
Article:
Stevenson, M.D. orcid.org/0000-0002-3099-9877, Wailoo, A.J. orcid.org/0000-0002-9324-1617, Tosh, J.C. et al. (8 more authors) (2017) The cost-effectiveness of sequences of biological disease-modifying antirheumatic drug treatment in England for patients with rheumatoid arthritis who can tolerate methotrexate. Journal of Rheumatology, 44 (7). pp. 973-980. ISSN 0315-162X

https://doi.org/10.3899/jrheum.160941

The cost-effectiveness of sequences of biological disease-modifying antirheumatic drug treatment within England for patients with rheumatoid arthritis who can tolerate methotrexate.

Authors

Stevenson Matt D, Wailoo Allan J, Tosh Jon C, Hernandez-Alava Monica, Gibson Laura, Stevens John W, Archer Rachel, Simpson Emma L, Hock Emma S, Young Adam, Scott David L

Abstract

Objective. To ascertain whether strategies of treatment with a biological disease-modifying antirheumatic drug (bDMARD) were cost-effective in an English setting. Results are presented for those patients with moderate-to-severe rheumatoid arthritis (RA) and those with severe RA.

Methods. An economic model to assess the cost-effectiveness of seven bDMARDs was developed. A systematic literature review and network meta-analysis was undertaken to establish relative clinical effectiveness. The results together with estimates of: Health Assessment Questionnaire (HAQ) score following European League Against Rheumatism response; annual costs, and utility, per HAQ band; trajectory of HAQ for patients on bDMARDs; and trajectory of HAQ for patients on non-biologic therapy (NBT) were used to populate the model. Results were presented as those associated with the strategy with the median cost-effectiveness. Supplementary analyses were undertaken assessing the change in cost-

effectiveness where only patients with the most severe prognoses on NBT were provided with bDMARD treatment. The cost per QALY values were compared with reported thresholds from the National Institute for Health and Care Excellence of £20,000 to £30,000.

Results. In the primary analyses, the cost per QALY of a bDMARD strategy was £41,600 for patients with severe RA and £51,100 for those with moderate-to-severe RA. Under the supplementary analyses the cost per QALY fell to £25,300 for those with severe RA and to £28,500 for those with moderate-to-severe RA.

Conclusion. The cost-effectiveness of bDMARDs in RA in England is questionable and only meets current accepted levels in subsets of patients with the worst prognoses.

Key Indexing Terms:

Arthritis, Rheumatoid; Antirheumatic agents; Cost-Benefit Analysis; Economics, Medical;

Departments and Institutions to which the work should be attributed:

School of Health and Related Research, University of Sheffield, Sheffield, UK

Department of Rheumatology, West Hertfordshire Hospitals NHS Trust, Hertfordshire, UK

Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK

Funding: Funding for this research was provided by the Health Technology Assessment programme of the National Institute for Health Research and the National Institute for Health and Clinical Excellence

Authors:

MD Stevenson, Professor of Health Technology Assessment, School of Health and Related Research, University of Sheffield, BSc, PhD

AJ Wailoo, Professor of Health Economics, School of Health and Related Research, University of Sheffield, BSc, MA, MSc, PhD

JC Tosh, Research Fellow in Health Economics, School of Health and Related Research, University of Sheffield, BA, MSc, PhD

M Hernandez-Alava, Senior Research Fellow in Econometrics, School of Health and Related Research, University of Sheffield, BSc, MSc, PhD

LA Gibson, Research Associate in Econometrics, School of Health and Related Research, University of Sheffield, BSc, MSc, PhD

JW Stevens, Reader in Decision Science, School of Health and Related Research, University of Sheffield, BSc, PhD

RJ Archer, Research Fellow, School of Health and Related Research, University of Sheffield, BSc, PhD

EL Simpson, Research Fellow, School of Health and Related Research, University of Sheffield, PhD

ES Hock, Research Fellow, School of Health and Related Research, University of Sheffield, BSc, MSc, PhD

A Young, Professor of Clinical Rheumatology, Centre for Lifespan and Chronic Illness Research, University of Hertfordshire

