Optimal management of RA patients who require Biologic Therapy (ORBIT) – a randomised controlled, non-inferiority study

Porter D[1*], van Melckebeke J[1], Dale J[2], Messow C-M[11], McConnachie A[11], Walker A[1], Munro R[2], McLaren J[3], McRorie E[4], Packham J[5], Buckley CD[6], Harvie J[7], Taylor P[9], Choy E[10], Pitzalis C[8], and McInnes IB[1].

[1] University of Glasgow
[2] Wishaw General Hospital
[3] Whytemans Brae Hospital, Fife
[4] Western General Hospital, Edinburgh
[5] Haywood Hospital, Stoke-on-Trent
[6] University of Birmingham
[7] Raigmore Hospital, Inverness
[8] Queen Mary University, London
[9] University of Oxford
[10] University of Cardiff
[11] Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow

* Corresponding author

Dr Duncan Porter
Consultant Rheumatologist
Gartnavel General Hospital
1053 Great Western Rd
Glasgow G12 0YN
duncan.porter@glasgow.ac.uk

00 44 141 452 6176

Abstract

Background

Tumour necrosis factor inhibition (TNFi) and B cell depletion are highly effective treatments for active rheumatoid arthritis (RA) but to date no randomised controlled trials have directly compared their safety, efficacy and cost effectiveness. This study was undertaken to test the hypothesis that using rituximab would be clinically non-inferior and cheaper compared to TNFi therapy in biologic-naive patients with RA.

Methods

An open label randomised controlled trial of two strategies of treatment over 12 months in patients with active, sero-positive RA and an inadequate response to synthetic disease modifying anti-rheumatic drugs (DMARDs). Patients were randomised (1:1) to receive either rituximab or TNFi (either etanercept or adalimumab) as their first biologic DMARD. Patients switched treatment to the alternative mode of action biologic in the event of drug-related toxicity or lack/loss of response. The primary outcome measure was the change in 28 joint count disease activity score (DAS28-ESR) between 0 and 12 months. The non-inferiority margin was specified as 0.6 DAS28-ESR units.

Findings

295 patients were randomised and treated with either rituximab or TNFi therapy. At baseline, there were no significant differences between the groups in age, gender, disease duration, disease activity or intolerance to methotrexate. After 12 months, the change in DAS28-ESR for patients randomised to rituximab-first (-2.7) was non-inferior to that for patients randomised to TNFi-first (-2.6) with the difference lying within the pre-specified non-inferiority limit of 0.6 units (estimated difference -0.19, 95% CI -0.51, 0.13; p=0.24). No between-group differences were found for the proportion of patients achieving good response (rituximab 43% v TNFi 40%), DAS28-ESR remission (rituximab 23% v TNFi 21%), ACR20 (rituximab 66% v TNFi 71%), ACR50 (rituximab 49% v TNFi 45%) or ACR70 (rituximab 25% v TNFi 23%) response. There were no differences in the change in health assessment questionnaire (HAQ) score, Hospital Anxiety and Depression (HAD) score or health-related quality of life. A higher proportion of patients switched from TNFi therapy to rituximab than *vice versa* (rituximab 19% v TNFi 32.5%, p=0.008). The health related costs associated with the rituximab-first strategy were lower than the TNFi-first strategy (£8391 v £10,356 per patient, p<0.001). In summary, starting treatment with rituximab is non-inferior to initial TNFi therapy in biologic-naïve patients with sero-positive RA, and is cost saving over 12 months.

Funding

The study was funded by Arthritis Research UK. Roche provided supplies of rituximab free of charge.

Trial Registration

ClinicalTrials.gov NCT01021735

Key Words

Rheumatoid arthritis; Tumour necrosis factor; etanercept; adalimumab; rituximab; cost effectiveness

Background

TNF inhibitor (TNFi) therapy is an integral component of the drug treatment of rheumatoid arthritis (RA) patients who fail to exhibit or maintain an adequate response to non-biologic Disease Modifying Anti-Rheumatic Drugs (nbDMARDs).[1] Five originator TNFi drugs (infliximab, etanercept, adalimumab, golimumab and certolizumab) have been granted marketing authorisation for the treatment of RA. They are effective in patients who are nbDMARD-naïve, respond inadequately to methotrexate (MTX-IR), or fail to respond to another TNFi (TNF-IR). Rituximab is an anti-CD20 monoclonal antibody that depletes a variety of pathophysiologic subsets within the B cell population. Rituximab is approved for use in TNF-IR patients[2-4] but it is also effective in patients who are nbDMARD-naïve or MTX-IR.[5] It is possible that rituximab is more or less effective than TNFi therapy in biologic-naïve patients but head to head trials have not been carried out. In placebo controlled studies, the overall response rates to TNFi or rituximab therapy are similar. However, important differences between the study populations make indirect comparison of limited usefulness, and the data are compatible with important clinical differences in safety, efficacy or cost effectiveness.

