Tumour necrosis factor-alpha inhibitors help control symptoms in active rheumatoid arthritis

Introduction

This article discusses use of the tumour necrosis factor (TNF)-alpha inhibitors, adalimumab, etanercept and infliximab, which have become available for treating adults with rheumatoid arthritis (RA) in the last few years. The evidence behind these agents and important safety considerations are considered in the context of recent NICE guidance (issued in October 2007).[1]

RA is a chronic progressive disabling autoimmune disease that occurs in 0.5% to 1% of the population. It is characterised by inflammation of the synovial tissue in the peripheral joints, which leads to swelling, stiffness, pain and progressive joint destruction.[2] Life expectancy is also reduced and the impact of RA on quality of life should not be underestimated. About half of all patients are unable to work within 10 years of diagnosis.[2] Therefore, recent advances in the management of this disease that might help to slow progression and reduce disability have been welcomed.

Treatment of RA aims to control pain, stiffness and inflammation, and to improve quality of life by reducing joint damage, disability and loss of function.[1,3] This involves using various combinations of drugs including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease modifying anti-rheumatic drugs (DMARDs).[4] Emphasis is now placed on early treatment with DMARDs to control symptoms, delay progression and reduce long-term disability.[5,6] Several non-biologic DMARDs are available, such as methotrexate and sulfasalazine, but they are not effective in all patients. Also, they can become less effective with time and their use is often limited by adverse effects.[3] However, these are still the first-choice DMARDs in RA[1,7,8] because the newer biologic DMARDs do not appear to improve clinical outcomes compared with these established agents when used as monotherapy.[9]

What are TNF-alpha inhibitors?

The TNF-alpha inhibitors are often referred to as biologic DMARDs.[4] Those currently licensed in the UK include:
adalimumab (Humira▼),
etanercept (Enbrel▼) and
infliximab (Remicade▼).

Their main effect is to inhibit TNF-alpha by blocking its interaction with cell surface receptors.[10] TNF-alpha is a cytokine involved in inflammation that is considered to be very important in the pathogenesis of RA.[3,11] Both adalimumab and infliximab are anti-TNF antibodies, whereas etanercept is a recombinant fusion protein.[12–14] Adalimumab and etanercept are injected subcutaneously and infliximab is given by intravenous infusion. These agents should not be confused with anakinra (Kineret▼) or rituximab (Mab Thera▼), which are also biologic DMARDs licensed for RA. NICE has recommended that anakinra should only be used for treating RA in the context of a long-term, controlled clinical trial[7] and rituximab should only be considered in severe disease after other DMARDs, including treatment with at least one TNF-alpha inhibitor.[8] In addition, another biologic DMARD, abatacept (Orenica▼) has recently been licensed for moderate to severe RA and is currently being reviewed by NICE.

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above: *rheumatoid arthritis is characterised by inflammation of the joints, which become swollen and stiff. This makes everyday tasks — and hobbies, such as photography — painful and difficult because of poor joint mobility*

When should they be used?

NICE recently recommended adalimumab, etanercept and infliximab as options for adults with active RA, who have already tried two DMARDs, including methotrexate (unless contraindicated). Active RA is defined as having a disease activity score (DAS28 — *see* Box 1) greater than 5.1, which has been confirmed on at least two occasions, one month apart. Each DMARD should usually be tried for six months, with two months at the standard dose, unless the dose or duration of treatment has been limited by significant toxicity.[1]

Usually, these agents should be used in combination with methotrexate. However, if methotrexate is considered to be inappropriate or if a patient is intolerant of this drug, adalimumab or etanercept can be used alone.[1] Infliximab is not licensed as monotherapy.[13]

Compared with placebo, these agents were effective treatments in patients with RA that is not well controlled by conventional DMARDs. In these patients, they improve symptom control and physical function as well as slowing radiographic changes.

