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Guidelines

Update on the British Society for Rheumatology guidelines for prescribing TNFα blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001)

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These guidelines have been developed for use by prescribing secondary-care rheumatologists. They are intended to indicate which adult patients with rheumatoid arthritis (RA) may benefit from the anti-tumour necrosis factor (anti-TNF) therapies, precautions that need to be taken in their use and to highlight potential side-effects from these therapies. The previous guidelines applied to the then available anti-TNF therapies (etanercept and infliximab) [1]. These current guidelines would apply to these two products together with adalimumab, which is a newly licensed anti-TNF therapy for RA. This is a rapidly changing field with new data emerging each month, so that it is vital that clinicians keep up to date with this area of practice. These guidelines can only incorporate information that was available to the authors at the time of their completion.

The guidelines have been drawn up by the above working party and have been approved by the British Society for Rheumatology (BSR) Standards, Guidelines and Audit Working Group (SGAWG). National Institute of Clinical Excellence (NICE) guidelines, Medline literature searches for published data on the anti-TNF drugs and data from the pharmaceutical companies producing anti-TNF agents have been used to draw together the updated guidelines. The guidelines were subject to a consultation process at the BSR Annual Meeting 2004 and feedback was received from BSR members, allied health professionals, patient representatives and members of the pharmaceutical industry. The BSR SGAWG will be responsible for initiating a further update of these guidelines in the future and for auditing their use.

The anti-TNF therapies are not necessarily the only treatment option available to patients who are eligible for treatment according to these guidelines—the potential risks versus the benefits need to be considered for each individual case. There will be circumstances in which rheumatologists will feel that there are other drugs that may be equally likely to produce a good clinical response.

In the UK all patients commenced on the following anti-TNF therapies need to be registered on the BSR biologics register (BSRBR): etanercept, infliximab, adalimumbab and anakinra. It is currently intended that data be collected on 4000 patients per anti-TNF therapy. Thereafter the BSR would recommend continued data collection, in the same format as for the BSRBR, at a local level. These guidelines will be updated as other anti-TNF treatments are included in the register. For further clarification before registration, please contact Dr Kath Watson, BSRBR Study Co-ordinator, arc Epidemiology Unit, Stopford Building, The University of Manchester, Oxford Road, Manchester M13 9PT, UK (Tel: 0161 275 1613, E-mail: biologics.register@man.ac.uk).

Adverse incidents/serious side-effects arising whilst on anti-TNF therapy should be notified immediately via the yellow card system, but also to the BSRBR via the 6-monthly review sheets. Rheumatologists have responsibility for supplying updated information to the BSRBR as required and as requested. Written consent will be sought from patients for their participation in this study via the BSRBR.

Eligibility for treatment with biologics therapies

Patients must:

1. Fulfil the 1987 criteria of the American College of Rheumatology classification criteria for a diagnosis of RA.
2. Have active RA (have a DAS28 score of >5.1). Measurements of disease activity should be made at two points, 1 month apart confirming on-going active disease.
3. Have failed standard therapy as defined by failure to respond or tolerate adequate therapeutic trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs)—intramuscular gold, hydroxychloroquine, sulphasalazine, penicillamine, azathioprine, methotrexate or leflunomide). One of the failed or not tolerated therapies must be methotrexate. Adequate therapeutic trial is defined as:
   (a) Treatment for at least 6 months, with at least 2 months at a standard target dose unless significant toxicity limited the dose tolerated.
   (b) Treatment for less than 6 months where treatment was withdrawn because of drug intolerance or toxicity, but normally after at least 2 months at therapeutic doses.

There may be circumstances when other DMARDs are relatively contraindicated, so that anti-TNF therapy may be considered very early in the course of the disease, and in patients in whom methotrexate has not been used. There are data to support these approaches with anti-TNF therapies working well in trials of early RA and in DMARD-naïve patients [2–17]. However, it is anticipated that in clinical practice it will be rare that circumstances arise necessitating use of anti-TNF therapy as a first-line therapy.

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Exclusion criteria

Reference should be made to the individual drug data sheets, but important exclusions include:

1. Women who are pregnant or breast feeding (see below).
2. Active infection [18–24].
3. Septic arthritis of a native joint within the last 12 months (based on opinion, but no good evidence).
4. Sepsis of a prosthetic joint within the last 12 months or indefinitely if the joint remains *in situ* (based on opinion, but no good evidence).
5. New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure (CCF) (see below).
6. Clear history of demyelinating disease (see below).

Extreme caution needs to be taken in those patients who are prone to infection, e.g. chronic leg ulcers, persistent or recurrent chest infections, in-dwelling urinary catheters. Patients infected with tuberculosis, hepatitis B and C and HIV are discussed below.

