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A randomised efficacy and discontinuation study of etanercept versus adalimumab (RED SEA) for rheumatoid arthritis: a pragmatic, unblinded, non-inferiority study of first TNF inhibitor use: outcomes over 2 years

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ABSTRACT

Objective: To compare adalimumab versus etanercept in patients with active rheumatoid arthritis (RA) to test the hypothesis that adalimumab was not inferior to etanercept in terms of drug continuation by a margin of 15% after 52 weeks of treatment.

Design: Pragmatic, randomised, parallel group, multicentre, unblinded and non-inferiority trial. Randomisation stratified by baseline use of methotrexate.

Participants: 125 adults with active RA despite treatment with two disease-modifying drugs (DMARDs), including methotrexate randomised (1 : 1) to adalimumab 40 mg alternate weeks or etanercept 50 mg weekly, added to existing medication.

Measurements: The primary outcome was proportion of patients continuing treatment after 52 weeks. Secondary outcomes included: disease activity score using 28 joints (DAS28), treatment satisfaction (TSQM V.2), health status (Euroqol-5D), drug toxicity and persistence with therapy after 2 years.

Results: Persistence with therapy was 65% for adalimumab versus 56.7% for etanercept (one-sided 95% CI for proportion still taking adalimumab minus proportion on etanercept ≥−7.9%); demonstrating non-inferiority at the 15% margin. After 2 years these figures were: adalimumab 58.3% and etanecept 43.3% (CI ≥−1.7%). The proportion of good, moderate and non-responders based on DAS28-C reactive protein, after 52 weeks, were 26.3%, 33.3% and 40.4%, respectively, for adalimumab versus 16.7%, 31.7% and 51.7%, respectively, for etanercept (p=0.158). Baseline median EQ-5D scores improved from 0.52 to 0.69 for adalimumab and from 0.52 to 0.64 for etanercept (p=0.046) after 52 weeks. Global satisfaction, effectiveness, side effects and convenience scores based on the TSQM were similar for both drugs. Fourteen serious adverse events occurred including two deaths from myocardial infarction, one patient with ovarian cancer and one with acute myeloid leukaemia.

Conclusions: Clinicians choosing a first tumour necrosis factor inhibitor for active RA, despite trying two DMARDs including methotrexate, may choose either adalimumab or etanercept in the knowledge that these drugs are similarly effective.

Clinical trial registration number: EU Clinical Trials Register 2006-006275-21/GB.

ARTICLE SUMMARY

Article focus

- Use of a first tumour necrosis factor (TNF) inhibitor for patients with active rheumatoid arthritis who have not responded to two disease-modifying drugs, including methotrexate.
- Comparative effectiveness study in a routine setting comparing two commonly used TNF inhibitors, adalimumab and etanercept, evaluated by drug survival or persistence with therapy over 2 years.

Key messages

- Adalimumab was not inferior to etanercept in terms of drug continuation over 2 years of therapy.
- Treatment satisfaction, adverse events and the proportion of good, moderate and non-responders for both drugs were comparable after 1 year.

Strengths and limitations of this study

- Pragmatic design reflecting routine care with 2 years of follow-up.
- Lack of blinding to treatment.
- A relatively wide non-inferiority margin of 15%.

INTRODUCTION

Pragmatic or practical clinical trials of drug treatments seek to help clinicians and patients decide between important

therapeutic choices. Such trials are therefore an essential element of comparative effectiveness research and especially important in rheumatoid arthritis (RA), a disease in which the range of efficacious treatment options, many of high cost, has widened in recent years.[1 2] American College for Rheumatology (ACR) guidelines for the treatment of RA recommend traditional disease-modifying drugs (DMARDs), especially methotrexate, in early and established RA of good prognosis provide for the addition of a tumour necrosis factor (TNF) inhibitor in poor prognosis patients.[3] Delayed use of TNF inhibitors may have detrimental effects on radiographic outcomes but not on disease activity scores and functional outcomes.[4 5] In the UK TNF inhibitors may only be used if patients with RA have active disease (defined by disease activity scores, DAS28, ≥5.1) despite at least two conventional DMARDs, including methotrexate.[6–9]

