

# British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005

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## Accepted for publication

20 June 2005

## Key words:

biologics, efalizumab, etanercept, guideline, infliximab, psoriasis

## Conflicts of interest:

C.H.S., grant/research trial support Wyeth, Serono, Schering Plough, consultant for Novartis; A.V.A., consultant for Schering Plough; J.N.W.N.B., consultant for Schering Plough, Wyeth, Biogen, Serono Novartis; grant/research trial support Schering Plough, Wyeth, Biogen, Serono; A.D.B., consultant for Wyeth, Serono, Schering Plough; grant/research trial support Wyeth, Serono; R.J.G.C., none; D.C., none; A.Y.F., consultant for Wyeth, Novartis, Serono, Amgen, Abbott; trial support; C.E.M.G., grant/research support Biogen, Serono, Amgen, Centocor; previous consultant for Serono, Wyeth, Schering Plough; K.J., none; N.J.McH., consultant for Aventis, Abbott; grant research support Wyeth; K.E.McK., none; N.J.R., grant/research support Serono; A.D.O., grant/research support Wyeth, Serono.

## Introduction

### Background

Psoriasis is a common, persistent, relapsing inflammatory skin disease that can be associated with significant morbidity. Quality of life studies in psoriasis reveal a negative impact on patients comparable with that seen in cancer, arthritis and heart disease.<sup>1–5</sup> Patients with severe disease constitute approximately 20–30% of all patients with psoriasis, often require systemic treatment, and represent a major economic burden to the Health Service.

All standard systemic therapies for severe disease are associated with the potential for major long-term toxicity, many are expensive, and a proportion of patients has treatment-resistant disease.<sup>6</sup> Biological therapies or 'biologics' describe agents designed to block specific molecular steps important in the pathogenesis of psoriasis and have emerged over the last 3–5 years as potentially valuable alternative therapeutic options.

Currently, biological therapies for psoriasis comprise two main groups: (i) agents targeting the cytokine tumour necrosis factor (TNF)- $\alpha$  (e.g. etanercept, infliximab, adalimumab) and (ii) agents targeting T cells or antigen-presenting cells (e.g. efalizumab, alefacept). Two of these, etanercept (Enbrel<sup>®</sup>) and efalizumab (Raptiva<sup>®</sup>) were licensed in 2004 in the U.K. for patients with moderate to severe psoriasis.

### Need for a guideline

These new treatments are relatively expensive and, given the widespread patient dissatisfaction with standard treatments,<sup>2</sup> demand is likely to be high. Clinical experience of biological therapies in dermatology is relatively limited and their

role in the context of existing standard systemic therapies, particularly with respect to efficacy and long-term toxicity, is uncertain. These guidelines have been developed to ensure that this new class of therapy is introduced in a systematic and planned way to achieve the greatest possible benefit to people with psoriasis, to facilitate safe and effective prescribing and to endorse the use of the British Association of Dermatologists (BAD) Biological Therapy Register as a mechanism for collecting long-term safety and efficacy data. The guideline group has sought to provide useful, evidence-based guidance based on systematic review of available literature, but acknowledges that additional funding may be required to implement guideline recommendations fully.

### Scope

These guidelines were developed in accordance with a predetermined scope, agreed by the guideline working group, and are as detailed below. For practical reasons, guidance is given only on those treatments that are currently licensed for use in psoriasis in the U.K. (etanercept, efalizumab) and infliximab. Although infliximab is currently unlicensed for use in psoriasis, a licence is anticipated in the near future, it is widely available, and it is currently the most extensively used biological therapy in dermatology clinical practice.

### Inclusions

Specific, evidence-based, recommendations cover the following clinical areas:

- Use of infliximab, etanercept and efalizumab in adult patients with psoriasis and, when relevant, psoriatic arthritis
- Which patients should be considered eligible for treatment
- Who should prescribe therapy and how to do so
- Definition of disease response and indications for stopping therapy

### Exclusions

- Agents licensed for use outside the U.K. (e.g. alefacept) or in clinical development for psoriasis (e.g. adalimumab)
- Use of biological therapies in children
- Use of biological therapies for indications other than psoriasis

### Methods

This guideline has been developed using BAD recommended methodology and the AGREE (Appraisal of Guidelines for Research and Evaluation) instrument. The guideline working group represents all relevant stakeholders including nurses, rheumatologists and patients. Draft guidance was made available for consultation and review by patients and the BAD membership prior to publication.

A literature review was performed by searching EMBASE and Medline databases (1990 to April 2005) for clinical trials involving efalizumab, etanercept and infliximab using an agreed protocol. Two reviewers screened all titles and abstracts independently, and full papers of relevant material were obtained wherever possible. Papers included as evidence were scored for strength of evidence using the instruments currently recommended by the Scottish Intercollegiate Guidelines Network and the National Institute for Clinical Excellence (Appendix 1). Additional *ad hoc* searches were done to address clinical questions that arose during the development of the guideline, and evidence was appraised in the same manner.

### Limitations of the guideline

These guidelines have been prepared for dermatologists on behalf of the BAD and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

### Plans for guideline revision

This field of therapeutics is in a rapid phase of development, and revision of the scope and content of these guidelines will therefore occur on an annual basis.

### Which patients should be considered for biological therapy?

Most patients with moderate to severe disease achieve satisfactory disease control (i.e. significant or complete clearing of disease) in the short term with at least one of the systemic agents currently available.<sup>6</sup> Long-term disease control frequently requires some form of continuous therapy and consequent, predictable risks of toxicity. At present, the risks and benefits of anti-TNF agents, or efalizumab, relative to standard systemic therapy, are unknown. Early, widespread use of these agents in uncomplicated moderate to severe psoriasis is inappropriate and is not supported by the licensed indications for etanercept or efalizumab.