DL Scott, Professor of Clinical Rheumatology, Department of Rheumatology, King's College Hospital NHS Foundation Trust, MD FRCP

Requests for reprints:

Matt Stevenson, 30 Regent Street, Sheffield, S1 4DA

Corresponding Author:

Matt Stevenson, 30 Regent Street, Sheffield, S1 4DA

Short Running Title:

Cost-effectiveness of bDMARDs.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive, irreversible, joint damage, impaired joint function, pain and tenderness caused by swelling of the synovial lining of joints and is manifested with increasing disability and reduced quality of life.(1) RA is associated with substantial costs both directly (drug acquisition and hospitalisation) and indirectly due to reduced productivity.(2) RA has long been reported as being associated with increased mortality,(3,4) particularly due to cardiovascular events.(5) A range of biological disease modifying anti-rheumatic interventions(bDMARDs) is available with proven efficacy compared with conventional disease modifying anti-rheumatic interventions(cDMARDs). However, these are expensive treatments, costing in the region of £9,000 per annum making decisions based on cost-effectiveness particularly important. In England, the National Institute for Health and Care Excellence (NICE) make recommendations on the use of new and existing medicines and treatments within the National Health Service. NICE guidance restricts the use of bDMARDs to patients who have failed at least two cDMARDs and who have a disease activity score in 28 joints (DAS28) > 5.1. For treatment to be continued patients need to demonstrate at least a moderate European League Against Rheumatism (EULAR) response by 6 months.

NICE decided to review guidance on the use of bDMARDs to allow a comparison between interventions and to consider extending existing guidance to patients with less severe RA. This paper reports the economic model structure, parameter inputs

and estimated cost-effectiveness of sequences of bDMARDs compared with no use of bDMARDs undertaken by the Assessment Group. This work formed part of the evidence base used by NICE to form the guidance for Technology Appraisal 375.(6) The economic model differs from previously published models by other researchers in that: it is based on EULAR response rather than American College of Rheumatology (ACR) responses that are not used in UK clinical practice; it used non-linear, Health Assessment Questionnaire (HAQ) score progression whilst on cDMARDs based on a comprehensive review and analysis of HAQ progression; it assesses the cost-effectiveness in moderate-to-severe, and severe RA patients independently; and it allows fully incremental analyses of treatment strategies using different first-line bDMARDs. This paper concentrates on the cost-effectiveness results for those patients who can tolerate methotrexate (MTX) with the results for strategies without MTX provided elsewhere.(7,8)

Methods

Economic model

An economic model was developed to estimate the cost-effectiveness within England of sequences of bDMARDs. The model is used to synthesis evidence from a range of sources, including clinical trials, in order to estimate the costs and health benefits of different treatments over patients' lifetimes. The ratio of additional cost to additional health benefits, measured in quality adjusted life years (QALYs), is the incremental cost effectiveness ratio (ICER). The ICER is compared with a published threshold (£20,000 - £30,000 per QALY in this instance for NICE) to help determine if new treatments will add more to population health than will be lost from the withdrawal of other NHS services. The conceptual model is depicted in Figure 1 and

took an NHS and Personal Social services perspective. The model used an individual patient, time to event approach using a lifetime time horizon with both costs and benefits discounted at 3.5% per annum in accordance with NICE recommendations.(9) Individual patients were sampled with characteristics resembling those in the British Society for Rheumatology Biologics Register (BSRBR). An outline of the methods is provided here: see Stevenson *et al*.(7) for full technical details.

The population evaluated.

Analyses were conducted separately for patients with moderate-to-severe RA (defined as those with a DAS28 score >3.2 and ≤5.1) and for patients with severe RA (defined as those with a DAS28 > 5.1). Patients with prior experience of MTX were sampled using patient characteristics from the BSRBR for those receiving their first bDMARD which allowed correlation to be maintained between the following characteristics: age; sex; disease duration; DAS28; previous DMARDs; HAQ score; and weight. Details of the midpoint values and distributions are provided elsewhere.(7)