The number of available TNF inhibitors for RA has increased but there is considerably more experience with adalimumab, etanercept and infliximab than more recently introduced agents. There are no published randomised trials comparing one TNF inhibitor directly with another. Observational studies have shown inconsistent differences between agents[10–12] but a recent mixed treatment comparison suggests that etanercept and certolizumab are more effective than other TNF inhibitors, especially when modelled on disability scores.[13]

The choice of first TNF inhibitor is an important milestone in the treatment pathway of a patient with RA. In the absence of trials comparing these agents directly, we conducted an unblinded pragmatic randomised non-inferiority trial of adalimumab versus etanercept, focusing on persistence with therapy as our primary outcome. Treatment persistence is an important determinant of the cost-effectiveness of these agents.[7–9] Our trial was planned at a time when only adalimumab and etanercept were approved for subcutaneous use in the UK and at a time when there were indications that persistence with etanercept was better than with adalimumab.[7]

METHODS

Design overview

This was a 52-week unblinded, randomised, non-inferiority, multicentre, parallel group comparison of adalimumab versus etanercept in patients with active RA despite prior or current use of two DMARDs including methotrexate (unless contraindicated). Data on a key outcome, persistence with therapy, were also collected at 104 weeks. There were no constraints on changes in the dose of methotrexate, use of other DMARDs including previously untried agents, or on use of oral, parenteral or intra-articular corticosteroids once patients were included in the study. This approach is consistent with a pragmatic approach reflecting routine care. Study approval was given by the Nottingham Research Ethics Committee 2 (Reference 06/Q2404/171).

Setting and participants

Patients over the age of 18 years, who met the ACR 1987 criteria for RA, were recruited from four hospitals in England. To be eligible, patients had to meet national criteria for treatment with a TNF inhibitor with regard to the lack of response to at least two DMARDs including methotrexate. Patients were excluded if the clinician caring for the patient believed that TNF inhibitors were unsuitable or it was believed that patients would be unlikely to understand study procedures or unwilling to comply. Patients treated previously with any licensed or experimental biological TNF inhibitor were excluded. Adherence to national guidance in relation to pretreatment screening, including for tuberculosis, was required.[6]

Randomisation and interventions

Patients were randomised to subcutaneous adalimumab 40 mg every other week or etanercept 50 mg weekly (1:1). Once enrolled, clinicians could modify drug doses within the constraints of the drug license for these agents. Randomisation was stratified according to the use of methotrexate at inception. A random sequence of numbers was generated, by computer, for patients on methotrexate and separately for patients not on methotrexate. Use of other DMARDs at the time of TNF inhibitors introduction was permitted but did not influence randomisation. Randomisation was done in random block sizes. Opaque, sealed envelopes of the allocation sequences were prepared and managed at the sponsoring centre by a member of staff not involved in the patient management. A log was kept and a copy of sequences was lodged with the Department of Research and Development at the sponsoring institution, in order that audits could be conducted, if necessary. This study was the subject of an audit by the UK Medicines and Health Care Regulatory Agency during its conduct.

Outcomes and follow-up

The primary outcome was the proportion of patients still taking the drug to which they were randomised 52 weeks after starting. Patients were deemed to be continuing treatment if an injection of adalimumab or etanercept had been used at the 12-month anniversary with a 2-week window before the anniversary and up to 6 weeks after the anniversary. Criteria for withdrawal were not stipulated, consistent with the concept of a trial replicating everyday practice—clinicians were free to make their own judgements about treatment modification, including drug cessation, during the trial. Secondary outcomes were the proportion of patients on treatment at 6 months and 104 weeks, the four variable disease activity score using 28 joints based on C reactive protein (CRP) (DAS28-CRP4), the proportion of patients discontinuing therapy for different reasons (classified by the treating clinician according to lack of efficacy, toxicity, both or other reasons), satisfaction with medication measured by the Treatment Satisfaction Questionnaire for Medication (TSQM VII),[14] health utility determined

by the Euroqol-5D questionnaire[15] (permission to use both was registered) and adverse effects defined by severity and body system.