These drugs are relatively new and the long-term effects of blocking TNF-alpha over many years are still largely unknown. Therefore, they should not be used before trying methotrexate or other DMARDs, even in severe and progressive disease,[1] despite this being a licensed indication.[12–14]

Are they effective in RA?

Several systematic reviews have shown that the TNF-alpha inhibitors are effective in treating adults with RA. A *Health Technology Assessment* (HTA) of these agents, used to inform the NICE guidance systematically reviewed 29, mainly high quality RCTs, including nine of adalimumab, 11 of etanercept and nine of infliximab, with follow-up ranging from four weeks to two years.[3] It found that, compared with placebo, these agents were effective treatments in patients with RA that is not well controlled by conventional DMARDs. In these patients, they improve symptom control and physical function as well as slowing radiographic changes in the joints. In addition, combining a TNF-alpha inhibitor with methotrexate appears to be more effective than using methotrexate alone in early disease, but the clinical significance of this benefit needs to be established. TNF-alpha inhibitors seem to be most cost-effective when used as a last active treatment.[3]

To interpret RA trials, it is important to understand the measures of response that are used as outcomes (*see* Box 1). Table 1 shows the effect of TNF-alpha inhibitors on these outcomes in the HTA. Most of the trials compared TNF-alpha inhibitors with placebo, either as monotherapy or used in combination with methotrexate. There were no head-to-head trials between TNF-alpha inhibitors.[3]

Compared with placebo

Five RCTs of adalimumab (n=1861), eight etanercept trials (n=1715) and two infliximab trials (n=895) compared these agents with placebo. They were used either alone or in combination with other DMARDs, such as methotrexate. In several trials patients had failed treatment with other DMARDs at entry. All TNF-alpha inhibitors were significantly more effective than placebo in established RA (*see* Table 1). Statistically significant improvements were seen in measures of symptom control, physical function and radiographic joint damage. In addition, fewer people withdrew from treatment compared with placebo.[3]

Compared with DMARDs

Only three RCTs comparing TNF-alpha inhibitors with other drugs were included in the HTA. These were all monotherapy comparisons against methotrexate (one adalimumab trial, n=531; and two etanercept trials, n=875; infliximab is not licensed as monotherapy).[3]

Adalimumab was slightly less effective than methotrexate at reducing symptoms and improving physical function in patients with early RA who had not tried methotrexate before, although this was not statistically significant (*see* Table 1). On the other hand, etanercept was slightly more effective than methotrexate in patients with early RA who were methotrexate naïve, and in more established RA in patients with no history of treatment failure with methotrexate. Statistically significant improvements were seen with etanercept for ACR20 in both studies and for ACR50 in patients with established disease. However, there were no statistically significant differences seen between etanercept and methotrexate in ACR70 or the HAQ (Table 1).[3]

Statistically significant improvements

Box 1. Common measures of disease activity and response to treatment in rheumatoid arthritis[1,3]

Disease activity score (DAS)

This is used in Europe and is calculated from a formula including counts for tender (53 joints) and swollen (44 joints) joints, an evaluation of general health by the patient (on a scale of 0 to 100) and a measure of circulating inflammatory markers (such as erythrocyte sedimentation rate; ESR).

DAS28 assesses only 28 joints:

High disease activity:	DAS28 > 5.1
Moderate disease activity:	DAS28 3.2 to 5.1
Low disease activity:	DAS28 < 3.2
Remission:	DAS28 < 2.6
Poor response to treatment:	DAS28 decrease ≤ 0.6 points
Moderate response to treatment:	DAS28 decrease ≥ 1.2 points & DAS28 ≥ 3.2 at endpoint
Good response to treatment:	DAS28 decrease ≥ 1.2 points & DAS28 < 3.2 at endpoint

American College of Rheumatology (ACR) response

This assesses the improvement in the number of tender and swollen joints and at least three of the following: observer evaluation of overall disease activity, patient evaluation of overall disease activity, patient evaluation of pain, a physical disability score, and improvements in circulating inflammatory markers. **ACR20, ACR50** and **ACR70** show a 20%, 50% and 70% improvement.