All biologics are expensive and the relative cost effectiveness of each therapy needs to be considered, but there is considerable uncertainty associated with health economic modelling. For example in the UK, the cost of TNFi therapy is approximately £9-10,000 per annum; rituximab costs ~£3,500 per treatment course, which needs to be repeated every 6-9 months giving an annual cost of £4700 - 7000. Were rituximab to prove as effective as TNFi therapy in biologic-naïve patients it could result in substantial reductions in healthcare costs. On the other hand, if TNFi therapy is more effective than rituximab therapy, it would be important to have good evidence to inform health technology appraisals which might otherwise conclude from the available evidence that rituximab offers a more cost-effective alternative.

The Optimal Management of RA patients who Require Biologic Therapy (ORBIT) study was designed to compare the efficacy, safety and cost-effectiveness of rituximab-first and TNFi-first strategies in biologic-naïve RA patients with active disease despite nbDMARD therapy. The hypothesis was that a treatment strategy that starts with rituximab, and switches to TNFi if required, would be non-inferior to a strategy that starts with TNFi therapy, and switches to rituximab if required. Further, the study sought to estimate the incremental cost effectiveness ratio (ICER) of the more effective drug (if it is associated with higher costs) or the total cost savings associated with prescribing the cheaper drug (if it is at least as effective as the more expensive drug).

Methods

The study protocol was approved by the West of Scotland Research Ethics Committee and registered with ClinicalTrials.gov (NCT01021735). All participants provided written, informed consent. Patients were recruited between 2009 and 2013 from 35 rheumatology departments in the United Kingdom. The study was an open label, randomised, controlled, non-inferiority trial comparing two strategies of biologic therapy in biologic naïve patients over 12 months.

Randomisation and masking

Patients were randomised in a 1:1 ratio to treatment strategy groups using a telephone-operated Interactive Voice Response System. Minimisation was used to ensure similar numbers of methotrexate intolerant patients were allocated to each group. All patients,

treating clinicians and research nurse were aware of treatment allocation. Analyses were conducted by statisticians who were masked to treatment allocation.

Inclusion/exclusion criteria

Adult patients (>18y) who fulfilled the 1987 ACR classification criteria for a diagnosis of RA were eligible for the study if they: 1. had active disease (DAS28-ESR>5.1) despite treatment with at least two nbDMARDs including methotrexate**;** 2. had not previously been treated with biologic therapy and; 3. were sero-positive for rheumatoid factor and/or anti-CCP antibodies. Patients were excluded if they: were pregnant or breast-feeding; were women of child-bearing potential (or men whose partners were women of child-bearing potential) who were unwilling to use effective contraception; had a history of another autoimmune rheumatic disease other than RA; had received recent (≤2 weeks) intra-articular or parenteral corticosteroids; had an active infection; had septic arthritis within a native joint within the last 12 months; had septic arthritis of a prosthetic joint within 12 months or indefinitely if the joint remained in situ; known HIV or hepatitis B/C infection; had latent TB infection unless they had completed adequate antibiotic prophylaxis; had malignancy (other than basal cell carcinoma) within the last 10 years; had New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure; had demyelinating disease; or had any other contra-indication to the study medications as detailed in their summaries of product characteristics.

Treatment

In the rituximab-first group, patients commenced rituximab, followed by TNFi therapy if rituximab was stopped because of inefficacy or toxicity. The TNFi-first group used the reverse sequence, starting with TNFi therapy before rituximab. Lack (or loss) of response was defined by a failure to achieve (or maintain) an improvement in disease activity score (DAS28-ESR) of >1.2 from baseline. However, at all times during the course of the study, the final decision about treatment resided with the patient and physician. Thus, the study aimed to capture the variety of real life treatment pathways that patients might follow, measuring the outcomes and relating these back to the original (randomised) treatment strategy.

Patients randomised to the rituximab-first group were given rituximab 1g by IV infusion on days 1 and 15. Pre-medication with oral paracetamol 1g, chlorpheniramine 10mg IV and methylprednisolone 100mg IV was given 30 minutes before each rituximab infusion. Patients who responded to rituximab were re-treated with rituximab after 26 weeks if there was still persistent disease activity (DAS28-ESR>3.2). Patients who flared, with a rise in DAS28-ESR>1.2 from the lowest DAS28-ESR recorded, could receive early re-treatment but no sooner than 20 weeks after the previous infusion. Patients randomised to the TNFi-first group were prescribed adalimumab (40mg every other week, sc) *or* etanercept (50mg/week, sc) according to the patient's and rheumatologist's choice.

Patients' disease activity was assessed every month for one year. Response was defined as an improvement in DAS28-ESR>1.2; good response when the DAS28-ESR fell to <3.2; and remission when the DAS28-ESR fell to <2.6. Patients could be switched to the alternative treatment after 12 weeks (or at any visit thereafter) if response was not achieved or maintained. Patients could switch therapy if drug-related adverse events occurred. Patients could be treated with non-steroidal anti-inflammatory drugs, analgesics and nbDMARDs. Changes in concomitant medication and their doses were

allowed and were recorded. Oral corticosteroids could be prescribed at a dose not exceeding prednisolone 10mg/day (or equivalent), but the dose had to remain stable throughout the trial. Intra-articular and intra-muscular triamcinolone could be used, but not within four weeks of the 6 and 12 month assessments, and all injection(s) were recorded.