Statistical analysis

The objective of this study was to test the hypothesis that adalimumab was not inferior to etanercept in terms of drug continuation (or withdrawal from treatment). A systematic review, done when this study was planned, indicated that there were important differences in continuation rates between etanercept, infliximab and adalimumab in established RA. For example, the relative risk of treatment cessation for any reason was 0.71 with adalimumab compared with 0.61 for etanercept when these drugs were combined with methotrexate and compared with methotrexate alone (Table 17 ref. [7]). These data were supported by observations after our study began which showed that the HR for drug withdrawal for adalimumab was 1.47 compared with etanercept.[11] We assumed that around 75% of patients would still be on the treatment a year after starting. We also assumed, by consensus, that a difference in continuation rates of 15% between etanercept and adalimumab was clinically important and would be sufficient for clinicians to choose one agent over another. We calculated that 124 patients (62 in each treatment group) would be required to have an 80% chance of ruling out a 15% difference with 95% confidence (one-sided analysis). These data correspond to an assumed scenario where the true proportion of patients taking adalimumab at 1 year would be 75% compared with 70% for etanercept.

Patients receiving at least one dose of treatment were included in the analyses. Fisher's exact tests were used for all comparisons of proportions. Mann-Whitney tests or unpaired t tests were used for all other comparisons, as appropriate.

RESULTS

Study enrolment began in May 2007 and the last patient was recruited in April 2010. Patients were approached about the study during routine clinic visits. A formal screening log was not maintained and our study was not resourced to monitor new prescriptions of TNF inhibitors for RA at the four hospitals that contributed patients. We know that at least 362 patients not included in this study started a TNF inhibitor during this period at the four participating centres, though we do not know what proportion of these patients were starting a first TNF inhibitor. A flow diagram of study participants is shown in figure 1.

