQ-5D score, SF-36 summary scores and Larsen score) were measured at baseline and 6 and 12 months. As there were not a significant number of zero values for the HAQ and other outcomes during follow-up, a linear regression model was used to analyse the change in these outcomes at 6 and 12 months. Thus, change was defined as either 12- or 6-month score minus baseline score. The unadjusted univariate analysis (model 1) was adjusted for region to account for design effect. The adjusted multivariable model (model 2) included sex, ethnicity, age, region, disease duration and baseline covariate as explanatory variables. Interactions between treatment and sex were assessed in the adjusted model 2 using the Wald test. The sex-specific interactions were not significant (for all outcomes $p > 0.70$). The treatment regression coefficient provided an estimate of the mean differences in HAQ, EQ-5D, SF-36 and Larsen scores.

For individual components of the SF-36 we used generalised estimating equations (GEEs) to estimate the effect of treatment including baseline values as a covariate for these outcomes. Working correlation matrices were unstructured, which was not unduly restrictive given that measurements were taken only at three time points. As the data were analysed longitudinally, time was included as a covariate in models 1 and 2. A final model tested specifically for interactions between treatment and sex and treatment and time using the Wald test. The sex-specific interactions were not significant (for all outcomes $p > 0.50$ in the overall test of all interaction terms). However, the interaction term between time and treatment was of borderline significance for some SF-36 domains (physical functioning, general health perception). We therefore report the period-specific treatment effect for those variables that had significant interaction terms.

Outcomes assessed every month

The DAS28 and its components were measured monthly and were therefore analysed separately. Changes in DAS28 and its components were analysed using GEEs to estimate the effect of treatment including baseline values as a covariate. Working correlation matrices were autoregressive with lag 1. In this analysis interactions between time and treatment and sex and treatment were also assessed and were

found to be non-significant. Treatment effects were examined as subanalyses in two periods (1–6 months and 7–12 months). The estimates were presented as mean treatment effects (beta coefficients) with 95% confidence intervals (CIs). The sandwich estimator of error was used with the aim of obtaining robust estimates of precision. Statistical significance was determined at the 5% level using a two-sided test throughout. These analyses were based on the assumption that patients stayed in their original randomised treatment arm and thus ignored subsequent treatment switches.

Exploratory analyses

The patients randomised to start cDMARDs fell into two categories. The first category included those patients who remained on cDMARDs throughout the TACIT trial. The second category included those patients who switched to a TNFi after ≥ 6 months because they had not fully responded to cDMARDs. The outcomes of these two categories of patients have been compared in a series of exploratory analyses, recognising that these are non-randomised in their original treatment arm. These analyses were carried out for all populations (ITT, complete case and per protocol).

Four additional analyses used all observed data only and missing data were not imputed. This approach was taken when patients were divided into discrete response categories. These analyses comprised: (a) changes in Larsen score; (b) the development of new erosions shown by categorical increases in Larsen score; (c) clinical response to treatment indicated by a decrease in DAS28 of ≥ 1.2; and (d) achieving remission indicated by a DAS28 of ≤ 2.6. Analytical approaches used specifically with all observed data were the construction of Kaplan–Meier plots and a comparison of treatments using the log-rank test.

Toxicity

The proportion of serious adverse events was compared across randomised groups using Fisher's exact test as appropriate.

Software specification

All data management and analyses were carried out using Stata version 12.0 (StataCorp LP, College Station, TX, USA) and the R statistical package (The R Foundation for Statistical Computing, Vienna, Austria[181]).

Economic evaluation methods

Costs

Unit costs were applied to resource use data to calculate cost per participant. Unit cost estimates, their sources and any assumptions made for their estimation are detailed in *Appendix 2*. Medication unit costs were converted into cost per mg based on the most cost-efficient pack size, choosing maintenance prices over initial treatment prices and generic prices over branded ones to obtain conservative estimates.

Total costs were computed for each participant at each assessment point from two perspectives: health and social care and societal. Health and social care costs included the costs of inpatient services, outpatient services, primary care services, other community-based services, social services, trial medications and other prescribed medications. Two sets of societal costs were calculated, one that included health and social care costs plus participant lost productivity because of absence from work and one that included health and social care costs, participant lost productivity because of absence from work and, additionally, the cost of social security benefit payments received.

For the economic evaluation, costs generated from the 3-month CSRI data were extrapolated (multiplied by 2) to cover the full 6 months before each follow-up point. All costs are reported in pounds sterling at 2010/11 prices. Discounting was not necessary as all costs were related to a 1-year period.

Outcome measures

Cost-effectiveness analyses were based on the primary outcome measure (the HAQ). Cost–utility analyses were based on QALYs derived from both the SF-36 and the EQ-5D. Utility weights appropriate to each measure were attached to the SF-36- and EQ-5D-produced health states at baseline and 6 and 12 months.[182,183] QALY gains between baseline and 6 months and between 6 months and 12 months were then calculated using the total area under the curve approach with linear interpolation between assessment points (and baseline adjustment for comparisons[184]).

Analyses, missing data and sensitivity analyses

Data were analysed using IMB Statistical Product and Service Solutions (SPSS) Statistics for Windows (version 20; IBM Coporation, Armonk, NY, USA) and Stata (version 11.2). Participants had individual unit costs applied based on the exact medication that they were prescribed, not on which arm they were in. Therefore, appropriate costs were applied regardless of switching during the trial.

Costs and outcomes were compared at 6 and 12 months and are presented as means and SDs. Mean differences and 95% CIs were obtained using non-parametric bootstrap regressions (1000 repetitions) to account for the non-normal distribution commonly found in economic data, with adjustment for region as this was a stratification factor in the randomisation process. Although this was a RCT and participants in all groups were expected to be balanced at baseline, baseline costs and outcomes could be predictors of follow-up costs. To provide more relevant treatment effect estimates,[185] regressions to calculate mean differences in costs at follow-up included covariates for baseline cost from the same cost perspective, baseline HAQ score, duration of illness, age, sex, region and ethnicity. Outcome comparisons (for the economic evaluation) at follow-up included covariates for baseline values of the same outcome plus baseline HAQ score, duration of illness, age, sex, region and ethnicity.

Data were entered via an EDC system using the MedSciNet database (MedSciNet AB, Stockholm, Sweden; http://medscinet.com) which was programmed to disallow individual-item non-response on the CSRI service use section. There was thus no item non-response for this part of the CSRI. For lost employment data, if the CSRI indicated that this was positive but the amount was missing, the mean lost employment cost for that arm at that time point (only for those who had lost employment and had valid data) was substituted. For social security benefit data, if the CSRI indicated that this was positive but the amount was missing, unit costs for specified benefits were applied. When receipt of benefits was positive but specific benefits were unspecified, the mean benefit cost for that arm at that time point (only for those who received benefits and had valid data) was substituted. For non-trial medication data, if the medication name was missing but other information (e.g. dose) indicated some use, an average prescription cost (from Department of Health prescription cost analyses; see http://data.gov.uk/dataset/prescription_cost_analysis_england) was assumed. If a medication name was provided but usage quantity was missing, an average prescription cost for that particular medication was assumed.

Analyses were based on available cases for each analysis, that is, they excluded non-responders to the CSRI, HAQ, EQ-5D or SF-36 at each time point if there were any. To explore the potential impact of excluding non-responders we examined the sociodemographic and clinical characteristics of those included in the analyses and those in the full sample. We also carried out an ITT analysis, imputing missing 6- and 12-month total costs and outcomes using the multiple imputation command in Stata (version 11). Imputations of missing 6- and 12-month costs were based on variables expected to predict follow-up costs: baseline HAQ score, duration of illness, age, sex, region, ethnicity, trial arm and equivalent baseline cost (and equivalent cost at 6 months for 12-month imputations). Imputations of HAQ scores at 6 and 12 months were based on baseline HAQ score, duration of illness, age, sex, region, ethnicity and trial arm (and HAQ score at 6 months for 12-month imputations). Imputations of missing QALYs at 6 and 12 months were based on baseline HAQ score, duration of illness, age, sex, region, ethnicity, trial arm and equivalent baseline utility score (and utility score at 6 months for 12-month imputations). Cost and outcome data for the resulting imputed full sample were analysed and presented as per the base (available) case data.

Cost-effectiveness and cost–utility analyses

Accounting for the three cost perspectives and three outcomes, there were nine possible cost–outcome combinations to consider in the economic evaluation. ICERs were calculated for any combination that showed both significantly higher costs and better outcomes in either the intervention group or the control group.

Uncertainty around cost-effectiveness/cost–utility was explored using cost-effectiveness acceptability curves (CEACs) based on the net-benefit approach. This followed the Bayesian approach to cost-effectiveness analysis outlined by Briggs.[186] These curves address some of the problems associated with examining ICERs and show the probability that one intervention is cost-effective compared with another other for a range of values that a decision-maker would be willing to pay for an additional unit of each outcome (i.e. per additional QALY or per additional point improvement in HAQ score). Net benefits for each participant were calculated using the following formula, where λ is the willingness to pay for one additional unit of outcome:

$$\text{Net benefit} = (\lambda \times \text{outcome}) - \text{cost} \quad (1)$$

A series of net benefits were calculated for each individual for λ values ranging between £0 and £50,000 per QALY gained and per point improvement on the HAQ. After calculating net benefits for each participant for each value of λ, coefficients of differences in net benefits between the trial arms were obtained through a series of bootstrapped linear regressions (1000 repetitions) of group upon net benefit, which included the baseline values of the same cost category and the same outcome as covariates plus baseline HAQ score, duration of illness, age, sex, region and ethnicity. The resulting coefficients were then examined to calculate for each value of λ the proportion of times that the cDMARDs group had a greater net benefit than the TNFi group. These proportions were then plotted to generate CEACs for all three outcomes from the health and social care perspective at 6 and 12 months.

Systematic review methods

The systematic reviews were carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist.[187]

Search strategies

Ovid MEDLINE and EMBASE were searched from 1946 to 2013. The terms used in the search strategies are found in *Appendix 5*. This was then limited to English language and clinical trials. The Cochrane Library was also searched using the terms 'early rheumatoid arthritis and combination therapy' or 'early rheumatoid arthritis and anti-TNF' for the early RA search and 'rheumatoid arthritis and combination therapy' or 'rheumatoid arthritis and anti-TNF' for the established RA search. The titles and abstracts were then assessed by two reviewers (MM, DS) independently. If there were any doubts regarding the eligibility of a particular study it was discussed between the two reviewers until agreement was reached.

Selection criteria

Early rheumatoid arthritis

The following criteria were used to select studies for evaluation:

(a) the study was a RCT
(b) patients fulfilled the ACR classification criteria for RA
(c) disease duration was < 3 years (this threshold was chosen to maximise the number of studies included in this systematic review)
(d) the 'treatment' arms comprised one or other or both of cDMARDs and TNFi/methotrexate
(e) the 'control' arm comprised DMARD monotherapy.

Established rheumatoid arthritis

The following criteria were used to select studies for evaluation:

(a) the study was a RCT
(b) patients fulfilled the ACR classification criteria for RA
(c) patients were treatment resistant to at least one previous DMARD given for at least 3 months
(d) the 'treatment' arms comprised one or other or both of cDMARDs and TNFi/methotrexate; when more than one dosage of TNFi was used the treatment arm that mirrored clinical practice the closest was chosen
(e) the 'control' arm comprised DMARD monotherapy.

Assessing the risk of bias

The risk of bias was assessed using criteria recommended by Viswanathan *et al.*[188]

Outcome measures

American College of Rheumatology responses and patient withdrawals because of inefficacy and toxicity

These dichotomous outcomes were used to calculate random-effects odds ratios (ORs) with 95% CIs. Patient withdrawals because of inefficacy and toxicity are routinely reported in clinical trials and are increasingly used as outcome measures. They have face validity and are used to assess effectiveness in clinical practice.

Health Assessment Questionnaire

Our meta-analysis included only studies reporting mean changes in HAQ scores; these were used to calculate random-effects weighted mean differences (WMDs).

Radiological progression

This was variously expressed as mean or median values, as changes over time or as final values. The meta-analysis included only studies reporting mean changes in radiological scores. To allow for different periods of observation, the annual rate of radiological progression was calculated (mean change in radiological score divided by duration of follow-up in years). As different radiological scoring systems were used (Sharp score, van der Heijde modified Sharp score and Larsen–Dale score), these were standardised as per cent maximal change (annual rate of progression divided by maximum possible score expressed as a percentage). The mean percentage annual changes were used to calculate random-effects WMDs.

Statistical analysis

Results were analysed using Review Manager 5.1.6 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). The random-effects model based on DerSimonian and Laird's method[189] was used to estimate the pooled effect sizes; this gives more equal weighting to studies of different precision than a simple inverse variance weighted approach, so accommodating between-study heterogeneity. For all meta-analyses we performed Cochran's chi-squared test to assess between-study heterogeneity and quantified I^2-statistics.[190,191] We considered a p-value < 0.05 as statistically significant.

In RCTs with two or more combination arms, the treatment arm with the best outcome was used. We also carried out sensitivity analyses using methotrexate monotherapy as the comparator arm. Methotrexate is the most commonly used DMARD monotherapy and is considered the most effective DMARD. Therefore, including this DMARD as a comparator ensures that trials had an effective comparator agent.

Chapter 3 Results

Introduction

Results of the Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

The results of the TACIT trial are presented in five sections. The first section describes screening, randomisation, patients studied and the treatments that they received. The second section describes the impact of treatment on disability, quality of life and erosive damage; these outcomes were assessed every 6 months and include the HAQ, which was the primary outcome. The third section describes the impact of treatment on disease activity; it focuses on the DAS28 and its individual components, with outcomes assessed every month. The fourth section describes adverse effects encountered during the trial and the final section reports the economic evaluation.

The report presents the results from the ITT and complete-case populations. The results of the per-protocol population were similar to those of the ITT population and these findings are considered only in summary form. However, detailed tables of the complete-case analyses are presented in *Appendix 3*.

Results of the systematic reviews

The two systematic reviews focus on early RA and established RA and these are reported after the trial results.

The Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial: screening, randomisation, patients studied and drug treatments

Screening and randomisation

Between September 2008 and December 2010 432 patients were screened at 24 rheumatology clinics in England. In total, 218 patients were excluded, 196 because they did not consent to participate and a further 20 because they were not eligible to participate; in addition, for two patients no reasons were recorded. The remaining 214 patients were randomised: 107 to receive cDMARDs and 107 to receive TNFis (*Figure 1*). The final assessment for the TACIT trial was in December 2011.

After randomisation three patients in the cDMARD group did not receive the intervention; this was because the patients changed their minds about participating in the trial after randomisation but before receiving treatment. There were also six patients in the TNFi group who did not receive the intervention. In three cases this was also because the patients changed their minds about taking part in the trial after randomisation but before receiving treatment. In one patient new information about a previous non-melanotic skin cancer resulted in the supervising rheumatologist considering that the patient should not receive biological treatment; in another patient the supervising rheumatologist changed his opinion about the suitability of the patient for intensive treatment; and the final patient mistakenly self-injected the TNFi, which had been delivered before the formal baseline assessment had been carried out.

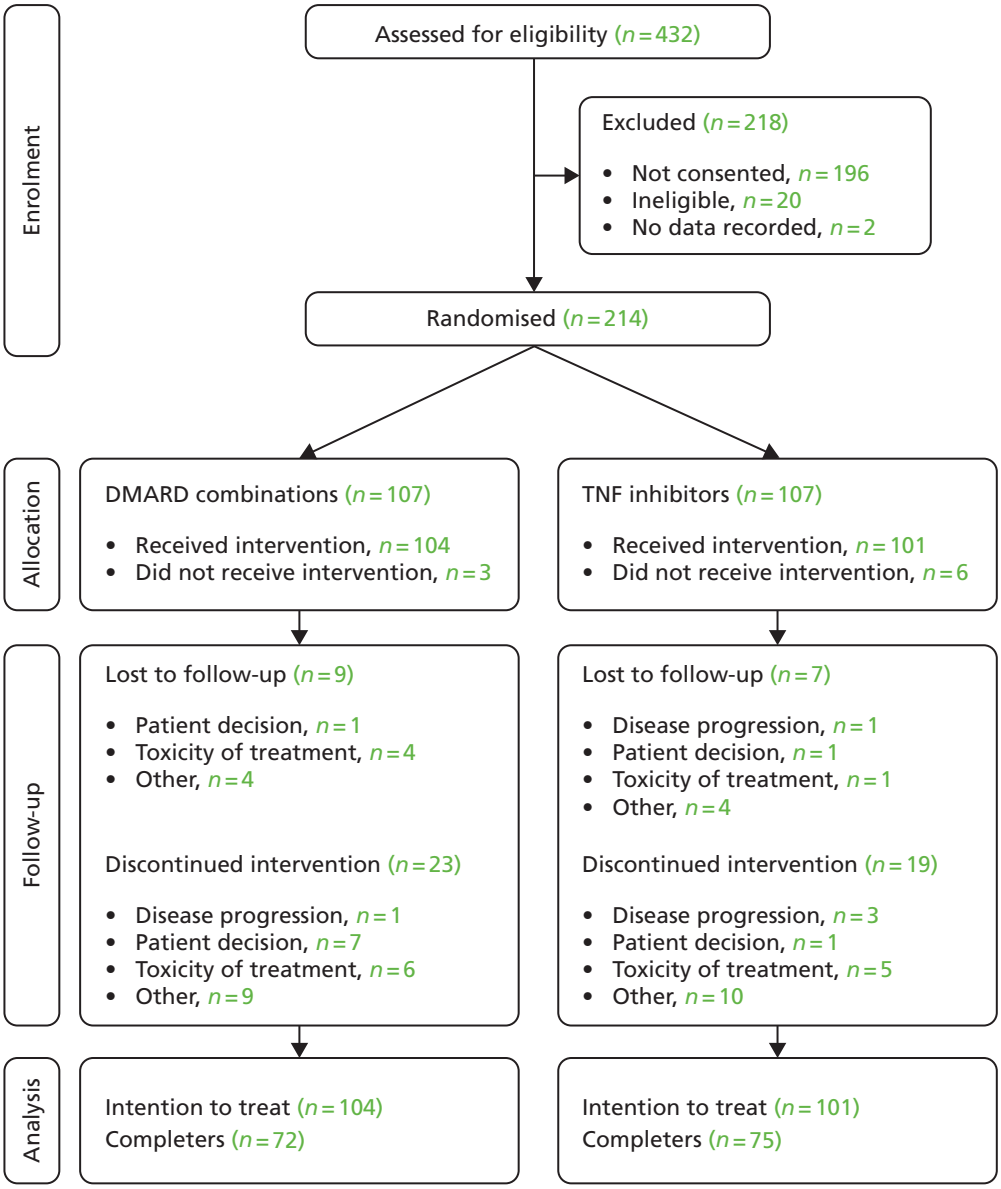

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram for the TACIT trial.

Patients studied

Although 214 patients were randomised (107 to receive cDMARDs and 107 to receive TNFis), only 104 patients started cDMARDs and 101 patients started TNFis and the trial report focuses on these 205 treated patients. Their baseline characteristics are summarised in *Table 3*. Both groups had similar demographic characteristics including region, sex, ethnicity, disease duration, weight and height. Most clinical variables were also similar between groups including DAS28, the individual components of the DAS28, HAQ and EQ-5D scores, and SF-36 domain and summary scores. The only variable to show a baseline difference was Larsen score, with a mean score of 45.1 (SD 41.9) in the cDMARD group and 37.9 (SD 38.8) in the TNFi group.

During the 12 months of the trial 16 out of the 205 treated patients (8%) were lost to follow-up, nine patients in the cDMARD arm and seven in the TNFi arm (see *Figure 1*). A further 42 out of the 205 patients (20%) discontinued their intervention but remained under follow-up; these comprised 23 patients in the cDMARD arm and 19 patients in the TNFi arm.

TABLE 3 Baseline demographic and clinical characteristics

Variable	cDMARDs ($N = 104$), *n* (%)	TNFis ($N = 101$), *n* (%)
Demographic variables		
Region		
London/south	65 (63)	63 (62)
Midlands	9 (9)	7 (7)
North	30 (29)	31 (31)
Age (years), mean (SD)	58 (13)	57 (11)
Sex		
Female	73 (70)	79 (78)
Male	31 (30)	22 (22)
Ethnic group		
White	89 (86)	92 (91)
Black (African, Caribbean, black other)	6 (6)	2 (2)
Asian (Bangladeshi/Indian, Pakistani)	8 (8)	6 (6)
Chinese	0 (0)	1 (1)
Other/mixed ethnic group	1 (1)	0 (0)
Disease duration (years), median (IQR)	4.4 (1.6–9.9)	5.9 (2.2–13.4)
Height (m), mean (SD)	1.64 (0.11)	1.66 (0.09)
Weight (kg), mean (SD)	78.3 (19.5)	80.6 (16.9)
BMI (kg/m^2), median (IQR)	28.5 (23.8–32.8)	29.0 (25.0–32.4)
Clinical variables		
DAS28, mean (SD)	6.21 (0.92)	6.30 (0.81)
Tender joint count, mean (SD)	16.4 (7.1)	17.5 (6.74)
Swollen joint count, mean (SD)	10.5 (6.1)	10.8 (6.74)
ESR (mm/hour), mean (SD)	33.1 (26.1)	30.1 (22.84)
VAS, mean (SD)	68.1 (19.7)	68.2 (21.30)
HAQ score, mean (SD)	1.80 (0.59)	1.90 (0.67)
Larsen score, mean (SD)	45.1 (41.9)	37.9 (38.8)
EQ-5D utility score, mean (SD)	0.39 (0.31)	0.35 (0.31)
SF-36 scores, mean (SD)		
Physical functioning	30.1 (22.6)	24.6 (21.0)
Role physical	14.9 (30.1)	12.4 (26.1)
Pain	28.1 (16.3)	26.3 (17.8)
General health perception	35.8(18.2)	31.4 (16.8)
Vitality	30.3 (21.4)	26.6 (19.0)
Social functioning	50.2 (25.2)	42.1 (25.3)
Role emotion	43.9 (44.9)	35.3 (44.9)
Mental health	61.9 (20.2)	58.8 (23.1)
PCS	28.4 (6.8)	27.3 (7.0)
MCS	43.4 (12.4)	40.7 (12.3)

BMI, body mass index; MCS, mental component score; PCS, physical component score.

In total, 10 out of 104 patients (10%) in the cDMARD arm stopped treatment because of toxicity, one (1%) stopped because of disease progression and 21 (15%) stopped for other reasons, including because a patient decided to stop treatment. In the TNFi arm six out of 101 (6%) patients stopped treatment because of toxicity, four (4%) stopped because of disease progression and 16 (16%) stopped for other reasons, including because a patient decided to stop treatment.

The main analysis evaluated 205 patients in the ITT group (104 in the cDMARD group and 101 in the TNFi group). The complete-case analysis evaluated the 147 completers (72 in the cDMARD group and 75 in the TNFi group).

Drug treatments

General

Drug treatments have been considered in two different ways: first, by describing treatments received by individual patients and, second, by reporting the numbers of prescriptions issued.

Patient received drug treatments in the TACIT trial using standard NHS prescribing mechanisms. DMARDs and steroids were prescribed from hospital pharmacies and were usually immediately available. TNFis were either delivered to patients' homes (adalimumab and etanercept) by a private company (Healthcare at Home, Burton on Trent, Staffordshire, UK) or given as day-case infusions (infliximab) in hospital. In both circumstances there were variable delays between making the clinical decision to initiate TNFis and starting treatment so that home deliveries or infusions could be arranged. These delays varied from weeks to months. In the group randomised to receive TNFis, the timing of the baseline assessment was adjusted to enable this initial assessment to coincide with delivery of the TNFis or the first infusion. However, when patients switched to start a TNFi (in the group randomised to start cDMARDs) or changed TNFis (in the group randomised to start TNFis), then the delay in starting a TNFi occurred with the trial time frame.

Individual treatments in the combination disease-modifying antirheumatic drug group

Most patients received combinations of two or three DMARDs during the course of the trial (*Table 4*). A minority had four or five DMARDs. As patients were receiving DMARDs when enrolled, combinations were usually given in a step-up approach. The most common combination was methotrexate and leflunomide. Other frequently used combinations included methotrexate and ciclosporin, methotrexate, sulfasalazine and hydroxychloroquine and methotrexate and gold. A variety of other combinations were used occasionally.

In total, 27 patients received glucocorticoids (steroids). In 24 patients these were given as oral prednisolone. Most of these patients receiving steroids (16 cases) had oral prednisolone combined with two DMARDs. An additional three patients received Depo-Medrone injections.

After 6 months, patients who had failed to achieve a decrease in DAS28 of ≥ 1.2 could receive a TNFi. Altogether, 46 out of 104 patients (44%) were recommended to switch to a TNFi. Three patients withdrew from the trial before starting a TNFi and therefore 43 out of 104 patients (41%) actually switched to a TNFi. The majority of these patients received adalimumab (see *Table 4*). The times at which the new treatments were actually started (as opposed to when they were recommended) are shown in *Figure 2*. TNFis were started after an average of 9 months (range 7–12 months).

TABLE 4 Individual treatment regimens in the cDMARD group

Therapies	No. of patients
No. of DMARDs combined	
One	0
Two	46
Three	48
Four	8
Five	2
Total	104
DMARD combinations	
Methotrexate/leflunomide	62
Methotrexate/ciclosporin	17
Methotrexate/sulfasalazine/hydroxychloroquine	13
Methotrexate/gold	10
Other	2
Total	104
Use of steroids	
Oral prednisolone	24
Depo-Medrone injections	3
Total	27
Switched to TNFis	
Adalimumab	25
Etanercept	14
Infliximab	4
Withdrew before starting[a]	3
Total	46

a Three patients were to have switched to a TNFi but never started because they withdrew from the trial.

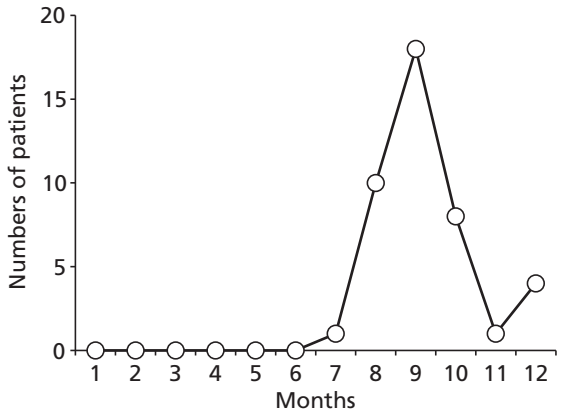

FIGURE 2 Actual month that TNFis were started in cDMARD patients switching to TNFis.

Individual treatments in the tumour necrosis factor inhibitor group

Most patients received adalimumab with etanercept and infliximab being used less often (*Table 5*). All patients received DMARDs: these comprised methotrexate (82 patients), sulfasalazine (13 patients), leflunomide (10 patients) and hydroxychloroquine (eight patients). In 13 patients the initial DMARD treatment involved a combination of two or more DMARDs. These combinations reflected pretrial treatment regimens and they were reduced to monotherapies during the trial.

In total, 19 patients received glucocorticoids (steroids). All of these patients received oral steroids with none receiving Depo-Medrone injections.

After 6 months 16 patients received a second TNFi. Four patients were subsequently recommended to switch to DMARDs; however, none of these patients completed the trial.

Numbers of prescriptions

Overall, 4608 prescriptions were issued in the TACIT trial, 2418 for patients in the DMARD group and 2190 for patients in the TNFi group (*Table 6*). The most widely used DMARD was methotrexate, followed by leflunomide, hydoxychloroquine and sulfasalazine. The most widely used TNFi was adalimumab.

TABLE 5 Individual treatment regimens in the TNFi group

Therapies	No. of patients
Initial TNFi	
Adalimumab	58
Etanercept	34
Infliximab	9
Total	101
Second TNFi	
Adalimumab	7
Etanercept	9
Infliximab	0
Total	16
Use of steroids	
Oral prednisolone	19
Depo-Medrone injections	0
Total	19

Note
All of the patients received concomitant DMARDs (usually methotrexate) but these are not shown in detail. Four patients were recommended to switch to DMARDs; however, none of these patients completed the trial.

TABLE 6 Monthly prescriptions for the cDMARD and TNFi groups[a]

Treatment	cDMARDs ($n = 104$)	TNFis ($n = 101$)	Total ($n = 205$)
Methotrexate	810	830	1640
Leflunomide	435	75	510
Hydroxychloroquine	355	72	427
Sulfasalazine	226	97	323
Ciclosporin	128	0	128
Gold injections	61	0	61
Penicillamine	26	0	26
Azathioprine	1	2	3
Prednisolone	199	134	333
Depo-Medrone	3	0	3
Adalimumab	112	580	692
Etanercept	49	331	380
Infliximab	13	69	82
Total	2418	2190	4608

a The numbers of prescriptions for each drug in each arm of the trial over the whole year of treatment are shown.

Disability, quality of life and erosive damage (assessed every 6 months)

The outcome measures specifically collected every 6 months include the primary outcome measure, HAQ score, and three secondary outcome measures – EQ-5D score, SF-36 scores and Larsen score for radiological progression.

Changes in Health Assessment Questionnaire scores

Primary outcome in intention-to-treat population

Initial HAQ scores were similar in patients randomised to receive cDMARDs (mean 1.80, 95% CI 1.68 to 1.91) and TNFis (mean 1.90, 95% CI 1.77 to 2.03) (*Table 7*).

After 12 months HAQ scores had changed by a mean of 0.45 (95% CI 0.34 to 0.55) in patients randomised to cDMARDs and by a mean of 0.30 (95% CI 0.19 to 0.42) in patients randomised to TNFis (see *Table 7*). The unadjusted and adjusted linear regression analyses (*Table 8*) showed that patients randomised to start cDMARDs had a greater reduction in HAQ score than those randomised to start TNFis. The unadjusted coefficient (adjusted for region only) was 0.14 (95% CI −0.01 to 0.29). After adjusting for demographic factors (age, sex, ethnicity, disease duration and region) and baseline score the adjusted coefficient was 0.15 (95% CI −0.003 to 0.31). The unadjusted linear regression analysis showed that the reduction in HAQ score was of borderline statistical significance in patients randomised to cDMARDs ($p = 0.075$). After adjusting for demographic factors and baseline score, the reduction in HAQ score was of stronger statistical significance in patients in the cDMARDs group ($p = 0.046$) (see *Table 8*).

TABLE 7 Primary and key secondary outcomes [mean scores and changes in scores (95% CIs)] by treatment group in the ITT population

	cDMARDs ($n = 104$)					TNFis ($n = 101$)				
Measure	Initial	6 months	12 months	Change 0–6 months	Change 0–12 months	Initial	6 months	12 months	Change 0–6 months	Change 0–12 months
HAQ score	1.80 (1.68 to 1.91)	1.52 (1.39 to 1.65)	1.35 (1.20 to 1.50)	0.28 (0.18 to 0.38)	0.45 (0.34 to 0.55)	1.90 (1.77 to 2.03)	1.55 (1.39 to 1.71)	1.59 (1.43 to 1.76)	0.35 (0.23 to 0.46)	0.30 (0.19 to 0.42)
EQ-5D score	0.39 (0.33 to 0.45)	0.53 (0.48 to 0.59)	0.59 (0.53 to 0.65)	−0.14 (−0.20 to −0.08)	−0.20 (−0.27 to −0.13)	0.35 (0.28 to 0.41)	0.52 (0.46 to 0.58)	0.49 (0.43 to 0.55)	−0.17 (−0.23 to −0.11)	−0.14 (−0.21 to −0.08)
Larsen score	45.1 (37.0 to 53.2)	45.9 (37.7 to 54.0)	46.3 (38.1 to 54.5)	−0.78 (−1.65 to −0.02)	−1.26 (−2.34 to −0.19)	37.9 (30.2 to 45.6)	38.7 (30.81 to 46.6)	39.3 (31.2 to 47.4)	−0.81 (−1.65 to 0.02)	−1.37 (−2.48 to −0.26)

Note
Changes in outcome measures over 6 months and 12 months are shown as the final value subtracted from the initial value. This means that improvements in HAQ score are positive but improvements in EQ-5D score are negative. With Larsen scores, negative changes represent worsening.

TABLE 8 Analysis of treatment effects on primary and secondary outcome measures: adjusted and unadjusted linear regression analyses of treatment effects in the ITT population

	Model 1 (unadjusted): treatment + region		Model 2 (adjusted): treatment + demographics + baseline score	
Outcome	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
Change in HAQ score				
12 months	0.14 (–0.01 to 0.29)	0.075	0.15 (0.00 to 0.31)	0.047
6 months	–0.07 (–0.22 to .08)	0.360	–0.08 (–0.23 to 0.07)	0.311
Change in EQ-5D score				
12 months	–0.06 (–0.15 to 0.04)	0.245	–0.11 (–0.18 to –0.03)	0.009
6 months	0.03 (–0.06 to 0.11)	0.500	0.01 (–0.07 to 0.08)	0.882
Change in Larsen score				
12 months	0.11 (–1.45 to 1.67)	0.891	0.35 (–1.37 to 2.06)	0.689
6 months	0.03 (–1.09 to 1.15)	0.958	0.24 (–1.02 to 1.51)	0.704
Change in SF-36 PCS				
12 months	–0.23 (–3.26 to 2.79)	0.880	–1.40 (–4.22 to 1.41)	0.327
6 months	2.66 (1.50 to 3.83)	<0.001	1.75 (0.64 to 2.86)	0.002
Change in SF-36 MCS				
12 months	0.42 (–3.51 to 4.35)	0.832	–1.73 (–5.07 to 1.61)	0.307
6 months	0.68 (–3.17 to 4.54)	0.728	–1.62 (–4.94 to 1.70)	0.336

MCS, mental component score; PCS, physical component score.
Demographics adjusted for are age, sex, ethnicity, disease duration and region. The reference group is cDMARDs.

The minimum clinically detectable difference in HAQ score is 0.22. The difference in HAQ change scores from 0 to 12 months between patients starting cDMARDs and those starting TNFis was 0.15 and the 95% CIs fell within 0.22 of this difference. The TACIT trial therefore provides no evidence of a clinically important difference in 12-month HAQ scores between groups.

Six-month outcomes in the intention-to-treat population

At 6 months the HAQ score decreased by a mean of 0.28 (95% CI 0.18 to 0.38) in patients randomised to cDMARDs and by a mean of 0.35 (95% CI 0.23 to 0.46) in patients randomised to TNFis (see *Table 7*). This difference was not significant in either the unadjusted or the adjusted model (see *Table 8*). The overall pattern of change is shown in *Figure 3*.

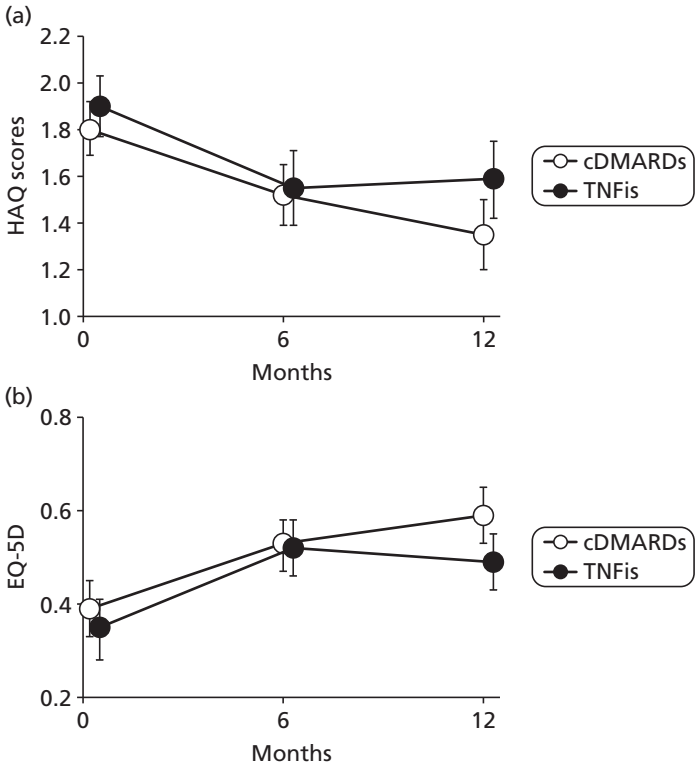

FIGURE 3 (a) Health Assessment Questionnaire; and (b) EQ-5D mean scores (95% CIs) by treatment group in the ITT population.