Outcome measures

Demographic data were collected at baseline; disease activity (DAS28-ESR and CRP) was assessed every month; and physical function (HAQ score), mood (HAD score) and health related quality of life (EQ-5D) were recorded every three months. Patients were asked to complete a diary to capture health care costs and employment data during a one month period every 6 months. The primary outcome measure was the change in DAS28-ESR between baseline and 12 months. Secondary outcome measures included: DAS28-ESR remission, good response, moderate response and non-response; ACR20/50/70 response; area under the curve of DAS28-ESR between baseline and 12 months; change in HAQ score; change in HAD score; change in EQ-5D; toxicity; and incremental cost effectiveness.

Sample size and power calculations

The study was powered to demonstrate non-inferiority of a rituximab-first strategy compared to TNFi-first strategy in the change from baseline DAS28 score after 12 months of treatment. If the true treatment effect difference is zero, and assuming a standard deviation of 1.6 units for the change in DAS28 after 12 months,[4] then 151 patients per group had 90% power to demonstrate non-inferiority between the study groups within a one-sided non-inferiority limit of 0.6 units which equates to the measurement error of DAS28-ESR.[6]

Statistical Analysis

The analysis of the primary outcome was carried out on the 'per protocol' population[7] and tested the null hypothesis that a rituximab-first strategy is inferior to a TNFi-first strategy, after adjustment for baseline DAS28-ESR using a linear regression model. Residuals were examined through residual plots and were found to be near-normal without any evidence of heteroscedasticity. The null hypothesis would be rejected if the upper limit of the 95% confidence interval in the difference in the mean change in DAS28-ESR (comparing rituximab-first to TNFi-first) was less than 0.6 units. If rituximab-first was found to be non-inferior to TNFi-first then the p-value and CI will be used in combination to assess whether rituximab-first is superior to TNFi-first therapy. Quantitative secondary outcomes were analysed in the intention to treat (ITT) population which was defined as those patients who were randomised and treated with at least one dose of study medication. For binary secondary outcomes the odds ratios of response were estimated from a baseline-adjusted logistic regression models. Adverse events were also analysed in patients who received at least one dose of study medication. No interim analyses were planned or undertaken. An independent data monitoring committee periodically reviewed the occurrence of all serious adverse events.

Health Economic Analysis

The economic analysis estimated the mean between-group difference in costs and quality-adjusted life years (QALYs) gained over 12 months. Costs were measured from the perspective of the health service, and the items of resource use collected included

costs of medicines, administering infusion, clinic visits, blood tests, radiology tests, endoscopy, other medicines used, and use of primary care and community services. Appropriate UK costs were applied using 2014 prices (Supplementary Table). QALYs were estimated from the area under the health utility curve, derived from EQ-5D questionnaire responses; the EQ5D was valued using UK time trade-off tariff values. Since all cost and QALY differences were estimated over the 12 month period from randomisation, discounting future costs and effects for societal time preference was not relevant.

Bootstrapping (5000 samples) and the method of recycled predictions were used to jointly estimate the mean between-group differences in QALYs and costs with 95% confidence intervals; these quantities are summarised and presented graphically in the incremental cost effectiveness plane.

Role of the funding source
The funders of the study played no part in study design, data collection, data analysis, data interpretation, writing the manuscript or the decision to submit the manuscript for publication.

Results

Three hundred forty four patients were screened for inclusion in the study, and 329 were randomised. 34 randomised patients (n= 21 to rituximab, and 13 to TNFi) did not receive any study medication because of inter-current illness or withdrawal of consent. The intention to treat population comprised 295 patients (144 rituximab-first, and 151 TNFi-first). 135 (94%) in the rituximab-first and 136 (90%) in the TNFi-first groups completed the follow-up period and were included in the per-protocol analysis of the primary outcome (Figure 1). In the TNFi-first group, 91 patients were treated with adalimumab and 60 were treated with etanercept. Baseline demographic characteristics and measures of disease activity were similar in the treatment groups (Table 1).

Disease Activity Outcomes

The per-protocol analysis demonstrated that the rituximab-first treatment strategy was non-inferior to the TNFi-first strategy, within the pre-specified non-inferiority limit of 0.6 units. The baseline-adjusted between-group difference in the change in DAS28-ESR between baseline and 12 months follow-up (Figure 2) was estimated as -0.19 (95% CI -0.51, 0.13), p=0.24. The upper confidence limit was less than the pre-specified inferiority margin, allowing rejection of the null hypothesis that the rituximab-first strategy is inferior to a TNFi-first strategy. No significant between group differences in DAS28-ESR were observed at any time point, and there was no difference in the area-under-the-curve (AUC) for the improvement in DAS28-ESR over 12 months (Supplementary Figure 3, mean difference in AUC= 64 units (95% CI -20, 147), p=0.13).

After 6 and 12 months, there were no significant differences in the proportion of patients achieving ACR20, ACR50, ACR70, DAS28-ESR remission, good response, moderate response or non-response (Table 2). The groups showed similar improvements in EQ5D health utility, EQ5D VAS and the Anxiety and Depression Scores of the HAD Scale after 6 and 12 month's follow-up. The rituximab-first group demonstrated a greater

improvement in HAQ over time (mean difference [95% CI] = -0.121 [-0.236, -0.006], p=0.039. Table 3).

