The clinical effectiveness and cost-effectiveness of treat-to-target strategies in rheumatoid arthritis: a systematic review and cost-effectiveness analysis

Allan Wailoo,1* Emma S Hock,1 Matt Stevenson,1 Marrissa Martyn-St James,1 Andrew Rawdin,1 Emma Simpson,1 Ruth Wong,1 Naila Dracup,1 David L Scott2 and Adam Young3

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

*Corresponding author a.j.wailoo@sheffield.ac.uk

Declared competing interests of authors: none

Published November 2017
DOI: 10.3310/hta21710

Scientific summary

Treat-to-target strategies in rheumatoid arthritis
Health Technology Assessment 2017; Vol. 21: No. 71
DOI: 10.3310/hta21710

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

Background

Patients with rheumatoid arthritis (RA) have seen dramatic improvements in their care in the last 20 years, particularly through the development of more targeted biologic disease-modifying antirheumatic drugs (bDMARDs) and non-bDMARDs. Treat to target (TTT) in rheumatology is a more recent concept encompassing a range of broad features. The central component of the TTT concept is the setting of a treatment target. Recommendations in RA typically specify low disease activity (LDA) or remission as an appropriate target, but, in addition to the setting of a target, there are a range of different features that lead to a continuum of ‘weak’ to ‘strong’ TTT principles. These can include an increased frequency of rheumatology visits for the assessment of the target and any associated changes in the management of the patient. Treatment changes within a TTT strategy may also be protocolised, specifying how treatments are to be altered in response to the target assessment.

Objectives

To identify and evaluate the evidence for the clinical effectiveness and cost-effectiveness of TTT strategies compared with routine care for adult patients with RA.

Methods

Review methods

Scoping searches were carried out to identify the extent of potentially relevant literature. Databases including MEDLINE and EMBASE were searched from 2008 to August 2016. A full systematic review of clinical effectiveness data was then conducted following the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched for evidence from studies of adults with clinically diagnosed RA, which included TTT. At a minimum, TTT had to include the setting of an explicit target.

Only randomised controlled trials were included. Data were extracted on measures of treatment goals, including the number/proportion of patients in each arm meeting the target; disease activity; mortality; health-related quality of life; serious adverse events (SAEs); treatments; and dosages given. The methodological quality of each included study was assessed.

Evidence examining the clinical effectiveness of TTT was synthesised according to the TTT comparison, namely (1) TTT compared with usual care; (2) a comparison of different targets against each other; and (3) a comparison of different treatment protocols against each other. Two trials did not fit into this framework and so were examined separately under ‘other comparisons’. Trials were further grouped according to whether or not they used early RA populations (disease duration < 3 years) or established RA populations.

A systematic review of cost-effectiveness was undertaken. Titles and abstracts were examined by one reviewer and a random 5% were checked by another reviewer. Study selection based on full texts was decided by two reviewers, with discrepancies resolved by discussion. Data were extracted by one reviewer using a standardised data extraction form and checked by a second reviewer.
**Evaluation of cost-effectiveness**

As study heterogeneity precluded meta-analysis, it was deemed most informative to analyse each study included in the clinical effectiveness review and to assess the implications of the results for the cost-effectiveness of each strategy. A simplistic approach was taken and costs that were assumed to be similar between arms were ignored.

**Results**

A total of 16,591 records were identified from electronic databases. Forty-two articles describing 16 trials were included in the review. Eleven trials examined an early RA population. Three trials examined an established RA population. Two trials examined populations that included both patients with early RA and those with established RA. The only trial rated as having a low risk of bias was the TICORA (Tight Control for RA) trial, which examined TTT compared with usual care in a mixed population.

Study heterogeneity precluded meta-analyses. This heterogeneity was evident in the substantial differences between studies in the targets that were set, the nature of the treatment protocol (where one existed) and the frequency of patient visits.

Overall, the evidence for TTT is mixed. For several outcome measures, studies produced a mixture of results or found no difference between TTT and conventional care. However, there does seem to be some support for the use of TTT in specific patient groups for some outcomes.

Two studies in patients with early disease found that TTT resulted in favourable remission rates, though in one case the findings were not statistically significant: an odds ratio (OR) of 0.52 [95% confidence interval (CI) 0.21 to 1.28] in the STRategies in Early Arthritis Management (aggressive therapy in patients with early arthritis results in similar outcome as conventional care) study at 2 years; an OR of 0.43 (95% CI 0.19 to 0.95) for Disease Activity Score, 28 joints (DAS28)-driven TTT at 1 year in the Treating to Twin Targets (T-4) study; and an OR of 0.21 (95% CI 0.10 to 0.47) for DAS28-driven and matrix metalloproteinase 3 (MMP-3)-driven TTT at 1 year in the T-4 study. The T-4 study found usual care to be more effective than the MMP-3 target (21% vs. 13%; OR 1.72, 95% CI 0.66 to 4.52). There were mixed findings for DAS28/Disease Activity Score, 44 joints (DAS44) and joint erosion, and no difference between targeted arms and usual care on Health Assessment Questionnaire (HAQ) score. There were no differences in the proportions of patients experiencing any adverse event (AE), SAE, death, withdrawals as a result of AEs or specific AEs.