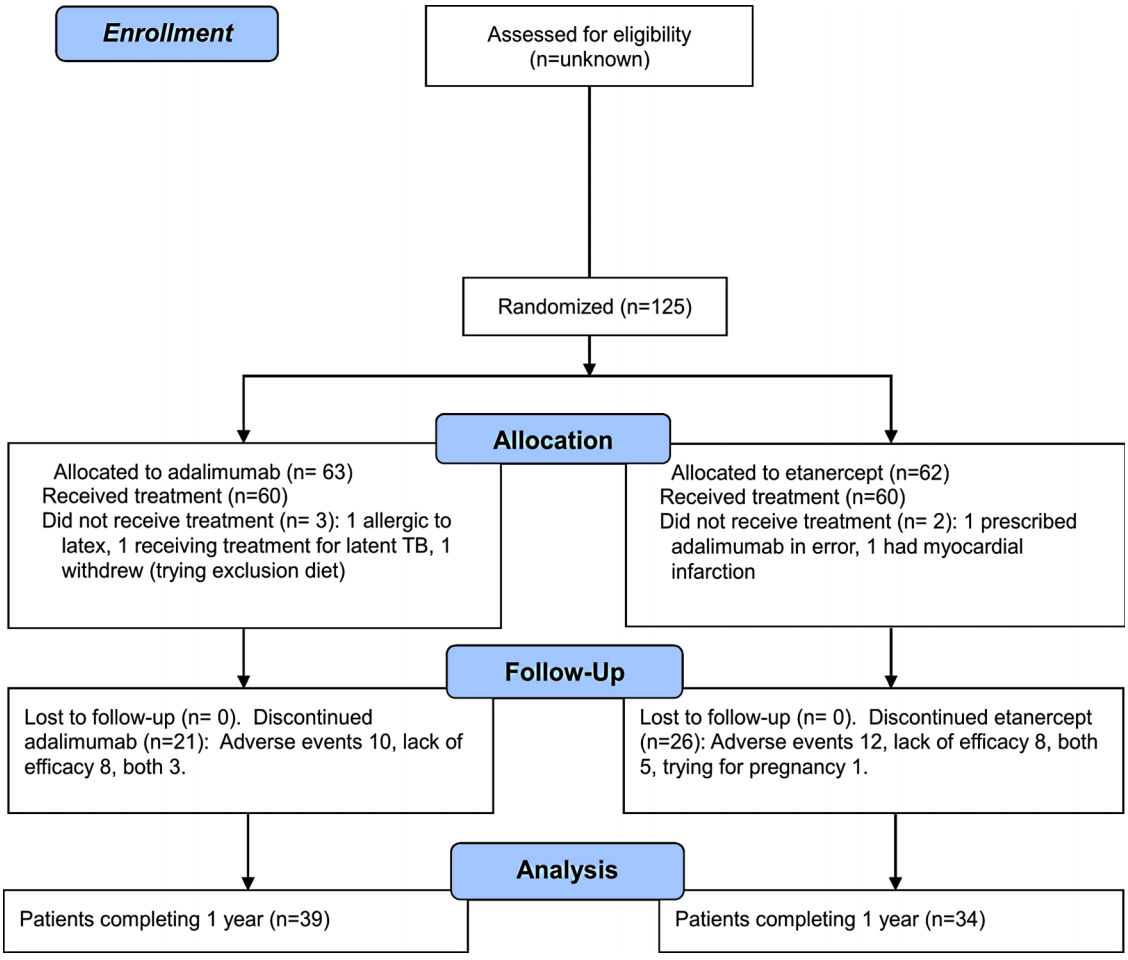

Figure 1 Consort flow diagram.

Table 1 Baseline characteristics of participants

	Adalimumab (n=60)	Etanercept (n=60)	All (n=120)
Age (years)	55.0 (12.5)	53.2 (13.4)	54.1 (12.9)
Female : male	45:15	42:18	87:33
Disease duration (years)	7.0 (3.3–13.0)	5.5 (2.0–14.5)	6.0 (2.0–14.0)
No. of DMARDs tried*	2 (2–3)	2 (2–3)	2 (2–3)
Concomitant MTX	40 (66.7%)	40 (66.7%)	80 (66.7%)
Median dose (mg/week)	20	17.5	20
Other DMARDs			
Azathioprine	1 (1.7%)	1 (1.7%)	2 (3.4%)
Hydroxychloroquine	12 (20%)	1 (1.7%)	13 (21.7%)
Leflunomide	5 (8.3%)	8 (13.3%)	13 (21.7%)
Penicillamine	1 (1.7%)	0	1 (1.7%)
Sulfasalazine	13 (21.7%)	8 (13.3%)	21 (35%)
RF or anti-CCP +ve	55 (91.7%)	51 (85.0%)	106 (88.3%)
Body mass index	29.1 (6.6)	27.2 (4.1)	28.2 (5.6)
On NSAIDs	35 (58.3%)	26 (43.3%)	61 (50.8%)
On oral prednisolone	20 (33.3%)	27 (45%)	47 (39.2%)
Median dose (mg/day)	10	7.5	10
DAS28 (CRP4)†	5.6 (0.9)	5.8 (0.9)	5.7 (0.9)
CRP (mg/l)	10 (5–22)	13 (5–31)	12 (5–25)
Patient global assessment of disease severity (0–100)	64 (23)	67 (21)	66 (22)

*DAS28 (CRP4): disease activity score based on 28 joint counts calculated using CRP. For three patients in each treatment arm DAS28 (ESR4) was substituted and in one case each DAS28 (CRP3) was substituted because of missing data.
†Including methotrexate and concomitantly used DMARDs. Only one patient (randomised to adalimumab) was not given methotrexate previously because of long-standing abnormalities of liver function.
CCP, cyclic citrullinated peptide; CRP, C reactive protein; DAS28, disease activity score using 28 joints; DMARDs, disease-modifying drugs; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor.
Values are mean (SD), n (%) or median (lower quartile–upper quartile).

The 60 patients receiving adalimumab and the 60 receiving etanercept form the modified intention-to-treat population. Key characteristics of patients are shown in table 1. It is worth noting that the median disease duration for the study population was 6 years, that 88% were rheumatoid factor or cyclic citrullinated peptide antibody positive, that 40% were on oral steroids at baseline and that a third of patients did not receive concomitant methotrexate but took a wide variety of other concomitant DMARDs. Imbalances in the use of hydroxychloroquine and the number of patients on oral steroids at baseline were noted.