To draw up eligibility criteria, 'severe' disease requires definition and should encompass objective measures of disease severity and the impact the disease has on quality of life.

All existing disease severity assessment tools are imperfect,<sup>7,8</sup> and most require some training to complete. The **Psoriasis Area and Severity Index (PASI)** score has been chosen for the purposes of this guideline as it has been widely used in clinical trials including those investigating

biological therapies. Furthermore, it is a validated measure of disease severity in chronic plaque psoriasis and is also appropriate to use as an objective measure of disease response.<sup>7</sup> A PASI score of > 10 (range 0–72) has been shown to correlate with a number of indicators commonly associated with severe disease such as need for hospital admission or use of systemic therapy.<sup>8</sup> Where the PASI is not applicable (e.g. pustular psoriasis), affected **body surface area (BSA)** should be used, with severe disease defined as > 10% area affected.<sup>8</sup>

#### Eligibility criteria

To be considered eligible for treatment, patients must have severe disease as defined in (a) **and** fulfil one of the clinical categories outlined in (b):

(a) **Severe disease** is defined as a PASI score of 10 or more (or a BSA of 10% or greater where PASI is not applicable) *and* a DLQI > 10. Disease should have been severe for 6 months, resistant to treatment and the patient should be a candidate for systemic therapy. In exceptional circumstances (for example, disabling acral disease), patients with severe disease may fall outside this definition but may be considered for treatment. (Strength of recommendation D, level of evidence 3).

#### AND

(b) **fulfil at least one of the following clinical categories** (Strength of recommendation B, level of evidence 1++ and formal consensus):

- (i) have developed or are at higher than average risk of developing clinically important drug-related toxicity and where alternative **standard therapy**<sup>a</sup> cannot be used
- (ii) are or have become intolerant to or cannot receive standard systemic therapy
- (iii) are or have become **unresponsive to standard therapy**<sup>b</sup>
- (iv) have disease that is only controlled by repeated inpatient management
- (v) have significant, coexistent, unrelated comorbidity which precludes use of systemic agents such as ciclosporin or methotrexate
- (vi) have severe, unstable, life-threatening disease (erythrodermic or pustular psoriasis)
- (vii) have psoriatic arthritis fulfilling the British Society for Rheumatology (BSR) eligibility criteria for treatment with anti-TNF agents,<sup>11</sup> in association with skin disease

<sup>a</sup>**standard systemic therapy** includes acitretin, ciclosporin, methotrexate, narrowband ultraviolet (UV) B and psoralen + UVA photochemotherapy (PUVA)

<sup>b</sup>**unresponsive to standard therapy** is defined as an unsatisfactory clinical response (a less than 50% improvement in baseline PASI score or percentage BSA where the PASI is not applicable, and a less than 5-point improvement in DLQI) to at least 3 months of treatment in the therapeutic dose range to the following treatments: ciclosporin 2.5–5 mg kg<sup>-1</sup> daily; methotrexate single weekly dose (oral, subcutaneous, intramuscular) 15 mg, max 25–30 mg; acitretin 25–50 mg daily; narrowband UVB or psoralen photochemotherapy (nonresponse, rapid relapse or exceeding recommended maximum doses) 150–200 treatments for PUVA, 350 treatments for narrowband UVB.<sup>12,13</sup>

The **Dermatology Life Quality Index (DLQI)** is a validated tool for the measurement of quality of life across all skin diseases in both trial and clinical practice settings<sup>9</sup> and a score of > 10 (range 0–30) has been shown to correlate with at least 'a very large effect' on an individual's quality of life.<sup>7,8,10</sup>

Patients with psoriasis may be considered eligible to receive treatment with a biological intervention when they fulfil the eligibility criteria as set out. However, the decision to proceed with treatment must be made in collaboration with the patient and must include a careful assessment of the associated risks and benefits.

## Who should prescribe biological therapy?

These treatments should be made available to all those patients fulfilling the currently recommended eligibility criteria. However, given (a) that few dermatologists have experience of their use in clinical practice, (b) the need to ensure collection of long-term data on efficacy and safety, and, (c) in the short term at least, to ensure that these agents are only used when alternative standard therapies are inappropriate, it is essential that all those which prescribed strictly to guidelines on prescribing practice and participate in the registration process.

Treatment should be initiated and monitored by consultant dermatologists experienced in managing difficult psoriasis. This should include knowledge and experience of standard therapies and management of those who fail to respond. They must be familiar with, and/or have access to health care professionals trained in the use of the tools recommended for determining treatment eligibility and disease response.

Supervising consultants will be responsible for ensuring that all patients receiving therapy are registered with the BAD Biological Therapy Register throughout the treatment period.

## Antitumour necrosis factor therapies

There are two anti-TNF agents in current use for psoriasis in the U.K., U.S.A. and Europe: etanercept (Enbrel<sup>®</sup>, Wyeth) and infliximab (Remicade<sup>®</sup>, Schering-Plough).

## Pharmacology

Etanercept is a human recombinant TNF receptor p75 fusion protein, formed by the fusion of the extracellular ligand-binding domain of human TNF receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. It also binds soluble and membrane-bound TNF- $\alpha$  with high specificity and affinity, preventing its binding to cell surface receptors and thus inhibiting its pro-inflammatory effects. In comparison with infliximab, etanercept forms less stable complexes with membrane-bound TNF and monomeric TNF, but it does bind significantly with the trimeric forms of soluble TNF.

