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

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Scientific summary

TACIT trial and associated systematic reviews
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Scientific summary

Background

Rheumatoid arthritis (RA) affects nearly 1% of adults in the UK. It causes joint inflammation, joint damage and extra-articular disease, and leads to disability and a reduction in quality of life. Core treatments are methotrexate and other disease-modifying antirheumatic drugs (DMARDs). Treating active RA can involve combination DMARDs (cDMARDs). Active RA patients in the UK who have failed methotrexate and another DMARD can receive tumour necrosis factor inhibitors (TNFis), which are both effective and expensive.

Objectives

Overall

We assessed whether or not RA patients eligible to receive TNFis achieve similar outcomes with cDMARDs in a head-to-head trial that compared both approaches [Tumour necrosis factor inhibitors Against Combination Intensive Therapy (TACIT)]. We also systematically reviewed published trials that assessed the efficacy of cDMARDs, TNFis with methotrexate and both approaches in patients with active RA.

The Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

The TACIT trial tested the hypothesis that patients with active RA meeting UK criteria for receiving TNFis gain equivalent benefit over 12 months at less expense and without increased toxicity if they start cDMARDs.

Systematic reviews

The systematic reviews assessed the efficacy and toxicity of cDMARDs and TNFis with methotrexate. They evaluated published randomised controlled trials that compared (1) cDMARDs with DMARD monotherapy; (2) TNFis plus methotrexate with methotrexate monotherapy; and (3) cDMARDs with TNFis plus methotrexate (head-to-head trials). The trials that enrolled patients with early RA were analysed separately from the trials that enrolled patients with established RA.

Methods

The Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

The TACIT trial was an open-label, 12-month, pragmatic, randomised, multicentre, two-arm trial. It compared cDMARDs with TNFis given with methotrexate or another DMARD in active, established RA. The 6-month non-responders in the cDMARDs arm could start TNFis and the 6-month non-responders in the TNFis arm could have a second TNFi. The Heath Assessment Questionnaire (HAQ), a patient-completed disability assessment, was the primary outcome measure. Secondary outcome measures included quality of life, joint damage, disease activity, withdrawals and adverse effects. An intention-to-treat (ITT) analysis used multiple imputation methods for missing data. The primary outcome was evaluated by linear regression with treatment, sex, ethnicity, age, region and disease duration as explanatory variables. The trial included an economic evaluation from both health and social care, and societal perspectives, linking costs with the HAQ and quality-adjusted life-years (QALYs) based on both the Short Form questionnaire-36 items (SF-36) and European Quality of Life-5 Dimensions (EQ-5D) at 6 and 12 months.

Systematic reviews

Ovid MEDLINE and EMBASE were searched from 1946 to 2012 for trials in English using the search term 'rheumatoid arthritis' with the search term 'DMARDs', 'TNFis' or 'combination therapy'. Treatment arms included cDMARDs or TNFi/methotrexate and control arms included DMARD monotherapy. Early RA trials enrolled patients with a duration of disease of < 3 years. Established RA trials enrolled treatment-resistant patients to at least one DMARD. The results were analysed using Review Manager 5.1.6 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects model estimated pooled effect sizes. Cochran's chi-squared test and I^2-statistics were used to assess heterogeneity.

Results

The Tumour necrosis factor inhibitors Against Combination Intensive Therapy trial

The TACIT trial screened 432 patients from 2008 to 2010 at 24 rheumatology clinics. Of these, 218 patients were excluded (196 did not consent) and 214 were randomised. Nine randomised patients withdrew before being treated (six decided not to participate); therefore, 104 patients started cDMARDs and 101 started TNFis. The initial demographic and disease assessments were similar between the groups. Over 12 months, 16 out of 205 were lost to follow-up (nine in the cDMARDs arm and seven in the TNFi arm). In total, 42 out of 205 discontinued their intervention but remained under follow-up (23 in the cDMARDs arm and 19 in the TNFi arm). ITT analysis evaluated all 205 patients. A secondary completer analysis evaluated 147 patients (72 in the cDMARDs arm and 75 in the TNFi arm). After 6 months, 42 out of 104 cDMARDs non-responders switched to TNFis.

Intention-to-treat analysis showed that reductions in HAQ score between baseline and 12 months were greater in the cDMARDs group [mean 0.45; 95% confidence interval (CI) 0.34 to 0.55] than in the TNFi group (mean 0.30, 95% CI 0.19 to 0.42). Adjusted linear regression showed that this was significant (coefficient 0.15, 95% CI −0.003 to 0.31; $p = 0.046$). Increases in EQ-5D score between baseline and 12 months were greater in the cDMARDs group (mean 0.20, 95% CI 0.13 to 0.27) than in the TNFi group (mean 0.14, 95% CI 0.08 to 0.21). Adjusted linear regression analysis showed that this difference was also significant (coefficient −0.11, 95% CI −0.18 to −0.03; $p = 0.009$). Changes between baseline and 6 months in HAQ and EQ-5D scores and between 6 and 12 months in radiological progression were similar between the groups.

Longitudinal analysis showed an overall difference between treatment groups in Disease Activity Score for 28 Joints (DAS28) over the whole 12 months. Patients randomised to the TNFi group had greater overall reductions in DAS28 than those randomised to cDMARDs; the adjusted general estimating equation showed a difference of −0.40 (95% CI −0.69 to −0.10, $p = 0.009$). Comparing the initial and final treatment periods showed different patterns of change. In the first 6 months DAS28 was lower in patients randomised to TNFis (coefficient −0.63, 95% CI −0.93 to −0.34; $p < 0.001$) whereas in the second period there was no difference between the groups (coefficient −0.19, 95% CI −0.55 to 0.18; $p = 0.317$).