The strategies evaluated within the economic model

The focus of the NICE appraisal was on the cost-effectiveness of the initial bDMARD which was one of: adalimumab (ADA); etanercept (ETN); infliximab (IFX); certolizumab pegol (CTZ); golimumab (GOL); tocilizumab (TCZ) and abatacept (ABT). ABT was available in both subcutaneous (SC) and intravenous (IV) formulations. The remaining treatments after all first line bDMARDs were assumed to

follow NICE guidance and were rituximab (RTX) + MTX, then TCZ + MTX, if TCZ + MTX was not used first-line, followed by a range of non-biologic therapies (NBT) which was a term defined to encompass a selection of non-biological treatments that clinicians may feel is appropriate for individual patients, typically MTX, and sulphasalazine.(10) All seven bDMARD strategies were compared against each other, and with a strategy of cDMARD (MTX) followed by NBT. It was assumed that in accordance with NICE guidance patients would have received at least two cDMARDs before considering the use of a bDMARD.(11)

The efficacy of bDMARDs, cDMARDs and NBT.

Literature searching was performed with a cut-off date of July 2013, as the Assessment Group report was submitted to NICE in August 2013. For inclusion in the network meta-analysis (NMA) a study needed to present information on ACR and/or EULAR response between 22 and 30 weeks inclusive and needed to recruit patients with moderate-to-severe RA or severe RA. These studies were deemed generalizable to the patients modelled.

This paper provides the results for studies conducted in patients without previous bDMARD experience: results including studies with a small proportion of bDMARD experienced people are provided elsewhere.(7) A NMA, implemented within a Bayesian framework, was undertaken to synthesise both direct and indirect evidence on relative EULAR responses produced by each intervention and assuming that cDMARDs could be grouped together. The analyses conducted for those with moderate-to-severe or severe RA was based on 16 randomised controlled trials.(12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29) Point estimates from the NMA for the interventions within the decision problem are shown in Figure 2. As

expected, bDMARDs are more efficacious than NBT. No EULAR data was available for ABT SC. Based on work undertaken by Malottki *et al*.(30) the efficacy of RTX+MTX was set equal to that for ABA IV + MTX. It was assumed that NBT provided no EULAR response.

The change in HAQ related to EULAR response

The change in HAQ score conditional on EULAR response was calculated using data (2417 Good EULAR responses and 5492 moderate EULAR responses) from the BSRBR. The average reductions in HAQ score were estimated to be 0.317 (standard error 0.048) for moderate responders and 0.672 for good responders (standard error 0.112).

The trajectory of HAQ while on bDMARDs or NBT

Three-year data from the BSRBR showed no evidence to challenge previous assumptions of no HAQ progression whilst a patient was on a bDMARD. For those patients on NBT, we used estimates from previous work by Norton *et al*.(31) which identified four distinct trajectories of HAQ in the Early Rheumatoid Arthritis Study (ERAS) and which showed that the rate of HAQ worsening decreases over time. These analyses were re-run incorporating covariates for patient characteristics (age; sex; disease duration; DAS28 score; and number of previous cDMARDs) with the results shown in Figure 3. For each individual patient the probabilities of belonging to each trajectory was calculated with the predicted HAQ progression being the weighted average of the four trajectories.

Alternative analyses were also undertaken to evaluate the ICERs if faster rates of HAQ progression were used. These analyses are described in detail in Gibson *et*

al.(32), which extended approach of Norton *et al* to assess the potential impact of patient dropout from the ERAS dataset on the four trajectories. We used the estimates that had the greatest rate of HAQ worsening over fifteen years to illustrate a lower limit of the ICER. The HAQ trajectories for the Gibson *et al*. analysis are shown in Figure 4. There was a delay between the Assessment Group being submitted to NICE and the final appraisal decision because the NICE appraisal process was suspended until these additional analyses were completed. In both the base case and supplementary analyses, it was assumed that that there was no further progression beyond 15 years, although a scenario which allowed the rate of progression seen between years 12 and 15 in trajectories three and four to be continued until 40 years was evaluated. Whilst the data to inform HAQ progression were relatively dated and do not reflect current first line cDMARD treatment these were believed appropriate to represent NBT in a population who had received at least 2 prior cDMARDs, and in the intervention strategy, bDMARDs.

