British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009

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Accepted for publication
25 August 2009

Key words
adalimumab, biologics, efalizumab, etanercept, guideline, infliximab, psoriasis, ustekinumab

Conflicts of interest
C.H.S., invited speaker and grant/research support Abbott, Janssen-Cilag, Schering-Plough, Serono, Wyeth; A.V.A., grant/research support Abbott, Janssen-Cilag, Schering Plough, Serono, Wyeth; J.N.W.N.B., advisory boards for Abbott, Janssen-Cilag, Novartis, Schering-Plough, Wyeth; grant/research support Abbott, Janssen-Cilag, Schering-Plough, Serono, Wyeth; A.D.B., advisory boards and grant/research support Janssen-Cilag, Schering-Plough, Serono, Wyeth; R.J.G.C., none; D.A.C., none; A.Y.F., consultant for Galderma, Novartis, Schering-Plough, Serono, Wyeth, Pfizer; joint copyright owner of the DLQI; C.E.M.G., advisory boards and invited speaker for Abbott, Janssen-Cilag, Merck-Serono, Novartis, Schering-Plough, UCB Pharma, Wyeth; grant/research support Amgen, Centocor, Merck-Serono, Wyeth; K.J., advisory boards for Abbott, Schering-Plough; educational support Merck-Serono; N.J.McH., advisory boards for Janssen-Cilag, Schering-Plough; grant/research support Abbott; K.E.McK., advisory boards for Abbott, Janssen-Cilag; N.J.R., advisory boards (nonpersonal) for Abbott, Basilea Pharmaceutica, Janssen-Cilag, Merck-Serono, Schering-Plough, Succinct Healthcare; grant/research support Stiefel Laboratories, AstraZeneca; A.D.O., advisory boards for Abbott, Merck-Serono, Schering-Plough; grant/research support Abbott, Janssen-Cilag, Serono, Wyeth.
This is an updated guideline prepared for the BAD Clinical Standards Unit, made up of the Therapy & Guidelines Subcommittee (T&G) and the Audit & Clinical Standards Subcommittee (A&CS). Members of the Clinical Standards Unit are: H.K. Bell (Chairman T&G), L.C. Fuller (Chairman A&CS), N.J. Levell, M.J. Tidman, P.D. Yesudian, J. Lear, J. Hughes, A.J. McDonagh, S. Punjabi, S. Wagle, S.E. Hulley and M.F. Mohd Mustapa (BAD Clinical Standards Administrator and Information Scientist).
Guidelines produced in 2005 by the British Association of Dermatologists; reviewed and updated June 2009.

DOI 10.1111/j.1365-2133.2009.09505.x

1.0 Background

Psoriasis is a common, chronic inflammatory skin disease which typically follows a relapsing and remitting course, and is associated with joint disease in approximately 25% of patients.[1] The significant reduction in quality of life and the psychosocial disability suffered by patients underline the need for prompt, effective treatment, and long-term disease control (reviewed[2,3]). Localized, limited disease can usually be managed satisfactorily with topical agents. Those with moderate to severe disease often require systemic treatment.

Phototherapy and traditional 'standard' systemic therapies, while often effective, can be associated with long-term toxicity; some are expensive, and some patients have treatment-resistant disease.[4] Also, phototherapy is not available to many due to geographical, logistical or other constraints. Patients themselves demonstrate high levels of dissatisfaction with standard approaches to treatment.[5,6]

Biologic therapies for psoriasis utilize molecules designed to block specific molecular steps important in the pathogenesis of psoriasis and now comprise a number of well-established, licensed, treatment options for patients with severe disease. Since 2005, when the British Association of Dermatologists (BAD) first published guidance on the use of biologic therapies in psoriasis,[7] much has changed. There is a substantial body of new evidence pertinent to the clinical use of these treatments, the U.K. National Institute for Health and Clinical Excellence (NICE) has approved the use of a number of biologic therapies in severe chronic plaque psoriasis and the BAD Biologic Interventions Register (BADBIR) has been successfully launched. Despite these developments, use of biologic therapy in clinical practice remains limited in the U.K., with a shortfall in funding cited as a significant obstacle to prescribing in approximately 40% of units recently surveyed.[8]

2.0 Purpose and scope

These guidelines have been revised and updated in accordance with a predetermined scope. This is based on the original scope used in 2005, and extended to include additional areas of practice. Recommendations in this guideline supersede those in the 2005 guideline.

The overall objective of these guidelines is to provide up-to-date, evidence-based recommendations on use of biologic therapies (infliximab, adalimumab, etanercept, ustekinumab) in adults and children with all types of psoriasis and, where relevant, psoriatic arthritis, for clinical staff involved in the care of patients treated with biologic therapies. Efalizumab remains in the scope of the guideline in relation to safety only, given that the European Medicines Agency has withdrawn the marketing authorization of this drug because of concerns over the development of progressive multifocal leukoencephalopathy (PML).

3.0 Exclusions

This guidance does not cover agents licensed outside the U.K. (alefacept) or use of biologic therapies for indications other than psoriasis and psoriatic arthritis.

4.0 Stakeholder involvement

The guideline working group represents all relevant stakeholders including dermatologists, nurses, rheumatologists and patients. Draft guidance was made available for consultation and review by patients, the BAD membership and the British Dermatological Nursing Group (BDNG). Advice relating to tuberculosis was reviewed and approved by the British Thoracic Society.

5.0 Methodology

The guideline has been developed using the BAD's recommended methodology[9] and with reference to the AGREE (Appraisal of Guidelines Research and Evaluation) instrument.[10] Recommendations were developed for implementation in the National Health Service using a process of considered judgment based on the evidence and an awareness of the European product licence of the various treatments.