Recent information from the BSR Biologics Register suggests that there may be higher levels of mortality in patients with pulmonary fibrosis treated with infliximab. At present there are more follow-up data available on infliximab-treated patients than for the other biologics. Increased mortality in patients with pulmonary fibrosis could occur with other biologics agents. Until further information is available, caution is needed when exposing RA patients with pulmonary fibrosis to anti-TNFα drugs. Such patients should be monitored closely for infection and any deterioration in pulmonary function.

Criteria for withdrawal of therapy

1. Development of drug-related toxicity [8–12, 16, 21, 25–28].
2. Inefficacy as indicated by failure of the DAS28 score to improve by >1.2 or to reduce to a score of $\leq$3.2 after 3 months of therapy. However, if other changes in therapy have occurred within the first 3 months (e.g. the treatment has allowed a reduction in steroid dose), treatment may be continued for a further 3 months, but should not be maintained for more than 6 months if the DAS28 responses are not achieved (this statement is based on opinion rather than evidence).
3. Severe intercurrent infection (temporary withdrawal).
4. Pregnancy (temporary withdrawal).

Which anti-TNF therapy should be used?

There is no current evidence to suggest that any type of anti-TNF therapy is more efficacious than the others [29, 30]. Selection of an anti-TNF agent will be based on patient preference and practical issues relating to drug administration and delivery. Etanercept and adalimumab do not require co-prescription with methotrexate, so that this is an attractive option in patients intolerant of this drug.

Should a patient who is failing to respond to one anti-TNF therapy have their treatment changed to an alternative anti-TNF agent?

There are a limited number of studies that have suggested that some patients who have shown no, or only a partial, response to anti-TNF therapy, can benefit from transferring to an alternative type of anti-TNF therapy. The current evidence suggests that infliximab can be useful when etanercept has failed, and vice versa [31, 32]. There is also evidence for adalimumab substitutions (currently in abstract form [33–38]).

Can DMARDs other than methotrexate be used in combination with anti-TNF therapies?

There are some published papers and abstracts highlighting that infliximab may be combined with leflunomide. The combination is efficacious; however, widespread use may be limited by adverse events which were common, and in some cases severe [39]. A pilot study using infliximab with azathioprine suggests the combination is clinically beneficial in severe RA refractory to azathioprine alone, but this has only been published in abstract form [40]. Until further evidence is forthcoming, methotrexate must remain the preferred drug for co-prescription with infliximab.

Although it is not necessary to co-prescribe methotrexate and etanercept, studies have addressed the possibility that the two together may be more efficacious than the individual agents [41–43]. There is good evidence to support this [42, 43]. In patients with inadequate response to etanercept, the addition of methotrexate is a useful option, and vice versa. Adalimumab has been shown to be useful in patients with an inadequate response to methotrexate [44] To ensure maximum efficacy, adalimumab should be administered in combination with methotrexate.

Is there a place for alteration in the dose or the frequency of administration of anti-TNF therapy?

Some patients who have responded well to anti-TNF therapy may be able to remain in remission with a reduced dose or reduced frequency of treatment, and in the absence of large trials each patient needs to have their regime tailored individually. Likewise there may be a proportion of patients on infliximab who would benefit from an increase in dose or in frequency of treatment when partial response only has been achieved with recommended dosage regimes [7, 45–47]. Adalimumab is licensed for weekly use for patients failing to respond to fortnightly injections.

In the absence of definitive data, the routine use of regimes which depart from those that are recommended cannot be supported as a general policy, and the majority of patients should stay on the recommended regimes.

Potential adverse effects related to anti-TNF therapy and guidance related to these

1. Serious infections, excluding tuberculosis

A number of serious infections including some fatalities have been reported in association with the anti-TNF therapies [7–24, 48–53].

Guidelines

- Anti-TNF therapy should not be started in the presence of serious infections.
- Anti-TNF therapy should be discontinued in the presence of serious infections, but can be re-continued once the infection has completely resolved.
- The effects of anti-TNF therapy are unknown for patients with HIV. There is a case report of an HIV patient with reactive arthritis receiving infliximab without any deleterious effects [54], but further data are needed. Infliximab has been used in six advanced HIV patients and there are abstracts reporting the use of infliximab in small numbers of HIV-positive Crohn's disease sufferers without any obvious deleterious effects [55–57]. However, until large-scale controlled studies are performed, anti-TNF therapy cannot currently be advised in patients who are HIV positive.
- Reports on the effects of anti-TNF therapy on hepatitis B patients are contradictory. There are case reports of severe

hepatitis reactivation [58, 59], with a more recent case report of no deleterious effects of anti-TNF therapy over 1 yr [60]. Until more definitive data are available, anti-TNF therapy should be avoided in patients with hepatitis B infection.
- Although larger and longer-term studies are needed, initial reports on the use of infliximab on patients infected with hepatitis C suggest no deterioration in hepatitis or viral load [60–62]. Similar data are also available in abstract form for etanercept (information from the drug company). However, there is a single published case of hepatitis C activation in a RA patient on etanercept [63]. Anti-TNF therapy may be used with caution in these patients.