The time to discontinuation of treatment and the assumed change in HAQ score post-discontinuation

The time to discontinuation of bDMARD treatment was estimated using the BSRBR. Separate analyses were undertaken for those with a good and moderate EULAR response with the gamma distribution providing the best fit from the parametric models considered (Weibull, exponential, log-logistic, log-normal, gamma and Weibull frailty models). The individual patient characteristics were used as covariates.

The median time to discontinuation was 1523 days for moderate responders and 3363 days for good responders. It was assumed that the distribution of time to

discontinuation was equal for all bDMARDs and also that this was applicable for cDMARDs. Patients were not assumed to discontinue NBT. Further details are provided in Stevenson et al. (7)

For all analyses it was assumed that any reduction in HAQ score provided by the initial response would be lost (commonly referred to as a 'rebound effect') once treatment was stopped.

The costs associated with treatment

The costs of each bDMARD and of MTX were taken from the British National Formulary.(33) The cost of MTX was assumed to approximate that of NBT. Both public (CTZ and GOL) and confidential (ABT and TCZ) Patient Access Schemes (PAS) were taken into consideration. In these PAS the first 12 weeks of CTZ treatment are provided free of charge, 100mg of GOL is provided at the same cost as 50mg, whilst ABT and TCZ are provided at a discount from the list price. Monitoring and administration costs were also included as detailed in Stevenson et al.(7)

Hospitalisation costs and patient utility

The hospitalisation cost data used in the model, conditional on HAQ score are shown in Table 1. These data were taken from the Abbvie company submission (34) and were derived from the Norfolk Arthritis Register database for Roche.(35) For calculating a patient's utility the mixture model proposed by Hernandez Alava et al was used (36,37) which required the pain score for each individual to be simulated from the HAQ score. This method uses a much larger sample size including patients

that span the entire range of disease; other published papers employ methods that have been shown to lead to biased utility estimates.

Indirect costs

In line with the NICE reference case (9) indirect costs such as lost productivity due to not working, were not included in our analysis.

Assumptions regarding mortality

It was assumed that bDMARD treatment would not influence the rate of mortality. This assumption was based on Michaud *et al*. (38) which concluded that changes in HAQ score did not contribute substantially to predictive values of mortality over and above the baseline values. The model assumes an increased hazard for mortality, compared with age and gender mortality rates (39), associated with baseline HAQ score category. These hazard ratios are provided in Table 1.

Adverse events associated with bDMARDs

A simplistic approach to estimating the impact of adverse events (AEs) associated with bDMARDs was taken. A review of AEs associated with bDMARDs estimated a serious infection was observed in 35 per 1000 patients (95% confidence interval 27 to 46) compared with 26 per 1000 patients (no confidence intervals presented) in patients receiving placebo.(40) As such it was assumed that 9 people per 1000 would have a serious infection which was associated with a cost of £1479 per episode and a QALY loss of 0.012 as detailed in Pfizer's submission to NICE.(41)

Ethical Approval

Ethical approval was not required in accordance with the policy of the institutions concerned.

Results

Due to there being only small differences in the discounted costs and discounted QALYs between many of the bDMARD sequences the incremental cost effectiveness ratio can be misleadingly volatile: accordingly, we present the average (median and mean) cost-effectiveness of the seven bDMARD sequences compared with NBT. Unfortunately, the absolute discounted costs and QALYs cannot be presented because of the risk of back calculation of commercial-in-confidence discounts. However, incremental QALY gains were between 1.5 and 2.0 and incremental costs were between £60,000 to £100,000. The ranges in the mean ICERs of the individual bDMARD strategies were relatively small, spanning £39,100 to £42,200 for patients with severe RA and from £48,800 to £52,300 for patients with moderate-to-severe RA. The deterministic base case ICERs (the median of the seven mean ICERs produced by the bDMARD strategies) for patients with severe RA is estimated to be £41,600 per QALY gained: for patients with moderate-to-severe RA the value is estimated to be £51,100. The mean ICERs (assuming equal use of all potential first line bDMARDs and weighting the individual cost and QALY gains for the seven strategies equaly) were marginally lower, being £41,100 for patients with severe RA and £50,300 for patients with moderate-to-severe RA. Probabilistic results were similar to the deterministic results: the median (mean)

ICERs for patients with severe RA were £41,300 (£40,700) and were £52,000 (£51,100) for patients with moderate-to-severe RA. As such, all sensitivity analyses were run deterministically to reduce computational time required. The absolute costs and QALYs gained for the TCZ first strategy differed from the remaining strategies as TCZ cannot be used after RTX, if TCZ was used as the first bDMARD.