Cochrane, EMBASE and Medline databases were searched between 1990 and June 2009 for clinical trials involving adalimumab, efalizumab, etanercept, infliximab and ustekinumab using an agreed protocol. Two reviewers screened all titles and abstracts independently, and full papers of relevant material were obtained. In relation to efficacy, only randomized controlled trials (RCTs) of high quality (1+ or more; see Appendix 1) were included for chronic plaque psoriasis, whereas in other clinical phenotypes, given the paucity of published data, all data were included. Data from each paper were extracted by two members of the guideline group using standardized literature evaluation forms in order to create evidence tables. Evidence on safety was extracted from literature on use of biologic agents for any indication in view of the relatively limited data specifically relating to use in psoriasis. The methodological limitations of the safety analysis are detailed in section 15. The guideline was peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines and Audit & Clinical Standards Subcommittees) prior to publication.

6.0 Limitations of the guideline

These guidelines have been prepared 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.

7.0 Plans for guideline revision

This field of psoriasis biologic therapeutics is in a rapid phase of development, and revision of the scope and content of the guidelines will therefore occur on an annual basis. Where necessary, the guideline will be updated via the BAD website, and a fully revised version is planned for 2012.

8.0 Which patients should be considered eligible for treatment?

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.[4] Long-term disease control frequently requires some form of continuous therapy and consequent, predictable risks of toxicity. At present, the risks and benefits of biologic therapies relative to standard systemic therapy are largely unknown. Widespread use of these agents in uncomplicated moderate to severe psoriasis is inappropriate and is not supported by the licensed indications for these drugs.

Eligibility criteria should encompass both objective measures of disease severity and the impact the disease has on quality of life. All existing disease severity assessment tools are imperfect[11–13] and most require some training to complete. The Psoriasis Area and Severity Index (PASI) is a measure of disease severity in chronic plaque psoriasis[12] and has been chosen for the purposes of this guideline as it has been widely used in clinical trials including those investigating biologic therapies, and has also been adopted by NICE. 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,[14] and reflects the minimal level of disease severity required for patient inclusion

in most of the clinical trials of biologic therapies to date. Where the PASI is not applicable (e.g. pustular psoriasis), body surface area (BSA) affected should be used, with severe disease defined as > 10% BSA affected.[14]

The Dermatology Life Quality Index (DLQI) is a validated tool for the measurement of quality of life across all skin diseases, including psoriasis, and has been used in both trial and clinical practice settings.[13,15] 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.[12,14,16]

8.1 Exceptional circumstances

When using the PASI and DLQI to determine whether or not a patient should be considered for biologic therapy, clinicians should take into account the applicability of these measures to each individual patient. There are circumstances where the use of these tools fails to give a sufficiently accurate assessment of the clinical situation. With respect to the PASI, this is especially pertinent in patients with localized disease that involves special 'high-impact' sites (genitalia, hands, feet, head and neck) where highly significant functional and/or psychosocial morbidity may exist with a PASI < 10. The DLQI may be a poor indicator of emotional disabilities resulting from psoriasis and the validity of the DLQI (and of other quality of life measures) may also be undermined due to linguistic or other communication difficulties.[13]

Recommendations: Eligibility criteria for biologic therapy

Patients with psoriasis may be considered eligible to receive treatment with any of the licensed biologic interventions when they fulfil the eligibility criteria set out below. However, the decision to proceed with treatment must be made in collaboration with the patient and include a careful assessment of the associated risks and benefits[17]

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** 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**. In exceptional circumstances (for example, disease affecting high-impact sites with associated significant functional or psychological morbidity such as acral psoriasis), patients with severe disease may fall outside this definition but should 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 D; level of evidence* 3, *and formal consensus*)

(i) where phototherapy[a] and alternative standard systemic therapy[b] are contraindicated or cannot be used due to the development of, or risk of developing, clinically important treatment-related toxicity.

(ii) are intolerant to standard systemic therapy

(iii) are unresponsive to standard systemic therapy[b]

(iv) have significant, coexistent, unrelated comorbidity which precludes use of systemic agents such as ciclosporin or methotrexate

(v) have severe, unstable, life-threatening disease

Eligibility criteria for patients with skin and joint disease

(i) patients with active psoriatic arthritis or skin disease that fulfils defined British Society for Rheumatology (BSR)[18] or BAD guideline criteria, respectively

(ii) patients with severe skin psoriasis and psoriatic arthritis who have failed or cannot use methotrexate may need to be considered for biologic treatment given the potential benefit of such treatment on both components of psoriatic disease

[a]Phototherapy may be inappropriate in patients (i) who have exceeded safe exposure limits (150–200 treatments for PUVA, 350 treatments for narrowband UVB[19,20]), (ii) who are non-responsive or relapse rapidly, (iii) who have a history of skin cancer or repeated episodes of severe sunburn, (iv) who are intolerant of UV exposure, especially if skin phototype I (sun-sensitive), or (v) for logistical reasons

[b]Standard systemic therapy includes ciclosporin (2·5 mg kg^{-1} daily; up to 5 mg kg^{-1} daily), and in men, and women not at risk of pregnancy, methotrexate [single dose (oral, subcutaneous, intramuscular) of 15 mg weekly; max 25 mg weekly] and acitretin (25–50 mg daily)

9.0 What is the definition of a disease response?

An adequate response to treatment is defined as **either** (i) a 50% or greater reduction in baseline PASI (PASI 50 response) (or % BSA where the PASI is not applicable) and a 5-point or greater improvement in DLQI[4,21–23] **or** (ii) a 75% reduction in PASI score compared with baseline (PASI 75 response). Initial response to therapy should be assessed at time points appropriate for the drug in question (Table 1).

For patients on tumour necrosis factor (TNF) antagonist treatment with psoriasis *and* psoriatic arthritis, treatment may be continued if there has been a sufficient response in at least one of these components (see BSR guidelines[18] for definition of disease response in psoriatic arthritis).