The effects of patients in the combination disease-modifying antirheumatic drug group switching to tumour necrosis factor inhibitors

In total, 58 of the 104 patients in the cDMARD group remained on cDMARDs and 46 switched to TNFis after 6 months. Over 12 months both sets of patients showed similar changes in HAQ score and there was no evidence of a difference between groups by linear regression analysis (*Table 9* and *Figure 4*). Comparing changes in HAQ scores in both of these groups using general estimating equations provided no evidence that there were any significant differences between the two groups in both an unadjusted and an adjusted model (*Table 10*).

Complete-case analysis

Initial HAQ scores and changes in HAQ scores were similar between patients randomised to cDMARDs and those randomised to TNFis. There was no evidence of any significant differences between groups (see *Appendix 3*, *Tables 50* and *52* and *Figure 28*). However, in the longitudinal analysis (see *Appendix 3*, *Table 55*), there was some evidence of a treatment difference in the unadjusted and adjusted models.

Changes in European Quality of Life-5 Dimensions scores

Intention-to-treat population

Initial EQ-5D scores were similar in patients randomised to receive cDMARDs (mean 0.39, 95% CI 0.33 to 0.45) and patients randomised to receive TNFis (mean 0.35, 95% CI 0.28 to 0.41) (see *Table 7*).

At 12 months EQ-5D scores changed by a mean of –0.20 (95% CI –0.27 to –0.13) in patients randomised to cDMARDs and by a mean of –0.14 (95% CI –0.21 to –0.08) in patients randomised to TNFis (see *Table 7*). There was no significant difference between groups in the unadjusted model (see *Table 8*). The adjusted model, in which the coefficient was –0.11 (95% CI –0.18 to –0.03), showed a significant change in EQ-5D score in patients randomised to cDMARDs compared with those randomised to TNFis ($p = 0.009$).

TABLE 9 Primary and key secondary outcomes [mean scores and changes in scores (95% CIs)] in the cDMARD group ($n = 104$) by treatment status

	Stayed on cDMARDs ($n = 58$)				Changed to TNFis ($n = 46$)			
Measure	Initial	6 months	12 months	Change 0–12 months	Initial	6 months	12 months	Change 0–12 months
HAQ score	1.82 (1.65 to 1.98)	1.42 (1.23 to 1.60)	1.38 (1.17 to 1.60)	0.43[a] (0.29 to 0.58)	1.77 (1.62 to 1.92)	1.64 (1.46 to 1.82)	1.31 (1.10 to 1.51)	0.46 (0.30 to 0.62)
EQ-5D score	0.35 (0.27 to 0.43)	0.57 (0.50 to 0.64)	0.61 (0.53 to 0.69)	−0.26[b] (−0.35 to −0.17)	0.44 (0.35 to 0.52)	0.49 (0.40 to 0.57)	0.57 (0.48 to 0.65)	−0.13 (−0.24 to −0.02)
Larsen score	44.7 (33.6 to 55.8)	45.3 (34.1 to 56.5)	45.9 (34.7 to 57.0)	−1.13[c] (−2.63 to 0.38)	45.5 (33.4 to 57.6)	46.5 (34.3 to 58.7)	46.9 (34.6 to 59.3)	−1.43 (−2.92 to 0.06)

a $p = 0.81$ comparing change at 12 months between groups by linear regression.
b $p = 0.069$ comparing change at 12 months between groups by linear regression.
c $p = 0.77$ comparing change at 12 months between groups by linear regression.

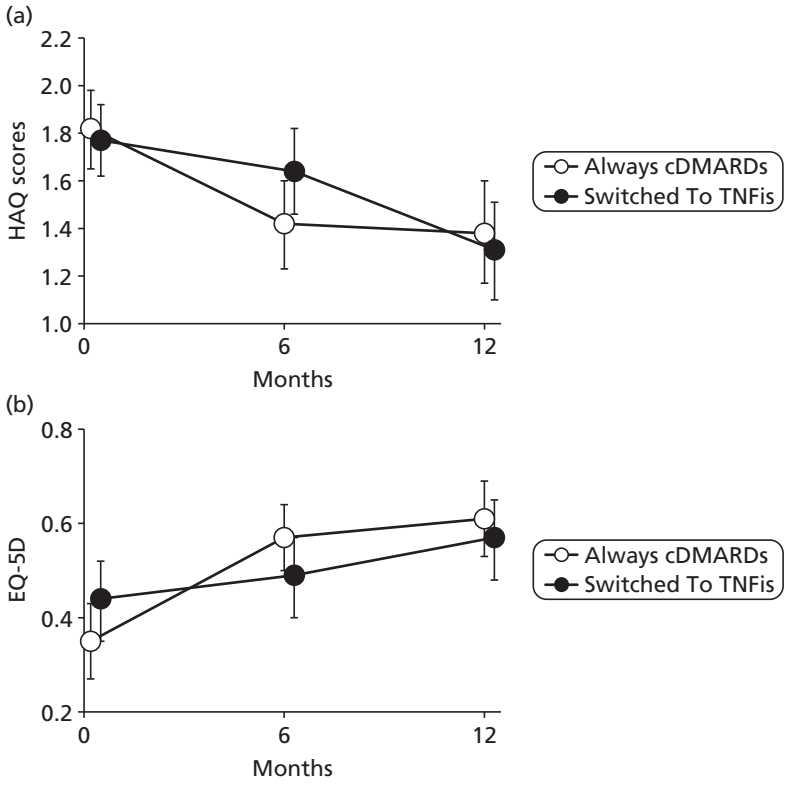

FIGURE 4 (a) Health Assessment questionnaire; and (b) EQ–5D mean scores (95% CIs) in cDMARD arm patients ($n = 104$) in the ITT population by treatment status.

TABLE 10 Effects on HAQ score in cDMARD arm patients ($n = 104$) in the ITT population by treatment status: adjusted and unadjusted assessments of treatment effect using GEEs

	Model 1 (unadjusted): treatment + region + time		Model 2 (adjusted): treatment + demographics + baseline score + time	
Outcome	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
Change in HAQ score				
12 months	0.14 (–0.03 to 0.31)	0.103	0.12 (–0.05 to 0.29)	0.185

Demographic variables are age, sex, ethnicity, disease duration and region. The reference group is no switch.

At 6 months EQ-5D scores changed by a mean of –0.14 (95% CI –0.20 to –0.08) in patients randomised to cDMARDs and by –0.17 (95% CI –0.23 to –0.11) in patients randomised to TNFis (see *Table 7*). The difference between treatment groups was not significant in either the unadjusted or the adjusted model (see *Table 8*). The overall pattern of change is shown in *Figure 3*.

The effects of patients in the combination disease-modifying antirheumatic drug group switching to tumour necrosis factor inhibitors

Over 12 months both sets of patients saw changes in EQ-5D scores (see *Table 9* and *Figure 4*). In patients remaining on cDMARDs, EQ-5D scores improved by a mean of –0.26 (95% CI –0.35 to –0.17) and in patients switching to TNFis, EQ-5D scores improved by a mean of –0.13 (95% CI –0.24 to –0.02). Comparing these changes in EQ-5D scores over 12 months by linear regression (see *Table 9*) showed that the difference was of borderline significance ($p = 0.069$).

Complete-case analysis

Initial EQ-5D scores and changes in EQ-5D scores were similar between patients randomised to cDMARDs and those randomised to TNFis. There was no evidence of any significant differences between groups (see *Appendix 3*, *Tables 50* and *52* and *Figure 28*).

Changes in Short Form Questionnaire-36 items scores

Intention-to-treat population

Changes in the SF-36 profiles and physical component score (PCS) and mental component score (MCS) are summarised in *Table 11*. There was a complex pattern of change. There were large mean changes (> 20) in the role physical domain at both 6 and 12 months in both groups. At 12 months physical functioning, pain, vitality, social functioning and role emotion showed changes of between 10 and 20 in both groups. General health perception and mental health showed smaller changes over 12 months (< 10) in both groups. We have not undertaken an in-depth statistical analysis of changes in the individual domains. However, longitudinal analyses assessing changes in these SF-36 domains at both 6 and 12 months (*Table 12*) mainly showed no significant differences between treatment groups in the unadjusted model or in the adjusted model.

Initial PCS scores were similar in the two groups: in patients randomised to cDMARDs the mean score was 28.4 (95% CI 27.1 to 29.7) and in patients randomised to TNFis the mean score was 27.3 (95% CI 25.9 to 28.7). At 12 months PCS scores changed by a mean of −6.0 (95% CI −8.1 to −3.8) in patients randomised to cDMARDs and by a mean of −5.8 (95% CI −7.9 to −3.7) in patients randomised to TNFis (see *Table 11*). There was no significant difference between the groups in the unadjusted or adjusted model on linear regression analysis (see *Table 8*). At 6 months PCS scores changed by a mean of −4.2 (95% CI −6.2 to −2.1) in patients randomised to cDMARDs and by a mean of −7.6 (95% CI −9.5 to −5.8) in patients randomised to TNFis (see *Table 11*). This difference was significant on linear regression analysis in both the unadjusted model (2.66, 95% CI 1.50 to 3.83; $p < 0.001$) and the adjusted model (−1.75, 95% CI 0.64 to 2.86; $p = 0.002$) (see *Table 8*).

Initial MCS scores were similar in the two groups: in patients randomised to cDMARDs the mean score was 43.4 (95% CI 41.0 to 45.8) and in patients randomised to TNFis the mean score was 40.7 (95% CI 38.3 to 43.1). At 12 months MCS scores changed by a mean of −5.0 (95% CI −7.8 to −2.2) in patients randomised to cDMARDs and by −5.4 (95% CI −8.2 to −2.7) in patients randomised to TNFis (see *Table 11*). There was no significant difference between the groups in the unadjusted or adjusted model (see *Table 8*). At 6 months MCS scores changed by a mean of −3.6 (95% CI −6.1 to −1.1) in patients randomised to cDMARDs and by a mean of −4.3 (95% CI −7.2 to −1.4) in patients randomised to TNFis (see *Table 11*). There was no significant difference between treatment groups in the unadjusted or adjusted model in linear regression analysis (see *Table 8*).

Complete-case analysis

Changes in SF-36 profiles and initial scores and changes in scores for the PCS and MCS were similar between patients randomised to cDMARDs and those randomised to TNFis. There was no evidence of a significant difference between groups in the longitudinal analysis (see *Appendix 3*, *Tables 51* and *53*).

Changes in Larsen scores

Intention-to-treat population

The initial Larsen scores differed between groups (see *Table 7*): in the cDMARD group the initial mean score was 45.1 (95% CI 37.0 to 53.2) and in the TNFi group it was 37.9 (95% CI 30.2 to 45.6). The Larsen score was the only clinical variable to show baseline differences and no clinical significance was attached to this difference.

TABLE 11 Short Form Questionnaire-36 items domain and summary scores [mean scores and changes in scores (95% CIs)] by treatment group in the ITT population

	cDMARDs ($n = 104$)					TNFis ($n = 101$)				
Domain	Initial	6 months	12 months	Change 0–6 months	Change 0–12 months	Initial	6 months	12 months	Change 0–6 months	Change 0–12 months
Physical functioning	30.1 (25.8 to 34.5)	36.7 (31.3 to 42.2)	42.1 (36.4 to 47.7)	−6.58 (−12.2 to −0.9)	−11.9 (−17.5 to −6.3)	24.6 (20.5 to 28.7)	40.0 (34.4 to 45.5)	37.8 (31.9 to 43.6)	−15.4 (−20.8 to −10.1)	−13.2 (−18.9 to −7.5)
Role physical	14.9 (9.1 to 20.7)	36.2 (28.0 to 44.3)	37.2 (28.2 to 46.1)	−21.3 (−30.7 to −11.8)	−22.3 (−31.9 to −12.6)	12.4 (7.3 to 17.5)	37.6 (29.2 to 46.1)	33.1 (24.4 to 41.8)	−25.2 (−33.6 to −16.9)	−20.7 (−29.5 to −11.9)
Pain	28.1 (25.0 to 31.3)	41.2 (37.4 to 45.1)	46.4 (41.5 to 51.2)	−13.1 (−17.5 to −8.7)	−18.2 (−23.5 to −12.9)	26.3 (22.8 to 29.8)	45.5 (40.9 to 50.0)	44.7 (40.0 to 49.4)	−19.2 (−24.1 to −14.3)	−18.4 (−24.0 to −12.9)
General health perception	35.8 (32.3 to 39.3)	40.9 (37.1 to 44.8)	44.6 (39.8 to 49.4)	−5.2 (−9.3 to −1.1)	−8.9 (−13.7 to −4.1)	31.4 (28.1 to 34.7)	44.1 (39.9 to 48.3)	39.6 (35.3 to 44.0)	−12.7 (−17.1 to −8.3)	−8.2 (−12.8 to −3.7)
Vitality	30.3 (26.2 to 34.5)	36.8 (32.5 to 41.2)	40.4 (35.3 to 45.5)	−6.5 (−11.3 to −1.7)	−10.1 (−14.9 to −5.2)	26.6 (22.9 to 30.3)	40.4 (35.9 to 44.9)	40.1 (35.4 to 44.8)	−13.8 (−18.4 to −9.2)	−13.5 (−18.5 to −8.4)
Social functioning	50.2 (45.4 to 55.1)	61.6 (56.4 to 66.8)	66.2 (60.6 to 71.8)	−11.4 (−16.6 to −6.1)	−16.0 (−22.0 to −9.9)	42.1 (37.1 to 47.0)	58.9 (53.6 to 64.3)	59.8 (54.0 to 65.5)	−16.8 (−22.8 to −10.9)	−17.7 (−24.2 to −11.1)
Role emotion	43.9 (35.2 to 52.6)	58.3 (49.3 to 67.3)	60.4 (50.8 to 70.0)	−14.4 (−25.1 to −3.6)	−16.5 (−28.0 to −5.0)	35.3 (26.5 to 44.1)	50.9 (41.7 to 60.1)	52.1 (42.7 to 61.5)	−15.6 (−26.8 to −4.3)	−16.8 (−28.3 to −5.3)
Mental health	61.9 (58.0 to 65.8)	68.1 (64.2 to 72.0)	70.4 (66.3 to 74.5)	−6.2 (−10.6 to −1.8)	−8.5 (−13.3 to −3.7)	58.8 (54.3 to 63.3)	65.8 (61.4 to 70.2)	67.8 (63.7 to 71.9)	−7.0 (−12.4 to −1.6)	−9.0 (−14.1 to −4.0)
PCS	28.4 (27.1 to 29.7)	32.6 (30.7 to 34.4)	34.4 (32.2 to 36.5)	−4.2 (−6.2 to −2.1)	−6.0 (−8.1 to −3.8)	27.3 (25.9 to 28.7)	34.9 (32.9 to 36.9)	33.0 (31.1 to 35.0)	−7.6 (−9.5 to −5.8)	−5.8 (−7.9 to −3.7)
MCS	43.4 (41.0 to 45.8)	47.0 (44.6 to 49.4)	48.4 (46.0 to 50.8)	−3.6 (−6.1 to −1.1)	−5.0 (−7.8 to −2.2)	40.7 (38.3 to 43.1)	45.0 (42.4 to 47.6)	46.1 (43.7 to 48.6)	−4.3 (−7.2 to −1.4)	−5.4 (−8.2 to −2.7)

TABLE 12 Longitudinal analysis of treatment effects on SF-36 domains: adjusted and unadjusted longitudinal analyses using GEEs in the ITT population

	Model 1 (unadjusted): treatment + region		Model 2 (adjusted): treatment + demographics + baseline score	
Variable	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
No period-specific treatment effects				
SF-36 role physical	−0.77 (−6.52 to 4.97)	0.793	0.40 (−4.74 to 5.53)	0.879
SF-36 pain	−1.50 (−4.76 to 1.76)	0.368	−0.21 (−2.95 to 2.53)	0.880
SF-36 vitality	−2.92 (−6.05 to 0.21)	0.067	−1.76 (−4.54 to 1.02)	0.215
SF-36 social functioning	−1.81 (−5.66 to 2.03)	0.356	1.80 (−1.43 to 5.04)	0.274
SF-36 role emotion	−0.43 (−7.64 to 6.78)	0.907	3.98 (−1.58 to 9.54)	0.160
SF-36 mental health	−0.31 (−3.46 to 2.85)	0.848	1.35 (−1.06 to 3.76)	0.272
Period-specific treatment effects *Period (1–6 months)*				
SF-36 physical functioning	8.69 (1.04 to 16.34)	0.026	5.52 (−1.74 to 12.77)	0.136
SF-36 general health perception	7.37 (1.43 to 13.30)	0.015	4.20 (−0.78 to 9.18)	0.098
Period (7–12 months)				
SF-36 physical functioning	1.16 (−6.49 to 8.81)	0.767	−3.12 (−10.44 to 4.19)	0.403
SF-36 general health perception	−0.79 (−7.24 to 5.66)	0.81	−4.14 (−10.05 to 1.76)	0.169

Demographics variables are age, sex, ethnicity, disease duration and region. The reference group is cDMARDs when appropriate.

Progression over 12 months was similar between the groups (*Figure 5*). With cDMARDs the Larsen score increased by 1.26 and with TNFis it increased by 1.37. Progression over 6 months was also similar. These differences between the treatment groups were not statistically significant (see *Tables 8* and *12*).

An exploratory analysis examined individual changes over 12 months using all observed data for both groups (*Figure 6*); this showed no evidence of a different pattern of progression between the groups.

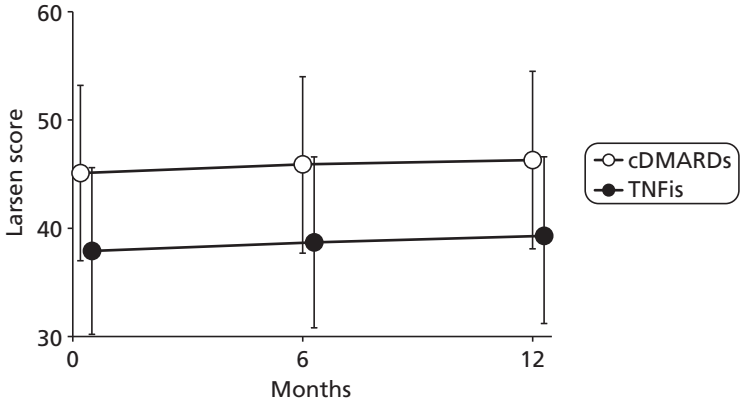

FIGURE 5 Mean Larsen scores (95% CIs) by treatment group in the ITT population.

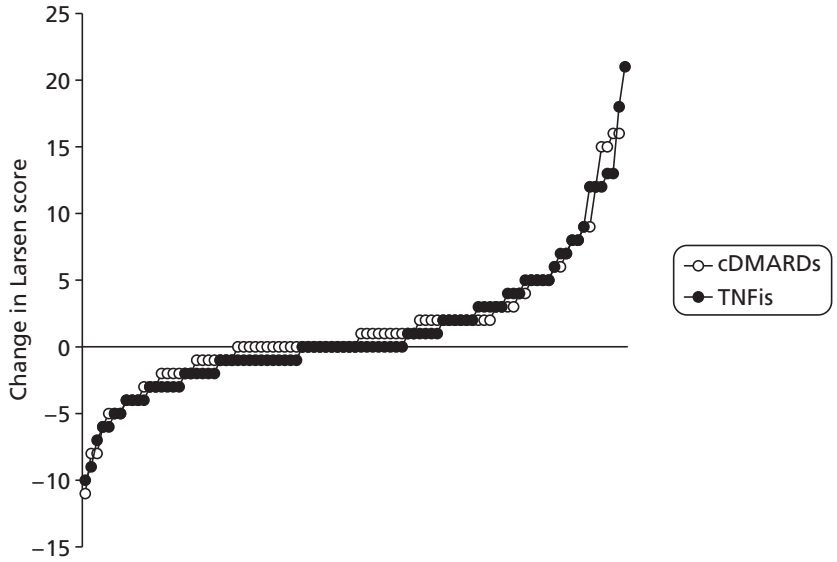

FIGURE 6 Individual changes in Larsen score over 12 months using all observed data.

Another exploratory analysis evaluated the development of one (increase in Larsen score of 2–5) or many new erosions (increase in Larsen score of > 5) using all observed data for both groups; this is summarised in *Figure 7*, showing that there were no differences between the groups. By the end of the trial, 23 out of 91 patients (25%) randomised to receive cDMARDs developed one new erosion and 12 out of 91 patients (13%) developed two or more erosions. In the group randomised to receive TNFis, 19 out of 93 patients (20%) developed one new erosion and 13 out of 93 patients (14%) developed two or more erosions.

The effects of patients in the combination disease-modifying antirheumatic drug group switching to tumour necrosis factor inhibitors

Over 12 months both sets of patients showed small increases in Larsen scores (see *Table 9*). In patients remaining on cDMARDs Larsen scores increased by a mean of −1.13 (95% CI −2.63 to 0.38) and in patients switching to TNFis Larsen scores increased by a mean of −1.43 (95% CI −2.92 to 0.06). Comparing these changes in Larsen scores over 12 months by linear regression provided no evidence that the difference was significant (see *Table 11*). We also examined individual changes over 12 months for both sets of patients using all observed data (*Figure 8*); this showed no evidence of a different pattern of progression between the two groups.

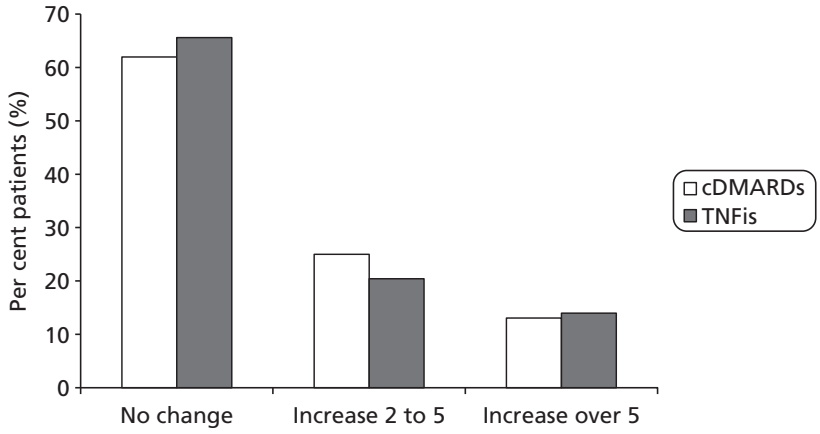

FIGURE 7 Development of new erosions over 12 months using all observed data.

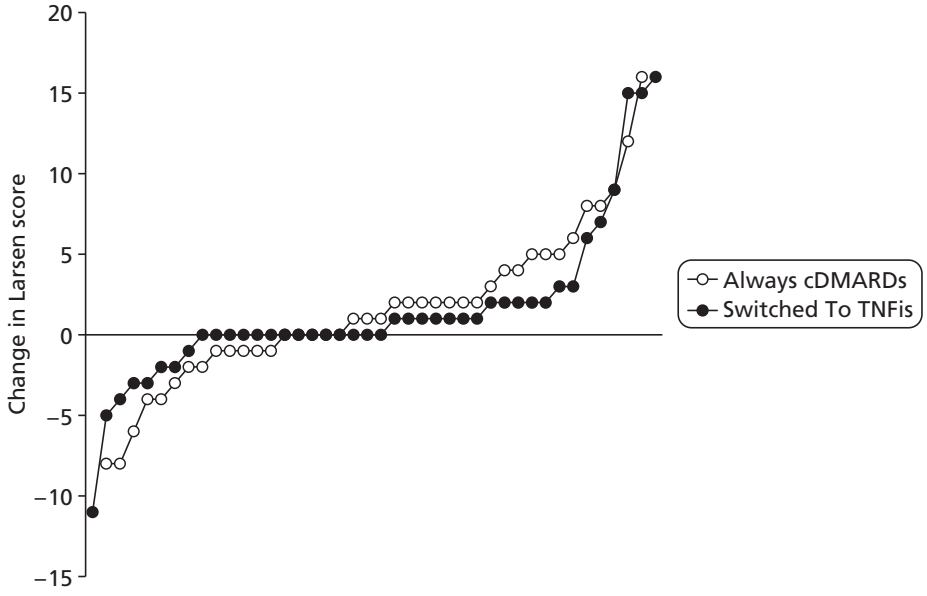

FIGURE 8 Individual changes in Larsen score over 12 months in the cDMARD group by treatment status using all observed data.

Complete-case analysis

Changes in Larsen scores were similar between patients randomised to cDMARDs and those randomised to TNFis. There was no evidence of a significant difference between groups (see *Appendix 3*, *Tables 50* and *53*).

Disease activity scores (assessed every month)

Outcomes that were collected monthly comprised the DAS28 and its components – tender joint count, swollen joint count, ESR and VAS patient global assessments. We assessed changes in DAS28 and changes in its components in the ITT population. We also assessed the occurrence of a clinical response (decrease in DAS28 of ≥ 1.2) and low DAS28 indicative of remission (DAS28 of ≤ 2.6) using all observed data; imputation was not undertaken for these summary data because evaluating clinical responses and DAS28 remissions were exploratory analyses rather than predefined analyses as explained in the statistical analysis plan (see *Chapter 2*).

Changes in Disease Activity Score for 28 Joints scores

Intention-to-treat population

Initial DAS28 were similar in both groups. In the cDMARD group the initial mean DAS28 was 6.21 (95% CI 6.04 to 6.39) and in the TNFi group the initial mean score was 6.30 (95% CI 6.14 to 6.46). The patterns of change are shown in *Table 13* and *Figure 9*.

By 6 months the DAS28 had fallen in the cDMARDs group to 4.78 (95% CI 4.45 to 5.12) and in the TNFis group to 4.23 (95% CI 3.89 to 4.58). By 12 months the DAS28 had fallen further in the cDMARDs group to 4.04 (95% CI 3.74 to 4.34) and in the TNFis group to 3.89 (95% CI 3.53 to 4.24). The initial change in DAS28 was greater in patients randomised to TNFis and there was a significant difference between groups within the first month of treatment. After 1 month the mean DAS28 in the cDMARDs group fell to 5.32 (95% CI 5.05 to 5.59) and the mean score in the TNFis group fell to 4.67 (95% CI 4.38 to 4.95, $p = 0.001$).

TABLE 13 Mean DAS28 and components scores (95% CIs) by treatment group in the ITT population

	cDMARDs ($n = 104$)					TNFis ($n = 101$)				
Month of assessment	DAS28	Tender joint count	Swollen joint count	ESR (mm/hour)	VAS	DAS28	Tender joint count	Swollen joint count	ESR (mm/hour)	VAS
0	6.21 (6.04 to 6.39)	16.38 (15.02 to 17.75)	10.51 (9.34 to 11.68)	33.14 (28.10 to 38.19)	68.13 (64.32 to 71.95)	6.30 (6.14 to 6.46)	17.48 (16.15 to 18.80)	10.79 (9.47 to 12.11)	30.13 (25.65 to 34.61)	68.18 (64.00 to 72.36)
1	5.32 (5.05 to 5.59)	11.81 (10.07 to 13.56)	6.76 (5.55 to 7.97)	32.44 (27.43 to 37.46)	54.87 (49.90 to 59.84)	4.67 (4.38 to 4.95)	10.69 (8.93 to12.46)	5.76 (4.53 to 6.99)	19.56 (15.78 to 23.34)	46.15 (41.09 to 51.20)
2	5.02 (4.76 to 5.27)	9.85 (8.36 to 11.34)	5.72 (4.72 to 6.72)	30.23 (25.51 to 34.95)	51.96 (47.22 to 56.70)	4.30 (3.98 to 4.61)	7.84 (6.47 to 9.21)	5.02 (3.74 to 6.31)	21.54 (17.27 to 25.81)	43.18 (38.14 to 48.22)
3	4.92 (4.63 to 5.21)	9.97 (8.36 to 11.59)	5.37 (4.26 to 6.47)	30.10 (24.81 to 35.39)	50.94 (45.74 to 56.15)	4.28 (3.95 to 4.60)	7.71 (6.12 to 9.31)	4.43 (3.27 to 5.59)	23.44 (19.08 to 27.80)	43.16 (38.10 to 48.23)
4	4.73 (4.45 to 5.02)	8.40 (7.03 to 9.78)	4.91 (3.85 to 5.97)	31.20 (26.05 to 36.36)	45.38 (39.69 to 51.07)	4.31 (3.97 to 4.64)	8.16 (6.54 to 9.78)	4.07 (2.95 to 5.20)	22.23 (18.31 to 26.15)	45.40 (39.48 to 51.31)
5	4.66 (4.36 to 4.96)	8.51 (6.98 to 10.04)	5.44 (4.33 to 6.55)	29.87 (24.95 to 34.79)	43.62 (37.87 to 49.37)	4.13 (3.81 to 4.44)	7.75 (6.06 to 9.45)	4.38 (3.15 to 5.62)	20.51 (16.96 to 24.06)	40.60 (35.02 to 46.18)
6	4.78 (4.45 to 5.12)	10.16 (8.39 to 11.93)	6.11 (4.74 to 7.49)	29.25 (24.16 to 34.33)	48.25 (42.42 to 54.09)	4.23 (3.89 to 4.58)	8.57 (6.87 to 10.27)	4.66 (3.41 to 5.90)	21.80 (17.64 to 25.96)	40.51 (34.98 to 46.03)
7	4.57 (4.27 to 4.87)	8.34 (6.68 to 10.01)	5.76 (4.53 to 7.00)	28.21 (23.03 to 33.39)	42.51 (36.95 to 48.07)	4.17 (3.81 to 4.53)	8.01 (6.35 to 9.67)	4.64 (3.34 to 5.93)	21.01 (17.18 to 24.85)	40.73 (34.72 to 46.73)
8	4.25 (3.92 to 4.59)	7.42 (5.98 to 8.85)	4.54 (3.43 to 5.64)	24.14 (19.29 to 28.99)	41.30 (35.45 to 47.14)	4.05 (3.69 to 4.41)	6.62 (5.14 to 8.09)	4.23 (3.04 to 5.42)	21.77 (17.57 to 25.97)	42.56 (36.91 to 48.22)
9	4.21 (3.87 to 4.56)	6.93 (5.40 to 8.47)	3.99 (2.98 to 5.00)	25.47 (20.57 to 30.37)	41.56 (35.78 to 47.35)	4.08 (3.73 to 4.42)	6.68 (5.14 to 8.22)	4.30 (3.07 to 5.52)	22.92 (18.62 to 27.21)	40.86 (35.36 to 46.36)
10	4.05 (3.73 to 4.37)	6.17 (4.74 to 7.60)	3.69 (2.78 to 4.61)	25.42 (20.44 to 30.40)	38.33 (33.02 to 43.65)	3.90 (3.56 to 4.24)	6.51 (4.90 to 8.12)	3.42 (2.33 to 4.51)	21.48 (17.34 to 25.62)	39.33 (33.64 to 45.03)
11	4.03 (3.74 to 4.31)	6.67 (5.09 to 8.25)	3.27 (2.31 to 4.24)	23.28 (18.69 to 27.87)	40.64 (34.69 to 46.59)	3.84 (3.48 to 4.20)	6.16 (4.57 to 7.76)	3.50 (2.25 to 4.75)	22.01 (17.73 to 26.28)	37.69 (31.82 to 43.56)
12	4.04 (3.74 to 4.34)	6.32 (4.88 to 7.77)	3.39 (2.63 to 4.14)	25.03 (20.41 to 29.65)	39.21 (33.23 to 45.19)	3.89 (3.53 to 4.24)	6.81 (5.22 to 8.40)	3.20 (2.25 to 4.14)	20.32 (16.04 to 24.59)	43.03 (36.79 to 49.27)

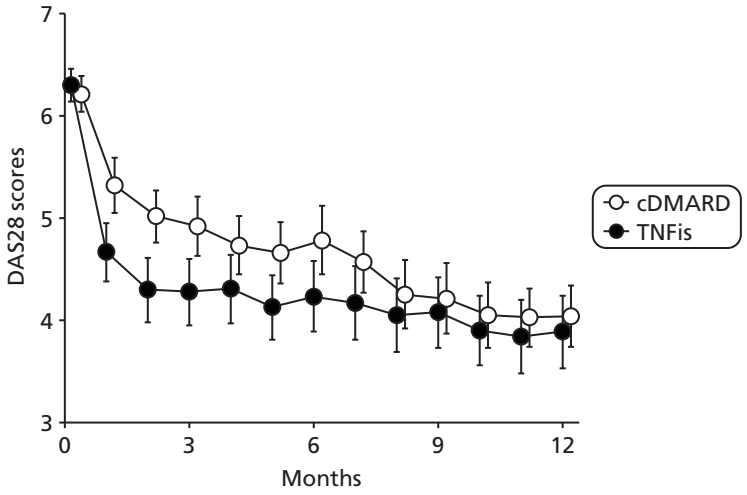

FIGURE 9 Mean DAS28 (95% CIs) by treatment group in the ITT population.

Longitudinal analysis (*Table 14*) showed that there was a significant difference between treatment groups over the whole 12-month period. Patients randomised to TNFis achieved greater overall reductions in DAS28 than those randomised to cDMARDs in both the unadjusted model (–0.48, 95% CI –0.79 to –0.17; $p = 0.002$) and the adjusted model (–0.40, 95% CI –0.69 to –0.10; $p = 0.009$). Comparing the initial and final treatment periods in the adjusted model showed a difference in the pattern of change. In the first 6 months there was a greater reduction in DAS28 in patients randomised to TNFis than in patients randomised to cDMARDs, with a coefficient of –0.63 (95% CI –0.93 to –0.34, $p < 0.001$).

TABLE 14 Longitudinal analysis of treatment effects on disease activity: analysis of changes in DAS28 and its components using GEEs in the ITT population

		Model 1 (unadjusted): treatment + region + time		Model 2 (adjusted): treatment + demographics + baseline score	
Time period	Variable	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
Months 1–6	DAS28	–0.68 (–0.99 to –0.37)	< 0.001	–0.63 (–0.93 to –0.34)	< 0.001
	Tender joint count	–2.42 (–4.22 to –0.63)	0.008	–1.79 (–3.31 to –0.26)	0.022
	Swollen joint count	–1.35 (–2.76 to 0.07)	0.062	–1.16 (–2.20 to –0.12)	0.029
	ESR (mm/hour)	–6.46 (–10.23 to –2.68)	0.001	–7.18 (–10.60 to –3.76)	< 0.001
	VAS	–6.97 (–13.10 to –0.84)	0.026	–6.41 (–11.66 to –1.15)	0.017
Months 7–12	DAS28	–0.31 (–0.69 to 0.07)	0.111	–0.19 (–0.55 to 0.18)	0.317
	Tender joint count	–1.10 (–3.22 to 1.01)	0.307	–0.13 (–1.79 to 1.53)	0.879
	Swollen joint count	–0.69 (–2.27 to 0.88)	0.388	–0.31 (–1.36 to 0.75)	0.570
	ESR (mm/hour)	–1.63 (–5.88 to 2.62)	0.452	–2.15 (–5.73 to 1.44)	0.241
	VAS	0.60 (–6.47 to 7.67)	0.867	2.04 (–4.08 to 8.17)	0.513
Months 1–12	DAS28	–0.48 (–0.79 to –0.17)	0.002	–0.40 (–0.69 to –0.10)	0.009
	Tender joint count	–1.69 (–3.50 to 0.11)	0.066	–0.93 (–2.36 to 0.51)	0.205
	Swollen joint count	–0.86 (–2.27 to 0.55)	0.233	–0.63 (–1.57 to 0.31)	0.186
	ESR (mm/hour)	–4.04 (–7.67 to –0.40)	0.029	–4.62 (–7.77 to –1.47)	0.004
	VAS	–2.83 (–8.85 to 3.20)	0.358	–1.96 (–7.04 to 3.11)	0.448

Demographics variables are age, sex, ethnicity, disease duration and region. The reference group is cDMARDs.