Efficacy measures

After 52 weeks, 39 of 60 or 65% (CI 51.6% to 76.9%) patients who started adalimumab were still taking the drug compared with 34 of 60 or 56.7% (CI 43.2% to 69.4%) for etanercept (figure 2). The one-sided 95% CI for the proportion still taking adalimumab minus the proportion on etanercept was ≥−7.9%, demonstrating that adalimumab was not inferior to etanercept at the 15% margin. After 104 weeks two patients allocated adalimumab had been lost to follow-up we assumed that these patients had ceased treatment thus: 35 of 60 or 58.3% (44.9% to 70.9%) were still taking adalimumab

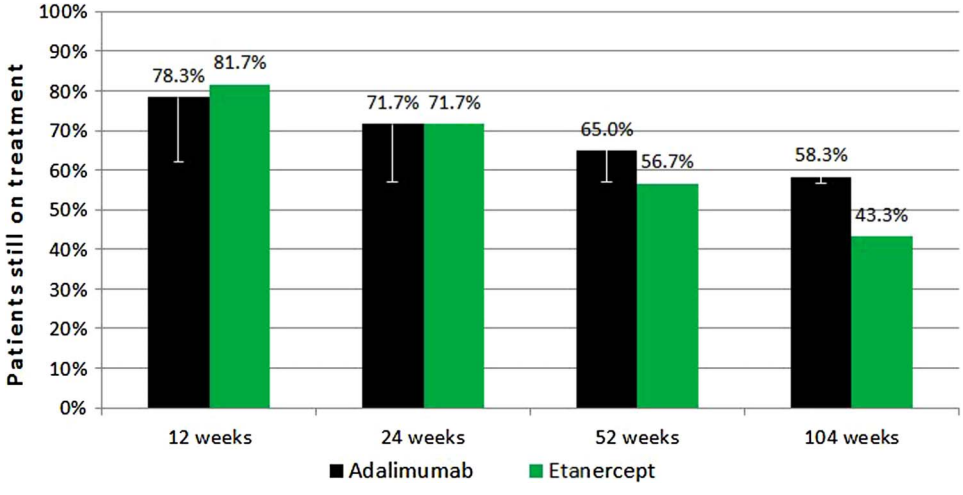

Figure 2 Patients still on treatment at key time points. Error bars show one-sided 95% CI required to demonstrate non-inferiority.

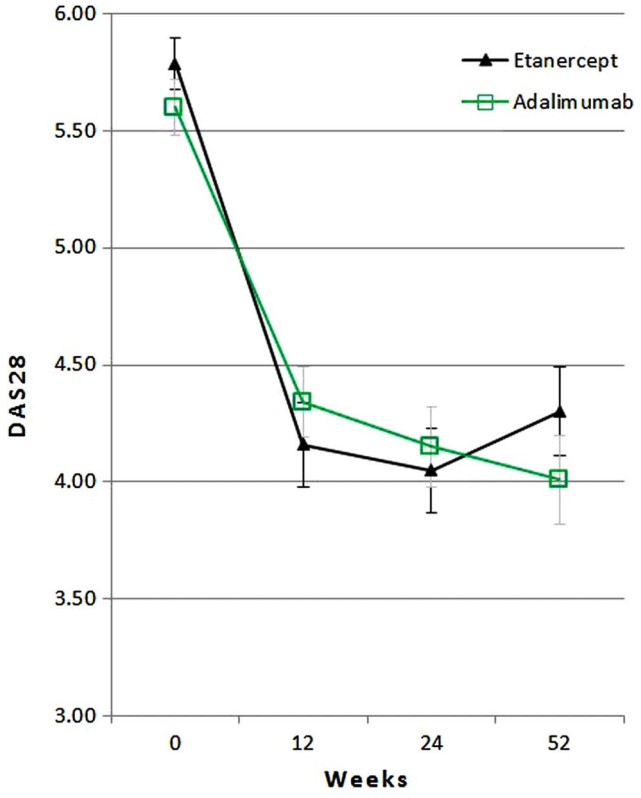

Figure 3 Comparison of disease activity scores over 1 year. Scores are disease activity score using 28 joints, DAS28 (CRP4). Where patients withdrew early data from the withdrawal visit were carried forward for all subsequent visits. DAS28 (CRP3) or DAS28 (ESR4), in that order, were substituted when it was not possible to calculate DAS28 (CRP4) because of missing data. Data are means, error bars show standard errors.

and 26 of 60 or 43.3% (30.6% to 56.8%), were still taking etanercept and the one-sided 95% CI for the difference in the proportions was ≥−1.7%. Changes from baseline to 3 and 12 months in CRP, DAS28, patient global assessment, tender and swollen joint count scores were similar for adalimumab and etanercept; there were no significant differences. DAS28 scores for patients completing 1 year are shown in figure 3. Secondary outcome data are shown in table 2.

