Reducing or stopping TNF-alpha inhibitors in people with rheumatoid arthritis and low disease activity

A Cochrane systematic review in 1203 people with rheumatoid arthritis and low disease activity found that, for up to a year, halving the dosage of etanercept compared to continuing the licensed dosage did not affect disease activity or function. However, slightly fewer people maintained low disease activity and a non-clinically significant worsening in radiographic damage was found. People who stopped etanercept rather than continuing it had a higher disease activity score and had worse function. Furthermore, people who stopped etanercept or adalimumab were almost half as likely to maintain low disease activity as those who continued their treatment and they also had non-clinically significant worsening in radiographic damage. This study has several limitations, including the lack of long-term data on disease progression and adverse effects.

Overview and current advice

The aim of treatment of rheumatoid arthritis (RA) is to induce remission of disease, control pain and inflammation, and reduce or prevent joint damage, disability and loss of function, thereby improving quality of life. Treatment includes various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and disease modifying anti-rheumatic drugs (DMARDs). DMARDs reduce symptoms and slow progression of structural damage and may be classified as conventional (for example methotrexate or sulfasalazine) or biological. Biological DMARDs include abatacept, rituximab, tocilizumab and the TNF-alpha inhibitors (such as adalimumab, certolizumab pegol, etanercept, golimumab and infliximab).

NICE has issued several pieces of guidance on the use of TNF-alpha inhibitors and other biological DMARDs in RA. A review of NICE guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis is currently in development and will update guidance on these drugs. Abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and tocilizumab are currently recommended as options for the treatment of adults who have both of the following characteristics:

- Active RA as measured by a disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

The biological DMARDs should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab, certolizumab pegol and etanercept may be given as monotherapy. Initiation and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents. Treatment should normally be started with the least expensive drug (taking into account administration costs, required dose and product price per dose).

With regards to dose and duration of these biological agents, escalation above the licensed starting dose is not recommended. NICE recommends only continuing treatment if there is an adequate response (an improvement in DAS28 of 1.2 points or more) at 6 months following initiation. After initial response, treatment should be monitored at least every 6 months with assessment of DAS28 and should be withdrawn if an adequate response (an improvement in DAS28 of 1.2 points or more) is not maintained. The NICE Pathway: rheumatoid arthritis brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams; it also gives details on what to use if people have an inadequate response or intolerance to drugs (including a TNF-alpha inhibitor). In addition, NICE has produced a useful algorithm on using biological DMARDs in RA and a clinical guideline on the management of RA in adults (next review March 2015).

In view of the adverse effects of TNF-alpha inhibitors, such as the increased risk of infections and lack of long-term safety data over many years, and their relatively high cost, an important clinical question remains unanswered. That is, whether people who respond to these drugs need to continue taking them indefinitely, or whether instead the dose can be reduced or they can be discontinued. In 2013, the European League against Rheumatism (EULAR) updated their recommendations for the management of RA with synthetic and biological DMARDs. Based mainly on data for TNF-alpha inhibitors, EULAR recommends that if a person is in persistent remission after having tapered glucocorticoids, tapering the biological DMARD can be considered, especially if this treatment is combined with a conventional systemic DMARD (such as methotrexate, sulfasalazine and leflunomide). Tapering is seen as either a dose reduction or an increase in the dosing interval. In cases of sustained long-term remission, EULAR recommends considering a cautious reduction of the conventional systemic DMARD dose, as a shared decision between patient and physician.

New evidence

A Cochrane systematic review of 6 randomised controlled trials (RCTs) and 1 open-label, non-randomised controlled trial compared the benefits and harms of down-titration (reducing the dosage or stopping treatment) of TNF-alpha inhibitors with usual care over 24 to 52 weeks in 1203 people with RA and low disease activity (definition varied but in the study that provided data on most outcomes mean DAS28 was 3.2 or less). Participants had RA for an average of 3.9 months to 14 years and had been using TNF-alpha inhibitors in standard (or lower) dosing regimens for more than 6 months before treatment was reduced or discontinued. The TNF-alpha inhibitors in the studies were etanercept and adalimumab and, in most cases, methotrexate was also taken. Most outcomes provided moderate quality evidence.