In total, 36 out of 104 patients in the cDMARDs group and 44 out of 101 in the TNFi group achieved DAS28 remission. The onset of remission did not differ between groups ($p = 0.085$ on log-rank test). Remissions did not always persist; however, the number of patients in remission gradually increased over time. Fewer than 5% of patients in the cDMARDs group were in remission by 3 months; this rose to 20% by 12 months. In the TNFi group, 16% of patients were in remission by 3 months; this increased to 32% by 11 months.

Ten patients in the cDMARDs group had a serious adverse event, compared with 18 in the TNFi group (one died from pneumonia). In total, 10 patients in the cDMARDs group and six in the TNFi group stopped treatment because of toxicity. The cDMARDs group reported 635 different adverse events, compared with 465 in the TNFi group.

The economic evaluation, which was within the trial and did not include an extension to a longer-term disease model, showed that the cDMARDs group had the same or better HAQ, SF-36 QALY and EQ-5D QALY outcomes at 6 and 12 months and significantly lower costs at both time points. From a health-care perspective, focusing on EQ-5D-based QALYs at 12 months using imputed data, the mean adjusted cost difference was −£1937 (95% CI −£2612 to −£1353) and the mean adjusted outcome difference was 0.02 (95% CI −0.00 to 0.05). Combination DMARDs had a higher probability of cost-effectiveness than TNFis at both time points and on all cost–outcome combinations (although based on the HAQ at 6 months, the probability of cost-effectiveness decreased with increased willingness-to-pay thresholds). These conclusions apply from both a health and social care perspective and a societal perspective.

Systematic reviews

The early RA review identified 32 trials (including 20–1049 patients), which enrolled over 8400 patients; 19 trials compared cDMARDs with DMARD monotherapy, 10 trials compared TNFi/methotrexate with methotrexate and three were head-to-head trials. Indirect comparisons showed that (1) more patients achieved American College of Rheumatology (ACR)20–ACR70 responses [odds ratio (OR) 1.76–2.81) with cDMARDs than with DMARD monotherapy and fewer withdrew for lack of effect (OR 0.47) and (2) more patients achieved ACR20–ACR70 responses (OR 1.88–2.22) with TNFi/methotrexate than with methotrexate and fewer withdrew for lack of effect (OR 1.42, 95% CI 0.87 to 2.34). Head-to-head trials showed no differences in ACR20 responses or inefficacy withdrawals but fewer ACR50 and ACR70 responses with cDMARDs (ORs 0.53 and 0.54 respectively). Indirect comparisons showed greater HAQ improvements with both combination regimens.

The established RA review identified 19 trials (including 40–982 patients), which enrolled over 5500 patients: 10 trials compared cDMARDs with monotherapy (six involving methotrexate), eight trials compared TNFi/methotrexate with methotrexate and there was also a single head-to-head trial. Indirect comparisons showed that (1) more patients achieved ACR20–ACR70 responses with cDMARDs than with monotherapy (OR 2.75–5.07) and fewer withdrew for inefficacy (OR 0.38) and (2) more patients achieved ACR20–ACR70 responses with TNFi/methotrexate than with methotrexate (OR 5.32–8.13) and fewer withdrew for inefficacy (OR 0.12). The head-to-head trial showed no difference in ACR20–70 responses between the two treatment arms. Indirect comparisons showed greater HAQ improvements with both combination regimens.

Conclusions

The TACIT trial showed that RA patients who have failed to respond to methotrexate and another DMARD show clinically important improvements over 12 months if initially treated with cDMARDs, reserving TNFis for non-responders to these combinations. These improvements were equivalent to those achieved by starting all patients on TNFis in line with current National Institute for Health and Care Excellence (NICE) guidance. The equivalence of cDMARDs with TNFis was confirmed in systematic reviews of published trials in both early RA and established RA.

Implications for health care

In patients with active RA who have failed to respond to initial DMARDs:

1. This study indicates that giving all patients intensive cDMARD therapy and reserving TNFis for 6-month non-responders may be effective and cost-effective.
2. Only a minority of patients achieve sustained remission with cDMARDs or TNFis, indicating that neither represents an ideal long-term treatment for all RA patients.

Recommendations for research

1. Identifying predictors of response to cDMARDs and TNFis will enable a move towards individualised treatment. This is of crucial importance as some patients respond well to cDMARDs whereas others respond well to TNFis, and prospectively identifying potential good responders should optimise treatment outcomes.
2. We need to define the most effective ways of using current treatments in strategy trials to examine novel ways of using high-cost treatments. Examples include identifying the benefits of short courses of biologics in early RA, in which the rapid effects of biologics may be very beneficial, and redefining the optimal duration of TNFi treatment in established RA.
3. There should be a greater emphasis on head-to-head trials of cDMARDs and TNFis compared with effective low-cost comparators when defining the overall benefits of high-cost treatments in RA. Placing excessive reliance on short-term placebo-controlled trials in conjunction with modelling of future benefits based on data from historical observational studies has limitations when defining optimal treatment pathways.

Trial registration

This trial is registered as ISRCTN37438295.

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