Infliximab is a human murine (25% murine) chimeric monoclonal IgG1 isotype antibody with a high binding affinity, avidity and specificity for TNF- $\alpha$ . It forms stable complexes with all forms of soluble and transmembrane TNF- $\alpha$ .

### Clinical effectiveness: etanercept

#### Induction and maintenance of remission

Several small phase II studies<sup>14,15</sup> and two key phase III<sup>16,17</sup> randomized controlled trials (RCTs) involving over 1000 patients with moderate to severe chronic plaque psoriasis, the majority of whom had received previous systemic treatment or PUVA, indicate that etanercept is an effective treatment for chronic plaque psoriasis. Efficacy is dose related, with 34% and 49% of patients receiving 25 mg and 50 mg twice weekly, respectively, achieving > 75% improvement in PASI (PASI 75 response) after 12 weeks of treatment. Continued treatment appears to improve response rates further, so that at 24 weeks, 44% and 59% of patients receiving 25 mg and 50 mg twice weekly, respectively, achieved a PASI 75 response. Studies up to a year show sustained efficacy over time, with no evidence of loss of efficacy with interrupted, repeat dosing.

Time to relapse, when defined as a 50% drop in the improvement in PASI achieved after 24 weeks of therapy, ranged from 70 to 91 days and appeared to be dose related (i.e. remission was maintained for slightly longer in the high dose group as compared with the low dose group). Of patients achieving a PASI 75 response at 24 weeks of therapy, 11% remained in remission at 1 year.

Treatment response in severe, recalcitrant disease, erythrodermic, pustular or other forms of psoriasis is unknown.

#### Dosing regimens

Etanercept is given as a self-administered subcutaneous injection and is licensed for use at both 25 mg and 50 mg twice

weekly. Although the percentage of patients achieving and maintaining remission is greater with the higher dose, this needs to be balanced against increased cost and risk of toxicity.

All the trials in psoriasis have been performed as monotherapy. In rheumatoid arthritis, however, etanercept has been safely combined with methotrexate.

### Clinical effectiveness: infliximab

#### Induction and maintenance of remission

Two randomized, placebo-controlled trials have been conducted in patients with moderate to severe, stable chronic plaque psoriasis. The larger study included patients who had received at least one systemic therapy prior to study entry.<sup>18,19</sup> Both trials demonstrated infliximab therapy to be highly effective at inducing disease remission. The onset of improvement occurs within the first 2–4 weeks of treatment and reaches maximum benefit by week 10 in the majority. Of patients receiving a standard induction course of therapy (5 mg kg<sup>-1</sup> at weeks 0, 2 and 6) 87% achieved a PASI 75 response. Time to relapse following successful 'induction' therapy is highly variable between individuals, and may depend on the initial dose given: 73% of those given 10 mg kg<sup>-1</sup> during induction maintained at least a 50% improvement in PASI scores at week 26 compared with 40% of those given 5 mg kg<sup>-1</sup>.<sup>18,20</sup>

There are no RCTs or other controlled trials examining treatment efficacy of infliximab in patients with recalcitrant disease or in other forms of psoriasis. Nevertheless, several case series indicate infliximab monotherapy to be of benefit in patients previously resistant to multiple systemic therapies<sup>21–25</sup> and there are several case reports documenting efficacy in severe unstable psoriasis and generalized pustular psoriasis.<sup>26,27</sup> Clinical experience within the guideline group further supports the value of infliximab in these clinical circumstances.

#### Dosing regimens

Infliximab is given by intravenous infusion over a period of 2 h. Dosing schedules vary according to the disease being treated, and have not been optimized for psoriasis. A standard induction course (5 mg kg<sup>-1</sup> at weeks 0, 2 and 6) may be followed by repeat single infusions at 8–12-week intervals.<sup>28</sup> No studies have established the optimal frequency or dose of repeat infusions required to achieve disease control. There is a suggestion, however, that once significant disease relapse has occurred, repeat infusions do not achieve the same rate of disease clearance as that seen on the initial three-dose induction treatment.<sup>18,20</sup> This latter possibility is supported by findings in Crohns disease, where the risk of developing treatment resistance to infliximab is reduced with maintenance (rather than as-required) infusions. In clinical practice, the risks of maintenance infusions must be balanced against the risks associated with disease relapse. For those patients with, for example, severely unstable disease, the benefits of maintaining

#### Etanercept: Clinical effectiveness

- Etanercept is effective in the treatment of chronic plaque psoriasis, with 38% and 54% of patients clear or nearly clear of disease after 12 weeks of treatment (25 mg twice weekly, 50 mg twice weekly, respectively). (Strength of recommendation A, level of evidence 1++).
- The current licence recommends intermittent courses no longer than 24 weeks, with the time to relapse being variable (around 12 weeks) and with similar response rates achieved with repeat dosing.
- Treatment should normally be initiated at 25 mg subcutaneously, twice weekly. However, response is dose dependent and the chances of responding to treatment are greater with 50 mg twice weekly. The choice of the higher dose should be made based on an individual patient basis. (Strength of recommendation B extrapolated from level of evidence 1++).
- Treatment may be continued according to clinical need, although long-term efficacy is only established in psoriasis for up to 2 years. (Strength of recommendation D, level of evidence 3).

disease control may outweigh risks associated with continued therapy.

### In combination with other therapies

Large trials in rheumatoid arthritis have demonstrated therapeutic benefits of infliximab in combination with methotrexate. The benefit of infliximab in combination with other agents in psoriasis is not established. Evidence from case series and clinical experience in psoriasis suggest that it can be given in combination with a number of systemic agents including methotrexate, ciclosporin, acitretin and hydroxycarbamide.<sup>21,23</sup> Circumstances where combination therapy may be used include when infliximab monotherapy has proved ineffective or, on initiation of therapy, where suddenly discontinuing existing standard therapy might result in unstable disease.