10.0 The interventions

10.1 Tumour necrosis factor antagonists

TNF is a proinflammatory cytokine produced by a wide variety of cell types including keratinocytes. It plays a central role in the pathogenesis of psoriasis, psoriatic arthritis and a number of other disease states. TNF is released from cells as a soluble cytokine (sTNF) following cleavage from its cell surface-bound precursor (transmembrane TNF, tmTNF). Both sTNF and tmTNF are biologically active, and bind to either of two distinct receptors: TNF receptor 1 (TNFR1, p55) and TNF receptor 2 (TNFR2, p75). This leads to NF-κB activation (which promotes inflammation) and/or cell apoptosis. In addition, tmTNF can

Table 1 Summary of interventions and criteria for treatment

Intervention	Dosing schedule according to licence[a]	NICE criteria	BAD criteria	Decision to continue treatment
Infliximab[b] (Remicade®; Schering-Plough, Welwyn Garden City, U.K.)	Adults: 5 mg kg^{-1} at weeks 0, 2, 6 and then every 8 weeks (intravenous)	Very severe plaque psoriasis, i.e. PASI ≥ 20, DLQI ≥ 18 *and* where CSA, MTX or PUVA has failed/cannot be used	Severe psoriasis, i.e. PASI ≥ 10, DLQI > 10 *and* qualifying criteria	14 weeks (licence); 10 weeks (NICE)
Etanercept[b] (Enbrel®; Wyeth, Maidenhead, U.K.)	Adults: 25 mg biweekly (50 mg once weekly up to 24 weeks); or 50 mg twice weekly up to 12 weeks reduced to once weekly thereafter (subcutaneous)	Severe plaque psoriasis, i.e. PASI ≥ 10, DLQI > 10 *and* where CSA, MTX or PUVA has failed/cannot be used	Severe psoriasis, i.e. PASI ≥ 10, DLQI > 10 *and* qualifying criteria	12 weeks (NICE, licence)
Etanercept (Enbrel®)	Children > 8 years: 0.8 mg kg^{-1} up to max 50 mg weekly (subcutaneous)	Not applicable; proposed for Single Technology Assessment (2009)	Severe psoriasis, i.e. PASI ≥ 10, DLQI > 10 *and* qualifying criteria	12 weeks (licence)
Adalimumab[b] (Humira®; Abbott, Maidenhead, U.K.)	Adults: 80 mg week 0, 40 mg week 1, then every other week (subcutaneous)	Severe plaque psoriasis, i.e. PASI ≥ 10, DLQI > 10 *and* where CSA, MTX or PUVA has failed/cannot be used	Severe psoriasis, i.e. PASI ≥ 10, DLQI > 10 *and* qualifying criteria	16 weeks (NICE, licence)
Ustekinumab (Stelara®; Janssen-Cilag, High Wycombe, U.K.)	Adults: 45 mg at week 0, 4 and then every 12 weeks; adults > 100 kg: 90 mg week 0, 4 and then 90 mg every 12 weeks (subcutaneous)	Severe plaque psoriasis, i.e. PASI ≥ 10, DLQI > 10 *and* where CSA, MTX or PUVA has failed/cannot be used.	Severe psoriasis, i.e. PASI ≥ 10, DLQI > 10 *and* qualifying criteria	28 weeks (licence); 16 weeks (NICE)

NICE, National Institute for Health and Clinical Excellence; BAD, British Association of Dermatologists; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; CSA, ciclosporin; MTX, methotrexate; PUVA, psoralen plus ultraviolet A. [a]Licensed indication for all therapies listed is 'treatment of patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA'. [b]Also licensed for use in **psoriatic arthritis**; approved by NICE provided the person has arthritis with three or more tender joints and three or more swollen joints, and at least two other disease-modifying antirheumatic drugs, given on their own or together, have not worked.

itself act as a ligand (via a process of *reverse signalling*) to induce cell activation, cytokine suppression or apoptosis of the tmTNF-bearing cell. Soluble forms of the TNF receptors also exist and, by binding and neutralizing sTNF, may act as natural TNF antagonists.

There are currently two approved groups of biologic agents that target TNF: anti-TNF monoclonal antibodies (adalimumab and infliximab), and sTNF receptors (etanercept). **Infliximab** is a chimeric human–murine monoclonal antibody (~ 25% mouse-derived protein) whereas **adalimumab** is fully human. **Etanercept** is a genetically engineered fusion protein composed of a dimer of the extracellular portions of human TNFR2 (p75) fused to the Fc domain of human IgG1. All three agents specifically bind both soluble and transmembrane forms of TNF and act by (i) blocking TNFR-mediated mechanisms and (ii) inducing tmTNF (reverse-signalling) events. Etanercept also binds members of the lymphotoxin family [LTα3 (also known as TNF-β) and LTα2β1] although the biological significance of this is unclear. Aside from the latter, there are important differences between the three agents with respect to pharmacokinetics, immunogenicity and structure-based mechanisms of action (only some of which are completely understood).[24] It is likely that these differences, in the context of the highly complex biology of TNF, account for observed differences in the efficacy and adverse events profile of TNF antagonists.

10.2 Efalizumab (now withdrawn – see section 15.3)

Lymphocyte function-associated antigen-1 (LFA-1) is a cell surface protein that binds to intracellular adhesion molecule (ICAM) 1–3 and plays a key role in T-lymphocyte recirculation, trafficking to sites of inflammation, antigen presentation by dendritic cells and other activated cells including keratinocytes, and T-cell costimulation. **Efalizumab** is a recombinant humanized IgG1 monoclonal antibody that binds specifically to the CD11a subunit of LFA-1, which by interfering with LFA-1/ICAM binding inhibits several key steps important in the pathogenesis of psoriasis including T-cell migration into the skin and T-cell activation. More recently, *in vivo* data have shown that efalizumab induces a state of reversible T-cell 'hyporesponsiveness' including downregulation of a number of T-cell surface molecules unrelated to LFA-1 both in the circulation and in psoriatic plaques.[25,26]

10.3 Ustekinumab

Interleukin (IL)-12 and IL-23 are heterodimeric cytokines secreted by activated antigen-presenting cells, and share a common protein subunit, p40. Of relevance to psoriasis, IL-12 activates CD4 and natural killer cells to induce expression of type 1 cytokines (TNF and interferon-γ) while IL-23 stimulates survival and proliferation of a subset of T cells that produce IL-17 (Th17 cells). Recent immunological[27] and genetic studies indicate a central role for IL-23 in the pathogenesis of psoriasis.[28] **Ustekinumab** is a fully human IgG1κ monoclonal antibody which acts as an IL inhibitor by binding with high affinity and specificity to the p40 protein subunit. It thus prevents IL-12 and IL-23 from binding to their IL-12Rβ1 receptor protein expressed on the surface of immune cells.