Treatment

A significantly higher number of patients in the TNFi-first group switched to treatment with rituximab than the number of rituximab-first patients who switched to TNFi treatment (33% vs 19% respectively, p=0.008). In the rituximab-first group, 2 patients switched treatment due to toxicity and 25 due to inefficacy. In the TNFi-first group, 3 patients switched due to toxicity and 44 switched due to inefficacy. In the rituximab-first group, 57 patients (39%) received 1 course of treatment, 77 (54%) received 2 courses and 10 (7%) received 3 courses. Of the 49 patients in the TNFi-first group who were switched to rituximab, 28 (57%) received 1 course and 21 (43%) received 2 courses.

In patients who switched treatment for inefficacy, there was no difference in DAS28-ESR at the point of switching (mean [SD] DAS28-ESR: rituximab-first 5.6 [0.9] v TNFi-first 6.3 [1.0]), and there were similar improvements in DAS28-ESR between the switch and month 12 visits (mean [SD] change in DAS28-ESR: rituximab-first -1.3 [1.5] vs TNFi-first -1.6 [1.5], p=0.44). More patients in the TNFi-first group achieved a good response after switching to rituximab than *vice versa* but this was not statistically significant (rituximab-first 69% vs TNFi-first 86%, p=0.13), and there was no difference in DAS28-ESR at 12 months in those who had switched (mean [SD]: rituximab-first 4.2 [1.5] vs TNFi-first 4.6 [1.1], p=0.32).

Adverse Events

One hundred thirty seven (95%) patients in the rituximab-first group and 143 (95%) patients in the TNFi-first group reported at least 1 adverse event during the follow-up period (Supplementary Table 5). In the rituximab-first group a higher number of patients reported diarrhoea (14% vs 6%, p=0.03) whilst, in the TNFi-first group a higher number of patients reported injection site reactions (2% vs 11%, p=0.003). There were 37 serious adverse events (SAE) reported in patients currently receiving rituximab (31 randomised to rituximab-first arm, and six following a switch from TNFi therapy); of these, 15/37 were deemed to be possibly, probably or definitely related to the rituximab. 26 patients experienced serious adverse events whilst receiving TNFi therapy (22 randomised to TNFi-first arm, and four following a switch from rituximab) of which 12/26 were deemed possibly, probably or definitely related to the TNFi therapy (p=0.27 for SAE occurring on rituximab vs TNFi). One patient in each group died during the study (rituximab – sepsis related to infected elbow prosthesis; TNFi – myocardial infarction).

Health Economic Outcomes

Healthcare-related costs, and Quality-Adjusted Life Years (QALYs) for each randomised group are shown in Table 4 and Supplementary Figure 4. The total healthcare-related costs were lower in the rituximab-first group (£9,405 vs 11,523, p<0.001). There was no difference in the mean AUC for EQ-5D (TNFi mean [SD] 0.519 [0.248] vs rituximab 0.546 [0.212], p=0.235) indicating no difference in QALYs gained. Using generalized linear regression models, age was a significant determinant of cost and EQ-5D but gender, baseline DAS28-ESR, and methotrexate tolerance were not independently associated with either (data not shown). Absenteeism costs were slightly lower in the

rituximab-first group (£6,296 vs £7,662 TNF). Given the lack of evidence of a QALY difference between groups, and the clear reduction in healthcare-related costs in the rituximab-first group, the incremental cost effectiveness ratio between treatment strategies was not relevant to the analysis, and a rituximab-first strategy can be judged as the more cost-effective option.

Discussion

Biologic DMARDs are the mainstay of therapy in moderate to severe RA. Many effective drugs are available that operate through discrete mechanisms of action. There is robust evidence for their efficacy in a variety of clinical settings; however, since there have been very few head-to-head clinical trials, there is a paucity of direct evidence about their comparative efficacy. The AMPLE study found that abatacept and adalimumab were similarly efficacious in biologic-naïve RA patients,[8] and the ADACTA study showed superiority of tocilizumab monotherapy compared to adalimumab monotherapy in biologic-naïve RA patients who were intolerant of methotrexate.[9] One study compared infliximab with etanercept, but was too small to provide reliable information about relative efficacy.[10] The RED-SEA study showed that adalimumab was non-inferior to etanercept in terms of persistence on therapy over 12 months, but was not powered to detect differences in efficacy.[11] The ORBIT study results are broadly similar to those reported in placebo-controlled randomized controlled trials of the individual drugs,[2, 4-5,12-16] but it is the first head to head RCT comparing B cell depletion with TNF inhibition in RA, and convincingly shows that a rituximab-first strategy in biologic-naïve RA is non-inferior to a TNFi-first strategy. The only notable difference between the strategies was that a higher proportion of patients continued on initial rituximab therapy, without the need to switch therapy, when compared to those randomised to TNFi-first therapy (81% persistence on rituximab v 68% persistence on TNFi, p=0.008).

Rituximab is only approved for use in patients who have failed TNFi therapy. An application to extend the license to biologic-naïve patients was rejected by the European Medicines Agency because of the rare occurrence of progressive multi-focal encephalopathy (PML). In this study, there were no differences observed in the rate, severity or relationship to study drug in serious adverse effects during the study period. This observation does not preclude the possibility of relevant differences in rare, but very serious, toxicity or differences in toxicity associated with long-term use. There were no cases of PML or demyelination, but two patients died - one from serious sepsis following rituximab therapy, and one from myocardial infarction on TNFi therapy.