In the second period there was no difference between groups, with a coefficient of –0.19 (95% CI –0.55 to 0.18, $p = 0.317$).

Complete-case analysis

Mean DAS28 fell in both groups with treatment (see *Appendix 3*, *Table 56* and *Figure 30*). Longitudinal analysis using GEEs showed that the decreases were significantly greater with TNFis (see *Appendix 3*, *Table 57*) in both the unadjusted model ($p < 0.001$) and the adjusted model ($p < 0.001$).

Changes in Disease Activity Score for 28 Joints components

Intention-to-treat population

Baseline tender joint counts, swollen joint counts, ESR and patient global assessments were similar in both groups and they all improved when patients received either cDMARDs or TNFis. The patterns of change are shown in *Table 13* and *Figures 10* and *11*.

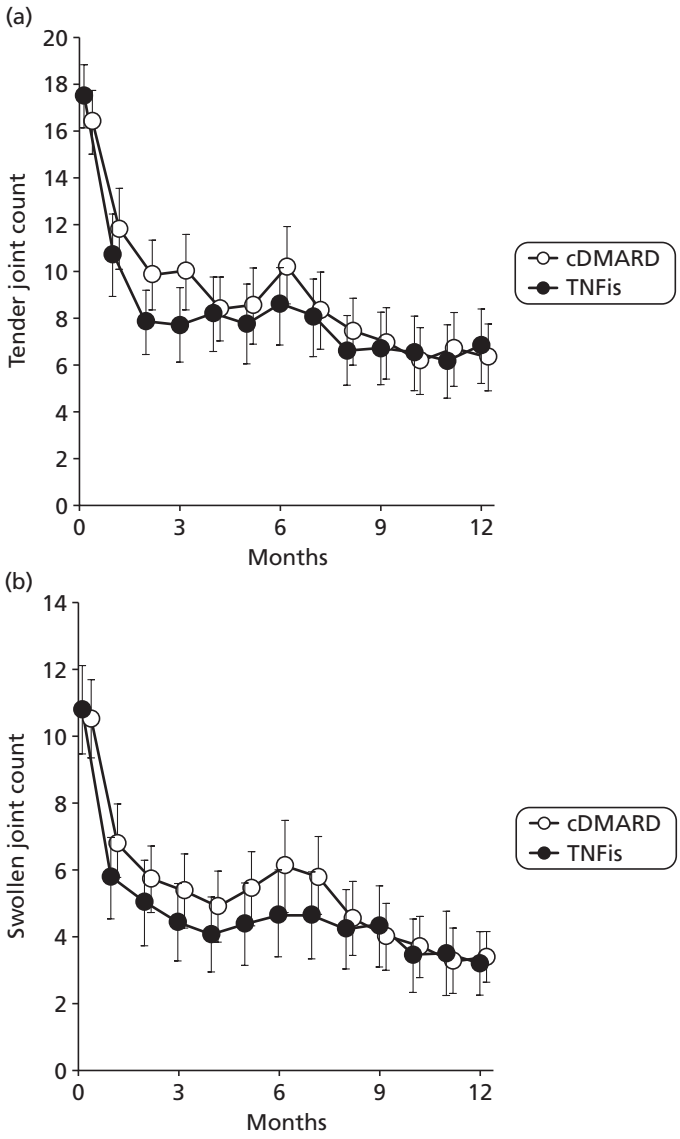

FIGURE 10 Mean tender and swollen joint counts (95% CIs) by treatment group in the ITT population. (a) Tender joints; and (b) swollen joints.

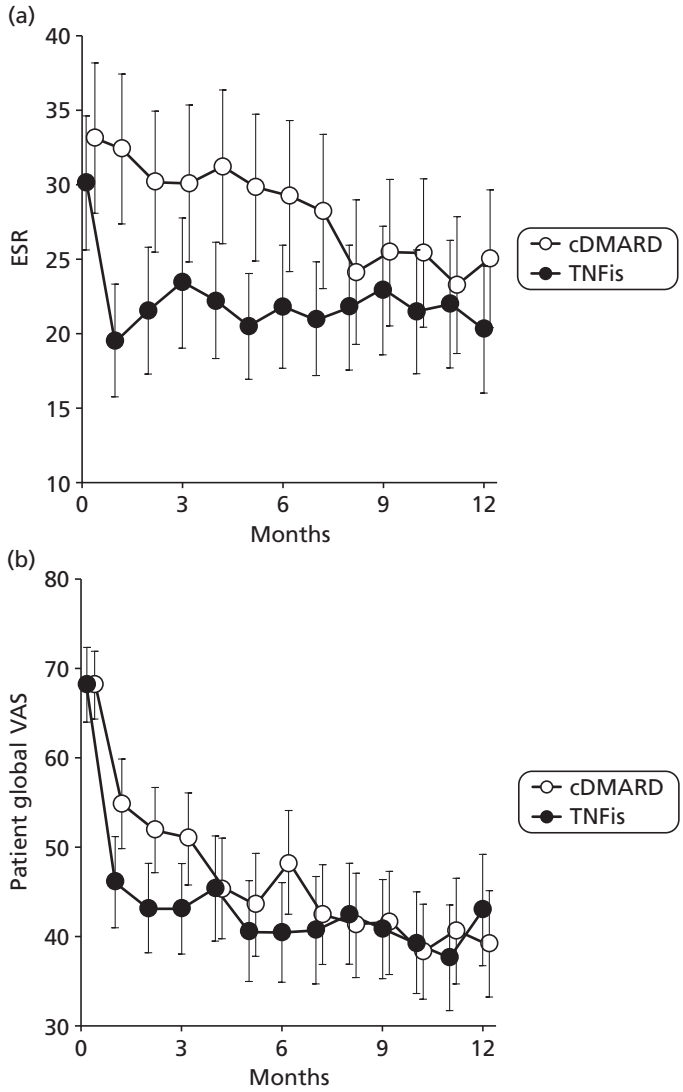

FIGURE 11 Mean ESR (mm/hour) and patient global VAS (95% CIs) by treatment group in the ITT population. (a) ESR; (b) patient global VAS.

Longitudinal analysis (see *Table 14*) showed that in the overall adjusted model changes in ESR were significantly different between patients randomised to cDMARDs and those randomised to TNFis; the decrease in ESR was significantly larger in the TNFis group (coefficient −4.62, 95% CI −7.77 to −1.47; $p = 0.004$). There were no significant differences between treatment groups in the other components over the whole 6 months.

In the first 6 months of treatment the adjusted mean treatment effects for all of the components were significantly greater in patients randomised to TNFis than in those randomised to cDMARDs. In the second 6 months there were no statistically significant differences between the groups.

The speed of onset of changes was particularly marked for the ESR in patients randomised to TNFis. With cDMARDs the ESR fell from an initial mean of 33.1 (95% CI 28.1 to 38.2) mm/hour to 32.4 (95% CI 27.4 to 37.5) mm/hour by 1 month. With TNFis the ESR fell from an initial mean of 30.1 (95% CI 25.7 to 34.6) mm/hour to 19.6 (95% CI 15.8 to 23.3) mm/hour by 1 month.

Complete-case analysis

Tender joint counts, swollen joint counts, ESR and patient global assessments improved in both patients receiving cDMARDs and patients receiving TNFis (see *Appendix 3*, *Table 56*). Longitudinal analysis (see *Appendix 3*, *Table 57*) showed that the improvements were significantly greater in the TNFis group for tender joint counts, swollen joint counts and ESR in both the unadjusted model and the adjusted model.

The effects of patients in the combination disease-modifying antirheumatic drug group switching to tumour necrosis factor inhibitors

Patients were selected to switch from cDMARDs to TNFis after 6 months if the change in DAS28 was < 1.2. As a consequence, the mean DAS28 for the switchers would be expected to be more than that in those who remained on cDMARDs. This difference is shown in *Table 15*, together with changes in the individual components of the DAS28, and is also illustrated in *Figure 12*. The difference is confirmed to be significant in the longitudinal analysis shown in *Table 16*. The adjusted model showed a significant reduction in DAS28 in the switchers. The same effect was seen for the components of the DAS28 and was most marked for tender joint count and patient global VAS score.

Achieving a clinical response

Time to achieve a response

An exploratory analysis examined the time taken to achieve a clinically meaningful response – a decrease in DAS28 of ≥ 1.2. The time to achieve a clinically meaningful response was compared between the groups using Kaplan–Meier plots (*Figure 13*). In total, 98 of 104 patients (94%) randomised to receive cDMARDs and 94 of 101 patients (93%) randomised to receive TNFis achieved such responses. The responses occurred sooner in the patients randomised to TNFis and this difference was significant in a log-rank test ($p = 0.035$). Patients randomised to receive cDMARDs who had a clinically meaningful DAS28 response achieved it within a mean of 3 months. Patients randomised to receive TNFis who had a clinically meaningful DAS28 response achieved it within a mean of 2 months.

Persistence of response

There was a complex pattern of achieving responses. In some patients the response was persistent and in others it was unsustained. Examples of these variations are shown in *Figure 14* for four patients randomised to the TNFi group. As a consequence of these variations we evaluated the frequency of response each month in the two treatment groups (*Figure 15*). There was a different pattern of response in the two groups. Patients randomised to cDMARDs showed a gradual increase in the rate of response from $\leq 45\%$ at 3 months or earlier to $> 70\%$ by 10 months. By contrast, patients randomised to TNFis achieved a response rate of $> 70\%$ by 2 months and the response rate remained at $> 70\%$ thereafter, with the highest response rate achieved in this group being 84% (achieved at month 11).

Impact of switching from combination disease-modifying antirheumatic drugs to tumour necrosis factor inhibitors

There was a difference in response rate between the patients randomised to cDMARDs who remained on cDMARDs and those who were randomised to cDMARDs but who switched to TNFis (*Figure 16*). Patients remaining on cDMARDs had a response rate of $> 50\%$ from 2 months onwards and after 6 months the response rate increased to $> 70\%$. Those patients who switched to TNFis had an initial response rate of $< 50\%$ and the response rate did not increase to 70% until 10 months.

TABLE 15 Mean DAS28 and component scores (95% CIs) in the ITT population cDMARD group ($n = 104$) by treatment status

	Stayed on cDMARDs ($n = 58$)					Changed to TNFis ($n = 46$)				
Month of assessment	DAS28	Tender joint count	Swollen joint count	ESR (mm/hour)	VAS	DAS28	Tender joint count	Swollen joint count	ESR (mm/hour)	VAS
0	6.10 (5.84 to 6.35)	15.05 (13.11 to16.99)	9.95 (8.45 to 11.44)	34.07 (27.29 to 40.85)	69.50 (64.19 to 74.81)	6.36 (6.12 to 6.60)	18.07 (16.24 to 19.89)	11.22 (9.34 to 13.10)	31.98 (24.26 to 39.70)	66.41 (60.88 to 71.95)
1	5.06 (4.69 to 5.42)	10.14 (7.78 to 12.49)	5.72 (4.39 to 7.06)	32.76 (26.01 to 39.50)	52.23 (45.54 to 58.92)	5.66 (5.26 to 6.05)	13.92 (11.39 to 16.46)	8.07 (5.93 to 10.21)	32.05 (24.35 to 39.74)	58.21 (50.74 to 65.68)
2	4.74 (4.40 to 5.07)	8.17 (6.33 to 10.00)	4.70 (3.49 to 5.92)	30.11 (24.05 to 36.18)	49.69 (43.34 to 56.05)	5.37 (4.99 to 5.75)	11.97 (9.64 to 14.30)	7.01 (5.38 to 8.64)	30.38 (22.77 to 37.98)	54.81 (47.50 to 62.13)
3	4.64 (4.27 to 5.01)	8.54 (6.58 to 10.50)	4.59 (3.08 to 6.09)	28.94 (21.86 to 36.03)	48.80 (41.44 to 56.16)	5.27 (4.81 to 5.72)	11.77 (9.12 to 14.42)	6.35 (4.69 to 8.00)	31.55 (23.45 to 39.66)	53.65 (46.32 to 60.98)
4	4.51 (4.15 to 4.87)	7.04 (5.44 to 8.64)	3.80 (2.59 to 5.00)	31.11 (23.79 to 38.43)	44.47 (36.92 to 52.02)	5.01 (4.54 to 5.49)	10.13 (7.78 to 12.47)	6.32 (4.52 to 8.12)	31.32 (24.17 to 38.47)	46.52 (37.63 to 55.41)
5	4.27 (3.90 to 4.65)	6.43 (4.64 to 8.23)	3.64 (2.46 to 4.81)	29.31 (22.87 to 35.76)	39.13 (31.94 to 46.32)	5.15 (4.68 to 5.62)	11.13 (8.73 to 13.53)	7.72 (5.85 to 9.59)	30.57 (22.88 to 38.27)	49.28 (40.01 to 58.55)
6	4.01 (3.61 to 4.40)	6.27 (4.35 to 8.19)	3.20 (1.78 to 4.62)	27.66 (20.92 to 34.40)	37.26 (29.75 to 44.78	5.76 (5.32 to 6.19)	15.07 (12.47 to 17.66)	9.78 (7.65 to 11.91)	31.24 (23.35 to 39.14)	62.11 (54.51 to 69.71)
7	4.09 (3.71 to 4.46)	5.85 (3.79 to 7.90)	3.91 (2.40 to 5.41)	28.87 (21.57 to 36.18)	38.04 (30.16 to 45.92)	5.18 (4.74 to 5.61)	11.49 (8.97 to 14.01)	8.11 (6.25 to 9.97)	27.37 (20.00 to 34.74)	48.15 (40.36 to 55.93)
8	4.13 (3.68 to 4.58)	6.26 (4.51 to 8.00)	3.55 (2.23 to 4.86)	24.88 (18.17 to 31.58)	42.35 (34.19 to 50.50)	4.41 (3.91 to 4.92)	8.87 (6.54 to 11.21)	5.79 (3.97 to 7.60)	23.20 (16.01 to 30.40)	39.97 (31.60 to 48.34)
9	4.15 (3.69 to 4.62)	5.75 (3.87 to 7.63)	3.46 (2.12 to 4.81)	26.58 (20.08 to 33.07)	43.31 (34.89 to 51.73)	4.29 (3.78 to 4.80)	8.43 (6.02 to 10.84)	4.64 (3.03 to 6.26)	24.07 (16.40 to 31.74)	39.36 (31.28 to 47.44)
10	3.91 (3.48 to 4.34)	5.23 (3.51 to 6.96)	3.35 (2.11 to 4.59)	25.67 (18.55 to 32.80)	37.16 (29.52 to 44.81)	4.23 (3.75 to 4.72)	7.35 (5.03 to 9.67)	4.12 (2.77 to 5.48)	25.10 (18.29 to 31.92)	39.81 (32.33 to 47.29)
11	3.87 (3.48 to 4.25)	5.44 (3.54 to 7.33)	2.63 (1.40 to 3.85)	22.65 (16.69 to 28.61)	40.56 (31.84 to 49.27)	4.23 (3.77 to 4.69)	8.22 (5.66 to 10.78)	4.09 (2.53 to 5.65)	24.08 (16.79 to 31.38)	40.74 (32.36 to 49.13)
12	3.91 (3.52 to 4.31)	5.37 (3.66 to 7.08)	2.87 (1.83 to 3.91)	26.39 (20.45 to 32.33)	38.33 (29.89 to 46.78	4.19 (3.73 to 4.66)	7.52 (5.08 to 9.97)	4.04 (2.93 to 5.15)	23.33 (15.89 to 30.76)	40.32 (31.89 to 48.75)

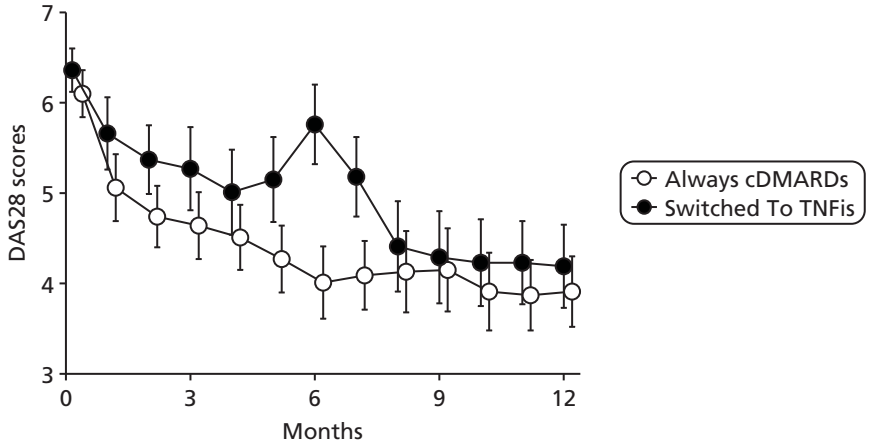

FIGURE 12 Disease Activity Score for 28 Joints mean scores (95% CIs) in patients in the cDMARD group ($n = 104$) by treatment status in the ITT population.

TABLE 16 Longitudinal analysis of treatment effects on disease activity in the cDMARD group ($n = 104$) by treatment status: analysis of changes in DAS28 and its components using GEEs in the ITT population

	Model 1 (unadjusted): treatment + region + time		Model 2 (adjusted): treatment + demographics + baseline score	
Variable	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
DAS28	0.35 (–0.03 to 0.74)	0.071	0.51 (0.16 to 0.86)	0.005
Tender joint count	0.69 (–1.47 to 2.85)	0.532	2.42 (0.75 to 4.10)	0.004
Swollen joint count	0.97 (–1.04 to 2.97)	0.344	1.94 (0.65 to 3.22)	0.003
ESR (mm/hour)	2.54 (–2.65 to 7.73)	0.338	2.44 (–1.97 to 6.84)	0.278
VAS	10.26 (2.70 to 17.83)	0.008	8.29 (2.14 to 14.44)	0.008

Demographics variables are age, sex, ethnicity, disease duration and region. The reference group is no switch.

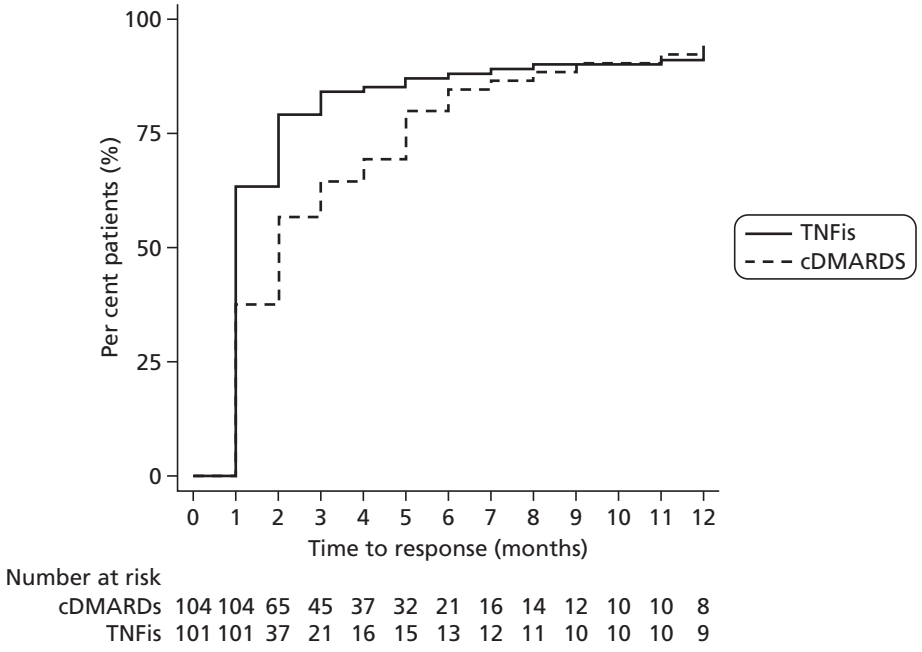

FIGURE 13 Time to achieve a response by treatment group. Kaplan–Meier plot of patients showing a reduction in DAS28 of ≥ 1.2 using all observed data.

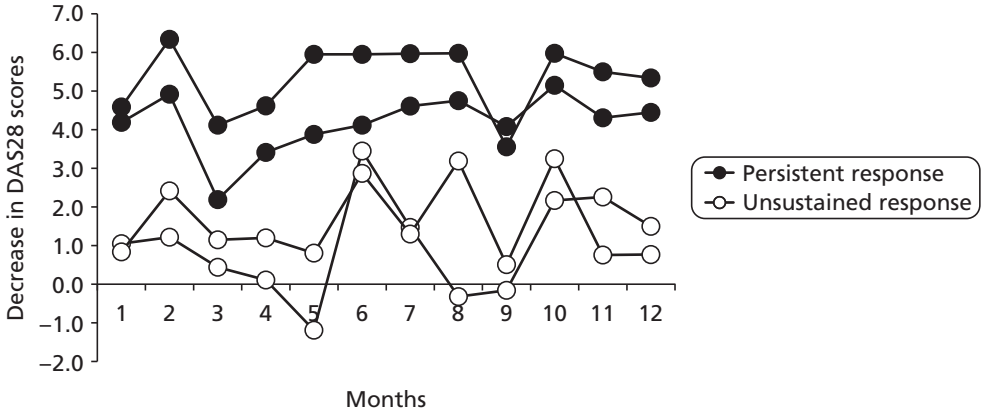

FIGURE 14 Examples of persistent and unsustained responses in four patients randomised to the TNFi group.

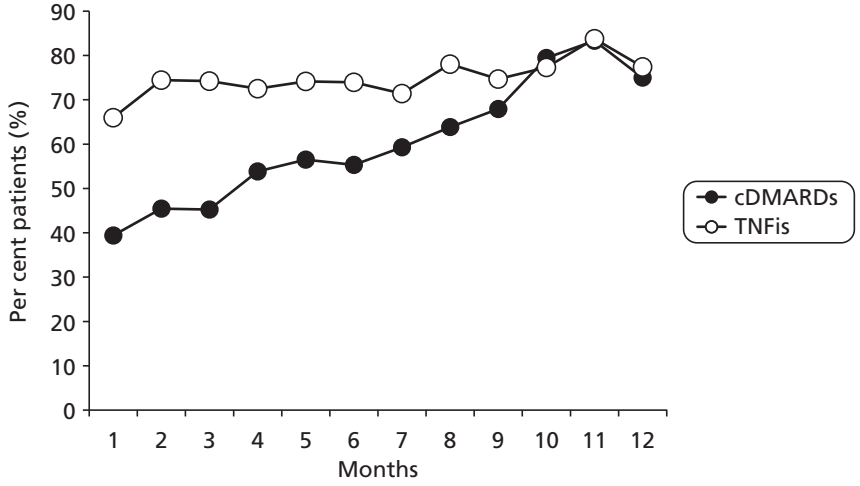

FIGURE 15 Frequency of response by treatment group: patients with a reduction in DAS28 of ≥ 1.2 using all observed data.

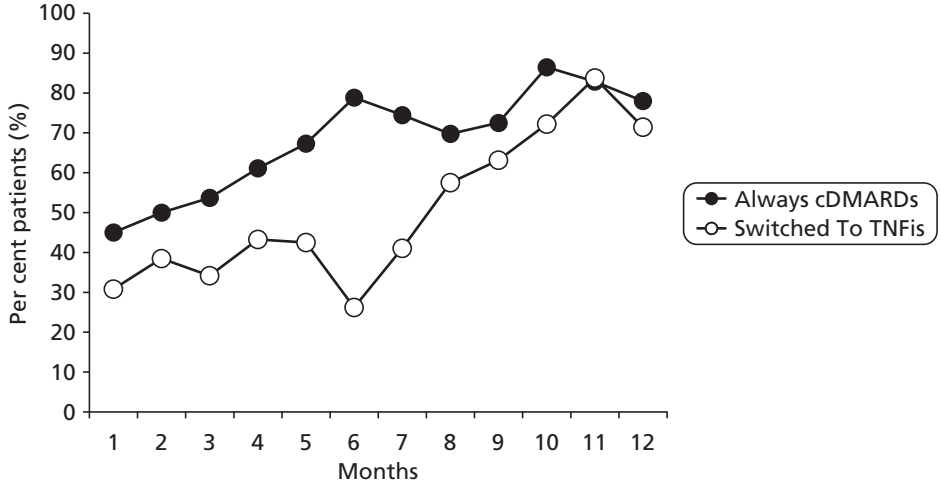

FIGURE 16 Frequency of response in cDMARD patients by treatment status: patients with a reduction in DAS28 of ≥ 1.2 using all observed data.

Achieving a Disease Activity Score for 28 Joints of ≤ 2.6

Time to achieve a Disease Activity Score for 28 Joints of ≤ 2.6

The time taken to achieve remission (DAS28 of ≤ 2.6) was compared using Kaplan–Meier plots (*Figure 17*). In total, 36 out of 104 patients (35%) randomised to receive cDMARDs and 44 out of 101 patients (44%) randomised to receive TNFis achieved remission at any time. There was no evidence that the speed of onset of remission was significantly different between groups ($p = 0.085$). Those patients randomised to receive both cDMARDs and TNFis who achieved DAS28 remission achieved it within a mean of 4 months.

Persistence of Disease Activity Score for 28 Joints of ≤ 2.6

There was a complex pattern of achieving remission. In some patients remission was persistent and in others it was unsustained. Examples of these variations are shown in *Figure 18* for four patients randomised to the TNFi group. As a consequence of these variations we have also evaluated the frequency of response each month for each group (*Figure 19*). There was a different pattern of response between the groups. Patients randomised to cDMARDs showed a gradual increase in the rate of response from ≤ 5% at 3 months or earlier to a maximum of 20% by 12 months. By contrast, those patients randomised to TNFis had achieved a remission rate of 16% by 3 months, which gradually increased to a maximum of 32% by 11 months.

Impact of switching from combination disease-modifying antirheumatic drugs to tumour necrosis factor inhibitors

There was a difference in response rate between the patients randomised to cDMARDs who remained on cDMARDs and those randomised to cDMARDs who switched to TNFis (*Figure 20*). In both groups < 10% of patients achieved a DAS28 of ≤ 2.6 at ≤ 5 months. From 6 to 12 months between 13% and 24% of patients remaining on cDMARDs and between 5% and 21% of patients who switched to TNFis achieved a DAS28 of ≤ 2.6.

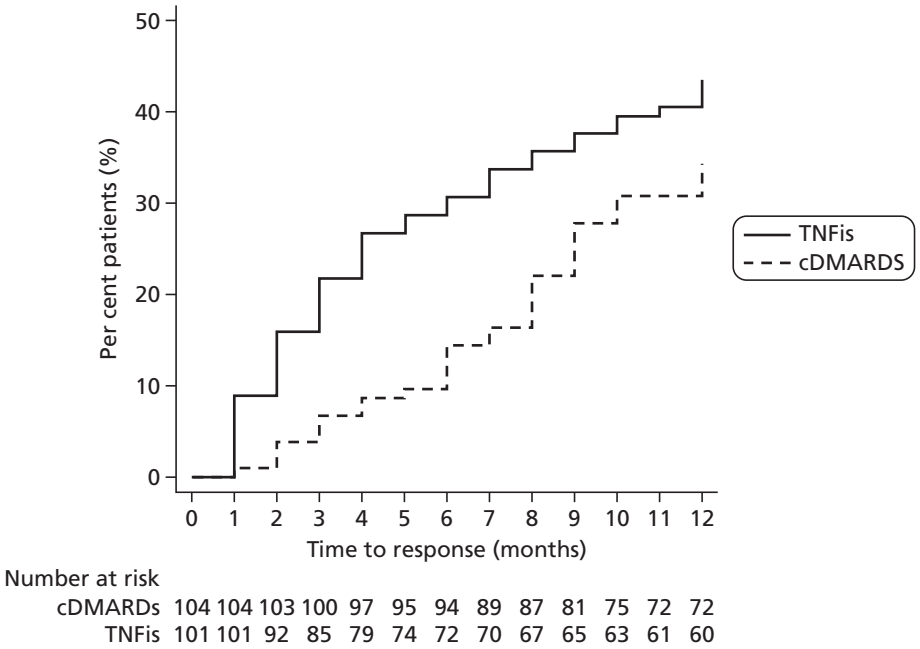

FIGURE 17 Time to achieve DAS28 remission by treatment group. Kaplan–Meier plot of time to achieve a DAS28 of ≤ 2.6 using all observed data.

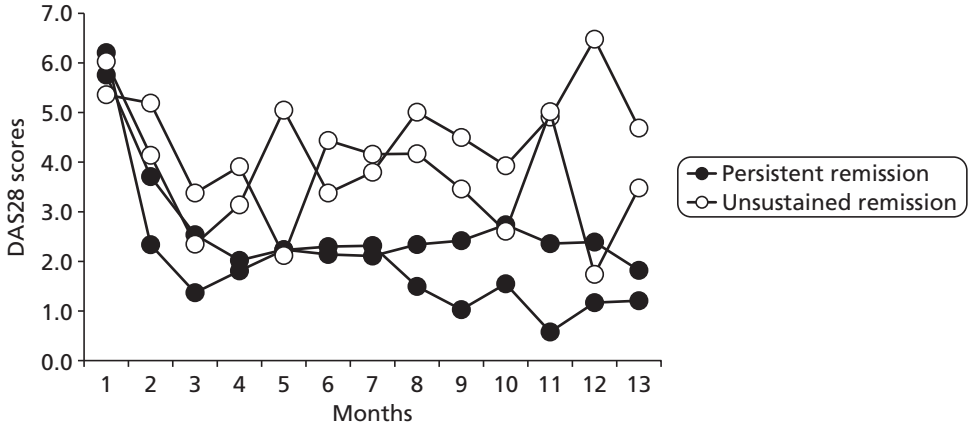

FIGURE 18 Examples of persistent and unsustained responses in four patients randomised to the TNFi group.

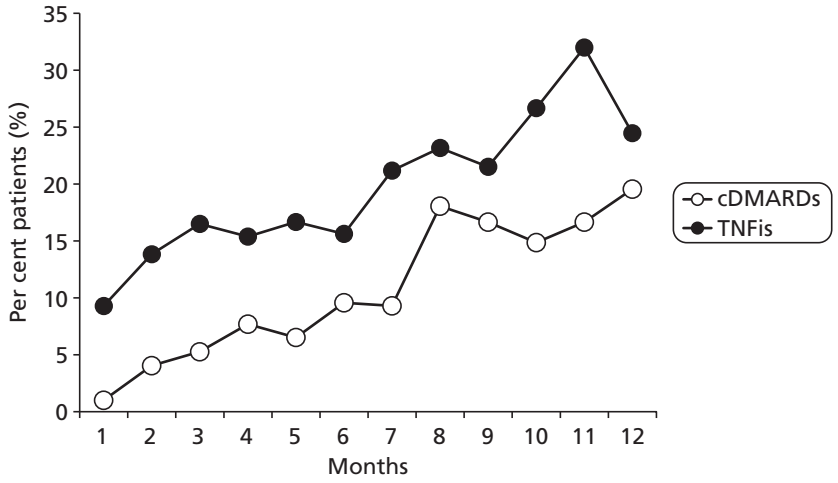

FIGURE 19 Frequency of response by treatment group: patients with a DAS28 of ≤ 2.6 using all observed data.

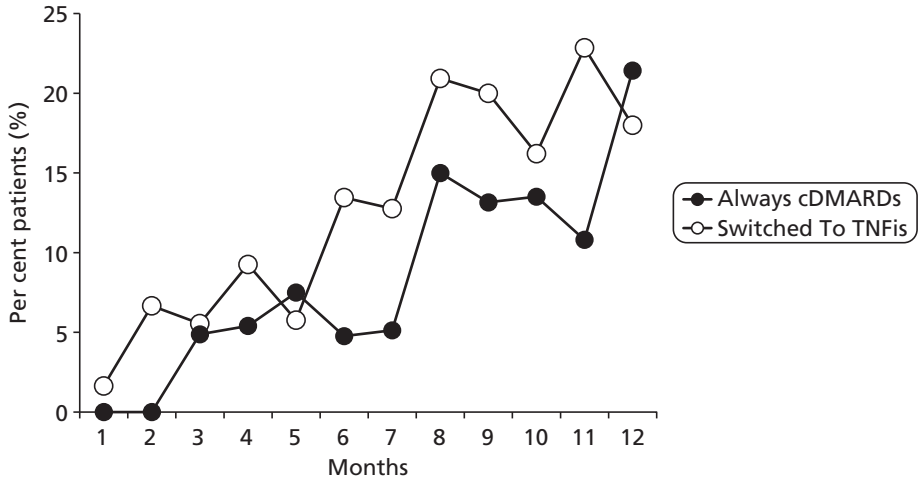

FIGURE 20 Frequency of remission in cDMARD patients by treatment status: patients with a DAS28 of ≤ 2.6 using all observed data.

Adverse events

Serious adverse events

In total, 10 patients in the cDMARDs group had a serious adverse event, eight in the first 6 months and two in the second 6 months (*Table 17*). Seven of these serious adverse events involved or prolonged inpatient treatment. In the TNFis group, 19 patients had a serious adverse event, six in the first 6 months and 13 in the second 6 months; 13 of these serious adverse events involved or prolonged inpatient treatment. One patient in the TNFi group died from pneumonia and multiple organ failure during the second 6 months of treatment. Cardiovascular, respiratory, digestive and genitourinary systems were most commonly involved. Although there were more serious adverse events in the TNFi group, there was no evidence of major clinically important differences between the treatment groups and the frequency of adverse events was not significantly different (Fisher's exact test $p = 0.110$).

Stopping treatment because of adverse events

In total, 10 out of 104 patients (10%) in the cDMARD arm and six out of 101 patients (6%) in the TNFi arm stopped treatment because of toxicity (see *Figure 1*). Although more patients withdrew from treatment because of toxicity in the cDMARDs arm, there was no evidence of major clinically important differences between the treatment groups and the frequency of withdrawals because of adverse events as this was not significantly different (Fisher's exact test $p = 0.441$).

Individual adverse events

There were 635 different adverse events reported by patients in the cDMARD group. The most frequent events are listed in *Table 18* and they are grouped by system involved in *Table 19*. All reported events are listed in *Appendix 4*.