Stanford Health Assessment Questionnaire (HAQ)

This is one component of the ACR criteria (above). It provides a score for the ability to perform daily activities, which ranges from 0 (least disability) to 3 (most severe disability).

Sharp Score

This measures joint damage radiographically (ie. by X-ray) and is based on joint-space narrowing and erosions. It is limited by the fact that it relies on plain radiographs which can be fairly insensitive to change. Also, variation in joint inflammation now seems to have a greater and more immediate impact on disability than slow damage seen radiographically.

Table 1. Results showing the effects of TNF-alpha inhibitors on the main outcomes in the HTA[3]

Comparison and TNF-alpha inhibitor	ACR 70 RR	ACR 70 NNT	HAQ change Mean difference*	Modified Sharp score Mean difference*
Compared with placebo:				
Adalimumab	**5.22** (3.45 to 7.89)	**7.7** (5.9 to 11.1)	**-0.31** (-0.36 to -0.26)	**-2.20 at one year** (-3.33 to -1.07)
Etanercept	**9.44** (3.98 to 22.38)	**7.7** (6.3 to 10.0)	**-0.50** (-0.59 to -0.42)	No data available
Infliximab	**3.16** (1.89 to 5.27)	**11.1** (7.7 to 20.0)	**-0.27** (-0.35 to -0.19)	**-5.70 at one year** (-8.58 to -2.82)
Compared with MTX:				
Adalimumab	0.99 (0.75 to 1.30)	–	0.00 (-0.13 to 0.13)	**-4.90 at two years** (CI not given)
Etanercept	1.23 (0.89 to 1.70)	–	-0.10 (-0.23 to 0.03)	**-0.97 at one year** (-1.65 to -0.29)
	1.46 (1.00 to 2.14)	–	-0.10 (-0.23 to 0.03)	**-2.28 at one year** (-4.11 to -0.45)
Infliximab	Monotherapy not licensed	Monotherapy not licensed	Monotherapy not licensed	Monotherapy not licensed
Anti-TNF + MTX vs. MTX:				
Adalimumab + MTX	**1.64** (1.30 to 2.07)	**5.6** (3.8 to 10.0)	-0.10 (-0.23 to 0.03)	**-4.40 at one year** (-6.14 to -2.66)
Etanercept + MTX	**2.53** (1.82 to 3.54)	**4.0** (3.0 to 5.9)	**-0.40** (-0.52 to -0.28)	**-3.34 at one year** (-5.12 to -1.56)
Infliximab + MTX	**1.57** (1.20 to 2.05)	**8.3** (5.3 to 20.0)	**-0.17** (-0.29 to -0.06)	**-3.28 at one year** (-4.55 to -2.01)

Key: NNT = Number needed to treat, calculated for data that are significantly different only. * Negative values favour the TNF-alpha inhibitor.
MTX = methotrexate. Figures in parentheses are 95% confidence intervals.
All figures in **bold type** show statistical significance in favour of the TNF-alpha inhibitor at p<0.05.
Figures in red type show RCTs in established RA and figures in grey type show those in early RA.
ACR20 results are not given above, but in all comparisons except for adalimumab compared with methotrexate ACR20 was statistically significant in favour of the TNF-alpha inhibitor.

were seen with both adalimumab and etanercept in slowing radiographic joint progression (measured by the modified Sharp score — see Table 1). However, the clinical significance of these differences compared with methotrexate was unclear.[3]