Additional deterministic results are presented alongside the base case results in Table 2. Assuming that only those patients with fastest HAQ progression would be treated with bDMARDs the cost per QALY was reduced to below £30,000. This value is particularly important as it is a reported upper limit for cost-effectiveness by NICE for treatments that are not classed as 'end of life' treatments.(6)

Discussion

The results from our primary analysis indicate that the ICER of a bDMARD strategy is in excess of £40,000 per QALY for those patients with severe RA and in excess of £50,000 for those patients with moderate-to-severe RA. Data presented elsewhere show that the values for monotherapy and for using bDMARDs before conventional DMARDs are greater than for our base case analyses.(7) All these values are greater than the threshold typically used by NICE for determining whether treatments should be recommended. However, there may be a number of factors that could reduce the ICER. These include: the emergence of biosimilars – two biosimilars for IFX and one for etanercept have already entered the UK market at prices below that of the branded equivalent; the fact that intensive treatment with conventional DMARDs may prevent those with the least severe prognosis, in terms of HAQ increase, being provided with bDMARDs as argued by clinical experts in the

appraisal process; the possible reduction in reducing the dose of bDMARDs for those in low disease activity or remission as summarised by Kuijper *et al.*(42) and Simpson *et al.*(43); and any potential mortality benefit associated with bDMARD treatment. Factors that could increase the ICER include: the possibility that second- and third-line bDMARD treatments are less efficacious than if they were used as a first-line bDMARD; that there may be HAQ increases while on bDMARDs; and should people with no EULAR response remain on treatment – analysis of BSRBR data show that a quarter of non-responders had treatment in excess of four years' duration.[7] Exploratory analyses indicate that if the price of bDMARDs (excluding RTX) were reduced by 50% the mean ICERs would reduce to £24,500 for patients with severe RA and £31,500 for patients with moderate-to-severe RA. Assuming that the efficacy of RTX and TCZ following a previous bDMARD were reduced by reallocating 10% of the patients with a Good EULAR response to having No EULAR response increased the mean ICERs to £41,600 and £52,100 for patients with severe RA and moderate-to-severe RA respectively. Assuming that those with No EULAR response did not cease bDMARD treatment at 6 months but incurred an additional 12 months' treatment cost increased the mean ICERs to £42,200 and £51,400 for patients with severe RA and moderate-to-severe RA respectively.

Limitations with this research include that it only includes studies with EULAR endpoints and that the literature search was completed in 2013, however, neither are expected to change the conclusions. Analyses contained in Stevenson *et al.*(7) showed that the results when all studies providing ACR data were synthesised and then mapped onto EULAR responses using data from the Veterans Affairs Rheumatoid Arthritis registry were similar to those produced by EULAR data alone.

A literature search of relevant clinical papers published since our review identified only two papers with data for the moderate-to-severe and the severe populations(44,45) and it is unlikely that these will change the broad conclusion regarding the cost-effectiveness of bDMARDs as a group at their current market prices. MTX was costed as oral tablets, rather than as an injection, which underestimates the cost of this treatment. This is unlikely to markedly affect the ICER as the use of MTX would be similar in both arms. The adopted method for generating utility estimates does not distinguish between reversible and irreversible damage within the HAQ score.

Despite the different modelling approach used within this research it is noted that the conclusions are similar to those of Joensuu *et al.*(46) which concluded that tumour necrosis factor inhibitors do not seem to be cost-effective at a threshold of €35,000 per QALY.