#### Infliximab: Clinical effectiveness

- Infliximab is effective in the treatment of chronic plaque psoriasis, with 90% of patients becoming clear or minimally affected at 10 weeks following 5 mg kg<sup>-1</sup> at weeks 0, 2 and 6. (Strength of recommendation A, level of evidence 1++).
- Infliximab therapy may be initiated at a dose of 5 mg kg<sup>-1</sup> at weeks 0, 2 and 6 and subsequent maintenance infusions (either 5 mg kg<sup>-1</sup> or 3 mg kg<sup>-1</sup>) given at 8-week intervals depending on clinical need and circumstances. (Strength of recommendation A, level of evidence 1++).
- In those patients who respond to therapy, regular maintenance infusions may avoid the risk of loss of efficacy seen in some patients receiving intermittent as-required repeat infusions on disease relapse. (Strength of recommendation D, level of evidence 3).
- Infliximab may also be of value in recalcitrant or unstable disease and in generalized pustular psoriasis. (Strength of recommendation D, level of evidence 3).
- Concomitant systemic therapies may be indicated for some patients with very severe or unstable psoriasis, although doses of these should be minimized. (Strength of recommendation D, level of evidence 3).

### Adverse effects and toxicity: Anti-TNF therapies

In general, infliximab and etanercept are well tolerated; detailed information on side-effects can be found in the relevant summary of product characteristics (SPC).<sup>28,29</sup>

Infections and malignancy are a significant clinical concern although the actual associated risks are unknown, particularly in psoriasis. Previous or concomitant immunosuppressant treatment and PUVA therapy may compound such risks. Additional, serious potential toxicities include demyelinating disease and heart failure.

### Allergic reactions (infusion/injection site reactions) and antibody development

*Etanercept.* Injection site reactions are the most frequently reported adverse event, and occur in 10–20% of patients.<sup>29,30</sup> These

comprise erythema, oedema and bruising, resolve spontaneously within 2–3 days, and tend to occur in the first month of therapy. Tolerance develops in most patients with continued use.

Antibodies to etanercept may develop in up to 6% of patients but data on the clinical relevance of these are scarce.<sup>29</sup>

*Infliximab.* Infusion reactions occurring during or within 1–2 h of treatment affect up to 20% of all patients treated and rarely may result in anaphylactic shock. Management of reactions will depend on the degree of severity. For mild to moderate reactions, the infusion rate may be slowed or temporarily interrupted until symptoms disappear, and symptomatic treatment given as appropriate (antihistamines, hydrocortisone, paracetamol). For more severe reactions, further infliximab is contraindicated, but does not necessarily preclude treatment with other anti-TNF agents.<sup>31</sup>

Antibodies to infliximab may develop during therapy. The frequency of infusion reactions is approximately 2–3 times higher in those with antibodies compared with those without, although overall, the presence of antibodies is poorly predictive of infusion reactions. The clinical significance of antibody development with respect to treatment outcome, and factors that increase risk of their development, are not established in psoriasis.<sup>19,20</sup> In other diseases, antibodies have been associated with a poorer therapeutic outcome, and risk of their development is reduced by giving continuous therapy (as opposed to episodic treatments), and concomitant methotrexate.

### Serious infections

Data from clinical trials in all diseases indicate that although infections are common, overall the rates of infection with these agents are no greater than with placebo. However, serious and opportunistic infections have been reported.<sup>32–37</sup>

Tuberculosis may be a risk particularly associated with anti-TNF agents, as TNF- $\alpha$  plays a key role in host defence against mycobacterial infection, particularly in granuloma formation (and hence containment of *Mycobacterium*) and inhibition of bacterial dissemination.<sup>38</sup> A postmarketing surveillance report in 2001<sup>33,39</sup> identified 70 cases of tuberculosis after treatment with infliximab for rheumatoid arthritis, other forms of arthritis and Crohns disease out of an estimated total of 147 000 people treated. Onset of infection occurred early in treatment, with 48 of 70 patients developing infection within the first three infusions. Most patients were also receiving one or more immunosuppressive agents (methotrexate, ciclosporin, azathioprine or corticosteroids). More than half had extrapulmonary disease, and a quarter disseminated disease. Atypical and extensive infection were thought to account for the high morbidity with at least four deaths directly attributed to tuberculosis infection. Most were assumed to be due to reactivation of latent infection as only a minority reported exposure to

tuberculosis and all had been living in the U.S.A. for at least 10 years. Based on this report, the risk of tuberculosis with infliximab has been estimated to be approximately six times that of untreated patients.<sup>39</sup> Risks of tuberculosis with etanercept may be less.<sup>36,37</sup> Only nine cases had been reported to the U.S. Food and Drug Administration (FDA) at the time of the report, with similar total numbers of patients receiving treatment. Although no cases of tuberculosis have been reported in clinical trials of either infliximab or etanercept in psoriasis, this probably reflects the limited numbers of patients treated and, possibly, monotherapy.

Other serious infections reported include sepsis secondary to *Listeria monocytogenes*<sup>35</sup> and histoplasmosis.<sup>34,36,37</sup> Most of these cases have occurred in association with infliximab treatment and, in most instances, additional immunosuppressant therapy.