The majority of patients in the rituximab-first group (93%) received four or fewer infusions (i.e. two courses) of rituximab. During the study period, the costs associated with the rituximab-first strategy were substantially lower than those in the TNFi-first group (mean annual cost per patient: rituximab-first £8391, TNFi-first £10,356). In the UK, widespread adoption of a rituximab-first strategy, in preference to TNFi-first therapy, would currently translate into very substantial budgetary savings for health services with no measurable loss of efficacy. However, the healthcare-related costs were dominated by drug acquisition and administration costs, which may vary significantly according to local procurement agreements. The availability of TNFi biosimilars at lower acquisition costs, or the use of lower doses of drugs (e.g. rituximab 500mg per infusion[17]) would also affect the relative cost effectiveness of the two strategies. There are other options that are available for biologic-naïve RA patients who require biologic therapy, and it is

possible that another drug/strategy would be even more cost effective than rituximab. The AMPLE study found that abatacept and adalimumab are equally efficacious, but as abatacept is more expensive than TNFi therapy, it is almost certain that a rituximab-first strategy will be more cost effective than an abatacept-first strategy. Because tocilizumab monotherapy is more effective than adalimumab therapy in patients who are unable to tolerate methotrexate, it is possible that tocilizumab is more cost effective than rituximab in this patient population and this requires further study. The TACIT study compared the efficacy of combination conventional DMARD therapy with TNFi in patients who met the British Society for Rheumatology/National Institute for Clinical Excellence (BSR/NICE) eligibility criteria for the use of TNFi therapy, and found that using combination DMARD was non-inferior to TNFi therapy, and substantially more cost effective.[18] A significant proportion (~40%) of patients randomised to combination DMARD therapy eventually required TNFi therapy, and the implication of the ORBIT study is that further savings could be made if patients who fail to make an adequate response to combination nbDMARD therapy were then treated with rituximab rather than TNFi therapy.

Our study has limitations: a wide range of clinical outcome measures were captured, but no radiographic outcomes were recorded. It is possible that a TNFi-first strategy would be associated with more or less radiographic joint damage, than a rituximab-first strategy. Secondly, the study was limited to patients who were sero-positive for rheumatoid factor and/or anti-cyclic citrullinated protein antibodies. Since response to rituximab is modestly greater in sero-positive patients[19] the results of this study should only be extrapolated to sero-negative patients with caution. Thirdly, patients who were intolerant of methotrexate were eligible for the study, even though rituximab is only approved for use in combination with methotrexate. However, this represents real life experience, and excluding patients who were intolerant of methotrexate would have limited the study's generalizability. Minimisation techniques were employed to ensure similar numbers of methotrexate-intolerant patients were randomised to each group, so this is unlikely to have significantly influenced the results. Fourthly, this was an open label study. Both patients and assessors were aware of the patients' treatment allocation and therefore there is a possibility of bias. There is no evidence that such bias existed, or which treatment arm was favoured if it did. A double-blind study design would have been more complex and costly, and been dependent on funding from three pharmaceutical companies, for example to provide matched placebo self-injection pen devices. The benefits accruing from delivering a true-to-life, investigator-initiated, charitably-funded RCT (and minimising the involvement of the pharmaceutical industry) were deemed to be more important and thus were given priority in study design. Fifth, when a patient had not responded, or lost response, the study team was advised to consider switching but treatment decisions were at the discretion of the treating physician in discussion with the patient – it is possible, therefore, that patients were kept on ineffective therapy but (on the other hand) the study will have captured usual practice. Disease activity at the point of switching was not significantly different in the two groups, arguing against any systematic bias in this regard. Finally, the 12 month follow-up period means that the study is unable to provide a comparative description of either strategy's long-term efficacy or safety. RA may affect an individual over several decades, and from a lifetime perspective, other factors are highly relevant – for example, the rates of long term drug continuation, the ability of each strategy to influence disease progression, and any effect on life expectancy.

In conclusion, initial therapy with rituximab is clinically non-inferior to and more cost effective than initial therapy with a TNFi drug in sero-positive RA patients who are eligible for biologic therapy in the UK.

Competing Interests

DP has received research funding, honoraria, and consultancy fees from Roche, Abbvie, Pfizer, UCB, BMS and MSD.
JvM has no competing interests
JD has received research funding from Pfizer, honoraria from Abbott, Janssen and MSD and support to attend academic meetings from Abbott and Pfizer
RM has received support to attend scientific meetings from UCB, Roche and Abbott
JMcL has received sponsorship to attend academic meetings from Roche, Pfizer and Abbott.
EMcR has received research funding, honoraria, and consultancy fees from Roche, Abbott, Pfizer, UCB, BMS and MSD.
JP has no competing interests
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AMcC has no competing interests
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Authors' contribution

DP (corresponding author) has full access to all the data and had the final responsibility for the decision to submit the manuscript for publication.
Study design: all authors
Data collection DP, JvM, JD, RM, JMcL, EMcR, JP, CB, JH, CP, PT, EC, IMcI
Analysis: AM, MM and AW designed the statistical and economics analyses, and analysed the data in discussion with the clinical authors
Interpretation: all authors
Writing: all authors

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References

1. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014 Mar 1;73(3):492–509.

2. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793–806.

3. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dorner T, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011 Jun;70(6):909–20.

4. KEYSTONE EC, Cohen SB, Emery P, Kremer JM, Dougados M, Loveless JE, et al. Multiple Courses of Rituximab Produce Sustained Clinical and Radiographic Efficacy and Safety in Patients with Rheumatoid Arthritis and an Inadequate Response to 1 or More Tumor Necrosis Factor Inhibitors: 5-Year Data from the REFLEX Study. J Rheumatol. 2012 Jan 1;39(12):2238–46.

5. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54(5):1390–400.

6. van Gestel AM, Prevoo MLL, van't Hof MA, van Rijswijk MH, Van De Putte LBA, Van Riel PLCM. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum. 1996;39(1):34–40.

7. Gomberg-Maitland M, Frison L, Halperin JL. Active-control clinical trials to establish equivalence or noninferiority: methodological and statistical concepts linked to quality. Am Heart J. 2003 Sep;146(3):398–403.

8. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013 Jan;65(1):28–38.

9. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial.

Lancet. 2013 Mar 18;381(9877):1541–50.

10. De Filippis L, Caliri A, Anghelone S, Scibilia G, Gullo Lo R, Bagnato G. Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. Panminerva Med. 2006 Jun;48(2):129–35.

11. Jobanputra P, Maggs F, Deeming A, Carruthers D, Rankin E, Jordan AC, et al. 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. BMJ Open. 2012;2(6).

12. Moreland LW. Etanercept Therapy in Rheumatoid Arthritis. Ann Intern Med. 1999 Mar 16;130(6):478.

13. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002 Jun 6;46(6):1443–50.

14. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. The Lancet. 2008 Aug 2;372(9636):375–82.

15. KEYSTONE EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400–11.

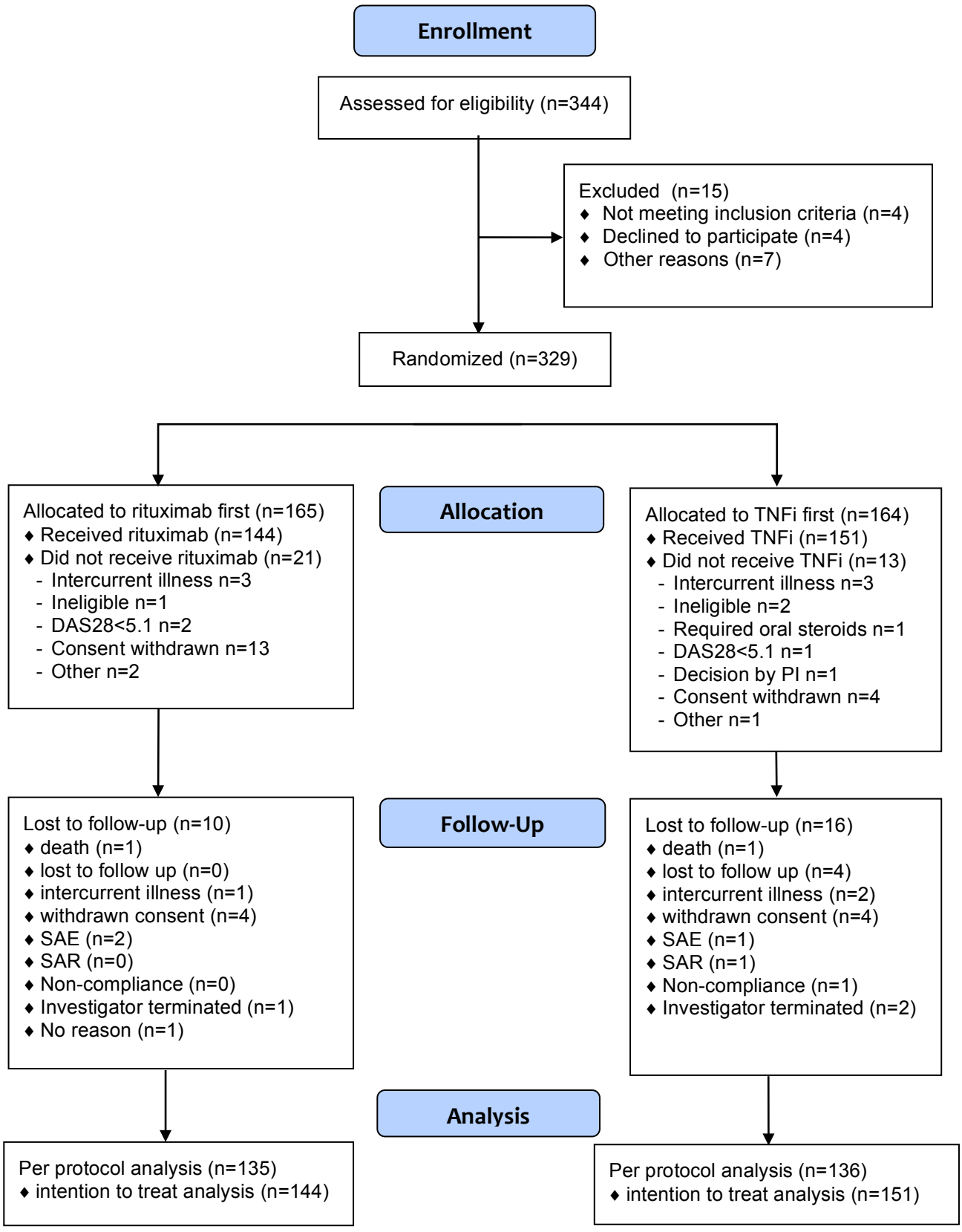
16. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006 Jan;54(1):26–37.