The supplementary analyses undertaken indicated that there may be subsets of patients in whom the use of bDMARDs may be cost-effective. Currently there are no agreed algorithms for identifying those patients who will have the worst prognoses on NBT. Research regarding prognostic factors in patients with RA could help identify those patients who could be treated cost-effectively with bDMARDs.

Conclusion

The estimate of the ICER for a bDMARD strategy in patients with severe and moderate-to-severe RA suggests that the use of bDMARDs has a greater cost per QALY than published NICE thresholds. However, the bDMARD strategies assessed

in this research fall within NICE's thresholds if it is assumed that only those patients with the worst prognoses on NBT are treated with bDMARDs.

Acknowledgements: The BSRBR for providing access to their data and expert advice on how to use it, in particular Rebecca Davies, Xuejuan Fan, Kath Watson and Kimme Hyrich; Sam Norton for providing data and expert analyses from the ERAS data set;

References

1 Scott DL, Steer S. The course of established rheumatoid arthritis. Best Pract Res Cl Rh 2007;21:943-67.

2 Allaire S, Wolfe F, Niu J, LaValley MP, Zhang B, Reisine S. Current risk factors for work disability associated with rheumatoid arthritis: Recent data from a US national cohort. Arthrit Care Res 2009;61:321-8.

3 Naz SM, Symmons DPM. Mortality in established rheumatoid arthritis. Best Pract Res Cl Rh 2007;21:871-83.

4 Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al. Mortality in rheumatoid arthritis over the last fifty years: Systematic review and meta-analysis. Joint Bone Spine 2013;80:29-33

5 Meune C, Touzé E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology 2009;48:1309-13.

6 National Institute for Health and Clinical Excellence (NICE). *Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed*; 2016.

7 Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technol Assess 2016;20(35).

8 Stevenson M. Additional analyses requested post consultation July 2015 https://www.nice.org.uk/guidance/TA375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-id537-committee-papers2

9 National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013 http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf

10 Brennan A, Bansback N, Nixon R, Madan J, Harrison M, Watson K et al. Modelling the cost effectiveness of TNF-α antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology 2007; 46: 1345-1354

11 National Collaborating Centre for Chronic Conditions (UK). Rheumatoid Arthritis: National Clinical Guideline for Management and Treatment in Adults: London: Royal College of Physicians; 2009

12 Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67:1096–103

13 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:e001395

14 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;381:1541–50.

15 van Vollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J. Atacicept in patients withrheumatoid arthritis and an inadequate response to methotrexate: results of a phase II, randomised, placebo-controlled trial. Arthritis Rheum 2011;63:1782–92.

16 Van De Putte LBA, Atkins C, Malaise M, Sany J, Russell AS, Van Riel PLCM, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508–16.

17 van Riel PL, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis 2006;65:1478–83.

18 Kameda H, Kanbe K, Sato E, Ueki Y, Saito K, Nagaoka S, et al. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumatol 2011;38:1585–92.

19 Machado D, Guzman R, Xavier R, Simon J, Ferdousi T, Pedersen R, et al. Combination Etanercept and Methotrexate Therapy Provides Better Outcomes Than Standard DMARD and Methotrexate Therapy in Rheumatoid Arthritis: Results From a Study in the Latin America Region. Presented at XVII

Congress of Pan American League of Associations of Rheumatology (PANLAR); Punta Cana, Dominican Republic; 17–21 April 2012.

20 Kim H-Y, Hsu P-N, Barba M, Sulaiman W, Robertson D, Vlahos B, et al. Randomised comparison of etanercept with usual therapy in an Asian population with active rheumatoid arthritis: the APPEAL trial. Int J Rheum Dis 2012;15:188–96.

21 Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis 2012;71:817–24.

22 Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis 2010;69:1129–35.

23 Kavanaugh A, Fleischmann RM, Emery P, Kupper H, Redden L, Guerette B, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study.

24 Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomised, 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;54:26–37.

25 Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis 2013;72:43–50.

26 Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of rheumatoid arthritis with humanised anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 2004;50:1761–9.

27 Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19:12–19.

28 Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 2008;58:2968–80.

29 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 anti-rheumatic drugs in established rheumatoid arthritis: the TACIT trial. Health Technol Assess 2013;18(66).

