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

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Scientific summary

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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.

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