Risks of anti-TNF treatment in the context of human immunodeficiency virus (HIV) infection are unknown, but severe disseminated opportunistic infections have been reported in those who are HIV positive.<sup>40</sup>

**Infection and anti-TNF agents**

- Actual risks of serious infections are unknown, particularly in those with psoriasis. Concomitant treatment with immunosuppressants or HIV infection may increase any risk. (Strength of recommendation D, level of evidence 3).
- Reactivation of tuberculosis may occur following treatment with anti-TNF agents, and the risks are greatest with infliximab. There appears to be a disproportionate risk of nonpulmonary and disseminated infection. (Strength of recommendation D, level of evidence 3).
- Patients with evidence of either active tuberculosis or previous, inadequately treated tuberculosis should receive antituberculous treatment prior to anti-TNF therapy.<sup>41,42</sup> (Strength of recommendation D, level of evidence 4).

**Cardiovascular disease**

Possible risks of anti-TNF therapy in the context of heart failure were first highlighted when trials in severe congestive cardiac failure [New York Heart Association (NYHA) class III and IV, left ventricular ejection fraction < 35%; Table 1] were prematurely discontinued due to failure to show benefit in the case of the etanercept studies, and an excess mortality with high-dose infliximab.<sup>43</sup> Clinical trial data in psoriasis and other diseases show no excess risk of heart failure although selection bias (i.e. exclusion of those at risk) may account for this. Forty-seven spontaneous reports to the FDA of new onset or worsening of pre-existing heart failure following either infliximab or etanercept were recently reviewed in detail.<sup>44</sup> The possibility of drug-induced pathology was supported by an apparent temporal association between introduction of drug and onset of symptoms (median onset 3 months with infliximab, 8.5 months with etanercept). Pre-existing risk factors

for heart disease were absent in 50% of cases, and complete resolution or substantial improvement of symptoms seen on withdrawal of drug in younger patients (< 50 years).

**Heart disease and anti-TNF agents**

- Anti-TNF agents should be avoided in patients with severe (NYHA class III or IV) congestive heart failure. (Strength of recommendation D, level of evidence 4).
- Those with milder disease should be carefully assessed prior to treatment, and treatment withdrawn at the onset of new symptoms or worsening of pre-existing heart failure. (Strength of recommendation D, level of evidence 4).

**Malignancy**

Safety data so far do not indicate increased rates of malignancy, including lymphoproliferative disorders, over the normal rates in the population. Patients who have received PUVA therapy may represent a particular at-risk group.

**Neurological disease**

TNF blockers as a class may be associated with the development of, or worsening of demyelinating disease. Lenercept, a soluble p55 receptor developed for the treatment of multiple sclerosis, was withdrawn from further development due to increasing severity and duration of symptoms in clinical trial subjects. Worsening of multiple sclerosis with infliximab and at least four cases of demyelination with etanercept (all of which resolved on drug cessation) have also been reported.<sup>45</sup>

**Table 1** New York Heart Association classification of heart failure symptoms

Class	Symptoms <sup>a</sup>
I	No limitations. Ordinary physical activity does not cause fatigue, breathlessness or palpitations (asymptomatic left ventricular dysfunction is included in this category)
II	Slight limitation of physical activity. Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, breathlessness or angina pectoris (symptomatically 'mild' heart failure)
III	Marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms (symptomatically 'moderate' heart failure)
IV	Inability to carry on any physical activity without discomfort. Symptoms of congestive cardiac failure are present even at rest. With any physical activity increased discomfort is experienced (symptomatically 'severe' heart failure)

<sup>a</sup>Patients with heart failure may have a number of symptoms, the most common being breathlessness, fatigue, exercise intolerance and fluid retention.

**Demyelination and anti-TNF agents**

- Infliximab and etanercept should not be given to people with a history of demyelinating disease or optic neuritis and treatment should be withdrawn if neurological symptoms develop. (Strength of recommendation D, level of evidence 4).

**Antinuclear antibodies and lupus-like syndromes**

Antinuclear antibodies and, less commonly, anti-double-stranded DNA antibodies may develop during therapy, but do not seem to be associated with symptoms or signs of lupus in the vast majority. Syndromes resembling drug-induced lupus have been reported and usually resolve on treatment withdrawal.

**Hepatitis**

Rare cases of severe hepatic reactions following infliximab therapy have been reported to the FDA (35 spontaneous reports received up to December 2004), with the onset of symptoms or signs occurring from 2 weeks to more than a year after initiation of treatment. A safety alert issued in December 2004 by Centocor recommends that infliximab treatment be stopped in the event of jaundice and/or marked elevations (> 5 times upper limit of normal) in liver enzymes.

The safety of TNF blockers in patients with chronic hepatitis B and C is not known.<sup>46,47</sup> Two limited studies of anti-TNF therapy in hepatitis C infection (a retrospective study of infliximab in 24 patients with rheumatoid arthritis and a phase II study examining efficacy of etanercept as an adjuvant to interferon and ribavirin in the treatment of hepatitis C infection<sup>46</sup>) did not demonstrate any significant adverse effects on viral load or liver function tests. Data on use of TNF blockers in the context of hepatitis B infection are limited to case reports, where concomitant or prior antiviral treatment was reported to be of benefit. However, recent consensus guidelines on use of immunosuppressant therapy (not specifically anti-TNF agents) in the context of hepatitis B recommend antiviral therapy prior to initiation of therapy or during treatment if hepatitis develops.<sup>48</sup>

**Hepatitis and anti-TNF agents**

- The safety of TNF blockers in patients with chronic hepatitis B and C is not known. For patients known to be hepatitis B or C positive, advice from a hepatologist should be sought prior to initiation of therapy. (Strength of recommendation D, level of evidence 4).

**Efalizumab****Pharmacology**

Efalizumab is a humanized form of a murine antibody directed against CD11a, the  $\alpha$  subunit of leucocyte function-associated antigen-1 (LFA-1). In vitro studies indicate that by binding

to LFA-1, efalizumab inhibits multiple pathogenic steps in psoriasis: T-cell activation, cutaneous T-cell trafficking and T-cell adhesion to keratinocytes.