The proportion of good, moderate and non-responders based on DAS28 at 52 weeks were 26.3%, 33.3% and 40.4%, respectively, for adalimumab versus 16.7%, 31.7% and 51.7%, respectively, for etanercept (p=0.158). Global satisfaction, effectiveness, side effects and convenience scores based on the TSQM (VII) were similar for both drugs.

Adalimumab led to slightly greater improvement in EQ5D utility scores than etanercept after 52 weeks of treatment (p=0.046, table 2). Using these data to estimate cost per quality adjusted life year (QALY), using drug costs alone, assuming annual drug costs for each agent of £9295 (€11 704) and ignoring other factors[16] yields costs per QALY of £54 676 (€68 843) for adalimumab and £77 458 (€97 528) for etanercept. None of the patients allocated adalimumab had increased the dose to 40 mg weekly after 52 weeks, though it is recognised that dose escalation may occur in up to 10% of patients.[17]

Twelve patients (20%) allocated adalimumab and completing 1 year of therapy discontinued at least one DMARD compared with eight patients (13.3%) allocated etanercept. The median dose of oral prednisolone in those completing 1 year of therapy fell from 10 to 5 mg in patients allocated adalimumab (n=7) compared with a fall from 7.5 to 2.5 mg for etanercept (n=19).

Adverse events

Fourteen serious adverse events occurred in 13 patients in this study: 6 allocated adalimumab and 7 etanercept. Serious events occurring within 2 weeks of study end or drug withdrawal are included. There were two deaths, both occurring in patients allocated adalimumab and resulting from ischaemic heart disease, one occurred a week after drug withdrawal. Another patient, allocated etanercept, was diagnosed with heart failure 2 weeks after drug withdrawal: an event believed to be possibly related to the treatment. This patient had discontinued treatment because of a skin rash prior to being diagnosed with heart failure. Two other events possibly related to therapy were acute cholecystitis (adalimumab) and a patient hospitalised with chest symptoms (etanercept). Malignancy developed in two patients, one each for etanercept (acute myeloid leukaemia) and adalimumab (ovarian cancer). In both cases, clinicians felt that these events were unlikely to be related to treatment. Other serious adverse events included hospitalisation for: a ruptured popliteal cyst; chest symptoms; syncope; suspected femoral fracture; angioedema and urticaria; stillbirth from pregnancy while on treatment and cellulitis.

A variety of other adverse events, with no notable differences between agents, were reported. A list of these events, classified according to the body system and based on published recommendations[18] is shown in table 3.

DISCUSSION

We have shown, in the first head-to-head randomised comparison of two TNF inhibitors for the treatment of RA in a study designed to reflect real clinical practice, that adalimumab is not inferior to etanercept in terms of persistence with therapy over 2 years. Other measures of efficacy were similar for these two agents including DAS28 responder status. An important strength of our study was a pragmatic design which, within the constraints of volunteer bias, provides data that are directly relevant to everyday practice. Inclusion and exclusion criteria were kept to a minimum. Our study design permitted modification or addition of DMARDs and corticosteroids whereby clinicians maximise opportunities to improve the disease control.