11.0 How effective is each intervention in chronic plaque psoriasis?

11.1 Etanercept

11.11 Etanercept in chronic plaque psoriasis

Three large RCTs demonstrate that etanercept is effective in chronic plaque psoriasis.[29–31] Onset of action is slower than that seen with the monoclonal antibodies, with clinically significant improvement in disease severity scores evident between 4 and 8 weeks after initiation of treatment.[30] Response is dose related, with 34% (25 mg biweekly) and 48% (50 mg biweekly) of patients achieving PASI 75 by 12 weeks (Table 2). Continuing therapy up to 6 months improves response rates further (43% and 57% for 25 mg biweekly and 50 mg biweekly, respectively).[29,30,32] While there are no RCT data establishing efficacy beyond 6 months, data from a 2-year, open-label etanercept 50 mg biweekly extension study[32] (following the phase III study reported by Tyring *et al.*[31]) suggest that efficacy is maintained for up to 1 year, with approximately 75% of patients maintaining their PASI 75 response over the ensuing year.

Overall, continuous therapy provides better disease control and higher levels of patient satisfaction compared with interrupted therapy. When treatment is stopped, disease relapses slowly: median time to disease relapse as defined by loss of PASI 50 in those who achieved PASI 75 after 24 weeks of continuous etanercept 25 or 50 mg biweekly, was 85 and 91 days, respectively, with no evidence of disease rebound. On re-treatment, mean PASI scores were similar, with the majority of patients achieving equivalent efficacy after 12 further weeks (i.e. 56% and 60% of PASI 75 responders achieved this level of efficacy on re-treatment).[33,34] Aside from objective measures of disease improvement (PASI, physician's global assessments), studies also report associated clinically meaningful improvements in quality of life measures,[35–37] reduction in fatigue and depression,[31] and increased proportions of patients in paid employment.[38,39] *Post hoc* analysis of two of these RCTs demonstrated that response rates in those over 65 years were the same as those under 65 years, although numbers in the older age group were small ($n = 77$).[40]

The 25 mg twice weekly and 50 mg once weekly dosing regimens are probably interchangeable given that their pharmacokinetic profiles are comparable,[41] that the number of patients achieving PASI 75 at 12 weeks following etanercept 50 mg weekly (in an RCT setting compared with placebo)[42] was comparable with that seen in other RCTs investigating etanercept 25 mg biweekly and that no significant differences

Table 2 Summary of the pooled results for efficacy from all clinical trials evaluated in the systematic review

	10–16 weeks				26 weeks		48–60 weeks		
	PASI 75	95% CI	PASI 90	95% CI	PASI 75	95% CI	PASI 75	95% CI	Comments
Etanercept 25 mg biweekly	0·34[29,30]	0·28–0·38	0·11[29,30]	0·08–0·15	0·43[29,30]	0·37–0·48	–	–	LOCF
Etanercept 50 mg biweekly	0·48[29–31]	0·44–0·52	0·21[29,30]	0·17–0·26	0·57[29,30,32]	0·52–0·6	0·6[32]	0·52–0·67	LOCF; patients continued on unlicensed dose after 12 weeks
Infliximab 5 mg kg^{-1} at 0, 2, 6 and every 8 weeks	0·79[52–56]	0·76–0·82	0·55[53,56]	0·50–0·60	0·74[53]	0·69–0·79	0·53[a53,54]	0·48–0·57	LOCF
Adalimumab 40 mg every other week	0·69[62–65]	0·66–0·79	0·43[62–65]	0·40–0·46	0·69[62,63,65,68]	0·66–0·72	0·62[62,68]	0·54–0·71	Nonresponder imputation
Ustekinumab 45 mg at 0, 4 and every 12 weeks	0·67[71,72]	0·63–0·70	0·42[71,72]	0·38–0·46	0·68[71,72]	0·65–0·72	–	–	Nonresponder imputation
Ustekinumab 90 mg at 0, 4 and every 12 weeks	0·72[71,72]	0·68–0·75	0·45[71,72]	0·42–0·49	0·75[71,72]	0·72–0·77	–	–	Nonresponder imputation

PASI, Psoriasis Area and Severity Index; PASI 75, 75% reduction in PASI score compared with baseline; PASI 90, 90% reduction in PASI score compared with baseline. [a]Continuous subgroup. For each of the outcomes the crude probability (not adjusted for the placebo response) of the biologic treatment achieving the specified endpoints is given followed by the 95% confidence interval (CI). Longer-term data are not directly comparable between studies due to differences in accounting for study drop outs. Last observation carried forward (LOCF) may overestimate efficacy whereas nonresponder imputation gives a more conservative estimate of efficacy.

were observed in mean PASI or DLQI in a cohort of patients receiving open-label etanercept 25 mg biweekly (at week 24) and etanercept 50 mg once weekly (at week 36).[43]

In the RCTs cited, the frequency of adverse events or serious adverse events in patients receiving etanercept was no greater than in the control patients, with the exception of injection site reactions.