**Clinical effectiveness****Induction and maintenance of remission**

Four large phase III studies involving over 2000 patients with moderate to severe plaque psoriasis, most of whom had received previous systemic therapy for psoriasis, have been published in full.<sup>49–52</sup> Overall, efalizumab appears to be effective in chronic plaque psoriasis, with 27% of patients receiving efalizumab 1 mg kg<sup>-1</sup> weekly achieving a PASI 75 response vs. 4% in the placebo group by week 12, and 19–32% achieving a physician's global assessment of clear or almost clear. Continuing therapy beyond 12 weeks may increase the response rate further.<sup>51,52</sup> In one study, 20% of patients who failed to achieve a PASI 75 response following 12 weeks of treatment did so after a further 12 weeks of treatment as compared with 7% who received placebo.

Duration of remission following discontinuation of therapy is variable. In one study approximately 30% of patients maintained at least a 50% improvement in PASI score for the 12-week follow-up period. Discontinuation of treatment may be associated with an exacerbation of psoriasis including development of pustular or erythrodermic disease.

**Dosing regimens**

The licensed dose of efalizumab is 1 mg kg<sup>-1</sup> weekly as a subcutaneous self-administered injection for 12 weeks following a first conditioning dose of 0.7 mg kg<sup>-1</sup>, with the recommendation that treatment be continued only in those who respond (defined in the SPC as a physician's global evaluation of good or better). Doses of 2 mg and 4 mg have also been investigated but do not confer any additional benefit. There is little information on the optimal dosing regimen for maintenance of remission, although one long-term open-label study demonstrated maintenance of efficacy over a period of up to 27 months with once-weekly doses of 1 mg kg<sup>-1</sup>.<sup>53</sup>

**Efalizumab: Clinical effectiveness**

- Efalizumab is effective in the treatment of moderate to severe chronic plaque psoriasis, with approximately one third of patients treated becoming clear or almost clear after 12 weeks. (Strength of recommendation A, level of evidence 1++).
- Duration of remission is variable on discontinuing therapy and may be associated with disease rebound. (Strength of recommendation D, level of evidence 4).
- The licensed weekly dose (1 mg kg<sup>-1</sup>) should be used and treatment discontinued after 12 weeks in those who do not respond. (Strength of recommendation A, level of evidence 1++).
- Therapy may be continued according to clinical need although data on long-term efficacy are limited to 27 months. (Strength of recommendation D, level of evidence 4).

## Adverse effects and toxicity

Safety data for efalizumab are more limited in terms of numbers of patients treated and duration of therapy when compared with what is known about anti-TNF therapies. However, in contrast to the safety data for infliximab and etanercept, all the information accrued for efalizumab is in patients with psoriasis.

Overall, efalizumab is well tolerated; detailed information on reported and potential adverse events are available in the SPC.<sup>54</sup> As with any drug of this class, clinical concern exists over the potential risk of serious infection and malignancy. There is no evidence so far that the rates of serious infection are increased. Similarly, rates of malignancy are no greater in those treated compared with controls, but the data are too limited to assess this risk properly.

## Influenza-like symptoms

Headache, fever, chills and myalgia commonly occur during the first few weeks of treatment but tend to resolve by the third or fourth week of therapy.<sup>49–54</sup>

## Thrombocytopenia

This occurs uncommonly (between 1 in 500 and 1 in 1000 patients), so platelet counts should be monitored.

## Skin

A transient, acute, pruritic eruption occurs commonly between weeks 4 and 10 in previously uninvolved flexural sites, and on the arms, neck and trunk. The eruption may be sudden and resemble pustules joining into plaques. This eruption is self-limiting and should be treated with topical steroids and not mistaken for a psoriasis flare. Flares of psoriasis are found

mainly in nonresponders on discontinuation of treatment. Usually this requires some systemic therapy for 6–8 weeks: for speed of action ciclosporin has been recommended although other second-line modalities have been used. The flare usually settles and intervention for this can then be safely withdrawn.

## Choice of agent to use

There are no studies directly comparing the efficacy of infliximab, etanercept and efalizumab. Extrapolating data from short-term, placebo-controlled studies of each individual drug suggests a possible rank order of efficacy, with infliximab being the most effective and efalizumab the least effective at 12 weeks. Over longer time periods, there is no robust evidence to indicate which agent is superior in terms of overall efficacy or safety, nor is there evidence to indicate that failure to respond to one biological therapy precludes response to another.

## How to prescribe biological therapies

### Role of specialist nurse

Safe prescribing of biological therapies requires good infrastructure and specialist nursing personnel. With additional training a nurse may take responsibility for a number of the tasks outlined in the patient pathway including screening, treatment administration, patient education, prescription coordination for home drug delivery, patient support, monitoring and data collection, e.g. PASI. A list of core competencies including cannulation skills is suggested by the Royal College of Nursing for rheumatology nurses involved in biological therapies.<sup>55</sup>

### Patient information and consent

Patients should be fully informed of the risks and benefits of biological therapies through detailed, collaborative discussion with the supervising consultant and clinical nurse specialist. Written information should be provided (available on the BAD website) and patients given adequate time to consider their decision. In clinical circumstances where these therapies are being used outside their licensed indications, written consent should be obtained.

### Registration

In the interest of acquiring long-term safety data a comprehensive national register is proposed. Once this is operative (expected in early 2006), all patients should be registered and followed up through this register.

### Pretreatment assessment

All patients should undergo a full clinical history, physical examination and further investigations as required, with particular reference to the known toxicity profile of the agent being considered.