Table 2 Key secondary outcomes*

	Adalimumab				Etanercept			
	Baseline (n=60)	3 months (n=47)	12 months (n=39)	12 months† (n=60)	Baseline (n=60)	3 months (n=49)	12 months (n=34)	12 months† (n=60)
CRP	10 (5–22)	6 (3–15)	5 (3–12)	6 (3–14)	12.5 (5–31)	5 (3–14)	7 (3–13)	9 (3–14)
DAS28 (CRP4)	5.8 (5.1–6.1)	3.9 (3.2–4.7)	3.5 (2.7–4.2)	4.4 (3.1–5.4)	5.7 (5.0–6.5)	4.0 (2.9–4.6)	3.6 (3.0–4.4)	4.6 (3.5–5.6)
EQ5D Utility Score‡	0.52 (0.06–0.66)	0.62 (0.59–0.76)	0.69 (0.59–0.76)	0.59 (0.52–0.69)	0.52 (0.06–0.69)	0.62 (0.52–0.76)	0.64 (0.52–0.80)	0.59 (0.24–0.73)
Patient global assessment (0–100)	70 (50–82)	35 (20–50)	25 (15–50)	49 (20–65)	70 (54–80)	43 (15–56)	34 (20–50)	50 (27–71)
Swollen joint count (28 joints)	9 (5–12)	4 (2–6)	2 (1–5)	4 (1–6)	9 (6–13)	3 (2–6)	2 (1–3)	5 (2–11)
Tender joint count (28 joints)	14 (9–20)	5 (2–8)	2 (1–4)	5 (1–14)	14 (8–20)	4 (2–8)	5 (2–7)	8 (4–14)
Treatment satisfaction score								
Global satisfaction	–	83 (67–100)	92 (75–100)		–	79 (58–92)	92 (75–100)	
Effectiveness score	–	67 (54–83)	83 (67–100)		–	67 (50–83)	83 (67–100)	
Side effects score	–	100 (83–100)	100 (83–100)		–	100 (83–100)	100 (92–100)	
Convenience score	–	89 (83–100)	83 (78–100)		–	86 (67–94)	89 (83–100)	

*Data are medians (lower quartile–upper quartile). The primary outcome was persistence with therapy: patients who discontinued therapy were not followed up to 1 year to ascertain secondary outcomes. Perprotocol data are shown here, unless stated otherwise.
†Data for the modified intention to treat population with baseline values carried forward for those who discontinued therapy within 1 year.
‡The change in EQ5D Utility Score from baseline to 12 months was significantly greater in patients treated with adalimumab than etanercept over 1 year (p=0.046).
CRP, C reactive protein; DAS28, disease activity score using 28 joints.

Table 3 Adverse events: patients reporting at least one episode by body system*

	Adalimumab (n=60)	Etanercept (n=60)
Serious adverse events		
All serious events	6	7
Serious events possibly related to treatment	1	2
Death	2	0
All adverse events		
General		
Fatigue	5	1
Fever, rigours, altered weight, headaches, sweating, hypoglycaemia, flushes, angioedema or suspected allergic reaction	8	18
Skin/integument		
Injection site reaction	9	19
Pruritus or rash (not bullous)	15	13
Cellulitis	1	0
Ophthalmic		
Conjunctivitis, visual disturbance, xerophthalmia or uveitis	2	2
ENT		
URTI or coryza symptoms	9	10
Others: rhinitis, epistaxis, cold sores, altered taste, stomatitis, mouth ulcers and hoarseness	5	10
Gastrointestinal		
Dyspepsia, abdominal pain, bloating, diarrhoea, nausea and vomiting	11	9
Cardiovascular		
Decreased cardiac function, phlebitis, Raynaud's, oedema, palpitations, bradycardia or hypertension	5	6
Pulmonary		
Cough or dyspnoea	9	7
Unspecified respiratory infection	4	3
Musculoskeletal		
Joint pain or swelling, spinal pain, muscle pain or cramps	20	24
Planned musculoskeletal surgery or fracture	2	2
Neuropsychiatric		
Anxiety, depression, mood disturbance or somnolence	5	6
Falls, impaired gait, peripheral neurological symptoms, vertigo and dizziness	6	7
Urinary symptoms		
Dysuria, urinary tract infection or difficulty passing urine	0	4
Abnormal laboratory tests		
Leukopaenia, neutropaenia, thrombocytopaenia, hyperglycaemia (fasting) and abnormal liver function	3	6

*Data are for 60 patients in each group. Number of events exceeds patient numbers.
ENT, ear, nose and throat; URTI, upper respiratory tract infection.

Drug cessation, or continued use, are key indicators of successful therapy in chronic disease, especially where the prospect of drug free remission is low[19] and drug costs are high. However in some circumstances drug persistence may simply reflect limited treatment options where clinicians and patients continue with a drug in the belief that continuing with something is better than nothing.[20] This latter scenario is less likely in our study as we studied first TNF inhibitor use and recruited patients between 2007 and 2010, a period when several new options for treating RA became available.