One small (n = 20 in each treatment arm) RCT has shown superior efficacy of etanercept 25 mg *once* weekly compared with acitretin 0·4 mg kg^{-1} daily at 24 weeks (see below).[44]

Given the role of TNF in adipocyte homeostasis, elevated levels of TNF in obese patients, and the fixed (nonweight adjusted) dosing regimen used for etanercept, decreased response rates may occur in heavier patients, particularly with low-dose etanercept. This is supported, in part, by pharmacological modelling (using published RCT data)[45] and data cited in the study by de Groot *et al.*[46]

11.12 Etanercept in chronic plaque psoriasis in combination with systemic therapies

Methotrexate

The combination of etanercept and methotrexate has been shown to be more effective in rheumatoid arthritis (RA) than either agent alone, with no significant additional toxicity. Limited data suggest that the addition of methotrexate may also confer improved etanercept efficacy in psoriasis. A small RCT (n = 59) investigated the efficacy and safety of introducing etanercept (25 mg biweekly) in patients already established on methotrexate, and reported significantly increased numbers of patients 'clear or nearly clear' at 24 weeks on combination therapy, as compared with those in whom methotrexate was discontinued.[47] A retrospective case series (n = 14) reported both improved efficacy with the introduction of methotrexate in patients on etanercept and loss of efficacy on withdrawal of methotrexate from patients on combination therapy.[48]

Acitretin

Data from a small RCT (n = 60) reported that the combination of etanercept 25 mg *once* weekly with acitretin 0·4 mg kg^{-1} daily is as effective as etanercept 25 mg *twice* weekly, and that both these interventions are more effective that acitretin alone.[44] These early data would suggest that in the short term at least, the combination may offer additional efficacy but, perhaps as importantly, there is no additional associated toxicity.

11.13 Quality of evidence

The patient cohort in the cited RCTs may not be representative of patients likely to be treated in clinical practice as entry to the studies required patients only to be considered suitable for, or have previously had, PUVA or systemic therapy. How-

ever, objective disease severity criteria were the same as those currently recommended by the BAD and NICE, and mean PASI scores on entry to studies were significantly higher (ranging from 16 to 18). Prospective case cohort studies of 'real life' practice report comparable response rates in 'high-need' patients who have previously failed multiple systemic therapies, all of which suggests that data from the RCTs can be extrapolated to clinical practice.[46,49,50] There is a lack of long-term RCT data beyond 6 months, and only limited data on re-treatment (of the two published studies available,[34,51] one is open label,[34] and both report outcome following one repeat cycle of treatment only).

Existing RCT data indicate that 50 mg biweekly is more effective than 25 mg biweekly, but there are no trial data indicating whether increasing the dose to 50 mg biweekly in patients who fail to achieve or maintain adequate responses on 25 mg biweekly results in improved disease control. This is especially pertinent given NICE guidance which currently limits treatment to the 25 mg biweekly dose (see below).

11.14 Licensed indications and existing NICE guidance (Table 1)

Etanercept is licensed for use in moderate to severe psoriasis at either 50 or 25 mg biweekly for the first 3 months, and 25 mg biweekly thereafter, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (SPC). NICE has approved use of etanercept in severe plaque psoriasis (subject to defined disease severity) at the 25 mg biweekly dose only, and did not find the 50 mg twice weekly dose cost effective, with therapy to be continued only in those patients achieving disease response at 3 months (Table 1).

Recommendations: Etanercept

- Etanercept is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8.0 (*Strength of recommendation A; level of evidence 1++*)
- Etanercept therapy may be initiated at either 50 or 25 mg twice weekly and disease response assessed at 3–4 months (*Strength of recommendation A; level of evidence 1++*)
- The choice of which dose to use will depend on clinical need, disease severity, body weight and, in the U.K., the dose that will be funded (*Strength of recommendation B; level of evidence 1++*)
- Patients established on etanercept 25 mg twice weekly may wish to consider switching to etanercept 50 mg once weekly as these two dosing regimens are equivalent in terms of efficacy (*Strength of recommendation A; level of evidence 1+*)
- In patients who respond, treatment may be continued according to clinical need, although long-term data on efficacy are limited to 2 years (*Strength of recommendation C; level of evidence 2+*)
- Treatment may be discontinued without risk of disease rebound, although there may be a lower response rate on restarting therapy (*Strength of recommendation B; level of evidence 1+*)
- Methotrexate may be recommended comedication in certain clinical circumstances, e.g. where it is required for associated arthropathy, or to improve efficacy (*Strength of recommendation B; level of evidence 1+*)

11.2 Infliximab

11.21 Infliximab in chronic plaque psoriasis

Three large RCTs[52–54] indicate that infliximab therapy is highly effective in chronic plaque psoriasis (Table 2[52–56]). Onset of action is rapid, with evidence of significant improvement within the first 2 weeks of treatment and maximum benefit by week 10 when 79% of patients achieve PASI 75 (Table 2) (and mean drop in DLQI of 10[54,57]). This response is largely maintained over time with 74%[53] and 53% achieving PASI 75 at 6 and 12 months, respectively (Table 2). Loss of efficacy correlates with development of antibodies to infliximab, which occurs in 19% of patients treated.[53] One RCT[54] (n = 835) investigated continuous vs. intermittent therapy (3 and 5 mg kg^{-1}) following a standard induction course (at 0, 2 and 6 weeks); continuous therapy at 5 mg kg^{-1} every 8 weeks achieved optimal control. Time to relapse in the intermittent arm (defined by loss of PASI 75) was stated as being 'between week 14 and 22 in the majority of patients' although data were not shown.[54] An early (small) dose-finding study[58] indicated that 50% (15/30) patients relapse (loss of PASI 75) by week 26. There are no published prospective trial data beyond 1 year.

Nail disease

One study prospectively assessed nail disease during therapy[53] using the Nail Psoriasis Severity Index (NAPSI) to assess a target, worst affected, nail: a 26·8% improvement in NAPSI from baseline was observed at week 10 with a maximum of 57·2% improvement reported at week 24. This was maintained until week 50. Numbers of patients with complete clearance of nail disease (from the target nail) continued to improve between weeks 24 and 50 (26·2% and 44·7%, respectively).

