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

Matt Stevenson,¹* Rachel Archer,¹ Jon Tosh,¹ Emma Simpson,¹ Emma Everson-Hock,¹ John Stevens,¹ Monica Hernandez-Alava,¹ Suzy Paisley,¹ Kath Dickinson,¹ David Scott,² Adam Young³ and Allan Wailoo¹

¹School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
²Department of Rheumatology, King’s College Hospital NHS Foundation Trust, London, UK
³Department of Rheumatology, West Hertfordshire Hospitals NHS Trust, Hertfordshire, UK

*Corresponding author

Declared competing interests of authors: David Scott has received honoraria within the last 3 years for providing advice to Merck Sharp & Dohme Corp., UCB Pharma and Bristol-Myers Squibb: these values were less than £1000. Additionally, David Scott has received grants from Arthritis Research UK and the National Institute for Health Research in connection with rheumatoid arthritis.

Published April 2016
DOI: 10.3310/hta20350
Scientific summary

Biologic DMARDs for the treatment of rheumatoid arthritis
Health Technology Assessment 2016; Vol. 20: No. 35
DOI: 10.3310/hta20350

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Scientific summary

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive, irreversible, joint damage, impaired joint function, and pain and tenderness caused by swelling of the synovial lining of joints and results in increasing disability and reduced quality of life. The primary symptoms are pain, morning stiffness, swelling, tenderness, loss of movement, fatigue and redness of the peripheral joints. RA is associated with substantial costs, both direct (associated with drug acquisition and hospitalisation) and indirect (owing to reduced productivity).

In 2010 the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) jointly published Rheumatoid Arthritis Classification Criteria, which focused on features at earlier stages of disease that are associated with persistent and/or erosive disease rather than defining the disease by its late-stage features. The classification criteria allocate scores to characteristics of joint involvement, serology, acute-phase reactants and duration of symptoms, to produce a score between 0 and 10, inclusive, with those scoring $\geq 6$ and with obvious clinical synovitis being defined as having ‘definite RA’ in the absence of an alternative diagnosis that better explains the synovitis.

There are an estimated 400,000 people in England and Wales with RA, and approximately 10,000 incident cases per year. The disease is more common in females (1.16%) than in males (0.44%), with the majority of cases being diagnosed when patients are aged between 40 and 80 years and with peak incidence in patients in their seventies.

Objectives

The key objectives of this report are twofold: to estimate the clinical effectiveness of seven biologic disease-modifying antirheumatic drugs (bDMARDs) – adalimumab (ADA; Humira®, AbbVie), etanercept (ETN; Enbrel®, Pfizer), infliximab [IFX; Remicade®, Merck Sharp & Dohme Corp. (MSD)], certolizumab pegol (CTZ; Cimzia®, UCB Pharma), golimumab (GOL; Simponi®, MSD), tocilizumab (TCZ; RoActemra®, Roche) and abatacept (ABT; Orencia®, Bristol-Myers Squibb) – in defined populations; and to estimate the cost-effectiveness of these interventions compared with conventional disease-modifying antirheumatic drugs (cDMARDs). These analyses incorporated the use of bDMARDs with and without methotrexate (MTX) where this was within licence.

Three populations were defined: population 1, adults with severe active RA not previously treated with cDMARDs; population 2, adults with severe active RA that has been previously treated with cDMARDs but not bDMARDs; and population 3, adults with moderate to severe active RA that has been previously treated with cDMARDs only, including MTX (unless contraindicated or inappropriate).

Methods

A systematic review of clinical effectiveness and safety evidence for interventions of interest was conducted. Where trials narrowly missed criteria (because of a small proportion of patients with prior bDMARD exposure or low prior MTX exposure), they were considered to inform sensitivity analyses. Separate network meta-analyses (NMAs) were undertaken for randomised controlled trials (RCTs) reporting EULAR and ACR data.
A mathematical model was constructed to simulate the experiences of hypothetical patients. The model was based on EULAR response data as these are most commonly used in clinical practice in England and Wales. Large observational databases, published literature and the results of the NMA were used to provide data for the model. The primary outcome measure was incremental cost per quality-adjusted life-year (QALY) gained.

**Results**

Sixty RCTs met the inclusion criteria for the systematic review of clinical effectiveness and safety evidence. Of these, 38 trials provided relevant ACR and EULAR response data for the NMA. In addition, 14 additional trials not meeting review criteria contributed data to NMA sensitivity analyses. Other relevant efficacy and safety outcomes were tabulated and discussed in a narrative synthesis. Generally, risk of bias was low overall, and low for baseline comparability, blinding, analysis by allocated treatment group and inclusion of ≥ 80% of participants randomised in the final analysis. There was greater risk of bias and a lack of clarity in many included trials for allocation sequence generation and concealment, and selective reporting of outcomes.

Although there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions for patients in population 1, IFX plus MTX was associated with the biggest increase in response rate and this was likely to be the most effective intervention. Other interventions were less effective and appeared to fall into three groups: (1) intensive cDMARDs and ADA plus MTX; (2) ETN, GOL plus MTX and step-up combination cDMARDs; and (3) ADA and cDMARDs.