One important limitation of our study was that only a proportion of patients treated with TNF inhibitors at the trial centres took part. We are unable to say precisely what proportion of eligible patients took part. We have no reason to suspect that patients were systematically excluded for reasons of disease severity or comorbidity or other factors that limit the generalisability of our findings. Patients, recruited to the British Society for Rheumatology Biologics register in 2008, a national registry to which our hospitals contribute patients, had disease of longer duration and higher DAS28 scores at baseline but a smaller proportion of patients on oral steroids.[21] We believe, most likely, that patients were not considered for inclusion because of practical considerations such as time constraints and concerns about loss of professional autonomy and patient choice.[22] Reasons clinicians' gave, in discussions as the trial proceeded, included a desire for less frequent injections, a preference for a drug with a shorter half-life in the case of etanercept, and concerns about self-administration of injections and thus a preference for infliximab.

Another potential limitation was our decision to test the hypothesis that adalimumab was not inferior to etanercept (a one-sided hypothesis) rather than demonstrate equivalence (a two-sided hypothesis). A smaller sample size was needed to answer the former question. This meant that the trial could be completed with fewer resources and in a timely manner, an important consideration for pragmatic trials.[23] One justification for hypothesising non-inferiority was data available at the time our study were planned[7] and indeed more recently[10–12] that continuation rates are better for etanercept than adalimumab. Such indirect comparisons of continuation rates however are insufficient for accepting the superiority of one agent over another—only direct comparisons, such as in our trial, can answer this question with confidence. A further limitation was a non-inferiority margin of 15%. This may be considered a wide margin. However, margins of such magnitude are used by drug manufacturers for securing regulatory approval for new agents.[24] A figure of 15% also contributed to a reduction in sample size and was justified on the basis of data from a systematic review[7] and consensus when this study was conceived. We also judged that clinicians would not necessarily be persuaded to change from a preferred drug option and the convenience of less frequent injections with adalimumab, unless the margin between drugs was of sufficient magnitude.

Our study may also be criticised for lack of blinding. Blinding would have been possible but would have increased study costs greatly and would have compromised our desire to create a real-world setting for our study. Observer blinding of the primary outcome, treatment continuation, was not feasible. It is possible that clinicians may have made extra efforts to persist with a particular TNF inhibitor if they had added faith in that agent. While such efforts may have biased outcomes in a trial of shorter duration we believe that efforts to maintain a particular therapy are much less likely to have been successful over 2 years. This is also true because use of a second TNF inhibitor, after lack of success with a first, has only been sanctioned in the UK lately.[25] We did not formally survey clinicians at participating centres regarding their beliefs about the relative effectiveness or toxicity of particular TNF inhibitors. For example, it is possible that some clinicians may have chosen etanercept in South Asian patients believing that a risk of unmasking tuberculosis was lesser with etanercept.[26]

Continuation rates in our trial were less than rates in some published observational cohorts of RA patients treated with TNF inhibitors but not all.[10–12 21] It seems unlikely that this is due to systematic differences in practice at study centres compared with the rest of the UK. It is more likely that contemporary cohorts of patients have treatment altered earlier than older cohorts given a wider availability of efficacious agents in the UK[25] and a desire for even better disease control. This view, surprisingly, is not supported by the most recent data (2008) from the BSRBR.[21] It is also worth noting that although only two-thirds of patients recruited were given methotrexate with etanercept or adalimumab, a wide range of other DMARDs were used as concomitant therapy (table 1); similar to data from the BSRBR.[21] We do not know whether differences in concomitant oral steroids or DMARDs, such as hydroxychloroquine, at baseline, might have influenced continuation rates for either TNF inhibitors. Differences reported between TNF inhibitors in observational studies become more marked with increasing follow-up. In our study the difference between adalimumab and etanercept widened after 2 years of follow-up.

In conclusion, clinicians needing to choose between adalimumab and etanercept, in a patient with active RA despite treatment with methotrexate and another DMARD, may choose either agent in the knowledge that continuation or persistence with therapy after 2 years is likely to be similar for these two agents.

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