11.22 Infliximab in chronic plaque psoriasis in combination with systemic therapies

There are no RCT data on use of methotrexate in combination with infliximab in psoriasis. In both RA and psoriatic arthritis, cotherapy with methotrexate is a licensed recommendation, and response rates (with and without methotrexate) are at least comparable in these disease indications. Higher serum levels of infliximab have been reported with methotrexate coadministration which may in part explain reports of improved efficacy. Methotrexate (low dose, 7·5 mg weekly) also reduces the incidence of antibodies to infliximab.[59–61]

11.23 Quality of evidence

The patient cohort in the cited RCTs may not be representative of patients likely to be treated in clinical practice. The mean PASI at baseline was ≥ 10 in all the studies cited. However, failure of previous systemic therapy was not an entry criterion, in that most studies required patients to be candidates for systemic therapy and/or failed topicals only. A subanalysis of patients in the study by Menter *et al.*[54] (continuous vs. intermittent) did, however, indicate that baseline PASI (< 20 vs. > 20) and the nature of previous treatments (including two or more systemic therapies, or biologic therapy) had no effect on treatment response.

The design of the study investigating continuous vs. intermittent infliximab therapy is problematic in that study visits occurred at monthly intervals: hence patients randomized to receive intermittent therapy could potentially receive infliximab at 4-weekly intervals (if PASI 75 was not maintained), and cumulative doses in both arms were reported as similar.

11.24 Licensed indications and existing NICE guidance (Table 1)

Infliximab is licensed for use (5 mg kg^{-1} every 8 weeks) in moderate to severe plaque psoriasis. NICE has approved use of infliximab in patients with 'very severe disease' (*sic*) (PASI ≥ 20, DLQI ≥ 18) with treatment beyond 10 weeks recommended only in those who achieve certain response criteria.

Recommendations: Infliximab

- Infliximab is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8·0 (*Strength of recommendation A; level of evidence 1++*)
- Infliximab therapy should be initiated at a dose of 5 mg kg^{-1} at weeks 0, 2 and 6 and disease response assessed at 3 months (*Strength of recommendation A; level of evidence 1++*)
- In patients who respond, subsequent infusions (5 mg kg^{-1}) should be given at 8-week intervals to maintain disease control although long-term data are available only up to 1 year (*Strength of recommendation A; level of evidence 1++*)
- Interrupted therapy should be avoided given the associated increased risk of infusion reactions and poorer disease control (*Strength of recommendation A; level of evidence 1+*)
- Methotrexate may be recommended comedication in certain clinical circumstances, e.g. where it is required for associated arthropathy, to improve efficacy or to reduce the development of antibodies to infliximab (*Strength of recommendation D; level of evidence 3*)

11.3 Adalimumab

11.31 Adalimumab in chronic plaque psoriasis

Three large RCTs demonstrate that adalimumab is a highly effective treatment for chronic plaque psoriasis (Table 2).[62–64] Onset of action is rapid, with significant improvements in disease severity evident within 2 weeks of treatment initiation[62] and maximal disease response seen between weeks 12 and 16. Response is dose related with 69% of patients achieving PASI 75 at week 12 with adalimumab 40 mg every other week[62–65] (i.e. the licensed dose for psoriasis), and 80% achieving PASI 75 with adalimumab 40 mg weekly.[62] Clinically relevant improvements in health-related quality of life indicators are also reported.[66] In one study,[62] a small subset of patients (n = 34) who had failed to achieve PASI 50 following at least 24 weeks of adalimumab every other week was escalated to the weekly dose for the remaining duration of the 60-week study (open-label); 40% of this cohort recorded PASI 50 responses, suggesting that dose escalation may further improve efficacy. Efficacy data are available up to 1 year, with no evidence of significant loss of response over time in those patients who respond and are continued on treatment.[63]

Loss of response on stopping treatment was also investigated in the third phase of the study reported by Menter *et al.*;[63] those who had maintained PASI 75 by week 33 were re-randomized to receive either placebo or a further 19 weeks of adalimumab (double blind). While mean time to relapse was not reported, 28% of patients receiving placebo relapsed (< PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to week 33) compared with 5% relapse in those continuing on adalimumab by week 52. As part of this study, patients who lost adequate response after re-randomization to placebo could enrol into the open-label extension phase of the trial (adalimumab 40 mg every other week). Re-treatment response rates in this group are stated (only) in the summary of product characteristics (SPC), where 38% (25/66) and 55% (36/66) regained PASI 75 response after 12 and 24 weeks, respectively. These response rates are lower than those reported following first treatment, suggesting that interrupted therapy may result in loss of treatment response.

Anti-adalimumab antibodies develop in 8·4% of patients and are associated with increased clearance and reduced efficacy of adalimumab (but not specific adverse events).

11.32 Adalimumab compared with standard systemic therapy in chronic plaque psoriasis

One RCT comparing efficacy of adalimumab (40 mg every other week) vs. methotrexate (7·5 mg initial dose weekly, increasing to a maximum of 25 mg weekly as tolerated) showed adalimumab to be significantly more effective than methotrexate by week 1, with 80% of patients achieving PASI 75 by week 16. This compared with surprisingly low methotrexate (36%) and high placebo (19%) response rates.[64] The latter are considerably higher than seen in other comparable placebo-treated cohorts where PASI 75 response rates are typically 5% or less. Improvements in DLQI and a number of other quality of life measures also indicated that adalimumab was the most effective intervention.[67] Overall, the incidence of adverse

events was similar in all three groups, with the exception of hepatic abnormalities which were significantly higher in patients on methotrexate.