Although there was uncertainty in, and overlap between, the effects of treatment on EULAR for interventions in populations 2 and 3 in the main trials, ETN plus MTX and TCZ plus MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: (1) TCZ, GOL plus MTX, ADA plus MTX, ABT intravenous (i.v.) plus MTX and grouped biologics; and (2) ETN, IFX plus MTX, ADA and intensive cDMARDs. The inclusion of the additional studies in which patients received prior biologics resulted in broadly the same groupings, although CTZ plus MTX was associated with an even bigger response than ETN plus MTX and TCZ plus MTX.

Although there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions in populations 2 and 3 in the main trials, ETN plus MTX, TCZ and TCZ plus MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: (1) ETN, GOL plus MTX, ABT subcutaneous plus MTX, ADA plus MTX, IFX plus MTX and ABT i.v. plus MTX; and (2) CTZ plus MTX, intensive cDMARDs and ADA. The inclusion of the additional studies in which patients received prior biologics suggested that CTZ plus MTX and ETN plus MTX resulted in the highest response rates. Other interventions appeared to give rise to broadly similar and slightly smaller response rates except for intensive cDMARDs and ADA which are associated with even smaller response rates.

The incremental cost per QALY of bDMARDs compared with a cDMARD-alone strategy is typically £40,000 when used in populations 2 and 3 and is greater in individuals with moderate to severe disease. The incremental cost per QALY increases (£50,000) for those who receive a bDMARD without MTX and is approximately £60,000 in population 1. A key parameter that affected the results is the assumed Health Assessment Questionnaire (HAQ) while on cDMARDs; if the values used in previous National Institute for Health and Care Excellence (NICE) appraisals were instead used, the incremental cost per QALY fell to approximately £38,000 for bDMARDs compared with cDMARDs alone. Fully incremental analyses were undertaken, but these could be misleading owing to the similarity in incremental costs per QALY for each bDMARD compared with cDMARDs alone, and the uncertainty in efficacy parameters. The data source used for establishing the relationship between HAQ and pain was also seen to influence the results markedly; the Assessment Group base case uses the estimate most favourable to the bDMARDs.
Discussion

There is no reason to believe that the results detailed in this report are not generalisable to the English and Welsh populations.

A strength of this report is that a systematic review of RCTs for bDMARDs in bDMARD-naive patients has been conducted. The primary outcome measures are EULAR or ACR response at 6 months and a formal NMA has been conducted to assess relative efficacy. Different analyses have been undertaken to assess the impact of including RCTs with a small proportion on patients with prior bDMARD use, and/or including RCTs when patients may have not had adequate prior MTX treatment.

A major strength of the cost-effectiveness analyses presented is that the Assessment Group has constructed a EULAR-based model that is much more appropriate to practice in England and Wales than previous ACR-based models. Estimates of incremental cost-effectiveness ratios (ICERs) for both EULAR data only, and when mapping ACR data to EULAR data indicate that the conclusions were not altered by restricting the selection of RCTs to only those that reported EULAR data.

An additional strength is that large observational databases were used to generate data on parameters such as HAQ change conditional on EULAR response and HAQ progression while on cDMARDs. This is preferable to data taken from relatively small RCTs of limited follow-up.

The model has known limitations. The plausible reduced efficacy of treatments when used subsequent to other treatments has not been formally incorporated. It is expected that this omission will favour bDMARDs. Lost productivity has not been included in the model, which may favour bDMARDs if it were included.

The analyses have assumed that the discontinuation rule specified by NICE has been strictly adhered to; data from the British Society for Rheumatology Biologics Register show that this is not the case. If such non-adherence continues, the ICERs will be considerably higher than those presented. Analysis of the impact has not been undertaken due to the possibility of back-calculation of commercial-in-confidence discounts offered through Patient Access Schemes.

Conclusions

The implications for the NHS are not known and it will be heavily dependent on the guidance produced by NICE.

Key research priorities include establishing, more precisely, HAQ progression while on cDMARDs; the relationship between HAQ score and utility; and the relationship between HAQ score and pain. Better evidence on the relative efficacies of bDMARDs and the reduction in efficacy when used after a different bDMARD would be beneficial, but it is acknowledged that large RCTs would be required to provide definitive answers.

Study registration

This study is registered as PROSPERO CRD42012003386.

Funding

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

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 11/74/01. The protocol was agreed in November 2012. The assessment report began editorial review in October 2013 and was accepted for publication in January 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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

© Queen’s Printer and Controller of HMSO 2016. This work was produced by Stevenson et al. under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
Health Technology Assessment Editor-in-Chief

Professor Hywel Williams  Director, HTA Programme, UK and Foundation Professor and Co-Director of the Centre of Evidence-Based Dermatology, University of Nottingham, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley  Director, NIHR Evaluation, Trials and Studies and Director of the HTA Programme, UK

NIHR Journals Library Editors

Professor Ken Stein  Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May  Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key  Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck  Chair in Public Sector Management and Subject Leader (Management Group), Queen’s University Management School, Queen’s University Belfast, UK

Professor Aileen Clarke  Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson  Director of NETSCC, HTA, UK

Ms Tara Lamont  Scientific Advisor, NETSCC, UK

Professor Elaine McColl  Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads  Professor of Health Sciences Research, Health and Wellbeing Research and Development Group, University of Winchester, UK

Professor John Norrie  Health Services Research Unit, University of Aberdeen, UK

Professor John Powell  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Jonathan Ross  Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: nihredit@southampton.ac.uk