Three RCTs (n=559) compared dosage reduction of etanercept with continuation. These compared either continuing the standard dosage of 25 mg by subcutaneous injection twice a week or 50 mg weekly (licensed dosages) with a reduced dosage of 25 mg weekly (not currently licensed for RA). Before dosage reduction, participants had low disease activity for between more than 3 months to
more than 11 months. Based on 1 study (n=404, 52 weeks), there was no statistically significant difference between continuing the standard dosage or reducing it on disease activity (measured by DAS28) or on function (measured by Health Assessment Questionnaire Disability Index [HAQ-DI]). However, the proportion who maintained low disease activity (3 studies, n=557, 24 to 52 weeks) was slightly lower among those on reduced doses of etanercept (61% versus 70%; Risk Ratio [RR] 0.87, 95% confidence interval [CI] 0.78 to 0.98). People with a reduced etanercept dosage also had slightly more radiographic damage (1 study, n=368, 52 weeks; measured by Sharp-van der Heijde score [mSvdH score] scale 0 to 448, higher score indicates greater joint damage, Mean difference 0.11, 95% CI 0.08 to 0.14), but this was not considered clinically meaningful.

Five studies (4 RCTs and one small controlled clinical trial, n=732) compared continuation of either adalimumab or etanercept, with its discontinuation. Participants had low disease activity for 4 weeks to 11 months or more, or were in remission. In 2 studies (n=436), people who stopped their TNF-alpha inhibitor had a higher mean disease activity score than those who continued it. The difference was statistically significant in the study on etanercept that provided most of the data (n=402, 52 weeks, DAS28-ESR mean difference 1.10, 95% CI 0.86 to 1.34). In addition, when all 5 studies were pooled, people who stopped their TNF-alpha inhibitor were almost half as likely to remain in low disease activity measured by DAS28 (38% versus 72%, RR 0.43, 95% CI 0.27 to 0.68). Furthermore, those who stopped their TNF-alpha inhibitor had slightly more radiographic damage (1 etanercept study, n=351, 52 weeks; mSvdH score mean difference 0.66, 95% CI 0.63 to 0.69; 1 adalimumab study, n=207, 52 weeks; mean change in mSvdH score 0.3 adalimumab discontinuation group and 0.1 for adalimumab group, no further data given). Function was also worse after stopping the TNF-alpha inhibitor (1 etanercept study, n=402, 52 weeks, HAQ-DI mean difference 0.30, 95% CI 0.19 to 0.41).

The limitations of this systematic review include that it only provides data on etanercept and adalimumab for discontinuation and only on etanercept for dose-reduction. Also, 5 of the 7 studies included were published in abstract form and the study that provided most of the outcome data was sponsored by a pharmaceutical company and so at high risk of bias. The studies were very different in both design and definition of treatment failure and they do not provide any information on the long-term effects of stopping or reducing TNF-alpha inhibitors beyond a year. It would be helpful to know what effect reducing or stopping TNF-alpha inhibitors would have on adverse effects, but data on this were inconclusive.

**Commentary**

**Commentary provided by Dr Jon Packham, Consultant rheumatologist, Honorary senior lecturer, Haywood Hospital, Stoke on Trent, UK**

Attempting to half the dosage of etanercept in people with RA and low disease activity (DAS 3.2 or less) may be an option in clinical practice for some people. It would seem sensible to follow EULAR recommendations on this (see above). Only 9% fewer patients failed to remain in disease remission following etanercept dose reduction to 25mg weekly. Patients within these studies are predominantly co-prescribed methotrexate; data on reducing etanercept dose when used as a sole agent are lacking. Reducing etanercept dose could reduce long term health costs and has the potential to reduce long term side effects (although no definite reduction in side effects has been shown to date). However, etanercept 25 mg weekly is not licensed in the UK for RA, is not available as an auto-injector pen and is not included in the NICE guidance on this drug.

If a reduction in etanercept dose is considered, regular (at least 3 monthly) DAS-28 assessments would need to be performed. A clear plan for dose escalation if control of disease activity was affected by the dose reduction should be in place. Adequate clinical capacity to perform these measurements
should be provided and factored into any potential health economic cost savings. NICE guideline definitions of inadequate response to treatment suggesting biologic inefficacy (and treatment withdrawal) should only be considered in patients receiving 50mg etanercept weekly.

Disease activity and function are more likely to worsen in patients stopping etanercept or adalimumab compared to those continuing treatment. Radiographic worsening at one year in both etanercept cessation and dose reduction groups was less than 1 point on a scale of 0 to 448 compared to people continuing etanercept, and was not clinically significant. However, radiographic damage has the potential to become cumulatively significant over time and longer follow up studies beyond a year are needed.

The evidence for reduction/cessation of biologics for people with RA who are in clinical remission is limited. There are limited data to inform dose reduction or cessation of biologics other than etanercept and adalimumab.

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The Cochrane Review had no sponsorship. The funding for most of the individual studies included was unclear. One study was funded by Pfizer.

References