Used in combination with methotrexate versus methotrexate alone

Four RCTs compared a TNF-alpha inhibitor used in combination with methotrexate with methotrexate alone (one adalimumab RCT, n=525; one etanercept RCT, n=459; and two infliximab RCTs, n=685). These were in patients who were either naïve to methotrexate, or had previously failed methotrexate.[3] All three agents used in combination with methotrexate were significantly more effective than methotrexate used alone in controlling symptoms of RA, improving physical function and slowing radiographic joint damage (Table 1).[3] The effectiveness of methotrexate in RA is well established and it is considered to be the standard DMARD against which other drugs should be assessed. Therefore, the clinical relevance of the benefits seen with TNF-alpha inhibitors used alone or in combination with methotrexate therapy over methotrexate alone still need to be determined.[3]

A recent Canadian HTA systematic review of etanercept and infliximab found that they had a small to moderate effect on clinical outcomes in RCTs longer than one year.[15] Both drugs, when used in combination with methotrexate, were more effective than methotrexate alone on outcomes such as ACR50 and DAS28. They also led to statistically significant — but not always clinically significant — improvements in radiological progression. However, a clear benefit was not seen when etanercept alone was compared with methotrexate alone.[15] This reinforces the NICE recommendations to use TNF-alpha inhibitors in combination with methotrexate where possible.[1] The NICE recommendations are further supported by a very recent meta-analysis which found no important differences between TNF-alpha inhibitors and non-biologic DMARDs in clinical outcomes (such as ACR 20, 50, or 70); only statistically significant improvements in radiographic outcomes with TNF-alpha inhibitors were seen.[9] However, clinical response rates and functional outcomes improved more with various combinations of biologic DMARDs plus methotrexate

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than with either methotrexate or a biologic DMARD used alone.[9]

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How safe are they?

Although many trials have found little difference in the incidence of adverse effects between TNF-alpha inhibitors and comparators,[3] some important safety concerns have emerged, particularly through post-marketing surveillance. The most common adverse effects reported with these agents are injection site or infusion reactions, infections and hypersensitivity reactions.[1] However, TNF-alpha inhibitors have also been associated with reports of cancer (for example, lymphoma), systemic lupus erythematosus and autoimmunity, demyelination and neurological complications, and haematological complications. In addition, worsening heart failure has been reported.[16]

The long-term effects of blocking TNF-alpha over many years are still largely unknown. Without sufficient long-term safety data, it is not possible to determine whether one drug is safer than another. Also, it is not always clear whether all adverse effects reported with specific agents are a class effect. For example, unlike adalimumab and infliximab, etanercept also binds to lymphotoxin-alpha, a cytokine that might be important in the control of infection and tumour growth, independent of TNF-alpha.[11]

A systematic review of infliximab and adalimumab RCTs suggests that the risk of serious infections (requiring antibiotics and/or hospital admission) is doubled. The number needed to harm (NNH) was 59 (95% CI 39 to 125) within 3 to 12 months.[11] Also, a recent retrospective US cohort study evaluated patients receiving etanercept, infliximab or adalimumab for up to 17 months. It suggested that the risk of hospital admission due to bacterial infection was doubled overall and quadrupled in the first six months.[17]

Serious infections have been reported particularly with concomitant use of etanercept with anakinra. Therefore, anakinra should not be used with any of the TNF-alpha inhibitors.[12–14] In addition, a large number of cases of tuberculosis (TB), particularly reactivation of latent TB, have been reported with these agents. This is most likely to occur within the first year of treatment.[16]

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above: *physical damage to the hand joints is evident here, although this lady can still manage to hold a hot cup of tea — and smile despite the discomfort she will be experiencing*

The systematic review of infliximab and adalimumab reported that the risk of malignancies was tripled in patients taking these agents, although the confidence intervals were wide (odds ratio [OR] 3.3, 95% CI 1.2 to 9.1; NNH 154 for 6–12 months' treatment).[11] It is unclear how much the various risks are influenced by the population being treated.[11,16,17] For example, patients with long-standing active inflammatory disease already have an increased background risk of lymphoma.[12]

Which agent should be used?