2. Tuberculosis

There have been a large number of cases of tuberculosis (TB) reported in association with the use of infliximab, and studies that demonstrate a significantly higher rate of TB in patients on this treatment compared with controls [64–66]. Cases of TB have also been reported in association with etanercept [64, 67] and adalimumab [68]. Reactivation of latent TB is highest in the first 12 months of treatment, so particular vigilance is required during this time [64, 66]. With infliximab, the majority of cases occurred within three cycles of treatment, with a median of 12 weeks after starting treatment, suggesting reactivation of latent TB as the main factor predisposing to TB [64, 66] in these cases.

Guidelines

- Prior to commencing treatment with anti-TNF, all patients should be screened for TB in accordance with the British Thoracic Society (BTS) guidelines [69]. Active TB needs to be adequately treated before anti-TNF therapy can be started.
- Prior to commencing anti-TNF therapy, consideration of prophylactic anti-TB therapy (as directed by the BTS guidelines) should be given to patients with evidence of potential latent disease (past history of TB treatment or abnormal chest X-ray raising the possibility of TB) after consultation with a local TB specialist.
- All patients commenced on anti-TNF therapies need to be closely monitored for TB. This needs to continue for 6 months after discontinuing infliximab treatment due to the prolonged elimination phase of infliximab.
- Patients on anti-TNF therapy who develop symptoms suggestive of TB should receive full anti-TB chemotherapy, but may continue with their anti-TNF therapy if it is clinically indicated (see the BTS guidelines on tuberculosis screening [69]).
- Anti-TNF therapy should only be resumed in accordance with the BTS guidelines and after agreement in collaboration with a TB specialist.

3. Surgical procedures

Treatment with infliximab, etanercept and adalimumab should be withheld for 2 to 4 weeks prior to major surgical procedures. Treatment may be restarted post-operatively if there is no evidence of infection and once wound healing is satisfactory (information provided by the drug companies).

4. Vaccination

The effects of anti-TNF therapies are unknown for most primary vaccinations and live attenuated vaccinations. A study on pneumococcal vaccination suggested patients on anti-TNF may not respond adequately to the vaccination [70]. If live vaccines are required they should ideally be given 4 weeks prior to commencing treatment or 6 months after the last infusion of infliximab (or potentially earlier if risks from not vaccinating are high) or 2–3 weeks after the last dose of etanercept (information available from the drug companies). Since no data are available, concurrent administration of live vaccines and adalimumab is not recommended (information available from the drug company). The BSR has a policy document on the use of vaccinations in patients on immunosuppressive therapy [71], and until further evidence is available these recommendations should be adhered to in patients on anti-TNF therapy.

5. Malignancy

There have been number of malignancies, including lymphoma, reported from studies and post-marketing surveillance in association with the anti-TNF therapies [62].

Guidelines

- There is no evidence currently for an increase in risk of solid tumours or lymphoproliferative disease with the anti-TNF therapies above that which would be expected in the RA population [73–75].
- Patients should be investigated for potential malignancy if clinically suspected and consideration should be given to stopping anti-TNF treatment if malignancy is confirmed.
- The effects of anti-TNF therapies are as yet unknown in patients with pre-existing malignancy or lymphoproliferative disease. Caution should be exercised in the use of anti-TNF therapies in patients with previous malignancy. The potential benefits of treatment need to be considered against the risks related to potential recurrence of the specific malignancy. If patients have been free of any recurrence of their malignancy for 10 yr there is no evidence for a contraindication to anti-TNF therapy.
- The effect on pre-malignant conditions such as Barrett's oesophagus, cervical dysplasia and large bowel polyps of anti-TNF therapies is unknown. Caution should be exercised in the use of anti-TNF therapies in such patients.

6. Systemic lupus erythematosus syndromes and autoimmunity

Rare cases of systemic lupus erythematosus (SLE) syndromes have been reported in association with the anti-TNF therapies [7, 8, 28, 76–82]. Symptoms resolved on discontinuing therapy—usually within 6 weeks to 14 months. There have been no fatalities or cases of major organ involvement in association with SLE-like syndromes developing in association with the anti-TNF therapies. There is no evidence that developing antinuclear antibodies, anti-DNA antibodies or anticardiolipin antibodies whilst on anti-TNF therapies increases the risk of developing clinical SLE-type syndromes.