Two studies in patients with established disease found that TTT may be beneficial in terms of LDA at 6 months, although, again, in one case the result was not statistically significant [an OR of 0.42 (95% CI 0.19 to 0.94) in the Fransen et al. study at 6 months; an OR of 0.81 (95% CI 0.45 to 1.45) using a DAS28 target in the Optimisation of Adalimumab study; and an OR of 0.91 (95% CI 0.50 to 1.66) in the same study using a swollen joint count (SJC) of 0 targets]. There was no difference between TTT and usual care in terms of DAS28, SJC, tender joint count or HAQ response. The proportion of patients who withdrew as a result of AEs (as reported in the Optimisation of Adalimumab study) and experienced specific AEs (dermatological and gastrointestinal AEs as reported in Fransen et al.) was lower in the TTT arms.

Of the trials that included both patients with early disease and those with established disease, only the TICORA trial found evidence favouring TTT in terms of remission at 18 months (65% vs. 16%; p < 0.0001). The TICORA trial also reported results in favour of a TTT approach compared with usual care in terms of American College of Rheumatology 20/50/70 response rates. The evidence, however, was equivocal for other outcome measures. A smaller proportion of patients reported any and specific AEs (dermatological, gastrointestinal and infectious AEs, significance not reported) in the TTT arm than the usual-care arm of the TICORA trial.
Support for TTT in early disease is stronger if evidence from the TICORA trial, which had an inclusion criterion of disease duration < 5 years, is considered generalisable to the early RA population.

There was little difference in outcomes where different targets were used as part of TTT strategies across all RA populations.

Two papers on the cost-effectiveness of TTT were identified. One, related to the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry, estimated that TTT would be dominant at 3 years. Savings compared with usual care were estimated at €462 (2011 values). The second, related to the BehandelStrategieën in Reumatoïde Artritis trial, estimated that step-up combination therapy was the most cost-effective strategy, even when compared with a strategy that included combination therapy with a biologic drug, and saved €2743 per patient (2008 values) compared with sequential monotherapy.

Literature relating to 16 studies was found. In five of these studies, and for low-risk patients (criteria not defined) in one study, no clear conclusion regarding cost-effectiveness could be made. In the remaining 10 studies, and for the high-risk patients (criteria not defined) in one study, we were able to estimate whether or not the strategy was likely to be cost-effective. Almost all of the estimates from these studies indicated that TTT would be considered cost-effective other than where the TTT strategy included the use of bDMARDs in early disease. No conclusions could be made in relation to TTT in established disease.

**Discussion**

Treat to target refers not to a single concept, but to a range of broad approaches to the treatment of patients with RA. The evidence reflects this, with studies exhibiting a great degree of heterogeneity, particularly in relation to the TTT strategies they sought to examine. Studies varied in terms of the treatment target, treatment protocols and frequency of assessments. Targets were often defined in terms of Disease Activity Scores, but different variants of the measure (DAS44, DAS28) and different cut-off points were used. Even in the case of TTT strategies that were broadly similar, the precise therapies used exhibited significant variation. For example, in those studies that used both a steroid step-down and a disease-modifying antirheumatic drug (DMARD) step-up combination treatment protocol, the doses of steroid varied substantially and the specific DMARD and dose also varied. This variation makes it complex to synthesise evidence and draw general conclusions. This applies equally to the assessment of clinical effectiveness and cost-effectiveness. This is further weakened by the risk of bias in many included studies. Despite this, there does seem to be some support for the broad TTT concept in RA, particularly in early RA, or for patients with a disease duration < 5 years if the TICORA trial is considered representative of early RA patients. However, it remains unclear which elements of TTT are important or if all are required. It is not possible to ascertain if it is the setting of a target, the more intensive management of patients or the treatment protocols that drive better outcomes. Furthermore, we cannot identify if any particular treatment target is more appropriate.

Owing to the heterogeneity of the evidence and the potential of changes in usual care across time, no modelling evaluating all strategies within a fully incremental analysis could be performed. For this reason, only those studies that have been trialled in the same study can be compared. In early RA, the components of care that together constitute ‘TTT’ are likely to form a cost-effective approach. There were insufficient studies in established RA to discern a pattern in cost-effectiveness.

**Conclusions**

Treat to target is a broad concept and does not refer to a single treatment strategy. In early RA there is some limited evidence to suggest that strategies that have been tested in clinical studies as TTT lead to better outcomes, particularly in terms of the number of patients achieving remission. In established disease
there is evidence that TTT leads to more patients achieving LDA. However, it is unclear which of the various elements of TTT drive these findings.

Intensive drug therapy is frequently included as part of TTT strategies that have been tested in trials. These trials do seem to indicate that intensive conventional disease-modifying antirheumatic drug (cDMARD) treatment is more cost-effective than routine practice, particularly in early RA. However, whether or not these results require the inclusion of a specific target in addition is uncertain. The use of bDMARDs before intensive cDMARDs as part of a TTT strategy is unlikely to be cost-effective.

Future trials comparing TTT with usual care and/or different TTT targets should use outcomes comparable with existing literature. Remission, defined in a consistent manner, should be the target of choice of future studies.

**Study registration**

This study is registered as PROSPERO CRD42015017336.

**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 funded by the HTA programme as project number 14/17/01. The contractual start date was in February 2015. The draft report began editorial review in October 2016 and was accepted for publication in April 2017. 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 2017. This work was produced by Wailoo 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 EME Programme, UK

NIHR Journals Library Editors

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

Professor Andrée Le May  Chair of NIHR Journals Library Editorial Group (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

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin  Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson  Director of the NIHR Dissemination Centre, University of Southampton, UK

Ms Tara Lamont  Scientific Advisor, NETSCC, UK

Dr Catriona McDaid  Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

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

Professor Geoffrey Meads  Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie  Chair in Medical Statistics, University of Edinburgh, 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 Riemisma  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 Snoooks  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

Professor Martin Underwood  Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, 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: journals.library@nihr.ac.uk