11.33 Adalimumab in chronic plaque psoriasis in combination with systemic therapies

The addition of methotrexate to adalimumab in RA results in reduced immunogenicity (i.e. a lower rate of anti-adalimumab antibody formation) and increased effectiveness (in part due to reduced clearance of adalimumab) with no increase in adverse events. No prospective studies have investigated the potential benefit of adalimumab in combination with methotrexate in psoriasis. In the ADEPT study, a *post hoc* analysis comparing those patients who were on a stable dose of methotrexate at initiation of adalimumab, and those who were not, suggests that for both skin and joint disease the combination of adalimumab and methotrexate is more effective than adalimumab alone, although the differences were only significant between the groups for the percentage achieving PASI 50.[65,68]

11.34 Quality of evidence

The patient cohort in cited RCTs may not be representative of patients likely to be treated in clinical practice. With the exception of the first (small) RCT[62] where entry disease severity comprised BSA > 5%, and studies on psoriatic arthritis where skin disease severity criteria were not set (mean PASI on entry 7)[65,68] all studies cited required PASI of at least 10 and/or BSA 10%, and mean disease severity scores on entry to psoriasis studies[63,64] tended to be significantly higher than this.

Previous use of systemic therapies was not an entry criterion for the RCTs cited, and of course, for the comparative study examining methotrexate vs. adalimumab, patients had to be treatment naive both to TNF antagonists and to methotrexate. One small (n = 30) open-label study evaluated the efficacy of adalimumab 40 mg *once* weekly in a cohort of patients with severe psoriasis who had failed both standard systemic therapy and other biologic therapies (including efalizumab, etanercept and infliximab).[69] By week 12, 87% of patients had achieved PASI 75, which represents a response rate comparable with that reported in the RCT by Gordon *et al.*[62] As adalimumab has only recently been licensed for use in psoriasis, few data exist on use outside clinical trials. The design of the study reported by Saurat *et al.*[64] has been criticized as favouring adalimumab, given that the maximum efficacy of methotrexate may not have been apparent by 16 weeks.

11.35 Licensed indications and existing NICE guidance (Table 1)

Adalimumab is licensed for use in moderate to severe psoriasis at 40 mg every other week (following 80 mg loading dose at week 0), with continued therapy beyond 16 weeks to be 'carefully reconsidered' in patients not responding within this time period; NICE has approved use of adalimumab (40 mg every other week) in severe plaque psoriasis (subject to defined disease severity) with continued therapy subject to adequate response at 16 weeks (Table 1).

Recommendations: Adalimumab

- Adalimumab is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8.0 (*Strength of recommendation A; level of evidence 1++*)
- Adalimumab therapy should be initiated according to the licensed dosing regimen (i.e. 80 mg subcutaneously at week 0, 40 mg at week 1, and then every other week thereafter) and disease response assessed at 3–4 months (*Strength of recommendation A; level of evidence 1++*)
- Consideration may be given to increasing the dose of adalimumab to 40 mg weekly in certain clinical circumstances (e.g. in those with PASI > 10 despite achieving a response[a] to adalimumab 40 mg every other week), although this is unlicensed and not approved by NICE (and in the U.K. may not be funded) (*Strength of recommendation A; level of evidence 1+*)
- In patients who respond, treatment may be continued according to clinical need although long-term efficacy data are available only up to 1 year (*Strength of recommendation A; level of evidence 1++*)
- If necessary, treatment may be discontinued without risk of disease rebound, although there may be a lower response rate on restarting therapy (*Strength of recommendation A; level of evidence 1+*)
- Methotrexate may be recommended comedication in certain clinical circumstances, e.g. where it is required for associated arthropathy, or to increase efficacy (*Strength of recommendation B; level of evidence 3*)

[a]as defined in section 9.0 (PASI 50, DLQI –5)

11.4 Ustekinumab

11.41 Ustekinumab in chronic plaque psoriasis

Three large RCTs[70–72] demonstrate that both doses of ustekinumab (i.e. 45 mg and 90 mg) are highly effective in psoriasis (Table 2); onset of action is evident within 2 weeks, with 67% and 72% of patients achieving PASI 75 by week 12 for the 45 mg and 90 mg doses, respectively, and maximal efficacy evident between week 20 and week 24. Disease responses are maintained with continued therapy for up to 1·5 years. On cessation of therapy, median time to relapse (i.e. loss of PASI 75) is 15 weeks, with no reports of rebound psoriasis. Similar response rates are achieved on re-treatment. While there is clearly a relationship between dose (serum drug levels) and response, this is not linear, as the 90 mg dose appears to be only slightly more effective than the 45 mg dose. Further, in partial responders, increasing the frequency of dosing to every 8 weeks (as compared with every 12 weeks), while increasing serum drug levels, significantly improves response rates only in those on the 90 mg regimen

[approximately 2/3 of partial responders (defined as > PASI 50, < PASI 75 at week 28) converted to responders (PASI 75) by week 52 with intensification of the 90 mg dose to 8-weekly]. Factors aside from the lower dose that are predictive of poorer response include higher body weight, previous poor response to at least one biologic therapy, longer duration of psoriasis and a history of psoriatic arthritis. While the inclusion criteria for these trials are comparable to those investigating other biologic therapies (PASI 12 and BSA 10% or greater), overall, the disease severity appears to be greater (mean PASI scores on entry around 20), with the majority of patients having received previous phototherapy and systemic therapy, and just over a third having received prior biologic therapy.

A phase II study has evaluated the use of ustekinumab in the treatment of psoriatic arthritis (n = 146, active: control allocation 1:1, dose regimen 90 mg weekly for 4 weeks). At week 12, 42% of patients achieved a clinical response [defined as a 20% improvement from baseline in the American College of Rheumatology (ACR20) core set measures].[73]

11.42 Ustekinumab compared with etanercept in chronic plaque psoriasis

A large (n = 903), phase III RCT indicates that ustekinumab is more effective than etanercept in the short term. The percentage of patients achieving PASI 75 by week 12 with ustekinumab 90 mg and 45 mg at week 0 and 4 was 74% and 68%, respectively, compared with 57% for patients randomized to etanercept 50 mg biweekly for 12 weeks.[74]

11.43 Licensed indications and existing NICE guidance (Table 1)

Ustekinumab is licensed for use in patients with moderate to severe psoriasis at 45 mg (or 90 mg if >100 kg) at week 0, 4 and then 12 weekly thereafter with consideration given to discontinuing therapy in those who have not responded by week 28. NICE has approved the use of ustekinumab in patients with severe plaque psoriasis (subject to defined disease severity criteria) with treatment to be continued beyond 16 weeks only in those who respond (Table 1).