17. Bredemeier M, de Oliveira FK, Rocha CM. Low- versus high-dose rituximab for rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care & Research. 2014 Feb;66(2):228–35.

18. Scott DL, Ibrahim F, Farewell V, O'Keeffe AG, Walker D, Kelly C, 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. BMJ. 2014 Oct;307(6901):425–8.

19. Isaacs JD, Cohen SB, Emery P, Tak PP, Wang J, Lei G, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis. 2013 Jan 1;72(3):329–36.

565 **Figure 1** Consort diagram
566



567 **Table 1** Baseline Characteristics - mean (SD) or %
568

	Rituximab-first n = 144	**Anti-TNF-first** n = 151
Age (years)	57 (10)	57 (10)
Gender - % female	72%	72%
Disease Duration (months)	8.0 (7.4)	6.7 (7.1)
DAS28-ESR	6.2 (0.9)	6.2 (1.1)
28 Tender Joint Count	17 (7)	16 (7)
28 Swollen Joint Count	9 (5)	9 (5)
Patient Global Health VAS (0-100)	67 (17)	66 (19)
Pain VAS (0-100)	62 (18)	63 (22)
Physician Global VAS (0-100)	63 (17)	62 (19)
CRP (mg/l)	19 (24)	21 (22)
ESR (mm/h)	32 (24)	37 (28)
HAQ (0-3)	1.7 (0.6)	1.8 (0.7)
EQ5D Health Utility Score	0.34 (0.32)	0.30 (0.33)
EQ5D VAS Score (0-100)	48 (22)	43 (23)
HADS Anxiety >11	29%	29%
HADS Depression > 11	22%	23%
Methotrexate Intolerance	26%	25%
Number of Concomitant DMARD*	1.0 (1.0-2.0)	1.0 (0-2.0)

569 ***** median (IQR)

Figure 2 Non-Inferiority Plot

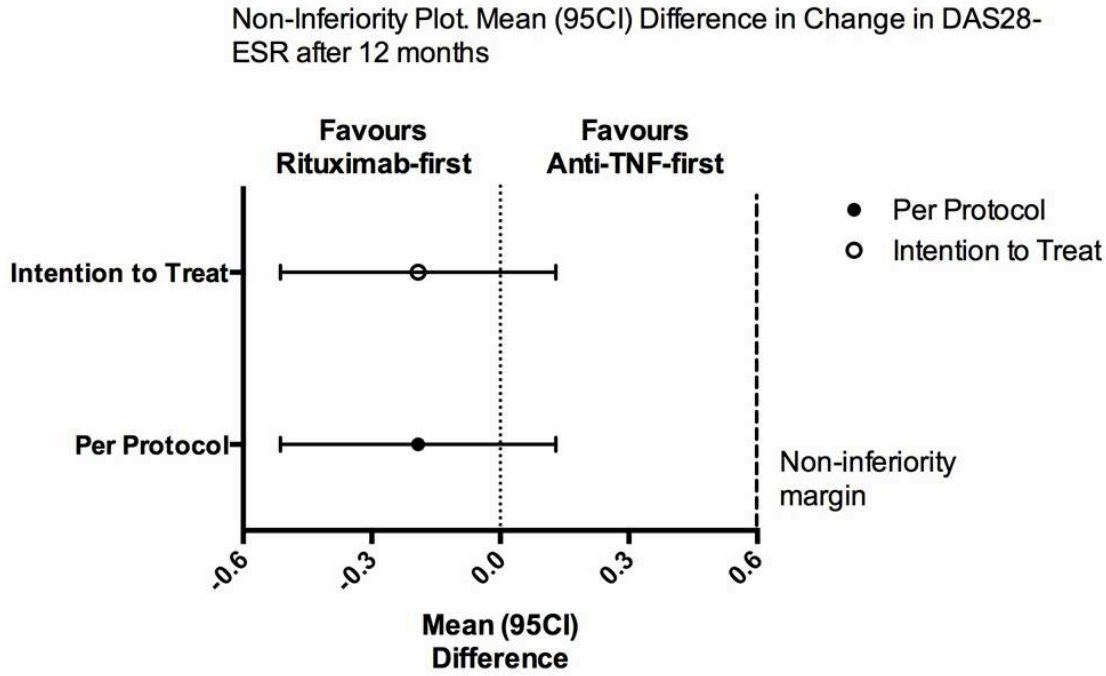


Table 2 Percentage of patients fulfilling response criteria after 6 and 12 months follow-up. Intention-to-treat population