TABLE 17 All serious adverse events

	cDMARDs			TNFis		
Adverse event	0–6 months	6–12 months	Total	0–6 months	6–12 months	Total
Cardiovascular	2	0	2	1	1	2
Digestive	0	0	0	2	2	4
Ear, nose and throat	0	0	0	0	1	1
Endocrine/metabolic	0	0	0	1	0	1
Genitourinary	3	0	3	0	1	1
Haematological	1	0	1	0	1	1
Mental	0	0	0	0	0	0
Musculoskeletal	0	0	0	0	1	1
Nervous system	0	1	1	1	1	2
Ophthalmological	0	0	0	0	0	0
Respiratory	2	1	3	1	2	3
Skin	0	0	0	0	2	2
Total	8	2	10	6	12	18
Patient died	0	0	0	0	1	1
Involved/prolonged inpatient hospitalisation	5	2	7	5	8	13
Life-threatening	1	0	1	0	1	1

TABLE 18 Most common adverse events[a]

Adverse event	No. of events	Percentage of total no. of adverse events
cDMARDs group		
Diarrhoea	30	4.7
Headache	30	4.7
Nausea	26	4.1
Vomiting	26	4.1
Chest infection	19	3.0
Flare of RA	17	2.7
Sore throat	15	2.4
Cold	12	1.9
Ulcers – mouth	12	1.9
Fatigue	11	1.7
Dizziness	9	1.4
Elevated alanine aminotransferase	7	1.1
Flu	7	1.1
High blood pressure	7	1.1
Itchy skin	7	1.1
Low white cell count	7	1.1
TNFis group		
Chest infection	27	5.8
Cold	16	3.4
Elevated alanine aminotransferase	16	3.4
Headache	15	3.2
Flare of RA	14	3.0
Sore throat	13	2.8
Diarrhoea	12	2.6
Urinary tract infection	9	1.9
Nausea	8	1.7
Breathlessness	7	1.5
Cold sore	7	1.5
Shoulder pain	6	1.3
Upper respiratory tract infection	6	1.3
Chest pain	5	1.1
Cough – productive	5	1.1
Fatigue	5	1.1
Injection site reaction	5	1.1
Vaginal thrush	5	1.1
Knee pain	5	1.1

a Adverse events accounting for > 1% of the total events are shown.

TABLE 19 All adverse events

Adverse event	cDMARDs group	TNFis group
Cardiovascular	22	17
Digestive	148	60
Ear, nose and throat	88	76
Endocrine/metabolic	7	7
Genitourinary	28	27
Haematological	25	10
Mental	24	15
Musculoskeletal	104	94
Nervous system	61	41
Ophthalmological	12	5
Respiratory	59	66
Skin	57	47
Total	635	465

There were 465 different adverse events reported by patients in the TNFis group. The most frequent events are listed in *Table 18* and they are grouped by system involved in *Table 19*. All reported events are listed in *Appendix 4*.

Chest infections (46 events), headaches (45 events), diarrhoea (42 events), nausea (34 events), sore throats (28 events), colds (28 events), elevated liver enzymes (alanine aminotransferase) (23 events) and fatigue (16 events) were the most common adverse events across both groups. Some types of adverse events spanned systems, in particular infections, which accounted for 112 adverse events in the cDMARDs group and 117 in the TNFis group.

There was no evidence of any major clinically important differences between the two treatment groups. However, the cDMARDs group had 37% more adverse events overall (635 vs. 465). This difference was mainly due to there being 88 more adverse events related to the digestive system (148 vs. 60) and 20 more adverse events related to the nervous system (61 vs. 41) in the cDMARDs group.

Economic evaluation

Response rates

The response rates for the CSRI and outcome questionnaires and the availability of trial medication data are summarised in *Tables 20–22* respectively. These were > 90% and were similar for all of the questionnaires at baseline and 6 and 12 months and across both trial arms.

Table 23 summarises the joint availability of both cost and outcome data (a requirement for the construction of CEACs) by outcome measure. In total, 191 of the 205 study participants (93%) had both cost and outcome data at 6 months' follow-up and 186–188 of the 205 study participants (91–92%) had both cost and outcome data at 12 months' follow-up. There were thus very few cases excluded from the available case analyses.

Tables 24–26 suggest that there were no notable differences in characteristics between the subsamples included in the available case analyses and the full sample.

TABLE 20 Client Service Receipt Inventory response rates

	Baseline		6 months		12 months	
Group	*n*	%	*n*	%	*n*	%
TNFis ($n = 101$)	101	100	97	96	93	92
cDMARDs ($n = 104$)	104	100	94	90	95	91
Total ($n = 205$)	205	100	191	93	188	92

TABLE 21 Health Assessment Questionnaire, EQ-5D and SF-36 response rates

	Baseline		6 months		12 months	
Group	*n*	%	*n*	%	*n*	%
HAQ						
TNFis ($n = 101$)	101	100	97	96	94	93
cDMARDs ($n = 104$)	104	100	94	90	95	91
Total ($n = 205$)	205	100	191	93	189	92
EQ-5D						
TNFis ($n = 101$)	101	100	97	96	93	92
cDMARDs ($n = 104$)	104	100	94	90	94	90
Total ($n = 205$)	205	100	191	93	187	91
SF-36						
TNFis ($n = 101$)	101	100	97	96	94	93
cDMARDs ($n = 104$)	104	100	94	90	95	91
Total ($n = 205$)	205	100	191	93	189	92

TABLE 22 Availability of trial medication data

	6 months		12 months	
Group	*n*	%	*n*	%
TNFis ($n = 101$)	97	96	94	93
cDMARDs ($n = 104$)	97	93	96	92
Total ($n = 205$)	194	95	190	93

TABLE 23 Availability of cost and outcome data by outcome measure

	6 months		12 months	
Group	*n*	%	*n*	%
HAQ				
TNFis ($n = 101$)	97	96	93	92
cDMARDs ($n = 104$)	94	90	95	91
Total ($n = 205$)	191	93	188	92
EQ-5D				
TNFis ($n = 101$)	97	96	92	91
cDMARDs ($n = 104$)	94	90	94	90
Total ($n = 205$)	191	93	186	91
SF-36				
TNFis ($n = 101$)	97	96	93	92
cDMARDs ($n = 104$)	94	90	95	91
Total ($n = 205$)	191	93	188	92

TABLE 24 Characteristics of the full sample and the subsample with cost and HAQ data

	Full sample ($N = 205$)		Subsample with 6-month cost and HAQ data ($N = 191$)		Subsample with 12-month cost and HAQ data ($N = 188$)	
Characteristic	*n*	%	*n*	%	*n*	%
Sex						
Male	53	26	45	24	46	25
Female	152	74	146	76	142	76
Ethnicity						
White	181	88	168	88	164	87
Other	24	12	23	12	24	13
Region						
London and south	128	62	127	67	121	64
Midlands	16	8	13	7	13	7
North	61	30	51	27	54	29
	Mean	SD	Mean	SD	Mean	SD
Age (years)	57.34	11.97	57.11	11.94	56.91	12.02
Duration of illness (years)	8.20	8.82	8.35	8.98	8.24	8.88
HAQ score at baseline	1.85	0.63	1.86	0.63	1.85	0.64

TABLE 25 Characteristics of the full sample and the subsample with cost and EQ-5D data

	Full sample ($N = 205$)		Subsample with 6-month cost and EQ-5D data ($N = 191$)		Subsample with 12-month cost and EQ-5D data ($N = 186$)	
Characteristic	***n***	**%**	***n***	**%**	***n***	**%**
Sex						
Male	53	26	45	24	45	24
Female	152	74	146	76	141	76
Ethnicity						
White	181	88	168	88	162	87
Other	24	12	23	12	24	13
Region						
London and south	128	62	127	67	121	65
Midlands	16	8	13	7	11	6
North	61	30	51	27	54	29
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	57.34	11.97	57.11	11.94	56.84	12.08
Duration of illness (years)	8.20	8.82	8.35	8.98	8.25	8.92
HAQ score at baseline	1.85	0.63	1.86	0.63	1.85	0.64
EQ-5D-based utility at baseline	0.37	0.31	0.37	0.31	0.37	0.31

TABLE 26 Characteristics of the full sample and the subsample with cost and SF-36 data

	Full sample ($N = 205$)		Subsample with 6-month cost and EQ-5D data ($N = 191$)		Subsample with 12-month cost and EQ-5D data ($N = 186$)	
Characteristic	***n***	**%**	***n***	**%**	***n***	**%**
Sex						
Male	53	26	45	24	46	25
Female	152	74	146	76	142	76
Ethnicity						
White	181	88	168	88	164	87
Other	24	12	23	12	24	13
Region						
London and south	128	62	127	67	121	64
Midlands	16	8	13	7	13	7
North	61	30	51	27	54	29
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	57.34	11.97	57.11	11.94	56.91	12.02
Duration of illness (years)	8.20	8.82	8.35	8.98	8.24	8.88
HAQ score at baseline	1.85	0.63	1.86	0.63	1.85	0.64
SF-36-based utility at baseline	0.54	0.11	0.54	0.11	0.54	0.11

Resource use

Resource use differences between the groups were not compared statistically, first, because the economic evaluation was focused on costs and cost-effectiveness/utility and, second, to avoid problems associated with multiple testing. Therefore, resource use patterns are described in *Tables 27–29* without statistical comparisons. Use of services appeared similar in both groups at all three time points. General practitioner (GP) surgery visits, practice nurse surgery visits, repeat prescription requests and hospital outpatient

TABLE 27 Resource use at baseline (in previous 3 months)

		cDMARDs group ($n = 94$)			TNFis group ($n = 97$)		
Resource use	Unit	No. of users	Mean use[a]	SD	No. of users	Mean use[a]	SD
GP							
At surgery	Visit	70	2	2	73	3	2
At home	Visit	3	1	1	3	1	1
Telephone call	Call	16	2	1	15	2	1
Repeat prescription request without GP contact	Prescription	93	3	2	92	3	2
Nurse							
At surgery	Visit	42	3	4	50	2	2
Telephone call	Call	6	1	< 1	7	1	< 1
Physiotherapist							
At hospital	Unit	7	2	2	9	2	1
At home	Visit	0	–	–	1	3	–
At GP surgery	Visit	2	11	13	1	3	–
Elsewhere	Visit	0	–	–	0	–	–
Occupational therapist							
At hospital	Unit	5	4	5	5	1	1
At home	Visit	3	2	1	5	1	1
At GP surgery	Visit	0	–	–	0	–	–
Elsewhere	Visit	0	–	–	2	2	< 1
Hospital services							
A&E	Unit	9	1	< 1	6	1	< 1
Hospital stay overnight	Night	4	2	1	3	12	6
Outpatient appointment	Unit	77	3	2	85	3	2
Social services							
Meals on Wheels	Meal	0	–	–	0	–	–
Home help	Visit	0	–	–	1	90	–
Social worker	Hour	0	–	–	2	3	1
Social worker telephone call	Call	0	–	–	3	1	< 1
Other health or social service	Contact	1	1	< 1	4	3	2
Non-trial medication	Medication	102	–	–	100	–	–

A&E, accident and emergency.
a Mean for users only.

TABLE 28 Resource use at 6 months' follow-up (in previous 3 months)

		cDMARDs group ($n = 94$)			TNFis group ($n = 97$)		
Resource use	Unit	No. of users	Mean use[a]	SD	No. of users	Mean use[a]	SD
GP							
At surgery	Visit	42	2	1	55	2	1
At home	Visit	2	1	< 1	3	2	1
Telephone call	Call	9	2	1	14	1	1
Repeat prescription request without GP contact	Prescription	63	3	1	70	3	1
Nurse							
At surgery	Visit	31	3	3	31	3	4
Telephone call	Call	2	2	1	2	1	< 1
Physiotherapist							
At hospital	Unit	8	4	3	4	3	1
At home	Visit	0	–	–	0	–	–
At GP surgery	Visit	2	3	< 1	1	1	–
Elsewhere	Visit	0	–	–	2	2	1
Occupational therapist							
At hospital	Unit	4	2	1	3	1	1
At home	Visit	2	1	< 1	4	1	< 1
At GP surgery	Visit	0	–	–	0	–	–
Elsewhere	Visit	1	1	–	0	–	–
Hospital services							
A&E	Unit	4	1	< 1	9	1	< 1
Hospital stay overnight	Unit/night	4	4	5	5	7	5
Outpatient appointment	Unit	55	3	2	58	3	1
Social services							
Meals on Wheels	Meal	1	60	–	0	–	–
Home help	Visit	1	1	–	2	46	63
Social worker	Hour	3	1	1	3	1	1
Social worker telephone call	Call	1	2	–	1	3	–
Other health or social service	Contact	3	31	51	3	14	11
Non-trial medication	Medication	88	–	–	94	–	–

A&E, accident and emergency.
a Mean for users only.

TABLE 29 Resource use at 12 months' follow-up (in previous 3 months)

		cDMARDs group ($n = 104$)			TNFis group ($n = 101$)		
Resource use	Unit	No. of users	Mean use[a]	SD	No. of users	Mean use[a]	SD
GP							
At surgery	Visit	60	2	1	58	2	2
At home	Visit	4	2	1	3	1	1
Telephone call	Call	16	1	1	13	1	1
Repeat prescription request without GP contact	Prescription	68	3	2	61	2	1
Nurse							
At surgery	Visit	24	2	1	31	2	2
Telephone call	Call	2	1	< 1	5	2	1
Physiotherapist							
At hospital	Unit	11	5	6	7	3	2
At home	Visit	0	–	–	0	–	–
At GP surgery	Visit	1	8	–	2	3	3
Elsewhere	Visit	1	1	–	1	2	–
Occupational therapist							
At hospital	Unit	6	2	1	1	1	–
At home	Visit	1	1	–	1	1	–
At GP surgery	Visit	0	–	–	0	–	–
Elsewhere	Visit	1	1	–	1	3	–
Hospital services							
A&E	Unit	10	1	< 1	5	1	1
Hospital stay overnight	Unit/night	5	2	1	2	11	13
Outpatient appointment	Unit	56	2	1	55	3	2
Social services							
Meals on Wheels	Meal	0	–	–	0	–	–
Home help	Visit	0	–	–	3	31	51
Social worker	Hour	1	1	–	2	2	< 1
Social worker telephone call	Call	2	2	1	1	1	–
Other health or social service	Service	2	19	16	2	1	< 1
Non-trial medication	Contact	90	–	–	91	–	–

A&E, accident and emergency.
a Mean for users only.

appointments were common in both groups at all time points, with other service use being relatively rare. The number of participants using non-trial medications was also similar in both groups at all time points.

Data on the use of NHS/social services-funded transport, equipment and home adaptations (costs of which are excluded from cost calculations) are presented in *Table 30*.

Costs

Cost components at baseline, 6 months and 12 months are summarised in *Table 31*. Costs for both groups were equivalent at baseline. Costs of social security benefits and employment losses are small compared to the cost of health and social care. At 6 and 12 months' follow-up all cost components remained equivalent between groups except for the cost of trial medications, which was significantly lower in the cDMARDs group (6-month adjusted mean difference −£3637, 95% CI −£3838 to −£3420; 12-month adjusted mean difference −£1894, 95% CI −£2320 to −£1427). The additional trial medication cost in the TNFis group overshadowed all other cost components in that group.

The increase in trial medication costs in the cDMARDs group between 6 and 12 months was due to a significant proportion of this group switching to the more expensive TNFis at 6 months because of non-response to cDMARDs by 6 months. Switching in the reverse direction was uncommon (a total of four participants) and so trial medication costs in the TNFis group did not fall a great deal between 6 and 12 months.

Table 32 shows total costs at 6 and 12 months from a health and social care perspective and the two societal perspectives that we adopted (with and without social security benefit costs). All figures (including those for trial medication) represent a 3-month period. The cDMARDs group has significantly lower total costs from all perspectives at both follow-up points. The difference is greater at 6 months than at 12 months because of the greater trial medication cost differential before switching taking place.

TABLE 30 Use of NHS/social services-funded transport, equipment and home adaptations at baseline and 6 and 12 months

	cDMARDs group			TNFis group		
Resource use	No. of users/ total no.	No. paid by NHS	No. paid by social services	No. of users/ total no.	No. paid by NHS	No. paid by social services
Baseline						
Transport	5/104	4	1	3/101	2	1
Equipment	4/104	1	3	2/101	0	2
Home adaptations	4/104	1	3	1/101	0	1
Other	2/104	1	1	3/101	1	2
6 months						
Transport	6/94	6	0	4/97	3	1
Equipment	2/94	0	2	4/97	0	4
Home adaptations	4/94	2	2	3/97	0	3
Other	0/94	0	0	2/97	0	2
12 months						
Transport	2/95	2	0	6/93	6	0
Equipment	3/95	1	2	2/93	0	2
Home adaptations	1/95	1	0	3/93	0	3
Other	1/95	0	1	1/93	0	1

TABLE 31 Cost components at baseline and 6 and 12 months

	TNFis group ($N = 101$)			cDMARDs group ($N = 104$)			Unadjusted difference[a]		Adjusted difference[b]	
Cost component	Valid *n*	Mean cost (£)	SD (£)	Valid *n*	Mean cost (£)	SD (£)	Mean (£)	95% CI (£)	Mean (£)	95% CI (£)
Costs at baseline										
Health and social care, excluding trial medication[c]	101	736	1082	104	601	476	−131	−379 to 97	–	–
Employment losses[c]	101	60	262	104	84	440	24	−66 to 131	–	–
Social security benefits[c]	101	71	76	104	63	67	−9	−29 to 12	–	–
Costs at 6 months										
Health and social care, excluding trial medication[c]	97	536	947	94	511	705	−27	−262 to 202	6	−217 to 206
Employment losses[c]	97	71	405	94	35	310	−35	−127 to 67	−35	−115 to 59
Social security benefits[c]	97	77	75	94	74	77	−2	−21 to 21	3	−15 to 19
Trial medication[d]	97	4166	1012	97	510	356	−3660[e]	−3855 to −3432	−3637[e]	−3838 to −3420
Costs at 12 months										
Health and social care, excluding trial medication[c]	95	659	1699	93	583	634	−74	−486 to 255	−24	−363 to 230
Employment losses[c]	93	19	132	95	2	18	−16	−46 to 2	−17	−42 to 2
Social security benefits[c]	93	85	83	95	77	84	−6	−32 to 16	5	−12 to 23
Trial medication[d]	96	3546	1631	94	1547	1547	−1988[e]	−2458 to −1555	−1894[e]	−2320 to −1427

a Comparisons include a covariate for region.
b Comparisons include covariates for equivalent baseline cost, baseline HAQ score, duration of illness, age, sex, region and ethnicity.
c Costs in the previous 3 months.
d Costs in the previous 6 months.
e Statistically significant.

Note
The most expensive treatment is shown first.

TABLE 32 Total costs at 6 and 12 months

Perspective	TNFis group (*N* = 101)			cDMARDs group (*N* = 104)			Unadjusted difference[a]		Adjusted difference[b]	
	Valid *n*	Mean cost (£)	SD (£)	Valid *n*	Mean cost (£)	SD (£)	Mean (£)	95% CI (£)	Mean (£)	95% CI (£)
Costs at 6 months										
Health and social care perspective, including trial medication	97	2547	1083	94	793	703	−1757[c]	−2006 to −1500	−1708[c]	−1973 to −1483
Societal perspective, including trial medication but excluding social security benefits	97	2617	1145	94	828	791	−1793[c]	−2050 to −1519	−1742[c]	−2024 to −1506
Societal perspective, including trial medication and social security benefits	97	2694	1148	94	902	802	−1794[c]	−2055 to −1515	−1742[c]	−2023 to −1506
Costs at 12 months										
Health and social care perspective, including trial medication	93	2411	1608	95	1493	1089	−907[c]	−1327 to −524	−817[c]	−1170 to −481
Societal perspective, including trial medication but excluding social security benefits	93	2430	1645	95	1494	1088	−924[c]	−1351 to −540	−840[c]	−1205 to −501
Societal perspective, including trial medication and social security benefits	93	2515	1637	95	1571	1100	−930[c]	−1363 to −541	−841[c]	−1200 to −508

a Comparisons include a covariate for region.
b Comparisons include covariates for equivalent baseline cost, baseline HAQ score, duration of illness, age, sex, region and ethnicity.
c Statistically significant.
All costs are for a 3-month retrospective period for all cost components, including trial medication.
Note
The most expensive treatment is shown first.

Costs from each of the societal perspectives are similar to those from a health and social care perspective because of the dominance of trial medication costs.

For the purpose of combining cost and outcome data for the cost-effectiveness/cost–utility analyses, all costs were equivalised to 6-month values. Trial medication costs were available for the 0- to 6-month and 7- to 12-month periods so all other costs were multiplied by 2 to represent 6-month rather than 3-month periods. The extrapolated figures are shown in *Table 33*. Imputing missing cost data (based on the extrapolated costs) for those lost to follow-up confirmed the findings from the unimputed available case analysis (*Table 34*).

Outcomes

The cDMARDs arm had an advantage of four points based on the SF-36-based utility scores at baseline but this did not carry through as an advantage in (baseline-adjusted) utility scores at either of the two follow-up points or in the resulting QALY estimates (*Table 35*). The cDMARDs group did, however, show advantages in terms of the HAQ and EQ-5D-based utility scores at 12 months, although the latter did not translate into an advantage in terms of the QALYs estimated from the EQ-5D. As with cost data, imputing missing outcome data for those lost to follow-up did not alter the conclusions from the available case analyses (*Table 36*).

TABLE 33 Costs extrapolated to 6-month periods for the cost-effectiveness and cost–utility analyses

	TNFis group ($N = 101$)			cDMARDs group ($N = 104$)			Unadjusted difference[a]		Adjusted difference[b]	
Perspective	Valid *n*	Mean cost (£)	SD (£)	Valid *n*	Mean cost (£)	SD (£)	Mean (£)	95% CI (£)	Mean (£)	95% CI (£)
Costs at 6 months										
Health and social care perspective, including trial medication	97	5238	2093	94	1538	1393	−3703[c]	−4175 to −3199	−3615[c]	−4104 to −3182
Societal perspective, including trial medication but excluding social security benefits	97	5379	2236	94	1607	1569	−3774[c]	−4298 to −3230	−3683[c]	−4198 to −3195
Societal perspective, including trial medication and social security benefits	97	5533	2241	94	1755	1591	−3778[c]	−4303 to −3230	−3684[c]	−4199 to −3194
Costs at 12 months										
Health and social care perspective, including trial medication	93	4866	3147	95	2718	1890	−2129[c]	−2941 to −1417	−1930[c]	−2599 to −1301
Societal perspective, including trial medication but excluding social security benefits	93	4904	3218	95	2722	1890	−2162[c]	−2977 to −1449	−1974[c]	−2648 to −1334
Societal perspective, including trial medication and social security benefits	93	5073	3208	95	2876	1914	−2175[c]	−2991 to −1465	−1977[c]	−2644 to −1338

a Comparisons include a covariate for region.
b Comparisons include covariates for equivalent baseline cost, baseline HAQ score, duration of illness, age, sex, region and ethnicity.
c Statistically significant.
Note
The most expensive treatment is shown first.

TABLE 34 Costs extrapolated to 6-month periods based on imputed data for the cost-effectiveness and cost–utility analyses

	TNFis group ($N = 101$)			cDMARDs group ($N = 104$)			Unadjusted difference[a]		Adjusted difference[b]	
Perspective	Valid *n*	Mean cost (£)	SD (£)	Valid *n*	Mean cost (£)	SD (£)	Mean (£)	95% CI (£)	Mean (£)	95% CI (£)
Costs at 6 months[c]										
Health and social care perspective, including trial medication	101	5234	2052	104	1520	1329	−3717[e]	−4205 to −32556	−3615[e]	−4067 to −3198
Societal perspective, including trial medication but excluding social security benefits	101	5373	2192	104	1594	1496	−3780[e]	−4341 to −3288	−3688[e]	−4195 to −3232
Societal perspective, including trial medication and social security benefits	101	5527	2197	104	1743	1518	−3784[e]	−4348 to −3298	−3691[e]	−4194 to −3246
Costs at 12 months[d]										
Health and social care perspective, including trial medication	101	4874	3023	104	2729	1816	−2137[e]	−2838 to −1516	−1937[e]	−2612 to −1353
Societal perspective, including trial medication but excluding social security benefits	101	4910	3092	104	2728	1818	−2173[e]	−2895 to −1535	−1971[e]	−2648 to −1377
Societal perspective, including trial medication and social security benefits	101	5080	3082	104	2887	1840	−2182[e]	−2885 to −1543	−1976[e]	−2668 to −1368

a Comparisons include a covariate for region.
b Comparisons include covariates for equivalent baseline cost, baseline HAQ score, duration of illness, age, sex, region and ethnicity.
c Missing data at 6 months imputed from baseline HAQ score, duration of illness, age, sex, region, ethnicity and trial arm as well as equivalent baseline costs.
d Missing data at 12 months imputed from baseline HAQ score, duration of illness, age, sex, region, ethnicity and trial arm as well as equivalent baseline costs plus equivalent 6-month costs.
e Statistically significant.

Note
The most expensive treatment is shown first.

TABLE 35 Outcomes at baseline and 6 and 12 months

	TNFis group			cDMARDs group			Unadjusted difference[a]		Adjusted difference[b]	
Outcome	Valid *n*	Mean	SD	Valid *n*	Mean	SD	Mean	95% CI	Mean	95% CI
Utilities and HAQ score										
Baseline										
SF-36 utility	101	0.52	0.11	104	0.56	0.10	0.04[c]	0.01 to 0.07	–	–
EQ-5D utility	101	0.35	0.31	104	0.39	0.31	0.04	−0.04 to 0.12	–	–
HAQ score	101	1.90	0.67	104	1.80	0.59	−0.10	−0.28 to 0.07	–	–
6 months										
SF-36 utility	97	0.59	0.13	94	0.62	0.12	0.03	−0.01 to 0.06	0.00	−0.03 to 0.03
EQ-5D utility	97	0.53	0.30	94	0.56	0.26	0.03	−0.05 to 0.10	−0.01	−0.08 to 0.06
HAQ score	97	1.55	0.83	94	1.52	0.65	−0.03	−0.22 to 0.19	0.07	−0.08 to 0.21
12 months										
SF-36 utility	94	0.60	0.14	94	0.64	0.13	0.04[c]	0.01 to 0.08	0.03	−0.00 to 0.07
EQ-5D utility	93	0.50	0.31	94	0.60	0.28	0.10[c]	0.02 to 0.19	0.10	0.02 to 0.18[c]
HAQ score	94	1.60	0.84	95	1.33	0.77	−0.27[c]	−0.51 to −0.04	−0.16[c]	−0.32 to −0.01
QALYs										
6 months										
SF-36 QALYs	97	0.28	0.05	94	0.30	0.05	0.02	0.00 to 0.03	0.00	−0.01 to 0.01
EQ-5D QALYs	97	0.22	0.14	94	0.24	0.12	0.02	−0.02 to 0.05	0.00	−0.02 to 0.02
12 months										
SF-36 QALYs	93	0.30	0.06	87	0.32	0.05	0.02	−0.00 to 0.03	0.01	−0.00 to 0.02
EQ-5D QALYs	92	0.26	0.13	88	0.29	0.11	0.03	−0.01 to 0.06	0.02	−0.01 to 0.05

a Comparisons include a covariate for region.
b Comparisons of HAQ scores include covariates for baseline HAQ score, duration of illness, age, sex, region and ethnicity; comparisons of utilities and QALYs include covariates for appropriate baseline utility, baseline HAQ score, duration of illness, age, sex, region and ethnicity.
c Statistically significant.
Note
The most expensive treatment is shown first.

TABLE 36 Outcomes for the cost-effectiveness and cost–utility analyses at 6 and 12 months: results based on imputed missing data

	TNFis group			cDMARDs group			Adjusted difference[a]		Adjusted difference[b]	
Outcome	Valid *n*	Mean	SD	Valid *n*	Mean	SD	Mean	95% CI	Mean	95% CI
6 months										
HAQ score[c]	101	1.55	0.82	104	1.51	0.64	–0.04	–0.24 to 0.16	0.07	–0.07 to 0.21
SF-36 QALYs[d]	101	0.28	0.05	104	0.29	0.05	0.02	0.00 to 0.03	0.00	–0.01 to 0.01
EQ-5D QALYs[d]	101	0.22	0.14	104	0.24	0.12	0.02	–0.02 to 0.05	–0.00	–0.02 to 0.02
12 months										
HAQ score[c]	101	1.59	0.83	104	1.35	0.74	–0.25[e]	–0.45 to –0.03	–0.16[e]	–0.30 to –0.02
SF-36 QALYs[d]	101	0.30	0.06	104	0.32	0.06	0.02	0.00 to 0.03	0.01	–0.00 to 0.02
EQ-5D QALYs[d]	101	0.26	0.13	104	0.29	0.11	0.03	–0.00 to 0.06	0.02	–0.00 to 0.05

a Comparisons include covariate for region.
b Comparisons of HAQ score include covariates for baseline HAQ score, duration of illness, age, sex, region and ethnicity; comparisons of QALYs include covariates for appropriate baseline utility, baseline HAQ score, duration of illness, age, sex, region and ethnicity.
c Missing values at 6 months imputed based on baseline HAQ score, duration of illness, age, sex, region, ethnicity and trial arm. Missing values at 12 months imputed based on the same predictors plus HAQ score at 6 months.
d Missing values at 6 months imputed based on baseline HAQ score, duration of illness, age, sex, region, ethnicity, trial arm and equivalent utility at baseline. Missing values at 12 months imputed based on the same predictors plus equivalent utility at 6 and 12 months.
e Statistically significant.

Note
The most expensive treatment is shown first.

Cost-effectiveness and cost–utility analyses

Table 37 presents the ICERs for the cost-effectiveness and cost–utility analyses based on costs from each perspective (based on extrapolations representing 6-month periods) and outcomes at 6 and 12 months. For the ICERs, the mean difference in the HAQ score was reversed (negatives turned to positives and vice versa) as a reduction in HAQ score indicates a better outcome. Of the 18 cost–outcome combinations, three showed statistically significant between-group differences for both costs and outcomes: at 12 months, the cDMARDs group dominated with the group having better outcomes (mean difference –0.16, 95% CI –0.32 to –0.01) and lower costs from a health-care perspective (mean difference –£1930, 95% CI –£2599 to –£1301), societal perspective excluding benefits (mean difference –£1974, 95% CI –£2648 to –£1334) and societal perspective including benefits (mean difference –£1977, 95% CI –£2644 to –£1338). These translated into ICERs of –£12,063, –£12,338 and –£12,356 per QALY respectively. All other cost–outcome combinations suggest that the cDMARDs group is superior, with equivalent outcomes achieved at a significantly lower cost. The conclusions remained the same when costs and outcomes for those lost to follow-up were imputed. It was not necessary to compute any ICERs as none of the combinations suggested a significantly better outcome at a significantly lower cost.

TABLE 37 Cost-effectiveness and cost–utility summary

	Cost per additional point improvement on the HAQ (£), cDMARDs vs. TNFis	Cost per additional QALY (SF-36 based) (£), cDMARDs vs. TNFis	Cost per additional QALY (EQ-5D based) (£), cDMARDs vs. TNFis
6 months			
Health and social care perspective	51,643	–3615	–3615
Societal perspective excluding benefits	52,614	–3683	–3683
Societal perspective including benefits	52,629	–3684	–3684
12 months			
Health and social care perspective	cDMARDs dominate: –12,063	–193,000	–96,500
Societal perspective excluding benefits	cDMARDs dominate: –12,338	–197,400	–98,700
Societal perspective including benefits	cDMARDs dominate: –12,356	–197,700	–98,850

Note
Only three cost–outcome combinations showed a significant difference: at 12 months the cDMARDs group had significantly lower costs and significantly better HAQ scores for all three perspectives.

Figures 21 and *22* show the probability that the cDMARDs group is cost-effective compared with the TNFis group for each outcome from a health and social care perspective at 6 and 12 months respectively. Both EQ-5D- and SF-36-based QALYs at each time point suggest that the probability that the cDMARDs group is cost-effective is ≥ 99% at all willingness-to-pay thresholds that were examined.

The probability that the cDMARDs group is cost-effective at 6 months based on the HAQ is 100% for willingness-to-pay thresholds of up to £10,000 per point improvement on the HAQ but decreases at higher willingness-to-pay thresholds. At 12 months the probability of cost-effectiveness is 100% for willingness-to-pay thresholds of up to £10,000 per point improvement on the HAQ and remains at 99% up to a threshold of £50,000.

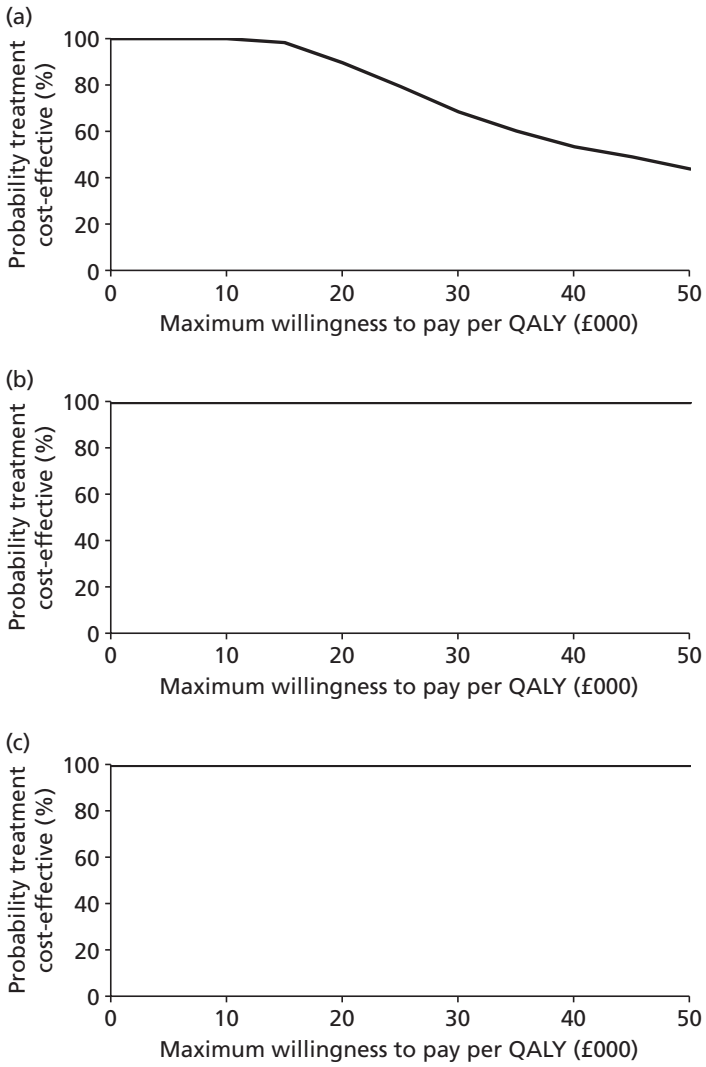

FIGURE 21 Cost-effectiveness acceptability curves at 6 months from a health and social care perspective for all outcomes. (a) HAQ; (b) SF-36; and (c) EQ-5D.

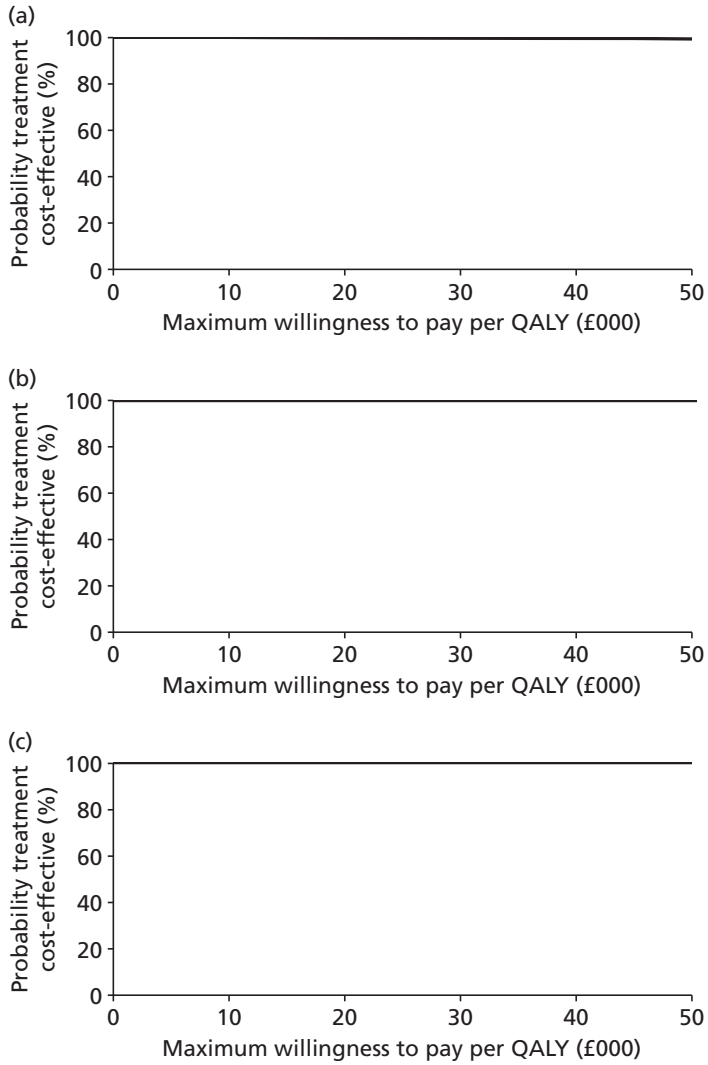

FIGURE 22 Cost-effectiveness acceptability curves at 12 months from a health and social care perspective for all outcomes. (a) HAQ; (b) SF-36; and (c) EQ-5D.