30 Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess 2011;15(14).

31 Norton S, Sacker A, Dixey D, Done J, Williams P, Young A. Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality. Rheumatology 2013;52:2016–24. http://dx.doi.org/10.1093/rheumatology/ket253

32 Gibson L, Hernandez Alava M, Wailoo A. Progression of disease in people with Rheumatoid arthritis treated with non biologic therapies. https://www.nice.org.uk/guidance/TA375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-id537-committee-papers-appendices-13192

33 Joint Formulary Committee. British National Formulary (online). URL: www.medicinescomplete.com/mc/bnf/current/index.htm (accessed 1 April 2013).

34 National Institute for Health and Care Excellence. Adalimumab, Etanercept, Infliximab, Certolizumab Pegol, Golimumab, Tocilizumab and Abatercpet for the Treatment of Rheumatoid Arthritis Not Previously Treated with Disease-Modifying Anti-Rheumatic Drugs Only. Submission by Abbvie. 2013

35 Wiles N.J., Symmons D. Resource use within the Norfolk Arthritis Register (NOAR) Cohort during the first five years of disease. 2005; Report for Roche.

36 Hernandez-Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology 2013;52:944–50.

37 Hernandez-Alava M, Wailoo A, Wolfe F, Michaud K. A comparison of direct and indirect methods for the estimation of health utilities from clinical outcomes. Med Decis Making 2013;34:919–30.

38 Michaud K, Vera-Llonch M, Oster G. Mortality risk by functional status and health-related quality of life in patients with rheumatoid arthritis. J Rheumatol 2012;39:54–9.

39 Office for National Statistics. Interim Life Tables: 2008–2010. URL: www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2008-2010/index.html (accessed 30 January 2013)

40 Singh JA, Wells GA, Christensen R, Tanjong GE, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011;2:CD008794.

41 National Institute for Health and Care Excellence. Etanercept for the Treatment of Rheumatoid Arthritis. (Review of TA Guidance 130, 186, 224, 234 and Part Review of TA Guidance 225 and 247). Multiple Technology Appraisal (MTA). Pfizer submission to NICE. 2013.

42 Kuijper TM, Lamers-Karnebeek FB, Jacobs JW, Hazes JM, Luime JJ. Flare Rate in Patients with Rheumatoid Arthritis in Low Disease Activity or Remission When Tapering or Stopping Synthetic or Biologic DMARD: A Systematic Review. J Rheumatol 2015; 42: 2012-22

43 Simpson EL, Hock ES, Stevenson MD, Wong R, Dracup N, Wailoo A et al. What is the added value of ultrasound joint examination for monitoring

synovitis in rheumatoid arthritis and can it be used to guide treatment decisions? A systematic review and cost-effectiveness analysis. Health Technol Ass. (In Press).

44 Takeuchi T, Miyasaka N, Zang C, Alvarez D, Fletcher T, Wajdula J et al. A phase 3 randomized, double-blind, multicentre comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Mod Rheumatol (2013) 23:623–633

45 Takeuchi T, Kaneko Y, Atsumi T, Tanaka Y, Inoh M, Kobayashi H, Amano K et al. Adding tocilizumab or switching to tocilizumab monotherapy in RA patients with inadequate response to methotrexate: 24 week results from a randomized controlled study (SURPRISE study). Ann Rheum Dis 2013;72(Suppl3):62

46 Joensuu JT, Huoponen S, Aaltonen KJ, Konttinen YT, Nordström D, Blom M. The cost-effectiveness of biologics for the treatment of rheumatoid arthritis: a systematic review. PLoS One 2015; 10: e0119683

Legends to Figures

Figure 1: Conceptual simplified schematic of the modelling process

Figure 2: The estimated EULAR response associated with each intervention

Figure 3: The trajectories used in the base case analyses for patients on non-biologic therapy

Figure 4: The trajectories used in the supplementary analyses for patients on non-biologic therapy.

Legends to Tables

Table 1: The assumed annual hospitalisation costs and the assumed hazard rate for mortality conditional on HAQ score

Table 2: The estimated deterministic ICERs for bDMARD strategies compared with a cDMARD strategy.