NICE recommends that treatment is normally started with the least expensive drug, based on a consideration of the administration costs, required dose and the product price per dose.[1] However, the agent chosen also depends on the individual patient and practical issues around administration and delivery of the drug (such as the route and dosing schedules).[1,16] Currently, there appears to be a lack of strong evidence suggesting that one agent is more effective than another.[1,3,10]

How should they be used?

Before starting a TNF-alpha inhibitor, it is important to weigh up the potential risks against the benefits expected for individual patients.[16] TNF-alpha inhibitors should be avoided in:[16]

- pregnancy or breast feeding
- active infection
- septic arthritis of a native joint within the last 12 months
- sepsis of a prosthetic joint within the last 12 months or indefinitely if the joint remains *in situ*
- heart failure — New York Heart Association grade 3 or 4
- clear history of demyelinating disease, such as multiple sclerosis.

Also, before starting treatment all patients should be screened for active and inactive TB.[16]

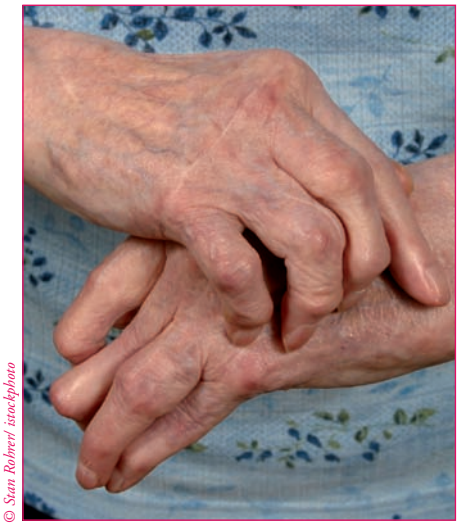
TNF-alpha inhibitor treatments should only be started by a specialist rheumatological team with experience in their use.[1] The team should also take responsibility for following up patients regularly to assess their response and adverse effects. [12–14,16]

Patients should be monitored at least every six months and TNF-alpha inhibitors only continued in patients who have an adequate response after the first six months. This is defined as an improvement in

DAS28 ≥ 1.2 points (*see* Box 1).[1] NICE does not recommend that the dose is increased beyond the licensed starting dose for each drug.[1]

If treatment is stopped during the first six months because of an adverse event an alternative TNF-alpha inhibitor may be considered if the risks and benefits are discussed with the patient and documented.[1] The draft NICE guidance, which discouraged trying another TNF-alpha inhibitor if the response was inadequate, was subject to appeal. This requires further consideration and NICE intend to issue more specific guidance in 2008.[18]

Patients should be monitored before, during and after treatment for signs of infection, blood dyscrasias, demyelinating disease and heart failure.[12–14,16,19] This includes a repeat chest x-ray after six months to screen for TB.[19] Patient leaflets from the Arthritis Research Campaign (ARC) may be



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useful when counselling patients about treatment.[20] Counselling points include asking patients to report signs and symptoms of TB, other infections and haematological reactions. A patient-alert card should also be provided, which can be used to record test results (for example, tuberculin skin tests).[12–14] It is also advisable to check full blood count, liver function and renal function before each infliximab infusion and monthly for patients receiving etanercept or adalimumab.[19] Reference to the respective summary of product characteristics should be made for specific administration details, monitoring and precautions for each drug.

TNF-alpha inhibitors are black triangle drugs. Therefore, all suspected adverse reactions should be reported to the Commission on Human Medicines (CHM). The British Society of Rheumatology Biologics Database is also monitoring the safety of these drugs (over five years; *see* www.medicine.manchester.ac.uk/arc/BSRBR for more information).

Conclusion

Etanercept, adalimumab and infliximab should be reserved for adults with active RA that is resistant to other DMARDs. They appear to improve symptoms, physical function and radiographic progression, at least in the first couple of years. However, longer-term studies assessing their effects on patient-oriented outcomes, such as quality of life, joint replacement and mortality are still needed. Post-marketing surveillance has raised several safety concerns with these agents. Therefore, pharmacists have an important role in ensuring that these drugs are used safely and that patients are counselled and monitored appropriately during treatment. ✣

Conflicts of interest

None.