Guidelines

- If symptoms of an SLE-like syndrome develop whilst on anti-TNF therapies:

  (a) anti-TNF treatment should be discontinued,
  (b) appropriate treatment should be initiated for the clinical symptoms and signs.

7. Congestive cardiac failure/cardiovascular disease

Following an increase in reported mortality and hospitalization in the infliximab-treated group in a placebo-controlled trial in

patients with cardiac failure, warning statements were issued in November 2001 with regard to the use of infliximab in patients with congestive cardiac failure/cardiovascular disease (CCF/CVD) [83, 84]. This usually occurred with high-dose regimes (such as 10 mg/kg). Etanercept may also adversely affect CCF [83, 85]. A more recent study suggests that heart failure may be more common in patients with RA than controls, and that anti-TNF may actually ameliorate heart failure in RA [86].

Guidelines

- Anti-TNF therapy should not be initiated in patients with New York Heart Association (NYHA) grade 3/4 CCF. It should be used in caution in patients with mild CCF.
- Patients should be carefully monitored for CCF whilst being treated with any anti-TNF therapy. If symptoms and signs of CCF are stable, treatment should still potentially be discontinued if the benefit of the anti-TNF therapy is only limited.
- Anti-TNF therapy should be discontinued if CCF increases whilst on treatment.

8. Demyelination and neurological complications

There are a number of reports of demyelination and acute neurological complications in association with the anti-TNF therapies. The cases reported thus far have usually responded to discontinuation of anti-TNF therapy and treatment for the acute demyelination when clinically indicated [7, 28, 87–89].

Guidelines

- Anti-TNF therapy should not be given when there is a clear history of demyelinating disease.
- Anti-TNF therapy may be best avoided if there is a possible history of demyelinating disease or a strong family history of demyelination.
- Anti-TNF therapy should be withdrawn if demyelination occurs.
- If a patient develops signs of demyelination whilst on anti-TNF therapy they should be referred to a neurologist for specialist investigation.

9. Haematological complications

There have been a few reports of haematological complications arising in patients treated with all three anti-TNF therapies [7, 28, 90–95]. Pancytopenia was fatal in some patients treated with etanercept and infliximab. No fatalities are reported from pancytopenia with adalimumab. Most patients were taking other potentially myelotoxic drugs and/or prednisolone at the time of the haematological abnormalities.

Guidelines

- If haematological complications arise whilst on anti-TNF therapies, these agents should be discontinued. Checking a full blood count periodically, and immediately if the patient is unwell, is recommended.

10. Pregnancy and lactation

There are no formal clinical studies of anti-TNF therapy in pregnancy or lactation. Animal models suggest no teratogenicity or risk of miscarriage. Some patients have become pregnant whilst taking anti-TNF therapy. There are no data to suggest any risk to the fetus, but insufficient data to warrant continuation of the therapy during pregnancy ([96–98] and information from the drug companies).

Because immunoglobulins are excreted in breast milk, the manufacturers of anti-TNF therapies advise no breast feeding. Due to the long half-life of infliximab it is recommended that patients do not breast feed until 6 months have elapsed from the last infusion.

Guidelines

- Safety of the anti-TNF therapies is unknown/has not been established through pregnancy or lactation.
- It is recommended that:

  (a) Pregnancy should be avoided whilst on anti-TNF therapies and effective contraception is strongly recommended to prevent pregnancy in women of child-bearing potential.
  (b) Breast feeding should be avoided with anti-TNF therapies.
  (c) Consideration should be given to stopping anti-TNF therapy if a patient becomes pregnant on treatment.
  (d) Infliximab is discontinued for 6 months before a female patient becomes pregnant or a male patient fathers a child. No data are currently available with regard to how long it takes for etanercept to be cleared from the reproductive organs. Abbott Laboratories recommend that adalimumab is discontinued for 5 months before a female patient becomes pregnant or a male patient fathers a child. The effect of adalimumab on sperm has not been studied so no specific recommendations can be made.

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Conflict of interest

The Working Party was set up independently of any input or funding from the manufacturers of the new biologic therapies.

Members of the Working Party were asked to clarify their relationships with the manufacturers of the new biologic therapies. Members were asked to declare if they, as individuals, had been sponsored to attend scientific or other meetings in the past 24 months or if they had a direct financial stake in the manufacturing companies. They were also asked if their units had received funding from the manufacturers to take part in clinical trials of the new biologic therapies. Organizations were asked to declare if they had received sponsorship from manufacturers of the new biologic therapies for activities related to the new therapies (either educational or promotional) or for activities not related to the new therapies.

The following replies were received:

- BSR has established a register which is funded by the manufacturers of biologic therapies; training for rheumatologists in data collection has also been funded by these manufacturers.
- The authors have declared no conflicts of interest.

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