Systematic reviews

Early rheumatoid arthritis

Trials

The preliminary search identified 463 papers, of which 36 were potentially relevant trials and were selected for full-text review (*Figure 23*). Of these, four trials were excluded: one included patients with a disease duration of > 3 years, two used treatment strategies in which the same approaches were included in both arms and one used steroids with methotrexate in the control monotherapy arm. The remaining 32 trials[68,111,147,171,192–219] formed the basis of this systematic review.

The baseline characteristics of the 32 RCTs are summarised in *Table 38*. The trials randomised between 20 and 1049 patients and enrolled over 8400 patients. In total, 19 trials compared cDMARDs with methotrexate,[68,111,171,192–207] 10 trials compared TNFis/methotrexate with methotrexate monotherapy[208–217] and three trials compared cDMARDs with TNFis/methotrexate directly (head-to-head trials).[147,218,219] The Optimal Protocol for Methotrexate and Adalimumab Combination Therapy in Early Rheumatoid Arthritis (OPTIMA)[217] and High Induction Therapy with Anti-Rheumatic Drugs (HIT-HARD)[216] studies withdrew anti-TNF treatment from 24 and 26 weeks, respectively; therefore, only outcomes at 24 and 26 weeks, respectively, were considered. The BeSt[220] and Swedish Farmacotherapy (Swefot)[221] trials initially published 12-month results and subsequently 24-month results.

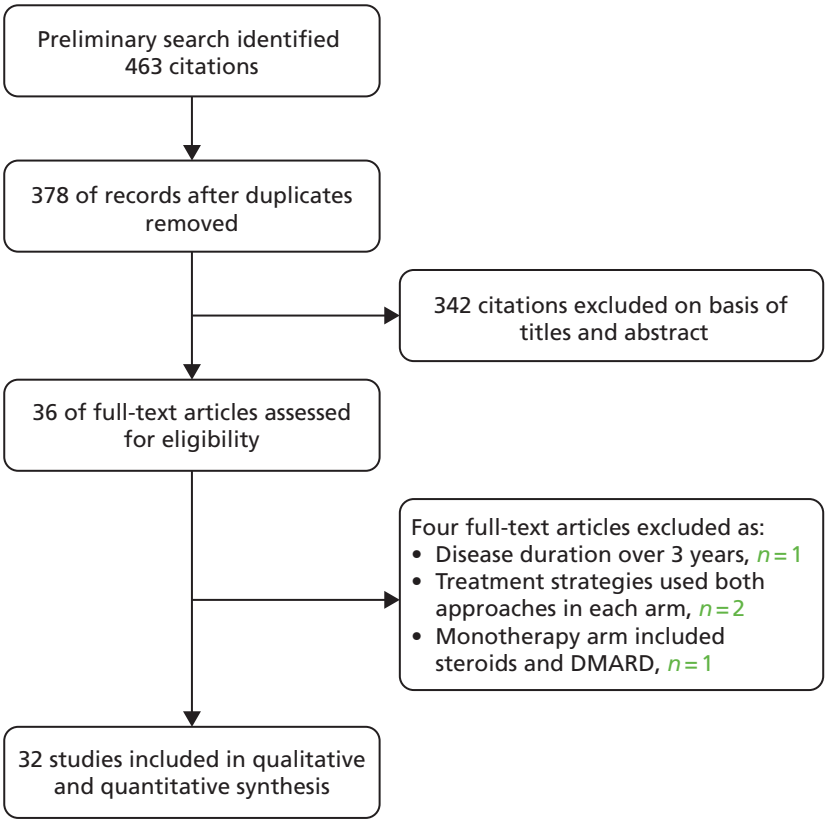

FIGURE 23 Selection of trials in early RA.

TABLE 38 Characteristics of included RCTs in early RA

Study	Year	Design	Cases	Max RA duration	Quality assessments				Follow-up	Combinations
					Allocation	Blinding	Analysed in original groups	Analysed for bias		
cDMARDs										
Boers *et al.*[68]	1997	Step-down	156	2 years	Unstated	Double	Yes	Yes	1 year	SSZ/MTX/prednisolone vs. SSZ
Haagsma *et al.*[192]	1997	Parallel	105	1 year	Unstated	Double	Yes	No	1 year	MTX/SSZ vs. SSZ vs. MTX
van den Borne *et al.*[193]	1998	Step-up	88	3 years	Central block randomisation	Double	Yes	No	0.5 years	Chloroquine/CsA vs. chloroquine
Dougados *et al.*[194]	1999	Parallel	209	1 year	Unstated	Double	Yes	No	1 year	MTX/SSZ vs. SSZ vs. MTX
Mottonen *et al.*[195]	1999	Step-down	199	2 years	Cards	Open	Yes	Yes	2 years	SSZ/MTX/HCQ/prednisolone vs. SSZ
Proudman *et al.*[196]	2000	Parallel	82	1 year	Centralised randomisation list	Open	Yes	Yes	1 year	CsA/MTX/IA methylprednisolone vs. SSZ
Ferraccioli *et al.*[197]	2002	Step-up	126	–	Unstated	Open	Yes	No	1.5 years	MTX/CsA vs. SSZ
Gerards *et al.*[198]	2003	Parallel	120	3 years	Computer generated	Double	Yes	No	1 year	CsA/MTX vs. CsA
Marchesoni *et al.*[199]	2003	Parallel	61	2 years	Randomisation list	Open	Yes	No	1 year	CsA/MTX vs. MTX
Capell *et al.*[200]	2004	Parallel	167	3 years	Unstated	Double	Yes	No	2 years	SSZ/prednisolone vs. SSZ
Grigor *et al.*[111]	2004	Step-up	111	5 years	Computer generated	Single	Yes	No	1.5 years	Intensive combinations vs. routine care
Miranda *et al.*[201]	2004	Parallel	149	2 years	Computer generated	Double	Yes	No	1 year	CsA/chloroquine vs. CsA
Ichikawa *et al.*[202]	2005	Parallel	71	2 years	Randomised by test drug number	Double	Yes	No	1.8 years	MTX/bucillamine vs. MTX vs. bucillamine
Sarzi-Puttini *et al.*[203]	2005	Parallel	105	3 years	Unstated	Open	Yes	Yes	1 year	CsA/HCQ vs. CsA/MTX vs. CsA
Svensson *et al.*[204]	2005	Parallel	259	1 year	Computer generated	Open	Yes	No	2 years	Prednisolone/DMARD vs. DMARD
Wassenberg *et al.*[205]	2005	Parallel	192	2 years	Computer generated	Double	Yes	No	2 years	Prednisolone/DMARD vs. DMARD

continued

TABLE 38 Characteristics of included RCTs in early RA (*continued*)

Study	Year	Design	Cases	Max RA duration	Quality assessments				Follow-up	Combinations
					Allocation	Blinding	Analysed in original groups	Analysed for bias		
Hetland *et al.*[206]	2006	Parallel	163	6 years	Computer generated	Double	Yes	Yes	1 years	MTX/CsA/IA beclamethasone vs. MTX/IA beclamethasone
O'Dell *et al.*[207]	2006	Parallel	66	1 year	Cards	Double	Yes	No	2 years	Doxycycline/MTX vs. MTX
Choy *et al.*[171]	2008	Step-up	467	2 years	Computer generated	Double	Yes	Yes	2 years	MTX vs. MTX + CsA vs. MTX + prednisolone vs. triple
TNFi/MTX										
Breedveld *et al.*[208]	2004	Parallel	82	3 years	Unstated	Double	Yes	No	2 years	Infliximab/MTX
St Clair *et al.*[209]	2004	Parallel	1049	3 years	Interactive voice response	Double	Yes	Yes	1 year	Infliximab/MTX
Taylor *et al.*[210]	2004	Parallel	24	3 years	Pharmacist randomisation	Double	Yes	No	1 year	Infliximab/MTX
Quinn *et al.*[211]	2005	Parallel	20	1 year	Adaptive stratified randomisation technique	Double	Yes	No	1 year	Infliximab/MTX
Breedveld *et al.*[212]	2006	Parallel	799	3 years	Unstated	Double	Yes	No	2 years	Adalimumab/MTX
Durez *et al.*[213]	2007	Parallel	44	1 year	Unstated	Open	Yes	No	1 year	Infliximab/MTX
Emery *et al.*[214]	2008	Parallel	542	2 years	Computer generated	Double	Yes	Yes	1 year	Etanercept/MTX
Soubrier *et al.*[215]	2009	Parallel	65	0.5 years	Unstated	Open	Yes	Yes	1 year	Adalimumab/MTX
Detert *et al.*[216]	2013	Parallel	172	1 year	Unstated	Double	Yes	Yes	0.5 years	Adalimumab/MTX
Kavanaugh *et al.*[217]	2013	Parallel	1032	1 year	Interactive voice response	Double	Yes	Yes	0.5 years	Adalimumab/MTX

Study	Year	Design	Cases	Max RA duration	Quality assessments				Follow-up	Combinations
					Allocation	Blinding	Analysed in original groups	Analysed for bias		
Direct comparisons										
Goekoop-Ruiterman *et al.*[147]	2005	All three	508	2 years	Variable block randomisation	Open	Yes	Yes	1 year	Step-up vs. step-down vs. infliximab
van Vollenhoven *et al.*[218]	2009	Step-up	487	1 year	Computer generated	Open	Yes	No	1 year	MTX/SSZ/HCQ vs. infliximab/MTX
Moreland *et al.*[219]	2012	Parallel	755	3 years	Computer generated	Double	Yes	Yes	2 years	MTX/SSZ/HCQ vs. etanercept/MTX

CsA, ciclosporin; HCQ, hydroxychloroquine; IA, intra-articular; MTX, methotrexate; SSZ, sulfasalazine.

Baseline characteristics

The baseline characteristics of the patients are summarised in *Table 39*. The average age ranged from 46 to 55 years in the TNFis/methotrexate RCTs, from 37 to 59 years in the cDMARDs RCTs and from 49 to 54 years in the direct comparison trials. Mean disease duration ranged from 0.5 to 3 years in the TNFis/methotrexate RCTs, from 0.5 to 3 years in the cDMARDs RCTs and from 1 to 3 years in the direct comparison trials. Not all trials reported initial DAS28; in the 14 trials in which this was recorded the mean score ranged from 4.8 to 6.7 with an overall average score of 5.58.

TABLE 39 Baseline characteristics in early RA trials in combined arms

Study	Cases	Age (years), mean (SD)	Female (%)	Baseline DAS28, mean (SD)
Indirect comparisons				
Boers *et al.*[68]	76	50 (11.9)	66	Not stated
Breedveld *et al.*[208]	82	50[a]	79	Not stated
Breedveld *et al.*[212]	268	51.9 (14)	72	6.3 (0.9)
Capell *et al.*[200]	84	55 (range 25–76)	65	Not stated
Choy *et al.*[171]	116	55	67	5.6 (1.2)
Detert *et al.*[216]	87	47 (12)	70	6.2 (0.8)
Dougados *et al.*[194]	68	52	77	DAS: 4.23
Durez *et al.*[213]	15	50 (9.9)	67	DAS28-CRP: 5.3 (1.1)
Emery *et al.*[214]	265	50.5 (0.9)	74	6.5 (1.0)
Ferraccioli *et al.*[197]	42	59 (7.7)	86	Not stated
Gerards *et al.*[198]	60	53 (10.6)	62	Not stated
Grigor *et al.*[111]	55	51 (15)	71	DAS: 4.9 (0.9)
Haagsma *et al.*[192]	36	57 (12.2)	66	DAS: 5.0 (0.8)
Hetland *et al.*[206]	60	53.2[a]	64	5.31 (1.34)
Ichikawa *et al.*[202]	24	49.1 (12.9)	71	Not stated
Kavanaugh *et al.*[217]	515	50.7 (14.5)	74	DAS28-CRP: 6.0 (1.0)
Marchesoni *et al.*[199]	30	46.6 (10.5)	93	5.2 (1.2)
Miranda *et al.*[201]	75	37 (11)	92	Not stated
Mottonen *et al.*[195]	97	47 (range 23–65)	58	Not stated
O'Dell *et al.*[207]	24	49.5	67	Not stated
Proudman *et al.*[196]	40	51 (13.7)	65	5.4 (1)
Quinn *et al.*[211]	10	51.3 (9.5)	Not stated	Not stated
Sarzi-Puttini *et al.*[203]	30	53 (10)	63	Not stated
Soubrier *et al.*[215]	65	46.3 (16.3)	79	6.31 (0.78)
St Clair *et al.*[209]	363	50 (13)	68	6.7 (1.0)
Svensson *et al.*[204]	119	51 (14)	65	5.28 (1.11)
Taylor *et al.*[210]	12	55 (11.8)	Not stated	5.4 (1.1)
van den Borne *et al.*[193]	30	51 (11.1)	73	Not stated
Wassenberg *et al.*[205]	80	53 (12.6)	75	Not stated

TABLE 39 Baseline characteristics in early RA trials in combined arms (*continued*)

Study	Cases	Age (years), mean (SD)	Female (%)	Baseline DAS28, mean (SD)
Direct comparisons				
Goekoop *et al.* (DMARDs)[147]	133	55 (14)	65	DAS44: 4.4 (0.9)
Goekoop *et al.* (TNFi/methotrexate)[147]	128	54 (14)	66	DAS44: 4.3 (0.9)
Moreland *et al.* (DMARDs)[219]	132	48.8 (12.7)	77	5.8 (1.1)
Moreland *et al.* (TNFi/methotrexate)[219]	244	50.7 (13.4)	74	5.8 (1.1)
van Vollenhoven *et al.* (DMARDs)[218]	130	52.9 (13.9)	78	4.79 (1.05)
van Vollenhoven *et al.* (TNFi/methotrexate)[218]	128	51.1 (13.3)	76	5.91 (0.93)

DAS44, Disease Activity Score for 44 Joints.
a Median.

American College of Rheumatology responses and withdrawals for inefficacy

Indirect comparisons showed that in trials of DMARD combinations (*Table 40* and *Figure 24*) more patients achieved ACR20–70 responses with combination therapy (OR 1.76–2.81) and less patients withdrew because of inefficacy with combination therapy (OR 0.47, 95% CI 0.34 to 0.64). In trials of TNFi/methotrexate combinations more patients achieved ACR20–70 responses with combination therapy (OR 1.88–2.22) and fewer patients withdrew because of inefficacy with combination therapy (OR 0.44, 95% CI 0.22 to 0.85). Sensitivity analysis of trials using only methotrexate monotherapy showed similar results.

Direct comparisons showed that there were no differences between DMARD combinations (*Table 41*) and TNFi/methotrexate with regard to ACR20 outcomes or patient withdrawals because of inefficacy. However, fewer patients achieved ACR50 and ACR70 responses using cDMARDs than using TNFi/methotrexate (ORs 0.54 and 0.53 respectively). A more detailed analysis of data from each of these trials is shown in *Figure 25*. Overall, there were small differences in favour of TNFi/methotrexate compared with cDMARDs at most time points but these were not always significant. There were also marked differences in response rates in the different trials.

Disability

In the indirect comparisons there were greater improvements in HAQ scores with both combination regimens when compared with DMARD monotherapy (OR –0.15, 95% CI –0.23 to –0.07) or methotrexate monotherapy (OR –0.17, 95% CI –0.33 to –0.01) (see *Table 40*). No RCTs that made a direct comparison between cDMARDs and TNFi/methotrexate reported HAQ outcomes.

Toxicity

Indirect comparisons (see *Table 40*) showed that more patients withdrew with DMARD combinations because of toxicity than with DMARD monotherapy (OR 1.50, 95% CI 1.11 to 2.03) or with methotrexate monotherapy (OR 2.69, 95% CI 1.49 to 4.83). There were no differences between TNFi/methotrexate and methotrexate monotherapy in terms of withdrawals because of toxicity. The direct comparisons showed no differences in patient withdrawal because of toxicity (see *Table 41*).

TABLE 40 Indirect comparisons in early RA: summary of meta-analysis of key outcomes – ACR responses, patient withdrawals, HAQ score and radiological progression

Outcome	Treatment regimen	Studies	Random-effects analyses OR (95% CI)
Categorical outcomes			
ACR20	DMARD combinations	14	1.76 (1.26 to 2.46)
	DMARD combinations (methotrexate only)	5	2.01 (1.08 to 3.72)
	TNFi/methotrexate	8	1.88 (1.61 to 2.19)
ACR50	DMARD combinations	13	2.34 (1.40 to 3.91)
	DMARD combinations (methotrexate only)	5	1.64 (1.15 to 2.34)
	TNFi/methotrexate	7	2.09 (1.80 to 2.43)
ACR70	DMARD combinations	8	2.81 (1.48 to 5.33)
	DMARD combinations (methotrexate only)	4	2.00 (1.32 to 3.02)
	TNFi/methotrexate	7	2.22 (1.78 to 2.76)
Inefficacy withdrawals	DMARD combinations	15	0.47 (0.34 to 0.64)
	DMARD combinations (methotrexate only)	7	0.52 (0.33 to 0.82)
	TNF/methotrexate	9	0.44 (0.22 to 0.85)
Toxicity withdrawals	DMARD combinations	15	1.86 (1.42 to 2.44)
	DMARD combinations (methotrexate only)	7	2.69 (1.49 to 4.83)
	TNFi/methotrexate	9	1.42 (0.87 to 2.34)
			WMD (95% CI)
Continuous outcomes			
Disability (HAQ)	DMARD combinations	7	–0.03 (–0.12 to 0.07)
	DMARD combinations (methotrexate only)	2	–0.17 (–0.33 to –0.01)
	TNFi/methotrexate	2	–0.16 (–0.24 to –0.08)
Radiological progression	DMARD combinations	7	–0.99% (–1.11% to –0.87%)
	DMARD combinations (methotrexate only)	4	–1.21% (–1.37% to –1.04%)
	TNFi/methotrexate	4	–0.61% (–0.79% to –0.43%)

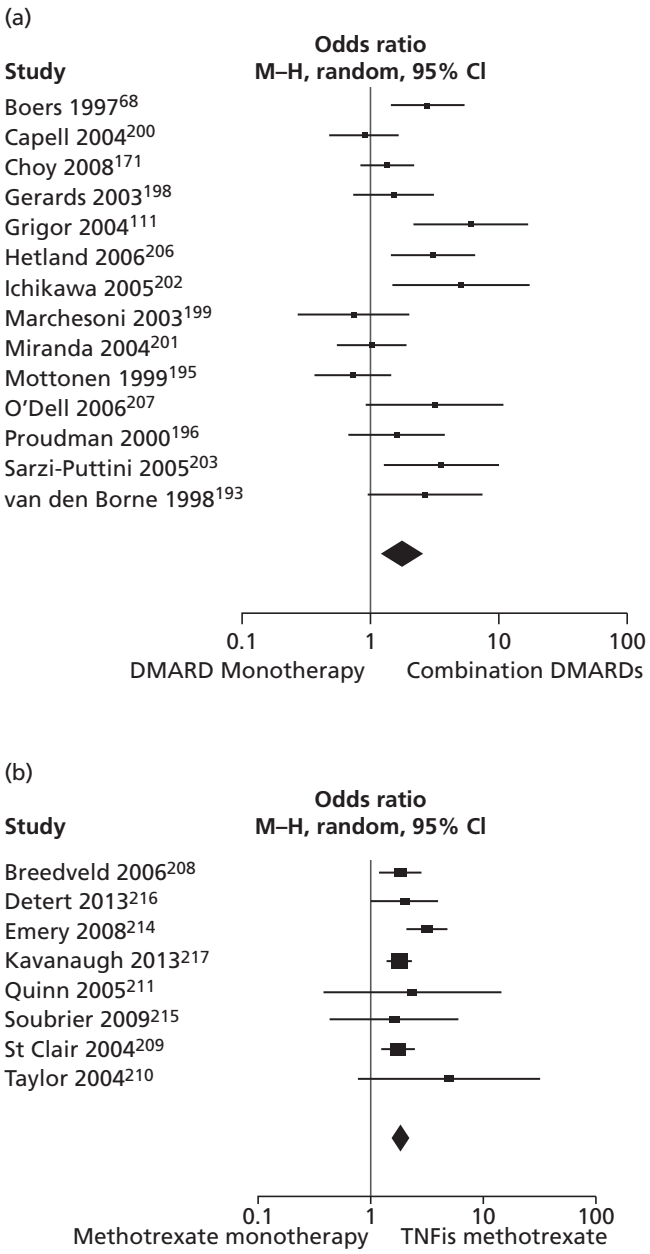

FIGURE 24 Forest plots of ACR20 responses in early RA: results for (a) cDMARD vs. methotrexate trials; and (b) TNFi/methotrexate vs. methotrexate trials.

TABLE 41 Direct comparisons (cDMARDs vs. TNFi/methotrexate) in early RA: summary of meta-analysis of all outcomes – ACR responses, patient withdrawals and radiological progression

Outcome	Studies	Random-effects analyses OR (95% CI)
Categorical outcomes		
ACR20	2	0.74 (0.42 to 1.29)
ACR50	1	0.54 (0.33 to 0.90)
ACR70	2	0.53 (0.36 to 0.79)
Inefficacy withdrawals	3	3.28 (0.51 to 21.28)
Toxicity withdrawals	3	1.63 (0.78 to 3.43)
		WMD (95% CI)
Continuous outcome		
Radiological progression	2	0.22 (–0.02 to 0.45)

Note
TNFi/methotrexate was the control group and cDMARDs was the comparison group (OR < 1 indicates reduced response.

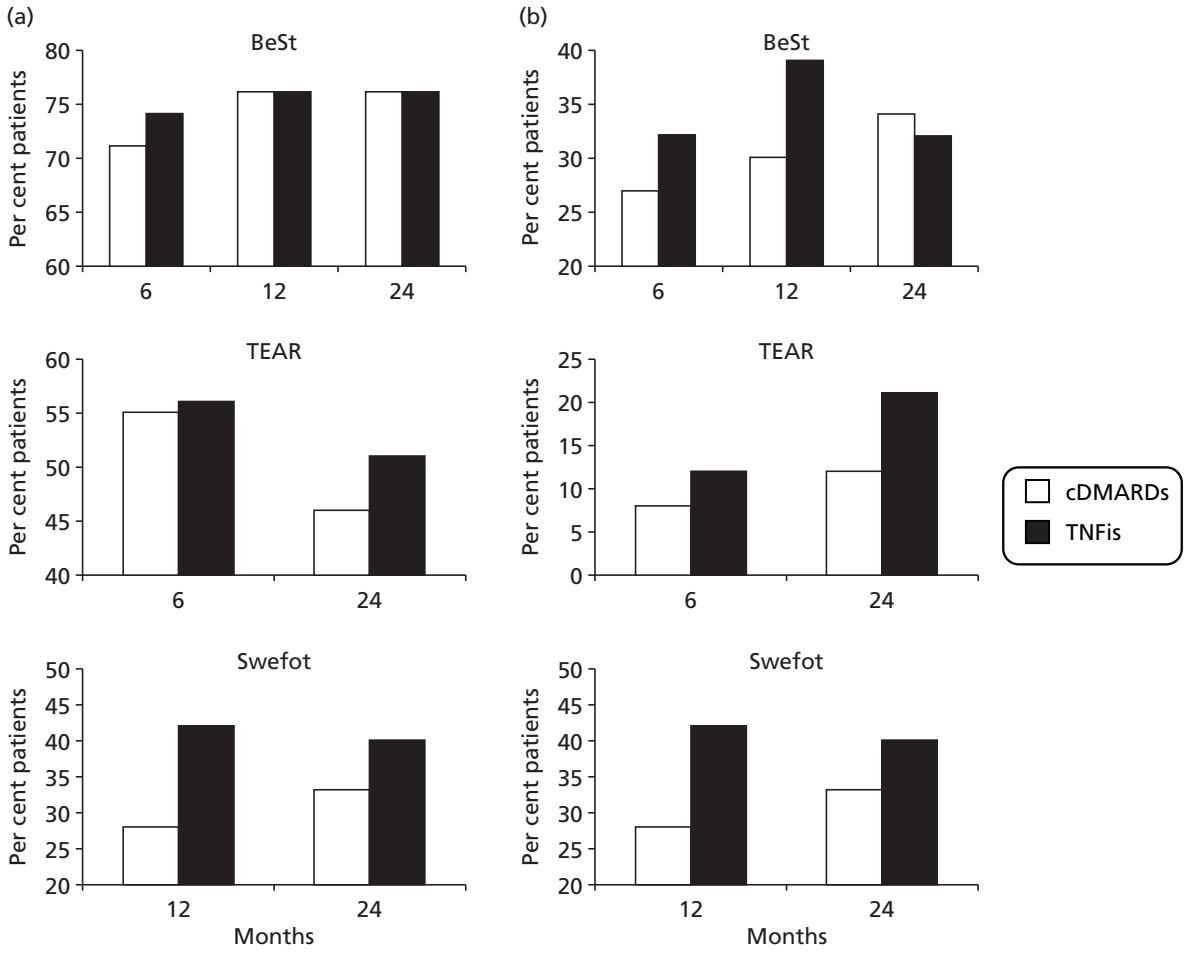

FIGURE 25 American College of Rheumatology responses in head-to-head trials in early RA. (a) ACR20; and (b) ACR70 responses from the BeSt,[147] Treatment of Early Aggressive Rheumatoid (TEAR)[219] and Swefot trials.[218] The trials variously reported outcomes at 6, 12 and 24 months.

Radiological progression

Indirect comparisons showed less erosive progression with both combination regimens compared with DMARD monotherapy (see *Table 40*). Sensitivity analysis of cDMARDs including only those trials in which the comparator was methotrexate monotherapy showed similar results. The direct comparison showed that there was no difference in radiological progression between cDMARDs and TNFi/methotrexate (see *Table 41*).

Heterogeneity

The cDMARD trials showed evidence of heterogeneity in ACR20 scores ($p < 0.007$), ACR50 scores ($p < 0.0001$) and ACR70 scores ($p = 0.02$). In contrast, the TNFi trials showed no heterogeneity. There was also no heterogeneity in the head-to-head trials.

Established rheumatoid arthritis

Trials

The preliminary search identified 3642 papers, of which 28 were potentially relevant and were selected for full-text review (*Figure 26*). Of these, nine studies were excluded: in four patients were treatment naive, in two patients had not received DMARDs for > 3 months, two did not specify previous DMARD treatment and one was a duplicate of an included study. The remaining 19 studies[66,67,170,222–237] were included in the systematic review and are summarised in *Table 42*. In total, 10 trials compared cDMARDs with DMARD monotherapy,[66,67,222–229] of which six used methotrexate monotherapy as the control arm,[66,67,222,223,227,229] and eight compared TNFi/methotrexate with methotrexate monotherapy,[170,230–236] with one involving infliximab,[170] two etanercept,[230,232] one adalimumab,[231] two golimumab[233,236] and two certolizumab pegol.[234,235] For the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO)[232] and Rheumatoid Arthritis Prevention of Structural Damage 1 (RAPID1)[234] trials, 2-year follow-up data were subsequently published.[238,239] Finally, one trial made a direct comparison between methotrexate/sulfasalazine/hydroxychloroquine and etanercept/methotrexate.[237]

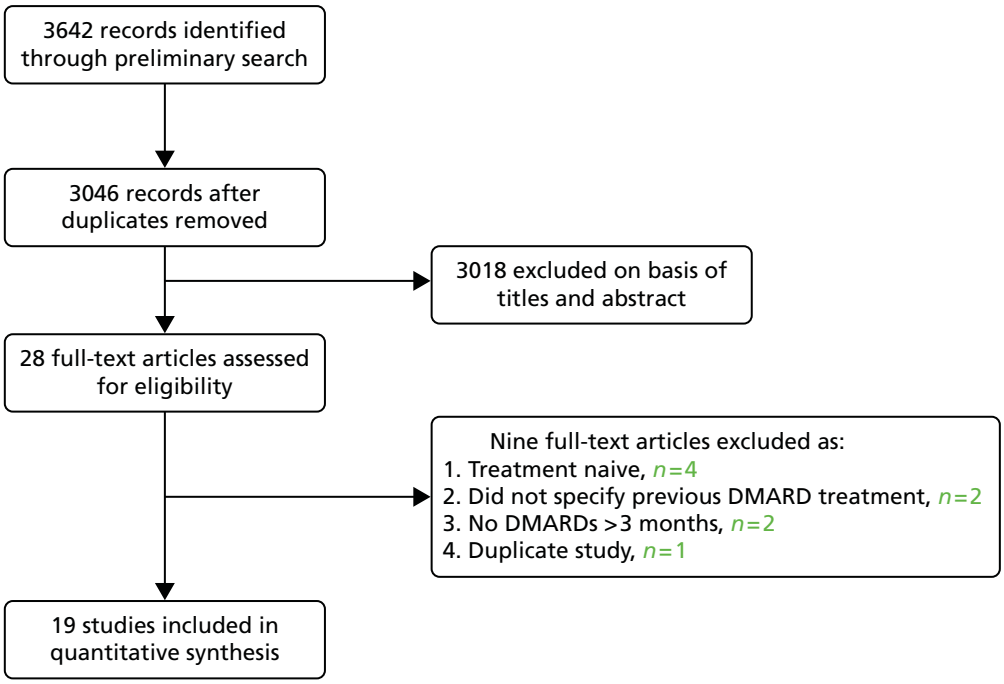

FIGURE 26 Selection of trials in established RA.

TABLE 42 Characteristics of RCTs in established RA

Study	Year	Cases	Refractory to treatment	Quality assessments				Follow-up	Treatment arms
				Allocation	Blinding	Analysed in original groups	Analysed for bias		
cDMARDs									
Ferraz *et al.*[222]	1994	82	Failed more than one DMARD	Unstated	Double	Yes	No	0.5 years	MTX vs. MTX/chloroquine
Tugwell *et al.*[66]	1995	148	MTX > 3 months	Unstated	Double	Yes	No	0.5 years	MTX vs. CsA/MTX
Willkens *et al.*[223]	1995	209	Resistant to penicillamine/gold	Permutated blocks	Double	Yes	Yes	1 year	MTX vs. MTX/AZA
Bendix *et al.*[224]	1996	40	Insufficient response to gold	Computerised	Double	Yes	No	0.5 years	PGT vs. PGT/CsA
O'Dell *et al.*[67]	1996	102	More than one DMARD	Cards	Double	Yes	Yes	2 years	MTX vs. MTX/SSZ/HCQ
Kremer *et al.*[225]	2002	263	MTX > 6 months	Computerised	Double	Yes	Yes	0.5 years	Leflunamide vs. leflunamide/MTX
Dougados *et al.*[226]	2005	106	Inadequate response to leflunomide	Unstated	Double	Yes	No	0.5 years	SSZ vs. leflunamide/SSZ
Lehman *et al.*[227]	2005	65	MTX > 12 weeks	Random number table	Double	Yes	Yes	1 year	MTX vs. MTX/IM gold
Karanikolas *et al.*[228]	2006	106	Refractory to more than one DMARD	Unstated	Open	Yes	No	1 year	Leflunamide vs. CsA/leflunamide
Capell *et al.*[229]	2007	191	SSZ > 6 months	Computerised	Double	Yes	No	1 year	MTX vs. MTX/SSZ

Study	Year	Cases	Refractory to treatment	Quality assessments				Follow-up	Treatment arms
				Allocation	Blinding	Analysed in original groups	Analysed for bias		
TNFis/MTX									
Weinblatt *et al.*[230]	1999	89	MTX > 6 months	Unstated	Double	Yes	No	0.5 years	MTX vs. etanercept/MTX
Lipsky *et al.*[170]	2000	428	MTX > 6 months	Unstated	Double	Yes	No	1 year	MTX vs. 3 mg infliximab/MTX
Weinblatt *et al.*[231]	2003	271	MTX > 6 months	Unstated	Double	Yes	No	0.5 years	MTX vs. 40 mg adalimumab/MTX
Klareskog *et al.*[232]	2004	686	More than one DMARD other than MTX	Centralised telephone	Double	Yes	Yes	0.5 years	MTX vs. etanercept/MTX
Kay *et al.*[233]	2008	172	MTX > 3 months	Unstated	Double	Yes	No	0.3 years	MTX vs. 50 mg golimumab/MTX
Keystone *et al.*[234]	2008	982	MTX > 6 months	Unstated	Double	Yes	No	1 year	MTX vs. 200 mg certolizumab/MTX
Smolen *et al.*[235]	2009	619	MTX > 6 months	Unstated	Double	Yes	Yes	0.5 years	MTX vs. 200 mg certolizumab/MTX
Kremer *et al.*[236]	2010	643	MTX > 3 months	Interactive voice response	Double	Yes	Yes	0.3 years	MTX vs. 2 mg/kg golimumab/MTX
Direct comparison									
O'Dell *et al.*[237]	2013	353	MTX > 3 months	Unstated	Double	Yes	No	1 year	MTX/SSZ/HCQ vs. etanercept/MTX

AZA, azathioprine; CsA, ciclosporin; HCQ, hydroxychloroquine; IM, intramuscular; MTX, methotrexate; PGT, gold aurothiomalate; SSZ, sulfasalazine.

Baseline characteristics

The baseline characteristics of the patients are summarised in *Table 43*. The trials enrolled between 40 and 982 patients; overall, > 5500 patients were randomised. The average age ranged from 49 to 59 years in the TNFi/methotrexate trials and from 44 to 56 years in the cDMARD trials. Mean disease duration ranged from 6.7 to 13 years in the TNFi/methotrexate trials and from 1–12.7 years in the cDMARDs trials. Disease activity, assessed using the DAS28 or its component parts, was reported in the majority of trials and showed active disease. In the six trials reporting initial DAS28, these ranged from a mean of 3.6 to a mean of 7.0, with an average of 5.75.