### Choice of agent to use

- Choice of agent efalizumab, etanercept or infliximab, will depend on the clinical pattern of psoriasis, pre-existing comorbidity, patient preference, prescriber preference and local facilities.
- Etanercept should be considered first choice for patients with significant, uncontrolled psoriatic arthritis (refer to BSR guidelines here,<sup>11</sup> but for this guideline skin disease identifies patient need). (Strength of recommendation D, level of evidence 4).
- For patients with stable psoriasis where a decision has been made to treat with an anti-TNF agent, etanercept should be used unless there are clear reasons not to do so. (Strength of recommendation D, level of evidence 4).
- Infliximab is useful in clinical circumstances requiring rapid disease control, e.g. in unstable erythrodermic or pustular psoriasis, due to its very rapid onset of action and high response rate. (Strength of recommendation D, level of evidence 4).
- For patients with a high risk of latent tuberculosis (and therefore requiring tuberculosis prophylaxis) or with evidence of demyelinating disease, efalizumab should be considered first choice. (Strength of recommendation D, level of evidence 4).



**Table 2** Exclusion criteria for antitumour necrosis factor (TNF) agents and efalizumab

Pregnant or breast feeding
Active infections. High risk include:
<ul style="list-style-type: none"> <li>• chronic leg ulcers</li> <li>• persistent or recurrent chest infections</li> <li>• indwelling urinary catheter</li> </ul>
Latent tuberculosis <sup>a</sup> (see Fig. 1)
Malignancy or premalignancy states excluding:
<ul style="list-style-type: none"> <li>• adequately treated non-melanoma skin cancer</li> <li>• malignancies diagnosed and treated more than 10 years previously (where the probability of total cure is very high)</li> </ul>
Demyelinating disease <sup>a</sup>
Congestive cardiac failure <sup>a</sup>
(New York Heart Association grade III or IV, see Table 1)
Relative contraindications:
<ul style="list-style-type: none"> <li>• Psoralen + ultraviolet A therapy &gt; 200 treatments, especially when followed by ciclosporin therapy</li> <li>• Human immunodeficiency virus-positive or AIDS</li> <li>• Hepatitis B or C virus-positive</li> </ul>

<sup>a</sup>These apply to anti-TNF agents only.

Specific exclusion criteria and recommended pretreatment investigations are listed in Tables 2 and 3. Assessment for risk of tuberculosis in patients considered for anti-TNF therapy is detailed in Figure 1.

**Table 3** Recommended pretreatment and monitoring investigations

		Pretreatment <sup>a</sup>	Monitoring <sup>a</sup>
Disease severity assessment			
Skin	PASI DLQI	Yes	At 3 months, then every 6 months
Joints (where applicable)	Follow recommended BSR guidelines for psoriatic arthritis	Yes	At 3 months, then every 6 months
General health (symptom enquiry and clinical examination)	Infection Demyelination <sup>b</sup> Heart failure <sup>b</sup> Malignancy (including skin)	Yes	At 3–6-monthly intervals
Assessment for latent tuberculosis <sup>b</sup>	See Fig. 1		
Blood tests	Full blood count	Yes	Efalizumab: monthly for the first 3 months, then every 3 months Tumour necrosis factor blockers: at 3 months, then every 6 months
	Creatinine, urea and electrolytes, liver function tests	Yes	At 3 months, then every 6 months
	Hepatitis B and C	Yes	–
	Human immunodeficiency virus	Consider testing in those at risk	–
	Autoantibodies <sup>b</sup> (antinuclear antibodies, antidouble-stranded DNA antibodies)	Yes	–
Urine	Urine analysis	Yes	At 3 months, then every 6 months
Radiology	Chest X-ray	Yes	–

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; BSR, British Society for Rheumatology. <sup>a</sup>Additional assessment and monitoring may be required in patients on concomitant therapy or in certain clinical circumstances. <sup>b</sup>Applies to tumour necrosis factor blockers only.

## Monitoring and assessment of disease response

Patients should be seen at 12 weeks to determine whether therapy should be continued, and thereafter at 3–6-monthly intervals. The need for monitoring biochemistry and haematology is less than that required for conventional drug therapies (Table 3) with the exception of platelet counts for patients on efalizumab. However, regular review of the clinical status of the patient is essential to ensure early detection of adverse effects, particularly infection.

## Adequate response to treatment

This is defined as a 50% or greater reduction in baseline PASI score (or percentage BSA where the PASI is not applicable) and a 5-point or greater improvement in DLQI within 3 months of initiation of treatment.<sup>7,9,10</sup>

Where arthritis has determined eligibility for treatment, please refer to the BSR guideline for psoriatic arthritis for the definition of treatment response.<sup>11</sup>

## Withdrawal of therapy

Therapy should be withdrawn after 3 months if there has not been at least a 50% improvement in baseline PASI score (or percentage BSA where the PASI is not applicable) and a 5-point or greater improvement in DLQI.