Samantha Lane, National Prescribing Centre, Liverpool, UK

Series editors:

Jonathan Underhill, National Prescribing Centre, Liverpool, UK

Scott Pegler, principal pharmacist, medicines information manager, Morriston Hospital, Swansea NHS Trust, UK

John Bane, medicine information/clinical trial pharmacist, Pharmacy Dept, Sheffield Childrens NHS Foundation Trust, Sheffield, UK

References

1. National Institute for Health and Clinical Excellence. *Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis.* Technology Appraisal; No. 130, Oct 2007. Accessed from www.nice.org.uk on 07.11.07.
2. National Institute for Health and Clinical Excellence. *Rheumatoid arthritis: the management and treatment of rheumatoid arthritis in adults.* Guideline Scope, Nov 2006. Accessed from www.nice.org.uk on 28.04.07.
3. Chen Y-F, Jobanputra P, Barton P *et al.* A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technol Assess* 2006; **10(42).**
4. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004; **350:** 2591–602.
5. Scottish Intercollegiate Guidelines Network. *Management of early rheumatoid arthritis: a national clinical guideline*; No. 48. Dec 2000. Accessed from www.sign.ac.uk on 28.04.07.
6. Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? *Rheum* 2001; **40:** 1211–20.
7. National Institute for Clinical Excellence. *Anakinra for rheumatoid arthritis.* Technology Appraisal; No. 72, Nov 2003. Accessed from www.nice.org.uk on 28.04.07.
8. National institute for Health and Clinical Excellence. *Rituximab for the treatment of rheumatoid arthritis.* Technology Appraisal; No. 126, August 2007. Accessed from www.nice.org.uk on 07.11.07.
9. Donahue KE, Gartlehner G, Jonas DE *et al.* Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med* 2008; **148** (early online publication). Accessed from www.annals.org on 23.11.07.
10. Gartlehener G, Hansen RA, Jonas BL *et al.* The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. *J Rhematol* 2006; **33:** 2398–408.
11. Bongartz T, Sutton AJ, Sweeting MJ *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; **295:** 2275–85.
12. Abbott Laboratories Ltd. Humira ▼ *Summary of Product Characteristics*, October 2007. Accessed from www.medicines.org.uk on 12.11.07.
13. Schering-Plough Ltd. Remicade ▼ *Summary of Product Characteristics*, July 2007. Accessed from www.medicines.org.uk on 12.11.07.
14. Wyeth Pharmaceuticals. Enbrel ▼ *Summary of Product Characteristics*, August 2007. Accessed from www.medicines.org.uk on 12.11.07.
15. Suarez-Almazor ME, Ortiz Z, Lopez-Olivio M *et al. Infliximab and etanercept in rheumatoid arthritis: a systematic review of long-term clinical effectiveness.* [Technology Report no 85]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007. Accessed from www.cadth.ca on 04.04.07.
16. Ledingham J and Deighton C on behalf of the British Society for Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). Update on the British Society for Rheumatology guidelines for prescribing TNF-alpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology* 2005; **44:** 157–63.
17. Curtis JR, Patkar N, Xie A *et al.* Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor-alpha antagonists. *Arthritis Rheum* 2007; **56:** 1125–33.
18. National Institute for Health and Clinical Excellence. NICE appraisal of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. Press Release, Oct 2007. Accessed from www.nice.org.uk on 11.11.07.
19. PRODIGY. *Monitoring People on disease-modifying drugs (DMARDs)*, October 2005. Accessed from www.cks.library.nhs.uk on 21.05.07.
20. Arthritis Research Campaign (ARC). Publications for people with arthritis. Accessed from www.arc.org.uk/arthinfo/patpubs.asp on 21.05.07.