TABLE 43 Baseline characteristics in established RA trials

Study	Year	Treatment	Age (years)	RF (% positive)	Disease duration (years)	DAS28	ESR (mm/hour)	SJC	TJC	PGA[a]
cDMARDs										
Ferraz *et al.*[222]	1994	MTX vs. MTX/chloroquine	50	71	9	–	–	–	–	–
Tugwell *et al.*[66]	1995	MTX vs. CsA/MTX	55	–	11	–	–	17	23	62
Wilkens *et al.*[223]	1995	MTX vs. MTX/AZA	54	–	8	–	–	–	–	–
Bendix *et al.*[224]	1996	PGT vs. PGT/CsA	55	81	11	–	–	–	–	–
O'Dell *et al.*[67]	1996	MTX vs. MTX/SSZ/HCQ	50	84	10	–	36	27	29	60
Kremer *et al.*[225]	2002	MTX vs. leflunamide/MTX	56	79	11	–	–	–	–	–
Dougados *et al.*[226]	2005	SSZ vs. leflunamide/SSZ	56	78	6	6.2	–	–	–	–
Lehman *et al.*[227]	2005	MTX vs. MTX/IM gold	51	67	3	–	29	11	21	42
Karanikolas *et al.*[228]	2006	Leflunamide vs. CsA/leflunamide	–	–	7	–	–	–	–	–
Capell *et al.*[229]	2007	MTX vs. MTX/SSZ	56	68	1	3.6	–	–	–	–
TNFis/methotrexate										
Weinblatt *et al.*[230]	1999	MTX vs. etanercept/MTX	48	84	13	–	–	–	–	–
Lipsky *et al.*[170]	2000	MTX vs. 3 mg infliximab/MTX	54	84	10	–	49	22	32	70
Weinblatt *et al.*[231]	2003	MTX vs. 40 mg adalimumab/MTX	57	369[b]	12	–	–	17	28	55
Klareskog *et al.*[232]	2004	MTX vs. etanercept/MTX	53	76	7	5.5	–	22	34	–
Kay *et al.*[233]	2008	MTX vs. 50 mg golimumab/MTX	57	–	6	6.4	–	14	28	70
Keystone *et al.*[234]	2008	MTX vs. 200 mg certolizumab/MTX	52	84	6	7.0	44	22	31	–
Smolen *et al.*[235]	2009	MTX vs. 200 mg certolizumab/MTX	52	76	6	–	29	21	30	61
Kremer *et al.*[236]	2010	MTX vs. 2 mg/kg golimumab/MTX	50	–	8	–	–	16	27	60

TABLE 43 Baseline characteristics in established RA trials (*continued*)

Study	Year	Treatment	Age (years)	RF (% positive)	Disease duration (years)	DAS28	ESR (mm/hour)	SJC	TJC	PGA[a]
Direct comparison										
O'Dell *et al.*[237]	2013	MTX/SSZ/HCQ	58	66	6	5.8	27	11	13	54
O'Dell *et al.*[237]	2013	Etanercept/MTX	56	70	4.9	5.9	30	11	13	56

AZA, azathioprine; CsA, ciclosporin; HCQ, hydroxychloroquine; IM, intramuscular; MTX, methotrexate; PGA, patient global assessment; PGT, gold aurothiomalate; RF, rheumatoid factor; SJC, swollen joint count; SSZ, sulfasalazine; TJC, tender joint count.
a Scored out of 100.
b IU/l.

American College of Rheumatology responses and withdrawals for inefficacy

In trials of DMARD combinations more patients achieved ACR20–70 responses with combination therapy (OR 2.75–5.07), as shown in *Table 44* and *Figure 27*. More patients withdrew with combination therapy (OR 1.51, 95% CI 1.02 to 2.25). Sensitivity analysis of RCTs that included a methotrexate monotherapy arm showed that more patients achieved ACR20–70 responses with combination therapy (OR 3.55–4.74) but few patients withdrew because of inefficacy (OR 0.34, 95% CI 0.20 to 0.59).

TABLE 44 Summary of outcomes in established RA trials

Outcome	Treatment	Studies	Random-effects analyses OR (95% CI)
Categorical outcomes			
ACR20	DMARDs (all)	6	2.75 (1.79 to 4.22)
	DMARDs (methotrexate only)	4	3.55 (2.43 to 5.17)
	TNFi/methotrexate	8	5.32 (3.03 to 9.34)
ACR50	DMARDs (all)	6	5.07 (3.10 to 8.29)
	DMARDs (methotrexate only)	4	4.70 (2.40 to 9.20)
	TNFi/methotrexate	8	8.13 (4.26 to 15.52)
ACR70	DMARDs (all)	5	4.85 (2.34 to 10.05)
	DMARDs (methotrexate only)	3	4.74 (1.65 to 13.61)
	TNFi/methotrexate	8	5.36 (2.92 to 9.83)
Inefficacy withdrawals	DMARDs (all)	10	0.38 (0.24 to 0.62)
	DMARDs (methotrexate only)	7	0.34 (0.20 to 0.59)
	TNFi/methotrexate	8	0.12 (0.06 to 0.25)
Toxicity withdrawals	DMARDs (all)	10	1.51 (1.02 to 2.25)
	DMARDs (methotrexate only)	7	1.58 (0.97 to 2.59)
	TNFi/methotrexate	8	0.94 (0.62 to 1.41)
			WMD (95% CI)
Continuous outcome			
Disability (HAQ)	DMARDs (all)	3	−0.19 (−0.27 to −0.10)
	DMARDs (methotrexate only)	1	−0.30 (−0.42 to −0.18)
	TNFi/methotrexate	1	−0.35 (−0.56 to −0.14)

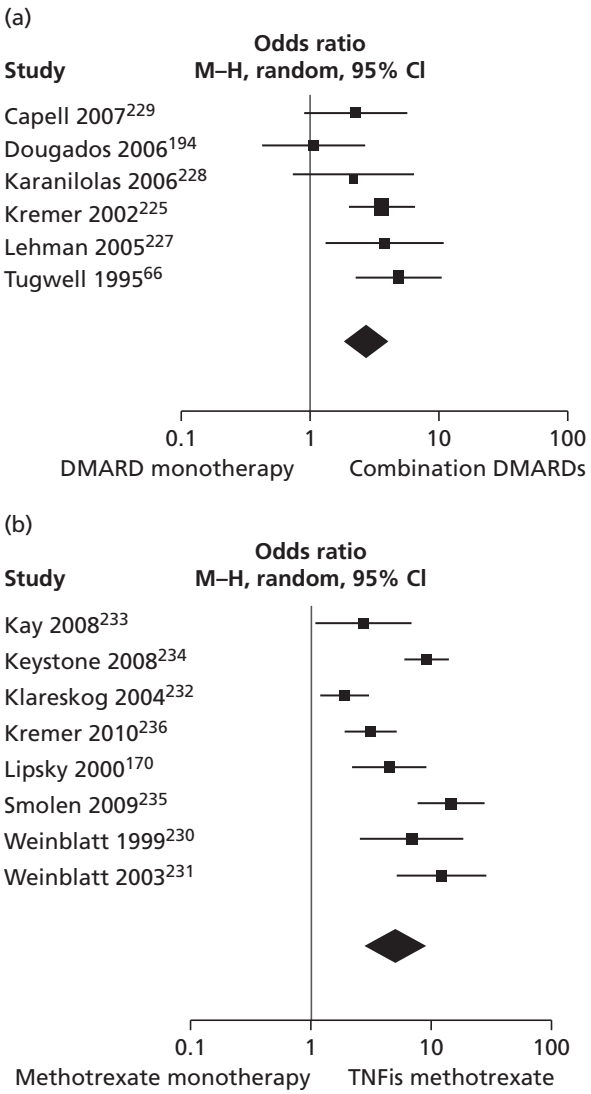

FIGURE 27 Forest plots of ACR20 responses in established RA: results for (a) cDMARD vs. DMARD monotherapy trials; and (b) TNFi/methotrexate vs. methotrexate trials.

In trials of TNFi/methotrexate combinations more patients achieved ACR20–70 responses with combination therapy (OR 5.32–8.13), as shown in *Table 44*. Fewer patients withdrew because of inefficacy with combination therapy (OR 0.12, 95% CI 0.06 to 0.25).

The trial comparing triple DMARD therapy with etanercept/MTX[237] showed no statistical difference between groups in ACR20 (57% vs. 66%), ACR50 (35% vs. 43%) and ACR70 (18% vs. 26%). This study did not report patient withdrawals for inefficacy.

Disability

Five randomised trials of cDMARDs reported change in HAQ scores (*Table 45*).[224–227,229] Only three of these trials reported both mean changes and SDs for these changes.[224–226] A combined analysis of these three trials' HAQ scores (see *Table 45*) showed that, overall, there were greater improvements with cDMARDs than with DMARD monotherapy (WMD –0.19, 95% CI –0.27 to –0.10). Only one of these RCTs used methotrexate as the monotherapy (see *Table 45*);[225] this trial also showed greater improvement with cDMARDs (WMD –0.30, 95% CI –0.42 to –0.18).

TABLE 45 Changes in HAQ scores in established RA trials

Study	Year	Treatment	Patients	HAQ change reported as	HAQ change scores
cDMARDs					
Ferraz *et al.*[222]	1994	MTX vs. MTX/chloroquine	34 vs. 34	–	
Tugwell *et al.*[66]	1995	MTX vs. CsA/MTX	73 vs. 75	–	
Willkens *et al.*[223]	1995	MTX vs. MTX/AZA	67 vs. 29	–	
Bendix *et al.*[224]	1996	PGT/placebo vs. PGT/CsA	21 vs. 19	Mean change (SD)	0 (0.4) vs. 0.1 (0.4)
O'Dell *et al.*[67]	1996	MTX vs. MTX/SSZ/HCQ	36 vs. 31	–	
Kremer *et al.*[225]	2002	MTX vs. leflunomide/MTX	133 vs. 130	Mean change (SD)	0.10 (0.43) vs. 0.40 (0.53)
Dougados *et al.*[226]	2005	SSZ vs. leflunomide/SSZ	50 vs. 56	Mean change (SD)	0.02 (0.36) vs. 0.09 (0.32)
Lehman *et al.*[227]	2005	MTX vs. MTX/IM gold	27 vs. 38	Mean % change (SE)	25 (7) vs. 38 (6)
Karanikolas *et al.*[228]	2006	CsA/leflunomide vs. CsA/leflunomide	36 vs. 35	–	
Capell *et al.*[229]	2007	MTX vs MTX/SSZ	54 vs. 56	Median change (IQR)	0.2 (−0.13 to 10.3) vs. 0.5 (−0.10 to −10.3)
TNFis/methotrexate					
Weinblatt *et al.*[230]	1999	MTX vs. etanercept/MTX	30 vs. 59	–	
Lipsky *et al.*[170]	2000	MTX vs. infliximab/MTX	88 vs. 86	–	
Weinblatt *et al.*[231]	2003	MTX vs. 40 mg adalimumab/MTX	62 vs. 67	Mean change (SD)	0.27 (0.57) vs. 0.62 (0.63)
Klareskog *et al.*[232]	2004	MTX vs. etanercept/MTX	228 vs. 231	Mean change (95% CI)	1.7 (1.6 to 1.8) vs. 1.8 (1.7 to 1.8) to 1.1 (1.0 to 1.1) vs. 0.8 (0.7 to 0.9)
Kay *et al.*[233]	2008	MTX vs. 50 mg golimumab/MTX	35 vs. 35	–	
Keystone *et al.*[234]	2008	MTX vs. 200 mg certolizumab/MTX	199 vs. 393	Median improvement (IQR)	0.25 (0.00 to 0.75) vs. 0.63 (0.25 to 0.88)
Smolen *et al.*[235]	2009	MTX vs. 200 mg certolizumab/MTX	127 vs. 246	Mean change (SE)	0.14 (0.04) vs. −0.5 (0.03)
Kremer *et al.*[236]	2010	MTX vs. 2 mg/kg golimumab/MTX		Mean % change	9.7 vs. 32.6

AZA, azathioprine; CsA, ciclosporin; HCQ, hydroxychloroquine; IM, intramuscular; MTX, methotrexate; PGT, gold aurothiomalate; SE, standard error; SSZ, sulfasalazine.

For TNFi/methotrexate combinations five trials reported change in HAQ scores (see *Table 45*).[231,232,234–236] In all of these trials there was an improvement in HAQ score in the combination arm. One trial reported mean (SD) change in HAQ score (WMD −0.35, 95% CI −0.56 to −0.14).[231]

The trial that made a direct comparison between methotrexate/sulfasalazine/hydroxychloroquine and etanercept/methotrexate reported mean HAQ scores at 48 weeks.[237] There was no difference in HAQ scores between triple DMARD therapy (0.93 ± 0.85) and etanercept/methotrexate (0.83 ± 0.81).

Toxicity

For cDMARDs, all 10 trials[66,67,222–229] reported patient withdrawals because of toxicity. The overall OR for withdrawal with combination therapy was 1.51 (95% CI 1.02 to 2.25). Seven[66,67,222,223,225,227,229] of these studies used methotrexate as the monotherapy arm; the OR for withdrawal was 1.58 (95% CI 0.97 to 2.59).

For TNFi/methotrexate combinations, eight trials[170,230–236] reported patient withdrawals because of toxicity. There were no significant differences between treatments, with an OR of 0.94 (95% CI 0.62 to 1.41).

The direct comparison trial[237] did not report patient withdrawals because of toxicity.

Heterogeneity

The cDMARD trials showed no evidence of heterogeneity in ACR20–70 scores. In contrast, the TNFi trials showed significant heterogeneity in ACR20 scores ($p < 0.00001$) and ACR50 scores ($p < 0.0002$) and borderline heterogeneity in ACR70 scores ($p = 0.06$).

Chapter 4 Discussion

The Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

Key findings

Patients with active established RA who meet current NICE criteria to receive TNFis achieve equivalent reductions in disability and improvements in quality of life over 12 months by treating initially with cDMARDs and reserving TNFis for cDMARD non-responders. The cDMARD strategy costs substantially less. However, neither treatment strategy was ideal. The majority of patients in both groups failed to achieve a DAS28 of ≤ 2.6, which is often considered to indicate remission.

The DAS28 improved more rapidly in patients receiving TNFis. Overall, monthly DAS28 were lower in patients receiving TNFis and more patients receiving TNFis achieved a DAS28 response (decrease in score of ≥ 1.2) within the first 6 months. This benefit of TNFis with regard to the DAS28 response particularly reflected rapid and sustained reductions in ESR in this group. However, the benefits of TNFis with regard to the DAS28 response were small and did not result in improvements in disability or quality of life. There was also no evidence that patients who received cDMARDs had more erosive progression. Larsen scores showed that both groups had comparable, minimal radiological progression.

Serious adverse events and withdrawals because of toxicity were equally common with cDMARDs and TNFis. However, the total number of adverse events, spanning both serious and more minor events, was higher with cDMARDs. This was most marked for adverse reactions involving the digestive system.

As TNFis are more expensive than cDMARDs, the economic evaluation showed that the cDMARD group was substantially more cost-effective, whatever approach was taken to assessing costs and relevant outcomes. This included incorporating societal costs such as lost time from work and social security benefit claims into the calculations.

In total, 44% of the patients in the cDMARD group were recommended to switch to a TNFi because their disease activity had not improved after 6 months of treatment. However, there was no evidence that patients who switched in this way had a worse quality of life, more disability or more erosive progression. There was therefore no evidence that these 'switchers' had any long-term disadvantages from taking cDMARDs for 6 months.

Limitations and sources of bias

Not all patients invited to participate agreed to do so; overall, 192 out of 432 patients (44%) declined to take part in the trial. We cannot be certain that the patients who did not consent to the trial would have responded in the same way as those who took part.[240] However, this is only one of a number of causes of bias in trials of long-term diseases[241] and does not seem a crucial factor compared with the range of issues influencing such trials. In addition, patient choice is of crucial importance and accepting that not everyone will agree to participate is an inevitable consequence of informed choice around clinical trials. In addition, as considered below, TACIT patients receiving TNFis were similar to those in the UK national register (see pp. 90).

Those patients who did not respond to cDMARDs in the TACIT trial were treated with TNFis. It could therefore be argued that over time the two arms of the trial become very similar if not identical. However, only a minority of patients were involved in switching, with 44% of patients who started cDMARDs switching to TNFis in the second 6 months. As a consequence, the two trial arms remained sufficiently different to make this a genuine comparison. Furthermore, the 6-month comparisons did not include any patients randomised to cDMARDs who had received TNFis (because no-one switched until after 6 months). Therefore, at 6 months there was a genuine head-to-head comparison within the TACIT trial. Switching between treatment strategies is normal clinical practice and over time many RA patients starting DMARDs or biologics will switch to other treatments.

The cDMARD treatment was not standardised and it could be argued that the therapy given was too heterogeneous, making it an intervention that could be difficult to reproduce. This is an intellectual challenge as the only way to standardise cDMARD treatment is to study early RA patients who are DMARD naive or study methotrexate non-responders. These patients do not meet existing NICE criteria for receiving TNFis. If anything, the cDMARD treatments used were too conservative. We had hoped that patients would receive more intensive treatment and more short-term steroids in the cDMARD arm. However, supervising clinicians and patients placed more emphasis on slowly changing treatment to limit toxicity rather that giving maximal-dose therapy as soon as possible. Over time we anticipate that the use of cDMARDs will increase and concerns about toxicity may consequently lessen. We also accept that some combinations may be more effective, although this could not be resolved in the TACIT trial. More trials of different cDMARDs would be needed to answer this question.

Steroid use in the cDMARD group, including intramuscular injections, was less than anticipated when designing the TACIT trial based on our previous experience with steroids in established RA.[242] UK rheumatologists may have concerns about treating many patients with steroids because of the risk of adverse events. However, the relatively limited use of steroids would serve to reduce rather than magnify the impact of cDMARDs. More intensive steroid use could make cDMARD treatment even more effective.

It could be argued that the same results could have been obtained from starting another DMARD monotherapy and that the use of intensive DMARD combinations in the TACIT trial was not needed. This is a theoretical rather than a practical issue as there is no reason to stop one DMARD and start another in active RA in the absence of adverse events. DMARDs often have long half-lives, particularly agents such as leflunomide. Consequently, washing out current DMARDs and then starting a new DMARD monotherapy has limitations for patients as well as being of limited interest as the toxicity of modern DMARDs used in combination is not excessive.

The use of DMARDs other than methotrexate in combination with TNFis could have reduced the efficacy of these treatments in some patients. However, to do otherwise would be to move away from current UK practice, in which a range of DMARDs are given with TNFis. There is some evidence supporting the use of these different DMARDs in combination, as shown in our systematic reviews.

The use of the HAQ as the primary outcome measure might be viewed by some experts as being inappropriate, as the opportunity to reverse HAQ scores decreases with increasing disease duration.[243,244] Although this is theoretically correct, both of our groups showed clinically relevant reductions in HAQ scores over 12 months. In addition, the disease duration of patients in the TACIT trial (median duration of < 6 years in both groups) was below that in the Phase III trials that have led to the approval of the different TNFis. Furthermore, the degree of reduction in HAQ scores in the TACIT trial was similar to that reported in previous trials of biologics. In our view, if TNFis do not substantially reduce HAQ scores compared with other treatments then their potential clinical value is limited.

The TACIT trial was not a blinded trial. It could be argued that being unblinded influenced patients and clinicians to favour cDMARDs inappropriately. However, it was impractical to have a fully blinded treatment strategy involving multiple drugs, all of which need careful monitoring. Given the enthusiasm of most clinicians and most patients for receiving high-cost biological treatment, we consider that unblinding would, if anything, benefit TNFis. The issue of blinding is related to a number of ethical matters; these are considered in detail in the subsequent section on ethical issues.

The TACIT trial and similar trials of efficacy are not able to completely assess the relative impacts of different types of adverse event on clinical outcomes. Many adverse events reported in patients taking cDMARDs in the TACIT trial, particularly gastroenterological events, may have been relatively minor. Many patients might have felt that the treatment was 'worth it', irrespective of these adverse events. Although we collected detailed information about such adverse events, we did not assess their specific impacts on patient outcomes and whether they affected patients' quality of life. We are therefore not able to fully determine the clinical consequences of such adverse events. Large long-term observational studies are needed to fully assess the impact of adverse events on treatment outcomes. Despite this limitation, the data that we collected in the TACIT trial on serious adverse events and adverse events linked to stopping treatment provided no evidence that there were more such events in the cDMARDs group than in the TNFis group.

The trial involved dividing patients into two groups after 6 months based on change in DAS28: responders and non-responders. This approach resulted in 46 out of 104 (44%) patients switching to TNFis after starting with intensive DMARDs. However, more than half (56%) of patients did not switch. This simple concept hides a more complex problem. Patients can fall on one side and then the other of such an arbitrary response without there being a major change in their condition, and the duration that patients remain within a defined state is not captured using such as approach, a problem discussed by Farewell and Su.[245] This general issue applies whenever arbitrary cut-offs are used at single time points in longitudinally collected data. It shows the difficulty of comparing the extent to which patients benefited from treatment.

Analytical issues

The TACIT trial was analysed on an ITT basis using multiple imputations and the primary outcome was compared using logistic regression methods. The HAQ is a complex assessment and it does not invariably behave as a conventional numerical scale.[246] There are identical issues with regard to the linearity of the scales of other key outcome measures, including the EQ-5D and Larsen scores. As both trial arms gave very similar outcomes using the HAQ, EQ-5D and Larsen scores, there is little merit in such an argument. In addition, the overwhelming balance of advice that we received favoured the analytical method that we preselected.

Not all of the outcomes confirmed equivalence. Changes in DAS28 and ESR favoured TNFis, particularly within the first 3–6 months. In part, this reflects the rapid onset of response with TNFis and the slow onset of response with DMARDs, which historically, and probably more accurately, used to be known as slow-acting drugs. Most DMARDs show maximal effects only by 6 months.

Measurement issues

There are several relevant measurement issues when measuring HAQ scores, radiological progression and DAS28. The HAQ was the primary outcome measure and its validity as an assessment instrument is therefore of most concern. The validity, reliability and responsiveness of the HAQ were reviewed by Linde *et al.*[158] Overall, the HAQ has appropriate measurement properties for a patient-generated outcome measure. It is not necessarily a simple scale and Rasch analysis by Wolfe[247] and Tennant *et al.*[246] have highlighted some relative weaknesses. Our own previous research contributions suggest that the HAQ is the best available measure to use in trials such as the TACIT trial.[145,248,249]

There is debate about the minimum clinically important difference in HAQ score in routine practice as opposed to clinical trials. Pope *et al.*[250] suggest that this is smaller than the difference that is considered important in trials. From this perspective the change in HAQ score in patients randomised to receive cDMARDs, which was overall 0.15 greater than that seen in patients randomised to receive TNFis, might be clinically relevant. However, this perspective appears questionable. We predetermined the minimum clinically important difference in HAQ score in trial settings and believe that it is inappropriate to change it retrospectively. It is also a theoretical rather than a practical issue as our aim was to show that the TNFi strategy was not better than the cDMARD strategy; showing that the cDMARD strategy has benefits is an identical conclusion in terms of its influence in clinical practice.

The use of Larsen scores to assess erosive damage merits consideration. The radiographs were all scored using the modified Larsen method by one investigator (DS), who has contributed to a number of published trials using this method and has achieved appropriate reproducibility of scoring.[171,242,251–260] There is debate about the relative merits of different approaches to scoring radiographs. The TACIT trial followed the approach taken in the British Rheumatoid Outcome Study Group (BROSG) trial in established RA[261] and we have no reason to doubt its validity or appropriateness.

The TACIT trial used the DAS28, which was scored by many clinicians in different clinics. Each centre received detailed information during initiation on the methods of scoring the DAS28.[262] However, we did not give either explicit standardisation training nor did we retrain observers periodically to assess whether or not they maintained consistent standards. There are challenges in assessing patients using the DAS28.[263] Although training increases clinicians' short-term agreement when measuring joint counts,[264] the overall benefit of such training is uncertain.[265] Training is useful within the national context to deliver high-quality care, but its value in an individual clinical trial is limited. As the TACIT trial is a strategy trial within routine care settings we consider that it needs to replicate standard methods and should not adopt more stringent approaches because these would limit its generalisability.

Strengths of the Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

The TACIT trial was undertaken in outpatient rheumatology clinics in England in conditions that, as far as is possible within a clinical trial, mirrored routine practice. The patients enrolled were typical of those treated within England and included patients from a range of ethnicities and levels of deprivation. They are similar to those reported in the British Society for Rheumatology (BSR) Biologics Register.[266] A comparison between patients enrolled in the BSR Biologics Register and those enrolled in the TACIT trial is shown in *Table 46*. As there is evidence that the patients enrolled in the BSR Biologics Register have changed over

TABLE 46 Comparison between patients enrolled in the BSR Biologics Register and TNFi patients in the TACIT trial

		BSR Biologics Register (by year)[235]								TACIT TNFi cases	
Outcome	Time	2001	2002	2004	2004	2005	2006	2007	2008	ITT	Completers
n		119	1206	2930	3138	1553	1056	782	432	101	75
Mean HAQ score	Baseline	2.21	2.14	2.10	2.04	1.98	1.95	1.87	1.87	1.90	1.84
	6-month change	0.26	0.33	0.32	0.32	0.34	0.33	0.33	0.32	0.35	0.41
	12-month change	0.31	0.33	0.33	0.33	0.34	0.35	0.34	0.37	0.30	0.38
Mean DAS	Baseline	6.77	6.75	6.67	6.56	6.51	6.41	6.34	6.38	6.30	6.28
	6-month change	2.08	2.20	2.17	2.33	2.33	2.29	2.26	2.31	2.07	2.35
	12-month change	2.03	2.33	2.35	2.41	2.46	2.38	2.46	2.32	2.41	2.84

time, data from all available years are shown. For the HAQ and DAS28, patients in the TACIT trial had similar initial scores and similar changes in scores (in the TNFi group) to those of patients most recently enrolled in the BSR Biologics Register.

The TACIT trial focused on patient-centred outcomes. We consider this vital because such patient-centred outcomes have a central place in clinical trials in RA. Changes in measures such as the ESR, although of interest to clinicians, are of limited value to patients. There are also concerns about the interobserver reproducibility of assessing joint counts.

The TACIT trial was of sufficient size to provide robust assessments of the changes in measures. In addition, it showed benefits favouring cDMARD treatment. In other words, cDMARDs give somewhat better outcomes than just achieving equivalence. Although we do not think that the trial shows that cDMARDs are preferable, the chance of the conclusions being incorrect and of TNFis being better appears remote.

The TACIT trial showed that only a minority of patients randomised to TNFis achieved DAS28 of ≤ 2.6 and the use of cDMARDs also resulted in relatively few DAS28 of ≤ 2.6. These low scores are often considered to reflect remission although, as discussed earlier, defining remission is an ongoing challenge. The frequency of such 'remission scores' in the TACIT trial is similar to that reported by both the BSR Biologics Register[266] and other international registers of patients receiving TNFis in routine clinical practice[267–271] (*Table 47*). In addition to achieving few single low DAS28 of ≤ 2.6, few TACIT trial patients achieve sustained remission. There is a need for more research on the nature and predictors of sustained low DAS28 and other indicators of remission, but this problem lies outside the remit of the TACIT trial.

TABLE 47 Disease Activity Score for 28 Joints remission rates in TNFi registries: comparison of DAS28 remission rates at 6 and 12 months in registries of RA patients receiving a first TNFi

	Registry							
	BSR BR[266]	CORONA[267]	DANBIO[268]	DREAM[269]	GISEA[270]	RABBIT[271]	Overall	TACIT
Patients, *n*	11,216	326	1839	1531	591	775	16,278	101
6-month DAS28 remission rate (%)[b]	14	25	21	27	26	–	17[a]	15
12-month DAS28 remission rate (%)[b]	16	29	–	–	–	16	17[a]	23

BR, Biologics Register; CORONA, Consortium of Rheumatology Researchers of North America; DANBIO, Danish Registry for Biological Therapies in Rheumatology; DREAM, Dutch Rheumatoid Arthritis Monitoring; GISEA, Gruppo Italiano di Studio sulla Early Arthritis (Italian Group for the Study of Early Arthritis); RABBIT, Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (Rheumatoid Arthritis – Observation of Biologic Therapy).

a Per cent patients achieving remissions in all studies with data at 6 or 12 months; larger studies had most influence on average per cent.

b Per cent patients from whom data were available at 6 or 12 months.

Economic evaluation

Key findings

The economic evaluation indicates that initiating treatment with cDMARDs produces similar HAQ and QALY outcomes at 6 months as initiating treatment with TNFis, at a significantly lower cost (from all cost perspectives). By 12 months, the cDMARD approach additionally brings advantages as measured using the HAQ (–0.16, 95% CI –0.32 to –0.01), although a difference of this size is not considered to be clinically significant and so this approach can thus be regarded as being clinically similar to the TNFi approach. The cost advantage in the cDMARDs group is almost entirely due to cDMARD medications being cheaper than TNFis.

In the cDMARDs group, costs at 12 months are significantly larger than at 6 months because of the high proportion of the group who switched from cDMARDs to TNFis at 6 months. Given that there is no outcome disadvantage in the cDMARD arm at 6 or 12 months, there may be some merit in a strategy of initiating treatment with cDMARDs as this incurs lower costs for those who remain on that treatment and delays the additional costs associated with TNFis for those who go on to switch treatment.

These findings are likely to be robust because of the breadth of the cost perspectives taken and the individual-level nature of the data, which represents the variation in the sample. A pragmatic trial design performed within NHS settings also makes the findings applicable to the NHS.

Limitations

The economic evaluation has one notable limitation. Taking a broader cost perspective and a multicentre approach necessitated collating data by self-report questionnaires, which carries the risk of recall bias. Although we collected the CSRI data at 6 and 12 months, we limited the recall period to the previous 3 months to guard against recall inaccuracies. The disadvantage of this approach was that it necessitated extrapolating cost data to represent the full 6-month periods. This approach may not accurately reflect any variations that may exist across the measured and non-measured periods. However, we did have data for trial medication use over the entire period of follow-up and any biases associated with recall of other resource use would not be expected to impact on the findings given the dominance of trial medication costs. We also have no reason to believe that any such recall bias would differ by randomisation group. We accept that there was a theoretical possibility that patients switching from cDMARDs to TNFis might have resulted in the introduction of some bias, although many patients did not switch treatment until month 9. It could also be argued that we should also have reviewed patients' medical records to ensure that no major health-care costs were missed. However, this would be unachievable over multiple sites that were dispersed throughout England and which collect clinical data in a variety of different ways. In any case, there is no evidence to suggest that the groups completed the CSRI in different ways. In addition, the differences in costs between groups were almost entirely accounted for by the treatment costs and all trial medication use was directly recorded each month for all patients in the trial.

Economic modelling

Our economic analysis used data from within the trial only. It could be argued that long-term modelling is needed to make a more convincing case for different treatment strategies including both the more extensive use of cDMARDs and the role of TNFis in non-responders to conventional DMARDs with active RA.

Marra *et al.*[126] have outlined the reasons for carrying out long-term modelling studies to justify the use of high-cost treatments including TNFis and other biologics in RA. Barton *et al.*[272] provide similar justifications. The key points are as follows:

- Randomised controlled trials of biological treatments for RA are too short to capture relevant long-term costs and outcomes. Decision models that extrapolate the evidence from RCTs to longer-term outcomes are needed to meet the requirements of policy-makers.

- Such models can link intermediate end points such as HAQ score with final health outcomes such as death, morbidity and employability.
- Because only a minority of RCTs collect relevant data about both costs and health-related quality of life, it is important to use economic models to relate clinical benefits to economic outcomes.
- The constraints inherent in all RCTs limit the generalisability of their findings for routine clinical care. Modelling can help translate their findings into different clinical settings.

Without the use of long-term modelling it would be challenging to justify the use of high-cost biologics such as TNFis in RA. However, this approach has been accepted and the balance of opinion, summarised by Bathon and McMahon,[273] is that TNFis are now the preferred next step when methotrexate and DMARD monotherapy have proved insufficient.

The economic case for using conventional DMARDs more intensively, including assessments of potential long-term benefits, is somewhat different. It has been reviewed by Fautrel,[274] who stressed the following key points:

- As RA medical costs increase with rising disability levels, delaying sustained disability by better disease control will have economic benefits.[275]
- These benefits will be largest when outcomes can be improved by optimising low-cost treatments, including conventional DMARDs and glucocorticoids.
- Early combination treatment with cDMARDs and glucocorticoids gives better efficacy at lower costs and its benefits extend over time.[276,277]
- Increasing the intensity of low-cost treatment, for example by adding modified-release prednisone to synthetic DMARDs, reduces the proportion of patients eligible for biologics, resulting in substantial cost savings. These economic benefits increase when the effects of modified-release prednisone persist.[278]

Other groups have provided evidence that cDMARDs are cost-effective in RA.[279,280] The evidence is strongest in early RA with there being less information about established disease.

Showing that the use of cDMARDs before the use of biologics such as TNFis is cost-effective in the long term requires different sorts of modelling studies from those required to establish the cost-effectiveness of TNFis. It requires information about the persisting effects of cDMARDs beyond 12 months, including evidence that their clinical benefits are sustained and more information about their potential long-term risks. None of this crucial information is currently available. The duration of both RCTs and observational studies is usually too short to provide definitive assessments of medium- to long-term RA outcomes. Despite the potential importance of long-term modelling, it falls outside the scope of our research goals in the TACIT trial. As cDMARDs have been used for many years without major toxicity concerns and as the TACIT trial shows that their use is cost-effective in the short term, we are unconvinced that there is a need to measure their overall long-term cost-effectiveness compared with biologics. Although we cannot estimate the overall extent of any savings, all of the evidence suggests that their use along the lines adopted in the TACIT trial is effective and cost-effective and has no identifiable risks.

Finally, we analysed patients from the economic perspective within their original groups. Although some patients in the cDMARD group switched to TNFis after 6 months, we have not analysed these separately from the economic perspective, although we have provided a separate analysis for clinical outcomes. From the clinical perspective we wished to make certain that there was no disadvantage for patients from either remaining on cDMARDs or switching to TNFis. Our analysis provided no evidence that this was the case in terms of disability, quality of life, disease activity or erosive damage. From the economic analysis it is unclear that comparisons of patients who remained on cDMARDs with those who switched to TNFis would provide relevant information. If all patients switched to TNFis this would clearly have meant that the cDMARDs strategy was not a viable strategy. However, enough patients remained on cDMARDs to ensure that there was still an economic benefit from the cDMARD strategy in the second 6 months of treatment.

Analysing data for patients who remained on cDMARDs separately from data for those who switched to TNFis in the second 6-month period would show that remaining on cDMARDs cost less; however, this inevitable finding might overemphasise the benefits of cDMARDs.

Clinical implications

This economic evaluation suggests that, at 6 months and 12 months following randomisation, cDMARDs are a more cost-effective treatment approach for RA as the cDMARDs group achieved similar outcomes as the TNFi group at a significantly lower cost.

Systematic reviews

Key findings

Compared with DMARD monotherapy, including methotrexate monotherapy, these systematic reviews show that combination treatment regimens involving either cDMARDs or TNFis with methotrexate were both superior in terms of ACR responses, reduced withdrawals because of lack of effect, reduced disability scores and reduced erosive progression. The findings are similar in early and established RA. The three head-to-head trials in early RA gave similar findings.

In our systematic review, HAQ scores showed a WMD in favour of cDMARDs, including methotrexate, of –0.30 and a WMD in favour of TNFis combined with methotrexate of –0.35. Interestingly, a systematic review of clinical trials of leflunomide in active RA,[281] one of the most intensively studied DMARDs, showed a WMD in favour of leflunomide at 6 months of –0.43 (95% CI –0.52 to –0.33) compared with placebo in three trials involving 387 patients receiving leflunomide and 292 control patients.[281] These results with leflunomide suggest that starting a new DMARD is likely to have the same impact on HAQ scores as starting a new biological treatment.

Compared with the substantial benefits of combination treatments, there appeared to be relatively little to choose between cDMARDs and TNFis combined with methotrexate. There are some potential benefits of TNFi/methotrexate combinations in that there appear to be fewer withdrawals for toxicity and there was some evidence that ACR responses occurred more rapidly with biological treatments. Not all evaluations have drawn a similar conclusion; some reviews conclude that biologics have more advantages than cDMARDs and others are less optimistic about combination treatment approaches in general. Of interest are two observational studies of the impact of DMARDs compared with TNFis. Analysis of data on DMARDs from a national register collected in Germany[271] and from an observational study in the UK[282] resulted in very different conclusions. The German register considered that DMARDs were relatively ineffective whereas the UK study found that they were often highly effective in patients who met the criteria for receiving TNFis. Non-randomised studies can often result in very different conclusions.