	Rituximab-first	Anti-TNF-first	Odds Ratio (95CI)
DAS28 Remission			
6 months	14%	16%	0.9 (0.4, 1.8)
12 months	23%	21%	1.1 (0.6, 2.1)
Good response			
6 months	29%	29%	1.0 (0.6, 1.8)
12 months	43%	40%	1.1 (0.7, 1.9)
Moderate response			
6 months	83%	76%	1.5 (0.8, 2.8)
12 months	87%	82%	1.5 (0.7, 2.9)
No response			
6 months	17%	24%	0.7 (0.4, 1.2)
12 months	13%	18%	0.7 (0.3, 1.3)
ACR20 response			
6 months	62%	66%	0.8 (0.5, 1.4)
12 months	66%	71%	0.8 (0.5, 1.4)
ACR50 response			
6 months	37%	41%	0.9 (0.5, 1.4)
12 months	49%	45%	1.2 (0.7, 1.9)
ACR70 response			
6 months	15%	17%	0.9 (0.5, 1.7)
12 months	23%	26%	0.8 (0.5, 1.5)

Definitions: DAS remission = DAS28-ESR<2.6; Good response = DAS28-ESR<3.2, with improvement from baseline >1.2; Moderate response = DAS28-ESR = 3.2-5.1 and improvement from baseline 0.6-1.2 or DAS28-ESR>5.1 and improvement from baseline >1.2; No response = DAS2828-ESR <5.1 and improvement from baseline <0.6 or DAS28-ESR >5.1 and improvement from baseline <1.2

Table 3 Mean (SD) change from baseline in functional ability, mood and health-related quality of life outcomes

	Rituximab-first	Anti-TNF-first	P*
HAQ			
6 months	-0.44 (0.6)	-0.31 (0.6)	0.039**
12 months	-0.49 (0.6)	-0.38 (0.5)	
EQ5D Health Utility Score			
6 months	0.2 (0.4)	0.3 (0.4)	0.90
12 months	0.2 (0.4)	0.3 (0.3)	
EQ5D VAS			
6 months	17 (30)	20 (28)	0.48
12 months	14 (34)	21 (32)	
HAD depression			
6 months	-2.0 (3.4)	-2.0 (3.4)	0.60
12 months	-2.1 (3.7)	-2.3 (3.4)	
HAD anxiety			
6 months	-1.7 (3.5)	-1.5 (2.9)	0.73
12 months	-2.0 (3.4)	-1.9 (3.2)	

HAD – Hospital Anxiety & Depression; HAQ – Health Assessment Questionnaire

* Treatment effect over time estimated from linear mixed effect model for rituximab-first vs TNFi-first adjusted for baseline variable and DAS28-ESR

** Estimated difference (95% CI) = -0.121 (-0.236, -0.006)

Table 4 Healthcare related costs and QALYs over 12 months

	TNFi-first	Rituximab-first	
Medicines, infusions, clinics	£10,356	£8,391	p<0.001*
Primary care	£370	£366	p=0.92
Blood tests, Xray	£163	£141	p=0.51
Total	£11,523	£9,405	p<0.001*
Bootstrap estimated mean cost difference (95% CI) = £1,999 (£2,755, £1440)			
Quality-Adjusted Life Years (1-EQ-5D AUC)			
QALYs	0.481	0.454	p=0.25
Bootstrap estimated mean QALY difference (95% CI) = 0.028 (-0.041, 0.094)			

* Wilcoxon

Research in Context

Evidence before this study

Biologic disease modifying anti-rheumatic drugs (DMARDs) are used in the treatment of moderate to severe rheumatoid arthritis (RA) following an insufficient response to conventional DMARDs. A Pubmed search was carried out on 1st February, 2016 using the search terms 'rheumatoid', rituximab', 'adalimumab', 'etanercept' and 'randomised controlled trial'. There have been several placebo controlled RCTs that have established the efficacy and safety of these biologic DMARDs; indirect comparisons of short term efficacy, effectiveness and drug continuation rates have suggested similar outcomes with rituximab and TNFi therapy, but no head to head comparisons have been undertaken.

Added value of this study

The ORBIT study is the first head to head study that directly compares the efficacy, safety and cost effectiveness of two strategies of care, and shows that a rituximab-first treatment strategy is non-inferior to a TNFi-first strategy. Very similar effects on disease activity, physical function, mood and health-related quality of life were observed. Fewer patients needed to switch from rituximab to TNFi therapy than vice versa, and there were no significant differences in the incidence of serious adverse events. Using rituximab-first was associated with significantly lower health related costs using UK 2015 prices

Implications of the available evidence

The relative cost-effectiveness of rituximab-first or TNFi-first treatment was dominated by drug acquisition and administration costs, which are context dependent - the price of biologic drugs varies according to local procurement agreements, and these are likely to be substantially affected by the advent of biosimilars that are cheaper than the originator drugs. This study suggests the cheapest drug is likely to represent the most cost effective option. However, the study has a 12 month horizon, and RA is a condition that may affect people over several decades. Consequently, the long term consequences of any differences in disease progression, effect on life expectance and/or drug discontinuation rates need to be evaluated.