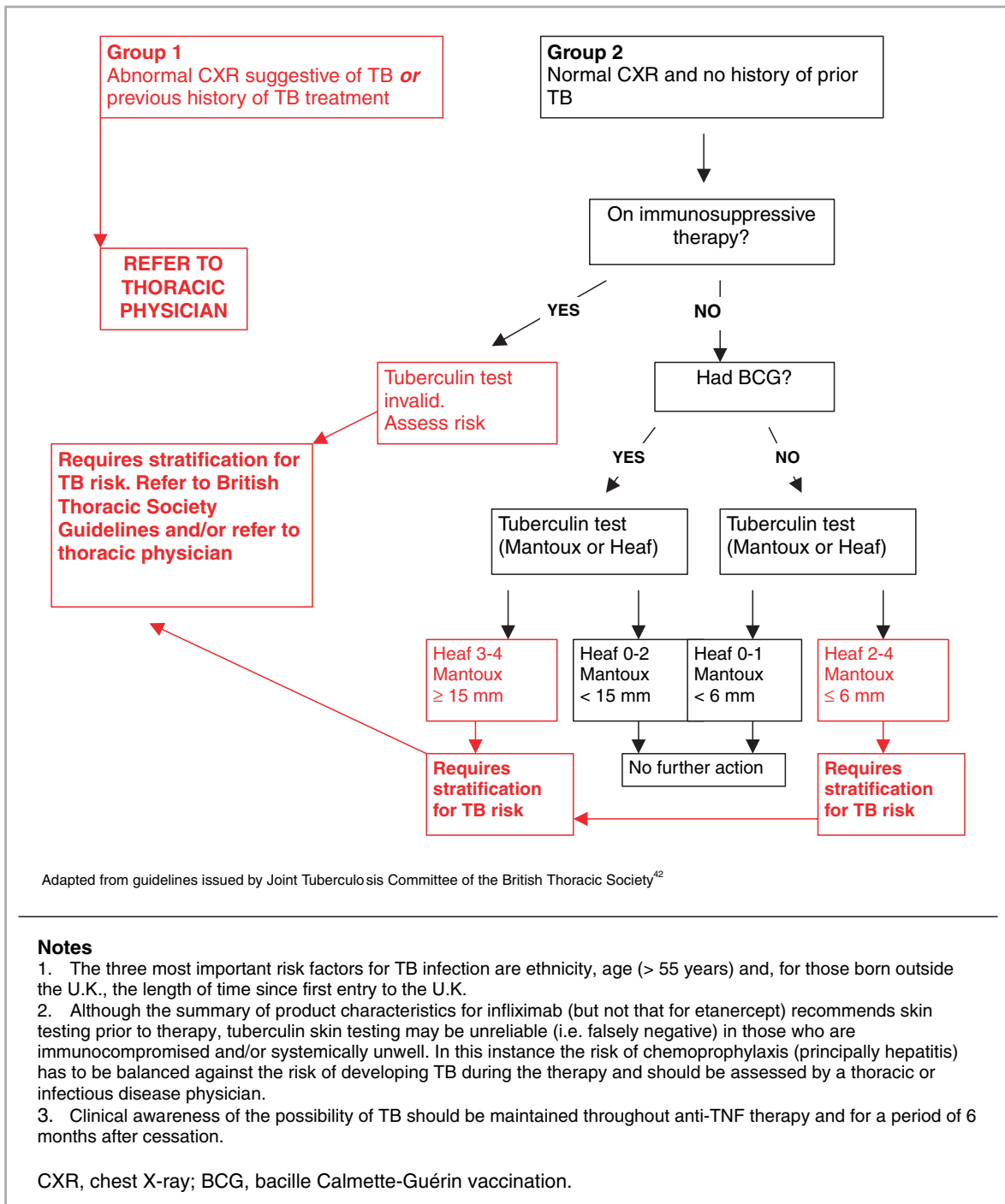


Fig 1. Algorithm for assessment and management of tuberculosis (TB) in patients scheduled for antitumour necrosis factor (TNF) therapy.

Withdrawal of therapy is also indicated due to the development of a serious adverse event. Adverse events which may justify the withdrawal of treatment include the following: malignancy (excluding nonmelanoma skin cancer); severe drug-related toxicity; pregnancy (temporary withdrawal); severe intercurrent infection (temporary withdrawal); major surgical procedures (temporary withdrawal in accordance with updated BSR guidelines<sup>11</sup>).

### Acknowledgments

The guideline was produced by the BAD independently of any funding body although the BAD does receive funding for its annual meeting from numerous commercial sponsors including the manufacturers of the biological therapies.

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## Appendix 1

Level of evidence and strength of recommendation. The published studies selected from the search were assessed for their methodological rigour against a number of criteria as currently recommended by the National Institute for Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network. The overall assessment of each study was graded using a code: '+ +', '+', or '-', based on the extent to which the potential biases have been minimized.

### Level of evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias <sup>a</sup>
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal <sup>a</sup>
3	Nonanalytical studies (e.g. case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. <sup>a</sup>Studies with a level of evidence '- ' should not be used as a basis for making a recommendation.

### Strength of recommendation

Class	Evidence
A	<ul style="list-style-type: none"> <li>At least one meta-analysis, systematic review, or RCT rated as 1++ , and directly applicable to the target population, <b>or</b></li> <li>A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ , directly applicable to the target population and demonstrating overall consistency of results</li> <li>Evidence drawn from a NICE technology appraisal</li> </ul>
B	<ul style="list-style-type: none"> <li>A body of evidence including studies rated as 2++ , directly applicable to the target population and demonstrating overall consistency of results, <b>or</b></li> <li>Extrapolated evidence from studies rated as 1++ or 1+</li> </ul>
C	<ul style="list-style-type: none"> <li>A body of evidence including studies rated as 2+ , directly applicable to the target population and demonstrating overall consistency of results, <b>or</b></li> <li>Extrapolated evidence from studies rated as 2++</li> </ul>
D	<ul style="list-style-type: none"> <li>Evidence level 3 or 4, <b>or</b></li> <li>Extrapolated evidence from studies rated as 2+ , <b>or</b></li> <li>Formal consensus</li> </ul>
D (GPP)	<ul style="list-style-type: none"> <li>A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group</li> </ul>

RCT, randomized controlled trial.