The main implication from our systematic review was the need for head-to-head studies that directly compare the clinical effectiveness and cost-effectiveness of cDMARDs with those of biologics in established RA. The TACIT trial fitted exactly with this requirement. A broader outstanding challenge is to identify how best to integrate the use of DMARD combinations with biologics so that the maximal number of patients achieve the best possible response in an effective and cost-effective manner. These issues extend beyond the TACIT trial and indicate the need for an ongoing research programme in the field.

Limitations

Our systematic reviews have several limitations. First, only three RCTs directly compared cDMARDs with TNFi/methotrexate combinations and all of these were in early RA. Although we have relied more on indirect comparisons, these are invariably less informative than direct comparisons. Second, there was diversity in the range of cDMARDs used and some are not commonly used in clinical practice, for example bucillamine and doxycycline. However, we felt that these agents should be included in the meta-analysis to avoid bias and because we are examining the concept of DMARD combinations rather than the effects of

specific combinations. Third, there were differences in the designs of the trials. Some trials, such as BeSt, used a tight-control regimen whereas others, such as the CARDERA trial, used a step-down design.

There are also technical limitations in assessing RA outcomes in trials. First, not all studies report the same measures in the same way. Such variability in reporting affected HAQ scores and radiological assessments. Second, not all studies had the same duration of treatment; early findings may mask longer-term limitations and therefore some comparisons may be flawed. Third, erosive damage was conventionally assessed using plain radiographs, and newer imaging methods, particularly ultrasound and MRI, may show benefits of one form of combination therapy that are not seen using conventional radiography. Fourth, reporting of adverse events is variable and assessing withdrawals because of side effects is open to criticism as a crude evaluation of a complex issue. A fifth problem is that conventional clinical measures may miss important improvements with biologics, for example work disability may be particularly reduced by TNFis. Finally, the studies may have recruited patients with different initial disease activities. We examined the entry criteria and baseline measures in all studies. Although they showed a degree of variability, all patients had active disease and there was no evidence that patients receiving cDMARDs had less active disease than those receiving TNFi/methotrexate combinations.

We mainly focused on trials in which methotrexate monotherapy was used as the control treatment. We considered that this provided the best approach for comparing cDMARDs with TNFi/methotrexate. On balance, we believe that it preferable to standardise different DMARD combinations against methotrexate monotherapy, especially in early RA, as trials with less effective monotherapy arms create uncertainty when interpreting the findings.

Strengths

Both systematic reviews were large and they each enrolled > 5000 patients. They also showed very similar findings and the head-to-head trials gave similar supportive results. The findings in the TACIT trial are replicated in the different trials comparing cDMARDs and TNFi/methotrexate combinations with DMARD monotherapy, indicating that the trial results are likely to be generalisable.

Ethical issues

Trial design

The last decade has seen substantial progress in trial designs.[283] Regulatory pathways that demonstrate efficacy of new therapeutic agents have been agreed. The use of pure placebo treatment beyond 12–16 weeks is no longer considered ethical and consequently background therapy and early rescue has become regular practice. Identification of rare adverse events associated with new therapies has resulted in intensive safety evaluation during RCTs, a greater focus on post-marketing surveillance and use of registries, particularly for biological agents such as TNFis.

A crucial question before starting the TACIT trial was whether or not the trial was genuinely ethical. This is because the TACIT trial potentially involved restricting access to TNFis in patients with RA who met the criteria to receive these agents. This section deals with the relevant ethical issues. Although observational studies often provide similar results to those of randomised trials,[284] these similarities are not universal,[285] and clinical practice is unlikely to change in the absence of clinical trials that establish equivalence between cDMARDs and TNFis

Risks and anticipated benefits for trial participants and society

Equipoise, or the uncertainty principle, is a key requirement for RCTs in which the best treatment must be unknown so that participants do not suffer harm by assignment to one particular arm.[286,287] Alternative ethical approaches to RCTs have not gained universal acceptance and strategies such as equipoise-stratified randomisation are not widely used.[288–291]

Equipoise in individual patients reflects not only the scientific probabilities of particular outcomes (known to trial clinicians) but also the value that individuals place on particular outcomes or risks (known only to individual patients). The solution to varying individual patient equipoise is genuine consultation with each patient about the choices using clear written information; similar approaches can be used with referring clinicians. It is difficult to ascertain the level of equipoise across the patient community for two reasons. First, patients hold highly variable views on the impact of and risks from adverse events to drug treatments. Second, patients also have highly variable views on the severity and ultimate outcome of RA.[292,293]

Community equipoise is essential for a RCT to be ethical. We considered that there was sufficient equipoise among rheumatologists on when to use TNFis to justify our proposed RCT. Rheumatologists vary markedly in prescribing these agents. Discussion with consultant rheumatologists suggests that TNFis are felt to be highly effective but there is debate on which patients should receive them (in terms of severity and stage of disease), on their long-term risks and benefits and on their advantages over maximal existing therapy. There is also uncertainty, especially among public health clinicians, about their cost-effectiveness.

Concerns for patients entering this trial

Apart from general concerns about randomisation, especially for individuals who do not perceive true equipoise between treatments, there was a specific emotive concern about 'entitlement' to anti-TNF agents. Initially, many UK patients believed that, compared with the USA and continental Europe, they were deprived of these agents on financial grounds. This was exacerbated by intense pharmaceutical company involvement with clinicians and some patient organisations and by media presentation of these agents as 'miracle cures'. Alternatives such as cDMARDs, which are relatively inexpensive and can be prescribed generically, have not received the same amount of attention either in the general media or in information provided to patient groups. As access to TNFis remains variable, patients and clinicians may perceive the proposed trial as an additional means of inhibiting access. However, a strategy is needed as biologics cannot be given 'on demand' in our resource-limited health system, because of their long-term costs (reflecting high production costs), the need for indefinite treatment, their uncertain cost-effectiveness and the many new biologics coming on stream (e.g. abatacept and rituximab).

Public issues and concerns

In the authors' opinion a national strategy for using TNFis is required, taking into account the extensive new emerging information about these treatments. The adoption of new agents goes through several phases. Initially, they are considered safe and effective. Adverse events are underestimated at this stage, reflecting selective recruitment to clinical trials, careful patient follow-up in trials, the expertise of the research clinicians and the small numbers of patients treated; efficacy is overestimated for similar reasons. The next phase of drug adoption involves a reaction against the agent precipitated by unexpected side effects and the recognition that the agent does not fulfil all of its initial promise. TNFis are leaving the initial phase as many patients do not respond, those who do respond require continual treatment and large studies have been published describing more accurately rare, serious complications such as infection and cancer. They now need to enter the final stage of drug adoption, in which their advantages and disadvantages are seen in a balanced light. We believe that the TACIT trial is therefore timely from the perspective of both patients and recruiting clinicians.

Informing potential participants of benefits and risks

Potential participants were identified by rheumatologists and specialist nurses in routine clinics at participating centres. They received a brief summary of relevant information about the trial including information on the key risks and benefits. Those patients who were interested received a full patient information sheet explaining in plain English the purpose of the study and the actual and potential risks and benefits of DMARD combination therapy compared with the risks and benefits of treatment with TNFis. The patient information sheet was drawn up by the investigators and patient representatives based on the analysis of risks and benefits in this application. Advice was sought from the full trial patient representatives group and the Trial Steering Committee before submission to the relevant research ethics committee.

Clinical implications

General implications

Tumour necrosis factor inhibitors and other biological treatments have revolutionised the treatment of RA and other inflammatory immune disorders. The TACIT trial underlines the need for patients to have ongoing access to these treatments. There is no evidence in the TACIT trial to indicate that TNFis do not have a crucial role in the treatment of RA.

Clinical implications

A range of leading experts helped devise existing NICE guidance for the use of TNFis in active RA,[81] which was based on extensive reviews of RCTs and associated observational studies. The rationale for using TNFis is mainly derived from extrapolating the results of these placebo-controlled trials using modelling studies that examine the health economic benefits of TNFis, with the help of historical data from observational studies. Before the TACIT trial there have been no head-to-head trials comparing TNFis with effective alternative treatments in established RA.

There have been three head-to-head trials of cDMARDs compared with TNFis in early RA. These trials all show that treatment strategies starting with cDMARDs or with TNFis give equivalent results over 12–24 months. As a consequence, there is no strong indication to start TNFis in preference to cDMARDs in early RA patients. Current NICE guidance, in our view, correctly recommends that cDMARDs are used in active early RA.[72]

The balance of current evidence suggests that the key role of TNFis in RA is in active disease that is not fully controlled by DMARDs. Placebo-controlled trials have established the efficacy of TNFis. Observational studies in registries have confirmed their safety. However, neither approach has identified how best to use them. We consider that defining their optimal use requires undertaking head-to-head trials of different treatment strategies. Although more than a decade has passed since their introduction, we still do not know their value as short-term tapered treatments or whether they should be given to selected subsets of patients.

If TNFis were low-cost treatments there would be little concern about their optimal use. However, they are among the most expensive of those treatments that are used for relatively common diseases. As a consequence, the payers for health care wish to ensure that their use delivers true ‘value for money’.

If TNFis ensured that most patients with active RA who received them entered a period of sustained remission, there would be relatively little difficulty defending their widespread use. However, the TACIT trial and all other trials and observational studies show that only a minority of patients with active RA who receive TNFis achieve sustained remission.

Tumour necrosis factor inhibitors are usually simple for patients to take, adverse events are relatively uncommon and the onset of their effect is usually fairly rapid. Therefore, if cost was not an issue most patients would probably prefer to take TNFis rather than try cDMARDs.[294] However, this is probably the wrong question to ask. As neither strategy in the TACIT trial ensured that most patients with active RA enter remission, the real need is to identify more effective and more cost-effective treatment strategies.

The TACIT trial therefore shows that the current approach to using TNFis in established RA, encapsulated within current NICE guidance, does not necessarily result in cost-effective outcomes in all patients. We do not consider that using cDMARDs followed by TNFis represents an ideal approach. Instead, further research is needed to identify more effective treatment strategies. For the present it appears preferable to ensure that patients with active established RA receive the most clinically effective and cost-effective treatment possible. From this perspective offering cDMARDs before TNFis appears to be appropriate and sensible.

The model of care used in the TACIT trial assumed that all patients with active established RA should be offered similar treatment. Using this approach some patients achieved a very good response with TNFis, a slightly small number of patients achieved a very good response with cDMARDs, a few patients achieved a very good response when they received TNFis after failing to respond to cDMARDs and most patients had a relatively poor response to all treatments. Universal treatment strategies do not appear to be very effective. The most sensible approach would be to individualise care.[295,296]

Research implications

Most clinicians consider that TNFis are highly effective treatments for active RA. However, we have found them to be no better than intensive cDMARDs for many patients. One reason for clinicians favouring them is their rapid onset of action. Another reason is that patients enrolled in early trials of biologics had more severe RA than is normally seen in current routine practice.[297] As a consequence, the benefits of biologics in these trials may have appeared greater that the benefit that would be likely to occur when they are used in routine practice settings. In addition, there is extensive evidence, at least in some countries, that patients starting biologics in clinical practice have far milder disease than patients in clinical trials,[298–301] making the translation of research findings into practice recommendations particularly challenging.

The TACIT trial was a strategy trial that required patients to attend outpatient clinics for monthly review and involved substantial efforts from both patients and the rheumatologists and specialist nurses in the collaborating centres. Before the start of the trial there were concerns about the ethics of asking patients to wait for biological treatments and whether or not patients would wish to participate. One important conclusion from the TACIT trial is that comparative trials of high-cost treatments are feasible in long-term disorders such as RA. Patients and clinicians are willing to take part in such trials and when they are undertaken in routine clinic settings they can deliver results of potential clinical relevance.

The TACIT trial involved giving patients intensive cDMARD treatments that were organised by specialist nurses and supervised by rheumatologists. Although some training was provided in the specific organisation of the trial, this did not include detailed training about how to deliver intensive DMARD combinations. Nevertheless, specialist nurses achieved this without any difficulties being encountered. A second general conclusion therefore is that rheumatology specialist nurses have sufficiently high levels of clinical skills to deliver more intensive DMARD combination therapy. It would therefore be possible to deliver this management strategy within existing specialist centres using currently available staff.

Finally, the costs of undertaking the TACIT trial merit consideration. The trial was funded by a substantial grant from the National Institute for Health Research Health Technology Assessment programme and without this grant it could not have been undertaken. However, the savings from not prescribing TNFis within the TACIT trial to patients who met the criteria for receiving theses biologics but who received cheaper DMARDs meant that the overall cost of the TACIT trial to the NHS was relatively small. Therefore, we consider that it is possible to undertake further strategy trials of high-cost treatments such as TNFis for minimal additional costs to the NHS as a whole. Many NHS patients receiving high-cost biologics for arthritis could be enrolled in strategy trials such as the TACIT trial to help the NHS identify the most effective and cost-effective ways to use high-cost treatments.

The TNFis used in the TACIT trial and a number of other biological agents in RA are licensed within Europe and North America for treating active RA. The Phase II and Phase III development programmes for these agents have all been funded by their manufacturers and have used broadly similar trial methods, focusing on patients who have failed to respond to treatments such as methotrexate either remaining on this treatment or taking an additional biologic. Such trial designs are efficient in establishing whether or not the biologics are effective. However, the regulatory process does not involve head-to-head comparisons of biologics with effective standard treatments. It is likely that the widespread adoption of the current approach by regulatory agencies might have overemphasised the benefits of biologics compared with other less expensive forms of treatment. Clearly this a complex issue as there is a balance between the complexity and duration of the regulatory process and the need to obtain full information about the

relative value of new treatments. In our view there are advantages in placing head-to-head trials with effective comparators at some point in the regulatory pathway, an assessment that has been made by others.[302,303]

Tumour necrosis factor inhibitors achieve rapid improvements in the ESR and other measures of disease activity compared with conventional DMARDs. Indeed, some licensed DMARDs, such as ciclosporin, have little impact on the ESR. The use of composite measures to assess treatment response in RA, such as the DAS28 and ACR response, is likely, in our opinion, to unduly favour TNFis. The impact of TNFis on measures such as the HAQ and EQ-5D, which are more reflective of patients' overall status, is less marked. We are unconvinced that the disproportionate impact of TNFis on laboratory measures such as the ESR is of clinical consequence, and it may lead to an overemphasis on improving laboratory as opposed to clinical measures. In the TACIT trial we found that this rapid improvement in ESR was not immediately related to decreases in clinical measures of direct importance to patients, such as falls in tender and swollen joint counts. The development of the current assessment methods in clinical trials in RA, which date back to the 1990s, is based on expert opinion rather than direct evidence. Although the approach is likely to reduce sample sizes in trials, it may favour some forms of treatment over others. One way of minimising this risk is to ensure that trials use a wide range of measures. Using changes in some measures, such as the DAS28, to model changes in other measures, such as the HAQ and EQ-5D, seems particularly inappropriate.

The economic case for using biologics such as TNFis in RA depends on extrapolating the results of placebo-controlled trials and using historical data from observational cohorts of previously treated patients. This approach involves two challenges. First, it is difficult to be certain how non-biological treatments would affect RA patients over time. Many of the models assume that they would not do well but there is limited evidence to support this view. Second, the data used for modelling are often historical and changes in the severity and natural history of treated RA may mean that these historical data have limited relevance to current patients. We consider that the economic rationale for using biological treatments should involve more emphasis on directly collected information from clinical trials and give less emphasis to theoretical modelling over long time frames.

Chapter 5 Conclusions

Key finding

The TACIT trial showed that RA patients who have failed to respond to methotrexate and another DMARD show clinically important improvements over 12 months if initially treated with cDMARDs, reserving TNFis for non-responders to these combinations. These improvements were equivalent to those achieved by starting all patients on TNFis with methotrexate or another DMARD monotherapy. The cost of the approach focused on using cDMARDs initially is approximately half the cost of using TNFis during the first 12 months of treatment. The equivalence of cDMARDs and TNFis is confirmed in systematic reviews of published trials in both early and established RA.

Health-care implications

The results from the TACIT trial, together with the results of the systematic reviews of previous trials of intensive cDMARDs and TNFis in active early and established RA, suggest that the following points could be considered when deciding how best to treat patients with active established RA who have not responded to methotrexate:

1. There is an extensive body of direct and indirect evidence which shows that giving such patients intensive cDMARD therapy and reserving TNFis for 6-month non-responders is clinically effective. Both EQ-5D- and SF-36-based QALY assessments suggest that cDMARDs are also cost-effective. A 6-month period of cDMARD therapy is sufficient to assess its effectiveness and there is no evidence that patients have any long-term disadvantages in terms of future disability, quality of life or joint damage from taking DMARD combinations for 6 months, even if they fail to respond.
2. In active established RA, starting treatment with either cDMARDs or TNFis results in equivalent clinically relevant improvements in disability and quality of life over 12 months. Immediately starting TNFis gives rapid early reductions in disease activity compared with starting cDMARDs but these improvements do not result in larger reductions in disability. There is no evidence that either strategy is associated with substantial erosive damage; radiological progression was minimal with both cDMARDs and TNFis.
3. Only a minority of patients achieve sustained remission with cDMARDs or TNFis. This suggests that neither approach should be considered an ideal long-term treatment strategy for all RA patients. Instead, they appear to be therapeutic options that decrease disability and reduce disease activity in some patients with active established RA.

Research implications

The TACIT trial raises many questions as well as providing some answers. There are a number of research areas that need to be taken forward. The following issues appear to be particularly important:

1. Identifying predictors of response to cDMARDs and TNFis will enable a move towards individualised treatment. This is of crucial importance as some patients respond well to cDMARDs whereas others respond well to TNFis, and prospectively identifying potential good responders should optimise treatment outcomes. In essence, there is a need to move away from the conventional 'one size fits all' approach to a more personalised clinical care approach. Research needs to focus on identifying predictors of response to these different treatment approaches. One possible implication is that national guidance on treatment decisions for specific interventions given to individual patients may not represent the most effective way of planning the delivery of care. Guidance might be most appropriate if it is moved from the general to the specific.

2. We need to define the most effective ways of using current treatments, including undertaking more strategy trials to examine novel ways of using high-cost treatments. Examples include identifying the benefits of short courses of biologics in early RA, in which the rapid effects of biologics may be beneficial, and redefining the optimal duration of TNFi treatment in established RA. Currently, once started, TNFis are continued if patients respond. However, this approach is based on custom and practice and has not been tested in clinical trials. The TACIT trial suggests that TNFis have dramatic immediate benefits but that, as currently used, these major improvements are present by 2 or 3 months and patients do not generally improve further. It is possible that short-term 'induction therapy' might be particularly useful with these treatments. Such an approach would change the cost base of using biological treatments.
3. There should be a greater emphasis on head-to-head trials when defining the overall benefits of high-cost treatments in RA. Extrapolating the results of short-term placebo-controlled trials and using observational studies to model economic benefits are less helpful in determining treatment pathways. Only head-to-head trials of treatment strategies including economic analyses can help drive forward innovative, cost-effective treatment approaches involving biologics. The results of the TACIT trial do not indicate that there should be less overall use of TNFis but that they are not being used in a highly effective manner.
4. A range of new non-biological treatments, particularly kinase inhibitors, is being developed for RA and some of these agents may soon be introduced into clinical practice. It is too early to judge the potential impact of these new treatments but it is likely that the treatment paradigm will change as a result. The TACIT trial highlights the limitations of our current treatment paradigm and therefore strengthens the case for developing new approaches to disease management.

The biologics revolution following the introduction of TNFis into routine clinical practice has changed RA care and, in our view, has benefited patients substantially. Clinicians and patients were keen to have access to these treatments when they first became available. As with all new treatments this is likely to have resulted in a relative overestimation of their clinical and economic benefits. Time and experience usually temper the initial enthusiasm for new treatments and this is likely to be the case with biologics for RA during the next decade. Trials such as the TACIT trial should help modify previous potential overenthusiasm for biologics in RA. However, the development of new agents is more likely to have a major impact, as novelty is a potent driver for changing behaviour. In our view it does not matter so much what drives change; the crucial point is to realise that some changes are needed.

Acknowledgements

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The TACIT trial involved a very large number of staff, who ran the trial, served on its various committees and were involved in recruitment and patient care within the trial. We are very grateful for all of their help.

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Appendix 1 Types of protocol deviations and permitted flexibilities

Deviation type number	Protocol deviation	Protocol criteria	Data Monitoring and Ethics Committee flexibility
1	Multiple DMARDs (while on TNFi)	Patients randomised to the TNFi arm are permitted to take one DMARD only (methotrexate unless contraindicated)	No flexibility
2	High-dose steroids	Not on high-dose steroids (in excess of 10 mg of prednisolone or equivalent per day at trial entry)	No flexibility
3	Trial medication given before baseline	Not expressly stated, but trial medication should commence immediately after the baseline outcome data are collected	No flexibility
4	Baseline outcome data (questionnaires) collected 3 months after starting trial medication	Not expressly stated, but trial medication should commence immediately after the baseline outcome data are collected	No flexibility
5	> 8 weeks off trial medication	A temporary interruption in trial medication of up to 8 weeks (consecutive) will be permitted if an adverse event or other unforeseen circumstance, deemed by the principal investigator to require stoppage of trial medication, has occurred	No flexibility
6	Ineligible – history of serious illness	No serious intercurrent illness	No flexibility
7	Changed treatment at 6 months despite improvement in DAS of > 1.2	At 6 months: no change in treatment if good response (≥ 1.2 fall in DAS)	No flexibility
8	Steroid injections given between screening and baseline	If a steroid injection is given before baseline, the baseline assessment should be delayed for 1 month after the date of the injection	Include in the ITT analysis and the per-protocol analysis but baseline screening assessment should be used rather than the one immediately following the steroid injection
9	Milestone assessments performed outside the visit window	Milestone assessments (6 and 12 months) must be performed within ±14 days of the estimated date of assessment; this was not defined in the protocol but as part of the TACIT Working Practice	Milestone assessments must be performed within ±31 days of the estimated date of assessment
10	Insufficient medication at baseline	At baseline, patients must be started on cDMARDs if in the DMARD arm and on a TNFi with accompanying DMARD if in the TNFi arm	Allow up to 1 month from baseline for the introduction of the second trial medication
11	Chest radiography not carried out prior to randomisation	Negative screen for tuberculosis (including chest radiography)	Local methods can be used
12	Patient not switched at 6 months	Patients assessed at 6 months: no change if good response (≥ 1.2 fall in DAS); change treatment from 6-month assessment if < 1.2 fall in DAS (change to second TNFi if in TNFi arm; change to first TNFi if in cDMARD arm)	Switch permitted at up to 9 months; however, the decision to switch is still based on the 6-month time point

Appendix 2 Health economic costs

This appendix contains the source data for costs used in the economic analysis.

TABLE 48 Unit costs for the health economic analysis

Item	Unit	Unit cost (£) (2010/11 prices)	Assumptions
GP			
At surgery[a]	Consultation	30	Per surgery consultation lasting 11.7 minutes. Includes direct care staff costs; excludes qualification costs
At home[a]	Home visit	99	Per home visit lasting 23.4 minutes. Includes direct care staff costs; excludes qualification costs
Telephone call[a]	Call	18	Per telephone consultation lasting 7.1 minutes. Includes direct care staff costs; excludes qualification costs
Repeat prescription request without GP contact[a]	Prescription	19	Assuming 5 minutes of GP time. Includes direct care staff costs; excludes qualification costs
Nurse			
At surgery[a]	Visit	11	Based on cost per hour of face-to-face contact. Excludes qualifications and assumes that each consultation lasts 15.5 minutes
Telephone call[a]	Call	7	Assumes that ratio of time spent on telephone consultation to time spent on face-to-face consultation is same as for GP (60.68%)
Physiotherapist			
At hospital[b]	Attendance	38	Physiotherapy Total Attendances – Adult (19 and Over) – service code 650A – Total OPATT table
At home[a,c]	Visit	58	Based on 2010/11 prices but with time estimates from 2009/10. Excludes qualification costs
At GP surgery[a,c]	Visit	27	Based on 2010/11 prices but with time estimates from 2009/10. Excludes qualification costs
Elsewhere[a]	Visit	27	Assumes same cost as physiotherapist at GP surgery as conservative estimate
Occupational therapist			
At hospital[b]	Attendance	56	Occupational Therapy Total Attendances – Adult (19 and Over) – service code 651A – Total OPATT table
At home[a,c]	Visit	57	Based on 2010/11 prices but with time estimates from 2009/10. Excludes qualification costs
At GP surgery[a,c]	Visit	20	Based on 2010/11 prices but with time estimates from 2009/10. Excludes qualification costs
Elsewhere[a]	Visit	20	Assumes same cost as occupational therapist at GP surgery as conservative estimate

continued

TABLE 48 Unit costs for the health economic analysis (*continued*)

Item	Unit	Unit cost (£) (2010/11 prices)	Assumptions
Hospital services			
A&E[b]	Attendance	108	Accident and Emergency Services: Not leading to Admitted – Index table
Hospital stay 1 night[b]	Bed-day	568	Non-Elective Inpatient (Short Stay) HRG Data – Index table (per 1 night)
Hospital stay > 1 night[b]	Bed-day	426	Weighted average of all Non-Elective Inpatient (Long Stay) HRG Data
Outpatient appointment[b]	Attendance	105	Total – Outpatient Attendances – Index table
Social services			
Meals on Wheels[a]	Meal	6	Average cost per local authority meal on wheels
Home help[a]	Visit	12	Assumes 30-minute visits. Based on cost per hour of face-to-face contact. Weighted average accounting for different rates for day/evening/weekday/weekends
Social worker[a]	Hour	152	Adult services – cost per hour of face-to-face contact. Excludes qualifications
Social worker telephone call[a]	Call	38	Assumes face-to-face consultation lasting 15 minutes
Other health or social service			
Community and outreach nurse[b]	Contact	50	Community and Outreach Nursing Services: Specialist Nursing – Index table – TCSCNSN
Dentist[b]	Attendance	78	TOCS tab: Community Dental Services – CN20
District nurse[a]	Contact	64	Assumes home visit lasting 1 hour
Orthotics[a]	Contact	16	Assumes podiatrist
Osteopath[d]	Contact	43	Assumes mid-point cost per session from range of £35–50 per 30- to 40-minute contact
Paramedic[b]	Contact	119	TPARO – Index table
Podiatrist[a]	Contact	16	Assumes 30-minute appointment
Medication[e]	Milligrams	Range < 0.01 to 296	
Social security benefits			
Attendance Allowance[f]	Benefit	60	Based on mean of high and low attendance allowance
Disability Living Allowance[f]	Benefit	41	Based on mean of care and mobility component
Council Tax Benefit[f]	Benefit	65	Based on single person aged 25+ years
Housing Benefit[f]	Benefit	65	Based on single person aged 25+ years
Incapacity Benefit[f]	Benefit	75	Based on the mean of lower and higher rates of short-term incapacity benefit under state pension age
Income Support[f]	Benefit	65	Based on single person aged 25+ years

TABLE 48 Unit costs for the health economic analysis (*continued*)

Item	Unit	Unit cost (£) (2010/11 prices)	Assumptions
Jobseeker's Allowance[f]	Benefit	65	Based on contribution-based jobseeker's allowance personal rates, aged 25+ years
Severe Disablement Allowance[f]	Benefit	59	Basic rate only
Statutory Sick Pay[f]	Benefit	79	
Working Tax Credit[g]	Benefit	37	Based on basic element only, £1920 per year divided by 52 weeks
Carer Allowance[f]	Benefit	54	
Child Benefit[g]	Benefit	20	Assumes one child only
Child Tax Credit[g]	Benefit	10	Based on basic element only, £545 per year divided by 52 weeks
Disability Working Allowance[g]	Benefit	51	Disabled person's tax credit replaced disability working allowance (see www.hmrc.gov.uk/dptctables/index.htm), £2650 per year divided by 52 weeks
Family Tax Credit[g]	Benefit	10	Child tax credit family element
Pension[f]	Benefit	98	Category A or B pension
Pension Credit[f]	Benefit	10	The maximum for a single person is £20.52 so divide by 2 for an arbitrary figure
Tax Credit[g]	Benefit	37	Assumes working tax credit

A&E, accident and emergency.

a Curtis L. Unit Costs of Health and Social Care 2011. Canterbury: Personal Social Services Research Unit, University of Kent; 2011.

b Department of Health. NHS Reference Costs 2010/11. URL: www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131145.xls (accessed 20 March 2012).

c Curtis L. Unit Costs of Health and Social Care 2010. Canterbury: Personal Social Services Research Unit, University of Kent; 2010.

d NHS Choices. Osteopathy. URL: www.nhs.uk/conditions/Osteopathy/Pages/Introduction.aspx (accessed 9 October 2012).

e British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. No. 60, September 2010. London: BMA and RPS; 2010.

f Department for Work and Pensions. Work and Pensions – Social Security Benefit Up-rating. URL: www.dwp.gov.uk/docs/benefitrates2010.pdf (accessed 26 March 2012).

g Institute of Fiscal Studies. Tax and benefit tables by the Institute of Fiscal Studies. URL: www.ifs.org.uk/ff/taxcredits.xls (accessed 26 March 2012).

TABLE 49 Trial medication unit costs

Medication	Preparation	Cost per mg (£)[a]	Cost per day if dose missing (£)[b]	Cost per medication if medication taken as required (£, assuming medication used for 1 month)[b]
Adalimumab	Injection	8.94	1399.73	1399.73
Azathioprine	Oral	0.01	0.28	8.27
Ciclosporin	Oral	0.02	3.09	92.67
Depo-Medrone	Injection	0.07	4.76	4.76
Etanercept	Injection	3.58	1002.12	1002.12
Folic acid	Oral	0.01	0.04	1.06
Gold injections	Injection	0.22	27.69	27.69
Hydroxychloroquine	Oral	< 0.00	0.17	4.95
Infliximab	Injection	4.20	419.62	419.62
Kenalog (Triamcinolone, Bristol-Myers Squibb)	Injection	0.04	1.92	1.92
Leflunomide	Oral	0.17	2.36	70.87
Methotrexate	Oral	0.05	5.01	5.01
Methotrexate	Injection	1.98	5.01	5.01
Methylprednisolone	Injection	0.04	47.64	47.64
Penicillamine	Oral	< 0.00	1.00	29.94
Prednisolone	Oral	0.06	0.09	2.58
Sulfasalazine	Oral	< 0.00	0.49	14.66

a British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. No. 60, September 2010. London: BMA and RPS; 2010.
b Department of Health. *Prescription Cost Analysis – England, 2011*. London: Department of Health. URL: www.hscic.gov.uk/pubs/prescostanalysis2011 (accessed August 2014).

Appendix 3 Complete-case population analysis

This appendix contains the tables and figures from the complete-case analysis.

TABLE 50 Primary outcome and other key secondary outcomes [mean (95% CI)] in the complete-case population by treatment group

Outcome	cDMARDs ($n = 72$)					TNFis ($n = 75$)				
	Initial	6 months	12 months	Change 0–6 months	Change 0–12 months	Initial	6 months	12 months	Change 0–6 months	Change 0–12 months
HAQ score	1.85 (1.71 to 1.99)	1.50 (1.34 to 1.66)	1.33 (1.16 to 1.51)	0.35 (0.23 to 0.48)	0.52 (0.41 to 63)	1.84 (1.68 to 2.00)	1.43 (1.24 to 1.63)	1.47 (1.27 to 1.66)	0.41 (0.26 to 0.55)	0.38 (0.24 to 0.51)
EQ-5D score	0.40 (0.32 to 0.47)	0.53 (0.47 to 0.60)	0.62 (0.56 to 0.69)	−0.14 (−0.21 to −0.06)	−0.22 (−0.31 to −0.14)	0.36 (0.29 to 0.43)	0.57 (0.50 to 0.63)	0.53 (0.46 to 0.60)	−0.21 (−0.27 to −0.14)	−0.17 (−0.24 to −0.10)
Larsen Score	47.3 (37.6 to 57.1)	48.1 (38.3 to 58.0)	47.4 (37.4 to 57.4)	−0.8 (−1.7 to 0.1)	−1.4 (−2.7 to −0.2)	34.7 (25.9 to 43.5)	34.4 (25.5 to 43.4)	35.1 (25.9 to 44.3)	−0.3 (−1.1 to 0.6)	−0.7 (−1.8 to 0.4)

TABLE 51 SF-36 domain and summary scores [mean (95% CI)] in the complete-case population by treatment group

	cDMARDs ($n = 72$)					TNFis ($n = 75$)				
Outcome	Initial	6 months	12 months	Change 0–6 months	Change 0–12 months	Initial	6 months	12 months	Change 0–6 months	Change 0–12 months
Physical functioning	30.8 (25.6 to 36.0)	36.5 (30.1 to 43.0)	42.8 (36.2 to 49.4)	−5.7 (−12.7 to 1.3)	−11.9 (−18.6 to −5.3)	25.8 (21.1 to 30.6)	44.3 (37.8 to 50.8)	40.3 (33.6 to 46.9)	−18.4 (−24.4 to −12.5)	−14.4 (−20.5 to −8.3)
Role physical	13.5 (7.1 to 20.0)	38.2 (28.4 to 48.0)	37.2 (26.8 to 47.5)	−24.7 (−35.6 to −13.7)	−23.6 (−34.3 to −13.0)	14.3 (7.8 to 20.9)	44.7 (34.7 to 54.6)	36.0 (26.2 to 45.9)	−30.3 (−40.8 to −19.9)	−21.7 (−31.7 to −11.7)
Pain	26.0 (22.6 to 29.4)	41.5 (36.8 to 46.1)	48.9 (43.5 to 54.2)	−15.5 (−20.9 to −10.1)	−22.9 (−28.7 to −17.0)	28.4 (24.3 to 32.4)	49.3 (44.3 to 54.3)	46.2 (40.7 to 51.7)	−21.0 (−26.8 to −15.1)	−17.9 (−24.2 to −11.5)
General health perception	34.7 (30.6 to 38.8)	40.0 (35.3 to 44.7)	45.1 (39.5 to 50.7)	−5.4 (−10.0 to −0.7)	−10.8 (−16.2 to −5.3)	31.6 (27.7 to 35.5)	47.3 (42.5 to 52.1)	40.7 (35.5 to 45.8)	−15.7 (−20.9 to −10.6)	−9.1 (−14.2 to −3.9)
Vitality	27.6 (23.1 to 32.0)	36.6 (31.3 to 41.9)	38.2 (32.4 to 44.0)	−9.0 (−14.7 to −3.4)	−10.6 (−16.1 to −5.1)	28.1 (23.6 to 32.6)	43.5 (38.3 to 48.7)	39.9 (34.3 to 45.5)	−15.5 (−21.0 to −10.0)	−11.8 (−17.8 to −5.8)
Social functioning	50.0 (44.4 to 55.6)	61.3 (54.9 to 67.7)	68.0 (61.7 to 74.2)	−11.3 (−17.6 to −5.0)	−18.1 (−25.0 to −11.2)	42.7 (36.9 to 48.4)	61.2 (54.9 to 67.5)	61.2 (54.6 to 67.7)	−18.5 (−25.7 to −11.3)	−18.5 (−26.4 to −10.6)
Role emotion	44.9 (34.2 to 55.7)	62.5 (51.9 to 73.1)	63.4 (53.0 to 73.9)	−17.6 (−31.0 to −4.2)	−18.5 (−31.8 to −5.2)	35.6 (25.2 to 45.9)	56.0 (45.2 to 66.8)	54.7 (43.9 to 65.4)	−20.4 (−34.0 to −6.9)	−19.1 (−33.2 to −5.1)
Mental health	61.6 (56.9 to 66.2)	68.3 (63.5 to 73.1)	71.9 (67.2 to 76.7)	−6.7 (−12.1 to −1.4)	−10.4 (−16.0 to −4.8)	59.8 (54.7 to 64.9)	68.5 (63.6 to 73.4)	68.4 (63.5 to 73.2)	−8.7 (−14.4 to −3.0)	−8.6 (−14.4 to −2.8)
PCS	27.9 (26.3 to 29.5)	32.3 (30.0 to 34.6)	34.3 (31.7 to 36.9)	−4.4 (−6.9 to −1.8)	−6.3 (−9.0 to −3.7)	27.9 (26.2 to 29.6)	36.7 (34.4 to 39.0)	34.0 (31.7 to 36.2)	−8.8 (−10.9 to −6.7)	−6.1 (−8.4 to −3.7)
MCS	43.2 (40.4 to 46.0)	47.7 (44.7 to 50.6)	48.9 (46.2 to 51.6)	−4.5 (−7.6 to −1.4)	−6.0 (−9.4 to −2.8)	41.0 (38.2 to 43.7)	46.2 (43.3 to 49.2)	46.5 (43.8 to 49.2)	−5.3 (−8.5 to −2.0)	−5.5 (−8.9 to −2.2)

TABLE 52 Linear regression for the adjusted and unadjusted treatment effect for the primary outcome measure (HAQ) in the complete-case population

	Model 1 (unadjusted): treatment + region		Model 2 (adjusted): treatment + demographics + baseline score	
Outcome	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
Change in HAQ score				
12 months	0.14 (–0.03 to 0.32)	0.108	0.15 (–0.03 to 0.32)	0.094
6 months	–0.06 (–0.25 to 0.13)	0.542	–0.08 (–0.271 to 0.10)	0.362

Demographics variables are age, sex, ethnicity, disease duration and region. The reference group is cDMARDs.

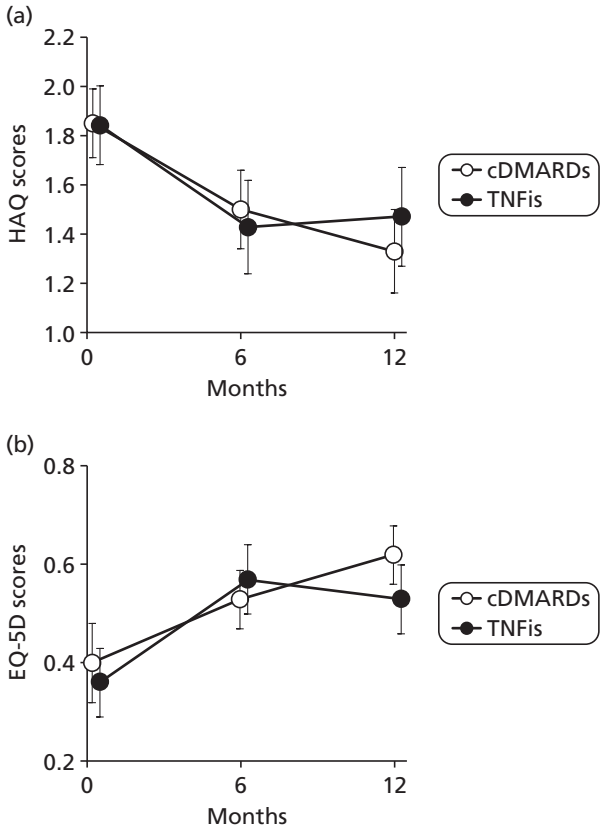

FIGURE 28 Changes in mean HAQ and EQ-5D scores (95% CIs) over 12 months in the complete-case population. (a) HAQ; and (b) EQ-5D.

TABLE 53 Longitudinal analysis comparing the effect of randomised treatment arm on primary and secondary outcome measures in the complete-case population using GEEs with unstructured correlation

	Model 1 (unadjusted): treatment + region + time		Model 2 (adjusted): treatment + demographics + baseline score + time	
Outcome	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
Larsen score	−0.58 (−1.86 to 0.69)	0.370	−0.46 (−1.91 to 0.98)	0.531
SF-36 role physical	1.39 (−10.75 to 13.52)	0.822	2.29 (−8.22 to 12.80)	0.669
SF-36 vitality	3.84 (−2.69 to 10.37)	0.249	3.66 (−1.82 to 9.14)	0.190
SF-36 social functioning	3.55 (−4.95 to 12.05)	0.413	−2.49 (−9.27 to 4.29)	0.472
SF-36 role emotion	1.11 (−15.37 to 17.59)	0.895	−7.00 (−18.40 to 4.39)	0.229
SF-36 mental health	−0.08 (−6.78 to 6.63)	0.982	−1.77 (−6.69 to 3.15)	0.480
SF-36 MCS	0.07 (−3.82 to 3.97)	0.971	−1.68 (−4.64 to 1.29)	0.268

Demographics variables are age, sex, ethnicity, disease duration and region. The reference group is cDMARDs.

TABLE 54 Primary outcome and other key secondary outcomes [mean (95% CI)] in the complete-case population cDMARD group by treatment status

	Stayed on cDMARDs ($n = 35$)				Changed to TNFis ($n = 37$)			
Outcome	Initial	6 months	12 months	Change 0–12 months	Initial	6 months	12 months	Change 0–12 months
HAQ score	1.91 (1.69 to 2.14)	1.35 (1.11 to 1.58)	1.39 (1.13 to 1.65)	0.53[a] (0.37 to 0.68)	1.79 (1.62 to 1.96)	1.64 (1.42 to 1.85)	1.28 (1.04 to 1.53)	0.51 (0.34 to 0.67)
Larsen score	54.2 (38.1 to 70.3)	54.8 (38.6 to 70.9)	55.5 (39.5 to 71.5)	−1.3[b] (−3.0 to 0.5)	40.8 (29.3 to 52.3)	41.8 (30.1 to 53.6)	39.4 (27.4 to 51.4)	−1.6 (−3.4 to 0.3)
EQ-5D score	0.38 (0.27 to 0.49)	0.63 (0.55 to 0.71)	0.68 (0.61 to 0.76)	−0.30[c] (−0.40 to −0.20)	0.41 (0.31 to 0.51)	0.44 (0.34 to 0.54)	0.56 (0.46 to 0.67)	−0.15 (−0.28 to −0.02)

a $p = 0.85$ comparing change at 12 months between groups by unpaired *t*-test.
b $p = 0.81$ comparing change at 12 months between groups by unpaired *t*-test.
c $p = 0.067$ comparing change at 12 months between groups by unpaired *t*-test.

TABLE 55 Adjusted and unadjusted treatment effect using GEEs for the primary outcome measure (HAQ) in the complete-case population cDMARD arm by treatment status

	Model 1 (unadjusted): treatment + region + time		Model 2 (adjusted): treatment + demographics + baseline score + time	
Outcome	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
Change in HAQ score				
12 months	0.22 (0.03 to 0.41)	0.025	0.20 (0.01 to 0.39)	0.039

Demographics variables are age, sex, ethnicity, disease duration and region. The reference group is no switch.

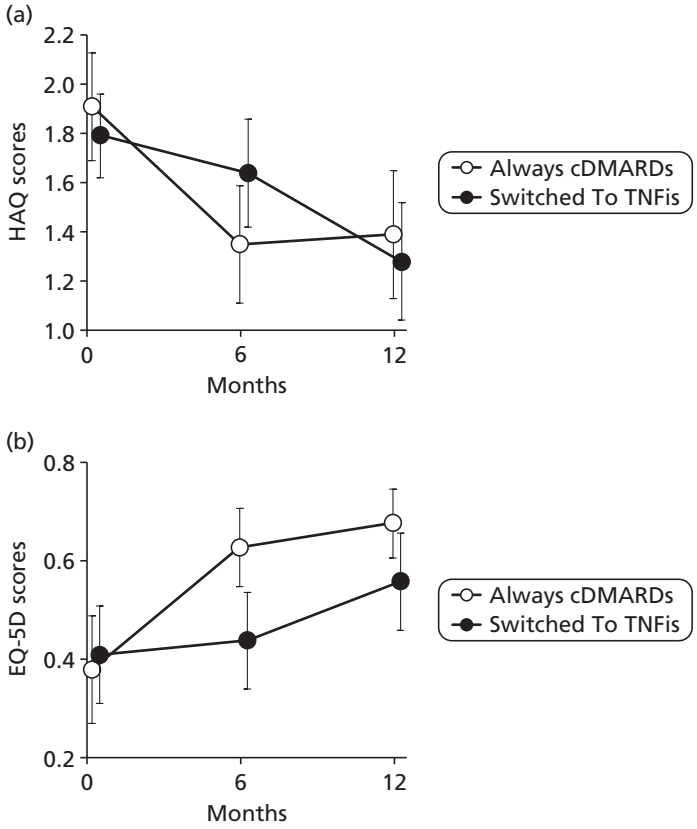

FIGURE 29 Changes in mean HAQ and EQ-5D scores (95% CIs) over 12 months in the complete-case population cDMARD arm by treatment status. (a) HAQ; and (b) EQ-5D.

TABLE 56 Mean DAS28 and component scores (95% CIs) by treatment group in the complete-case population

	cDMARDs ($n = 72$)					TNFis ($n = 75$)				
Month of assessment	DAS28	Tender joint count	Swollen joint count	ESR (mm/hour)	VAS	DAS28	Tender joint count	Swollen joint count	ESR (mm/hour)	VAS
0	6.20 (5.98 to 6.42)	15.96 (14.47 to 17.45)	10.01 (8.58 to 11.45)	34.17 (28.04 to 40.30)	67.42 (62.74 to 72.10)	6.28 (6.10 to 6.47)	18.17 (16.66 to 19.68)	11.28 (9.66 to 12.90)	26.12 (21.72 to 30.52)	67.56 (62.97 to 72.15)
1	5.36 (5.05 to 5.68)	11.43 (9.44 to 13.41)	6.80 (5.32 to 8.28)	33.40 (27.50 to 39.30)	54.54 (48.47 to 60.60)	4.56 (4.24 to 4.88)	10.92 (8.89 to 12.95)	5.18 (3.90 to 6.46)	16.51 (12.91 to 20.10)	44.07 (38.34 to 49.79)
2	5.01 (4.70 to 5.31)	9.30 (7.65 to 10.95)	5.89 (4.67 to 7.10)	31.03 (25.14 to 36.92)	50.09 (44.22 to 55.95)	3.99 (3.64 to 4.33)	7.48 (5.98 to 8.98)	4.44 (3.05 to 5.83)	16.79 (12.27 to 21.31)	41.14 (35.32 to 46.96)
3	4.91 (4.55 to 5.27)	9.48 (7.61 to 11.35)	5.58 (4.20 to 6.95)	30.65 (24.58 to 36.72)	49.99 (43.70 to 56.27)	4.06 (3.70 to 4.41)	7.20 (5.52 to 8.88)	4.03 (2.75 to 5.30)	18.68 (15.04 to 22.32)	41.12 (35.32 to 46.92)
4	4.69 (4.37 to 5.01)	8.38 (6.71 to 10.05)	4.76 (3.44 to 6.09)	30.93 (25.30 to 36.55)	41.93 (35.47 to 48.38)	4.14 (3.75 to 4.52)	8.19 (6.36 to 10.03)	3.88 (2.70 to 5.05)	18.00 (14.33 to 21.67)	41.65 (35.21 to 48.09)
5	4.61 (4.25 to 4.97)	8.37 (6.62 to 10.12)	5.73 (4.30 to 7.16)	28.74 (23.26 to 34.22)	41.91 (35.10 to 48.73)	3.87 (3.52 to 4.22)	7.03 (5.15 to 8.90)	3.75 (2.62 to 4.88)	16.21 (13.13 to 19.29)	39.01 (32.96 to 45.07)
6	4.70 (4.29 to 5.11)	9.78 (7.70 to 11.86)	5.97 (4.28 to 7.66)	28.61 (22.68 to 34.55)	46.76 (39.59 to 53.93)	3.93 (3.56 to 4.30)	7.80 (5.88 to 9.72)	3.96 (2.67 to 5.25)	17.77 (13.94 to 21.61)	36.64 (30.78 to 42.50)
7	4.55 (4.19 to 4.91)	8.54 (6.61 to 10.46)	5.83 (4.38 to 7.28)	28.44 (22.33 to 34.54)	40.96 (34.46 to 47.46)	3.82 (3.44 to 4.19)	7.00 (5.23 to 8.77)	3.76 (2.44 to 5.09)	17.47 (13.51 to 21.44)	37.63 (31.17 to 44.08)
8	4.20 (3.84 to 4.57)	7.29 (5.62 to 8.96)	4.46 (3.18 to 5.74)	25.14 (19.41 to 30.87)	39.43 (33.15 to 45.71)	3.57 (3.21 to 3.93)	5.24 (3.77 to 6.70)	3.13 (1.97 to 4.28)	16.90 (13.02 to 20.78)	37.63 (31.17 to 44.08)
9	4.10 (3.74 to 4.45)	6.50 (4.94 to 8.06)	3.82 (2.75 to 4.88)	26.25 (20.51 to 31.99)	37.93 (31.89 to 43.97)	3.76 (3.41 to 4.11)	5.95 (4.36 to 7.53)	3.54 (2.27 to 4.81)	17.18 (13.96 to 20.40)	37.66 (32.12 to 43.20)
10	3.94 (3.61 to 4.27)	5.97 (4.42 to 7.52)	3.64 (2.66 to 4.62)	26.17 (20.54 to 31.80)	35.90 (30.37 to 41.43)	3.54 (3.19 to 3.90)	5.51 (3.85 to 7.16)	2.93 (1.80 to 4.06)	16.97 (13.15 to 20.79)	34.75 (28.83 to 40.67)
11	3.95 (3.63 to 4.28)	6.35 (4.65 to 8.06)	3.25 (2.23 to 4.28)	24.01 (18.71 to 29.31)	37.73 (31.37 to 44.10)	3.54 (3.17 to 3.91)	5.23 (3.68 to 6.79)	3.25 (1.89 to 4.61)	17.49 (13.66 to 21.33)	32.25 (26.14 to 38.35)
12	3.92 (3.58 to 4.26)	5.82 (4.16 to 7.48)	3.14 (2.28 to 4.00)	25.03 (19.27 to 30.79)	36.38 (29.76 to 42.99)	3.44 (3.09 to 3.79)	5.59 (3.93 to 7.24)	2.55 (1.66 to 3.43)	15.07 (11.36 to 18.78)	36.97 (30.38 to 43.57)

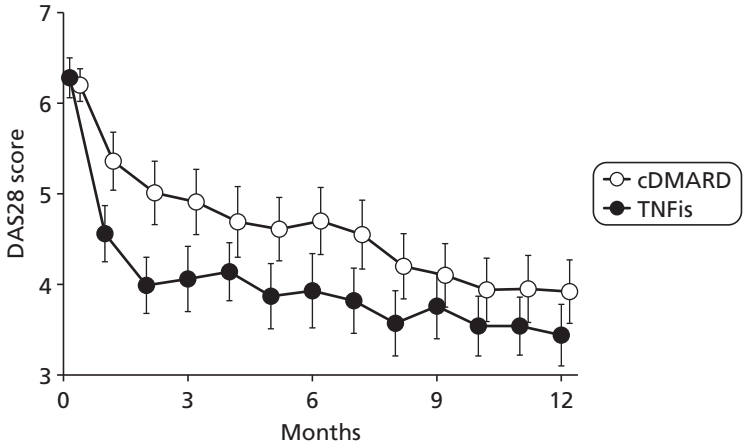

FIGURE 30 Complete-case analysis: mean change in DAS28 (95% CI) by treatment group.

TABLE 57 Longitudinal analysis comparing the effect of randomised treatment arm on disease activity score (DAS28) and its components in the complete-case population using GEEs

		Model 1 (unadjusted): treatment + region + time		Model 2 (adjusted): treatment + demographics + baseline score + time	
Time period	Variable	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
Months 1–6	DAS28	−1.06 (−1.41 to −0.71)	< 0.001	−1.02 (−1.37 to −0.68)	< 0.001
	Tender joint count	−4.37 (−6.40 to −2.35)	< 0.001	−3.14 (−4.99 to −1.29)	0.001
	Swollen joint count	−3.33 (−4.95 to −1.71)	< 0.001	−2.52 (−3.70 to −1.33)	< 0.001
	ESR (mm/hour)	−5.95 (−10.33 to −1.56)	0.008	−9.20 (−13.02 to −5.37)	< 0.001
	VAS	−10.08 (−17.08 to −3.07)	0.005	−9.07 (−15.36 to −2.78)	0.005
Months 6–12	DAS28	−0.69 (−1.11 to −0.27)	0.001	−0.58 (−0.97 to −0.18)	0.004
	Tender joint count	−3.65 (−5.93 to −1.37)	0.002	−2.12 (−3.92 to −0.32)	0.021
	Swollen joint count	−2.81 (−4.71 to −0.91)	0.004	−1.71 (−2.84 to −0.57)	0.003
	ESR (mm/hour)	−2.71 (−7.38 to 1.96)	0.255	−5.01 (−9.06 to −0.95)	0.016
	VAS	−2.73 (−11.16 to 5.71)	0.527	−1.47 (−8.53 to 5.60)	0.684
Months 1–12	DAS28	−0.92 (−1.29 to −0.55)	< 0.001	−0.82 (−1.18 to −0.46)	< 0.001
	Tender joint count	−4.26 (−6.42 to −2.11)	< 0.001	−2.71 (−4.50 to −0.92)	0.003
	Swollen joint count	−3.11(−4.85 to −1.37)	< 0.001	−2.05 (−3.13 to −0.97)	< 0.001
	ESR (mm/hour)	−5.20 (−9.52 to −0.88)	0.018	−7.96 (−11.58 to −4.35)	< 0.001
	VAS	−6.55(−14.17 to 1.07)	0.092	−5.55 (−11.90 to 0.81)	0.087

Demographics variables are age, sex, ethnicity, disease duration and region. The reference group is cDMARDs.

Appendix 4 Adverse events

This appendix contains details of all of the adverse events reported in the trial.

TABLE 58 Adverse events in the cDMARD group

Adverse event	Frequency	Per cent
Abdominal discomfort	3	0.47
Ache – arms	1	0.16
Ache – back	1	0.16
Ache – ear	1	0.16
Ache – entire body	3	0.47
Ache – foot (left)	1	0.16
Ache – hands	1	0.16
Anaemia	1	0.16
Bilateral lower lobe bronchiectasis	1	0.16
Bladder irritation	2	0.31
Blepharitis – eye (right)	1	0.16
Blurred vision	3	0.47
Blurred vision (right eye)	2	0.31
Breast lump (right)	1	0.16
Breathlessness	4	0.63
Bruising – arm (left)	1	0.16
Bruising – arm (right)	1	0.16
Bruising – flank (left)	1	0.16
Bruising – thigh (left)	1	0.16
Bruising – thigh (right)	1	0.16
Burning on micturition	1	0.16
Burning sensation – arm (right)	1	0.16
Burning sensation – shoulder (right)	1	0.16
Cardiac palpitations	2	0.31
Carpal tunnel syndrome	1	0.16
Cellulitis – shin (right)	1	0.16
Chest infection	19	2.99
Chest tightness	3	0.47
Cold	12	1.89
Cold sore	1	0.16
Collapse	1	0.16
Constipation	4	0.63

continued

TABLE 58 Adverse events in the cDMARD group (*continued*)

Adverse event	Frequency	Per cent
Cough	5	0.79
Cough – dry	4	0.63
Cough – productive	6	0.94
Cramp – legs	3	0.47
Cramp – stomach	2	0.31
Cutaneous vasculitis	1	0.16
Cyst – breast (right)	1	0.16
Cyst – kidney (right)	1	0.16
Depression	2	0.31
Diarrhoea	30	4.72
Diverticular disease	1	0.16
Dizziness	9	1.42
Dry mouth	3	0.47
Dry skin	1	0.16
Ear infection (left)	1	0.16
Eczema – lower legs	1	0.16
Elevated alkaline phosphatase	2	0.31
Elevated alanine aminotransferase	7	1.1
Elevated aspartate aminotransferase	1	0.16
Elevated cholesterol	2	0.31
Elevated creatinine	3	0.47
Elevated CRP	3	0.47
Elevated ESR	2	0.31
Elevated gamma-glutamyl transferase	3	0.47
Elevated globulin	1	0.16
Elevated liver enzyme	3	0.47
Enlarged axillary lymph nodes (left)	1	0.16
Epigastric pain	1	0.16
Exacerbation of hypertension	1	0.16
Exhaustion	1	0.16
Fall	4	0.63
Fatigue	11	1.73
Fever	6	0.94
Fibromyalgia	1	0.16
Flare of RA	17	2.68
Flatulence	1	0.16
Flexor tendonitis	2	0.31
Flu	7	1.1

TABLE 58 Adverse events in the cDMARD group (*continued*)

Adverse event	Frequency	Per cent
Flushed	2	0.31
Funny taste in mouth	1	0.16
Gallstones	1	0.16
Gastroenteritis	1	0.16
Gingivitis	1	0.16
Gum disease	1	0.16
Haematemesis	1	0.16
Haematuria	1	0.16
Haematuria – macroscopic	1	0.16
Haematuria – microscopic	1	0.16
Haemoptysis	1	0.16
Hair loss	1	0.16
Headache	30	4.72
Head cold	3	0.47
Hearing – diminished	1	0.16
Heartburn	4	0.63
Hiatus hernia – moderate size	1	0.16
High blood pressure	7	1.1
Hot flush	4	0.63
Hot flushes	1	0.16
Hypoglycaemia	2	0.31
Increased frequency of defecation	2	0.31
Increased urine frequency	1	0.16
Indigestion	3	0.47
Infected eyes	1	0.16
Infection – foot (left)	1	0.16
Inflamed eye (right)	1	0.16
Injection site reaction	1	0.16
Insomnia	1	0.16
Intermittent visual disturbance – eye	1	0.16
Itchy skin	7	1.1
Joint pain – feet	1	0.16
Joint pain – generalised	3	0.47
Laryngitis	1	0.16
Lesion – spleen	1	0.16
Lethargy	2	0.31
Leucocytes in urine	2	0.31

continued

TABLE 58 Adverse events in the cDMARD group (*continued*)

Adverse event	Frequency	Per cent
Lightheadedness	3	0.47
Loose stools	3	0.47
Loss of appetite	5	0.79
Low blood pressure	1	0.16
Lower back pain	1	0.16
Low creatinine	1	0.16
Low haemoglobin	2	0.31
Low iron level	1	0.16
Low platelet count	3	0.47
Low white cell count	7	1.1
Lymphadenopathy lungs	1	0.16
Lymphopenia	4	0.63
Migraine	4	0.63
Multiple liver cysts	1	0.16
Muscle ache – generalised	1	0.16
Muscle ache – shins	3	0.47
Muscle ache – shoulder	1	0.16
Nausea	26	4.09
Neutropenia	1	0.16
Night sweat	4	0.63
Nitrites in urine	2	0.31
Nosebleed	2	0.31
Oedema – feet	1	0.16
Pain – abdominal	4	0.63
Pain – ankle (left)	2	0.31
Pain – arm (left)	1	0.16
Pain – arm (right)	2	0.31
Pain – back	5	0.79
Pain – entire body	3	0.47
Pain – eye (left)	1	0.16
Pain – feet	4	0.63
Pain – first metatarsophalangeal joint (right)	1	0.16
Pain – foot (left)	3	0.47
Pain – groin (left)	1	0.16
Pain – hand (right)	1	0.16
Pain – hip (left)	1	0.16
Pain – hip (right)	2	0.31
Pain – knee (left)	1	0.16

TABLE 58 Adverse events in the cDMARD group (*continued*)

Adverse event	Frequency	Per cent
Pain – knee (right)	3	0.47
Pain – left side	1	0.16
Pain – leg (right)	1	0.16
Pain – neck	5	0.79
Pain – shoulder (left)	4	0.63
Pain – shoulder (right)	5	0.79
Pain – shoulders	4	0.63
Pain – wrist (left)	1	0.16
Pain – wrist (right)	3	0.47
Parotid enlargement (bilateral)	1	0.16
Peripheral neuropathy	1	0.16
Pins and needles – arms (both)	1	0.16
Pneumonia	2	0.31
Protein in urine	5	0.79
Pruritus – arms	1	0.16
Pulmonary fibrosis	1	0.16
Raised temperature	2	0.31
Rash – arm (left)	2	0.31
Rash – arm (right)	1	0.16
Rash – arms	3	0.47
Rash – back	4	0.63
Rash – cheek (right)	1	0.16
Rash – entire body	6	0.94
Rash – face	3	0.47
Rash – heel (right)	1	0.16
Rash – leg (left)	2	0.31
Rash – leg (right)	2	0.31
Rash – legs	4	0.63
Rash – neck	2	0.31
Rash – torso	4	0.63
Rectal bleeding	2	0.31
Redness – eye (right)	2	0.31
Reduced appetite	2	0.31
Rigours	1	0.16
Runny nose	1	0.16
Shaking	1	0.16
Shingles	3	0.47

continued

TABLE 58 Adverse events in the cDMARD group (*continued*)

Adverse event	Frequency	Per cent
Shortness of breath	1	0.16
Sinusitis	3	0.47
Skin infection – breast (right)	1	0.16
Skin lesions	1	0.16
Sore gums	2	0.31
Sore lips	1	0.16
Sore mouth	4	0.63
Sore throat	15	2.36
Stomach ache	1	0.16
Sweating	1	0.16
Swelling – ankle (both)	2	0.31
Swelling – calf (left)	1	0.16
Swelling – face (right side)	1	0.16
Swelling – upper lip	1	0.16
Swine flu	1	0.16
Swollen gums	4	0.63
Swollen temporomandibular joint	1	0.16
Synovitis – metatarsophalangeal joint	1	0.16
Tachycardia	1	0.16
Taste – metallic	1	0.16
Tendonitis – achilles	1	0.16
Thrush – mouth	2	0.31
Tingling – mouth area	3	0.47
Tonsillitis	1	0.16
Tooth extraction	5	0.79
Tooth infection	2	0.31
Torn muscle – lower back	1	0.16
Transient ischaemic attack	1	0.16
Ulcerative skin lesion – breast (right)	1	0.16
Ulcers – mouth	12	1.89
Urinary incontinence	1	0.16
Urinary tract infection	6	0.94
Verruca	1	0.16
Vomiting	26	4.09
Weight gain	1	0.16
Weight loss	5	0.79
Total	635	100

TABLE 59 Adverse events in the TNFis group

Adverse event	Frequency	Per cent
Abnormal vaginal bleeding	1	0.22
Abscess – axilla (left)	2	0.43
Abscess – tooth	2	0.43
Ache – back	2	0.43
Ache – ear	2	0.43
Ache – ear (left) with discharge	1	0.22
Ache – entire body	4	0.86
Ache – hand (right)	1	0.22
Ache – neck	1	0.22
Ache – tooth	3	0.65
Anxiety	1	0.22
Baker's cyst	2	0.43
Blocked eustachian tube (right)	1	0.22
Blurred vision	1	0.22
Breast lump (right)	1	0.22
Breathlessness	7	1.51
Broken arm (right)	1	0.22
Bruising – limbs	1	0.22
Bruising – thigh (left)	1	0.22
Bruising – thigh (right)	1	0.22
Burning sensation – neck (right hand side)	1	0.22
Cardiac palpitations	2	0.43
Carpal tunnel syndrome	3	0.65
Cellulitis – leg (right)	2	0.43
Chest infection	27	5.81
Chest pain	5	1.08
Choking – on waking up	1	0.22
Cold	16	3.44
Cold hands and feet	1	0.22
Cold sore	7	1.51
Congested ears	1	0.22
Constipation	2	0.43
Cough	4	0.86
Cough – dry	4	0.86
Cough – productive	5	1.08
Cramp – abdominal	1	0.22
Cyst – liver	1	0.22

continued

TABLE 59 Adverse events in the TNFis group (*continued*)

Adverse event	Frequency	Per cent
Deep vein thrombosis	1	0.22
Depression	1	0.22
Diarrhoea	12	2.58
Diverticular disease	1	0.22
Dizziness	4	0.86
Drop in estimated glomerular filtration rate	1	0.22
Dry feet with flaky skin and blotches	1	0.22
Dry throat	3	0.65
Dyspareunia	1	0.22
Ear infection (left)	2	0.43
Eczema – all over body	1	0.22
Elevated alkaline phosphatase	2	0.43
Elevated alanine aminotransferase	16	3.44
Elevated cholesterol	2	0.43
Elevated gamma-glutamyl transferase	1	0.22
Elevated globulin	1	0.22
Elevated liver enzyme	1	0.22
Elevated potassium	2	0.43
Elevated protein (blood)	1	0.22
Exacerbation of bronchiectasis	1	0.22
Exhaustion	1	0.22
Fall	2	0.43
Fatigue	5	1.08
Fatty liver	2	0.43
Fever	2	0.43
Flare of RA	14	3.01
Flexor tendonitis	2	0.43
Flu	4	0.86
Folliculitis	1	0.22
Fracture – foot (left)	1	0.22
Fungal infection – nail (big toes)	1	0.22
Gastroenteritis	1	0.22
Gum infection	1	0.22
Haematuria – macroscopic	2	0.43
Haematuria – microscopic	1	0.22
Haemostatis	1	0.22
Hair loss	1	0.22
Headache	15	3.23

TABLE 59 Adverse events in the TNFis group (*continued*)

Adverse event	Frequency	Per cent
Head cold	1	0.22
Hearing – diminished	1	0.22
Heartburn	3	0.65
Hot flushes	1	0.22
Impaired walking	1	0.22
Increased urine frequency	1	0.22
Indigestion	1	0.22
Infected eyes	2	0.43
Infection – big toe nail (right)	1	0.22
Injection site reaction	5	1.08
Insect bite	3	0.65
Insomnia	1	0.22
Intermittent flashing lights – both eyes	1	0.22
Intermittent headache	1	0.22
Itchy skin	3	0.65
Joint stiffness – generalised	1	0.22
Lethargy	4	0.86
Leucocytes in urine	1	0.22
Loose stools	1	0.22
Lower back pain	2	0.43
Low platelet count	1	0.22
Low white cell count	1	0.22
Malaise	1	0.22
Medial epicondylitis – (left)	1	0.22
Medial epicondylitis – (right)	1	0.22
Muscle ache – shoulder	1	0.22
Nasal congestion	2	0.43
Nausea	8	1.72
Neck – stiff	3	0.65
Neutropenia	3	0.65
Nose – left axillary lymphadenopathy	1	0.22
Numbness – legs	1	0.22
Numbness – lips	1	0.22
Numbness – toes	1	0.22
Oedema – feet	2	0.43
Oedema – foot (right)	2	0.43
Ovarian cyst	1	0.22

continued

TABLE 59 Adverse events in the TNFis group (*continued*)

Adverse event	Frequency	Per cent
Pain – abdominal	3	0.65
Pain and redness – index distal interphalangeal joint (right)	1	0.22
Pain – ankle (left)	3	0.65
Pain – arm (left)	1	0.22
Pain – back	4	0.86
Pain – entire body	2	0.43
Pain – eye (left)	1	0.22
Pain – foot (left)	1	0.22
Pain – foot (right)	4	0.86
Pain – hand (right)	1	0.22
Pain – hip (left)	3	0.65
Pain – hip (right)	3	0.65
Pain – knee (left)	3	0.65
Pain – knee (right)	5	1.08
Pain – leg (left)	1	0.22
Pain – legs	1	0.22
Pain – neck	2	0.43
Pain – ribs (left)	1	0.22
Pain – shoulder (left)	3	0.65
Pain – shoulder (right)	6	1.29
Pain – wrist (left)	1	0.22
Photosensitivity	1	0.22
Pins and needles – feet	1	0.22
Pins and needles – hands (left and right)	1	0.22
Plantar fasciitis	3	0.65
Pleurisy	1	0.22
Pneumonia	2	0.43
Protein in urine	1	0.22
Pruritus	1	0.22
Raised temperature	1	0.22
Raised white blood cell count	1	0.22
Rash – arms	2	0.43
Rash – back	1	0.22
Rash – entire body	1	0.22
Rash – face	2	0.43
Rash – hand (right)	1	0.22
Rash – legs	1	0.22
Rash – torso	4	0.86

TABLE 59 Adverse events in the TNFis group (*continued*)

Adverse event	Frequency	Per cent
Red and sore eyes (both)	1	0.22
Restless legs	2	0.43
Rigours	1	0.22
Runny nose	3	0.65
Scalp rash	2	0.43
Shaking	1	0.22
Shingles	3	0.65
Shortness of breath	1	0.22
Sinusitis	1	0.22
Skin infection – ankle (left)	1	0.22
Skin lesions	2	0.43
Skin nodules – back	1	0.22
Skin nodules – face	1	0.22
Soft tissue nodule – both feet	1	0.22
Sore mouth	1	0.22
Sore throat	13	2.8
Streptococcus A infection – vaginal	1	0.22
Superficial thrombophlebitis	1	0.22
Swelling – ankle (both)	2	0.43
Swelling – ankle (left)	1	0.22
Swelling – knee (left)	2	0.43
Swelling – lower jaw	1	0.22
Swelling – wrist (right)	1	0.22
Thrush – mouth	2	0.43
Thrush – vaginal	5	1.08
Tonsillitis	4	0.86
Tooth extraction	2	0.43
Tooth infection	3	0.65
Trace glucose in urine	1	0.22
Ulcers – mouth	4	0.86
Ulcers – vascular	1	0.22
Upper respiratory tract infection	6	1.29
Urinary incontinence	1	0.22
Urinary tract infection	9	1.94
Uterus fibroid	1	0.22
Vaginal dryness	1	0.22
Vasovagal attack	4	0.86

continued

TABLE 59 Adverse events in the TNFis group (*continued*)

Adverse event	Frequency	Per cent
Vomiting	3	0.65
Weight gain	1	0.22
Whitening of nails	1	0.22
Total	465	100

Appendix 5 Systematic review search strategies

Search strategy for early rheumatoid arthritis

1. Early Rheumatoid Arthritis.mp
2. Early RA.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
3. infliximab.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
4. etanercept.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
5. adalimumab.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
6. golimumab.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
7. certolizumab [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
8. anti-TNF.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
9. biological products.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
10. methotrexate.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
11. cyclosporin.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
12. sulphasalazine.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
13. hydroxychloroquine.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
14. prednisolone.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
15. immunosuppressive agents.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
16. combination DMARDs.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
17. combinatin atreatment.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
18. combination anti-rheumatic drugs.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
19. combination therapy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
20. leflunomide.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
21. 1 or 2
22. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 18 or 19
23. 20 and 21
24. remove duplicates from 23
25. limit 24 to clinical trial
26. limit 25 to english language

Search strategy for established rheumatoid arthritis

1. Rheumatoid Arthritis.mp
2. RA.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
3. infliximab.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
4. etanercept.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
5. adalimumab.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
6. golimumab.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
7. certolizumab [mp=ti, ab, ot, nm, hw, kf, ps, rs, ui, an, sh, tn, dm, mf, dv, kw]
8. anti-TNF.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
9. biological products.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
10. methotrexate.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
11. cyclosporin.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
12. sulphasalazine.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
13. hydroxychloroquine.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
14. prednisolone.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
15. immunosuppressive agents.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
16. combination DMARDs.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
17. combinatin atreatment.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]

18. combination anti-rheumatic drugs.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
19. combination therapy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
20. leflunomide.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
21. 1 or 2
22. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 18 or 19
23. 20 and 21
24. remove duplicates from 23
25. limit 24 to clinical trial
26. limit 25 to english language

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HS&DR
HTA
PGfAR
PHR

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