Recommendations: Ustekinumab

- In light of limited patient exposure, ustekinumab should be reserved for use in patients with severe psoriasis who fulfil the stated disease severity criteria AND where TNF antagonist therapy has failed or is contraindicated – refer to section 8.0 (*Strength of recommendation A; level of evidence 1+*)
- For logistical and safety reasons, drug injections should be supervised by a health care professional (*Strength of recommendation D (GPP); level of evidence 4*)

12.0 How effective are biologic therapies in pustular psoriasis and palmoplantar pustulosis?

12.1 Localized disease

There are two disabling and difficult-to-treat conditions affecting the hands and feet in which localized pustules are associated with psoriasis elsewhere on the body.

The more common of these, chronic palmoplantar pustulosis, has in the past been termed chronic palmoplantar pustular psoriasis. There is, however, evidence to suggest that, although it is associated with psoriasis in up to about 20% of cases, it is a distinct disease with a different clinical and genetic profile.[75] This evidence is strengthened by the almost complete lack of reports of benefit from TNF antagonists but, conversely, an increasing number of reports of new-onset palmoplantar pustulosis in patients with conditions other than psoriasis treated with these agents.[76,77] A recent small pilot study found no benefit over placebo of etanercept 50 mg given twice weekly for 12 weeks.[78] TNF antagonists should therefore be avoided in these patients.

The second condition is acropustulosis (acrodermatitis continua) of Hallopeau. Although uncommon, acropustulosis can result in considerable morbidity from an intense pustular inflammation centred around the terminal phalanges and often sufficiently severe to destroy the nail plate. It is commonly associated with a destructive arthritis of adjacent joints. It is recognized that patients with acropustulosis are at risk of developing generalized pustular psoriasis.

There are no controlled trials of interventions for acropustulosis. It is frequently unresponsive to conventional systemic antipsoriatic agents. There are now at least 10 case reports of significant benefit from TNF antagonists (etanercept, infliximab and adalimumab) for this rare but disabling condition. This contrasts with only two reports of failure to respond and, in one of those cases, the patient subsequently responded to a different TNF antagonist. If acropustulosis has a major impact on quality of life, it is therefore reasonable to recommend a trial of one of these agents.

12.2 Generalized pustular psoriasis

Publications concerning biologic treatments for generalized pustular psoriasis are limited to case reports and small series, reflecting the fact that these drugs are relatively new in the treatment of psoriasis, and that generalized pustular psoriasis is a very rare disorder. Infliximab has been used in the treatment of severe generalized pustular psoriasis with generally positive results. A 39-year-old man with severe generalized pustular psoriasis responded rapidly to infliximab with complete disease clearance which allowed withdrawal of all conventional systemic psoriasis treatments.[79] A follow-up study of three patients with generalized pustular psoriasis included two who cleared completely with infliximab treatment, while

one was left with residual keratoderma.[80] On stopping infliximab following a variable number of infusions, two of these three relapsed, while disease remission was maintained in one. Additional case reports and a small case series (n = 3) confirm efficacy for infliximab in the treatment of generalized pustular psoriasis.[81–84] Etanercept has also been shown to be of benefit in generalized pustular psoriasis. One case series (n = 6) reports clinical efficacy of etanercept in generalized pustular psoriasis at 50 mg biweekly, but not at 25 mg biweekly, with maintenance of response for up to 48 weeks.[85] One report confirms efficacy for etanercept in a single patient with generalized pustular psoriasis following withdrawal of ciclosporin,[86] and a second, use of etanercept in generalized pustular psoriasis following induction of remission with infliximab.[87]

Reports of biologic therapies for generalized pustular psoriasis in childhood are limited to two cases: a 3-year-old child cleared rapidly with infliximab and was switched successfully to etanercept after 12 months of infliximab infusions.[88] A 15-year-old girl with severe generalized pustular psoriasis treated with ciclosporin, methotrexate and adalimumab cleared completely by 2 months.[89]

Thus, for patients with generalized pustular psoriasis, experience of treatment with biologic agents is currently limited to infliximab, etanercept and adalimumab. These initial case reports and small case series are generally positive and justify formal clinical trials to assess safety and efficacy in more detail in this difficult patient group.

13.0 How effective are biologic therapies in erythrodermic psoriasis?

TNF antagonists are reported to be of benefit in this form of psoriasis, which given that many cases evolve from chronic plaque disease is perhaps not surprising. A case series of 10 patients with erythrodermic psoriasis responded well to etanercept 25 mg twice weekly. The mean PASI decreased from 39·1 to 5·1 at 24 weeks, when 60% had achieved PASI 75.[90]

Three of five erythrodermic patients achieved PASI 75 with repeated infusions of infliximab 5 mg kg^{-1}.[80] There are also several case reports of successful treatment of erythrodermic psoriasis, including life-threatening disease, with infliximab therapy,[91–95] one clearing with a single infusion.[96] Infliximab was also successful in three patients who experienced erythrodermic flares when transitioning from efalizumab to etanercept.[97] No evidence was found concerning the efficacy of adalimumab in erythrodermic patients.

Recommendations: Use of biologic therapy for special types including pustular and erythrodermic psoriasis

- Biologic therapies cannot at present be recommended for palmoplantar pustulosis
- TNF antagonists may be considered for patients with severe, disabling acropustulosis (acrodermatitis continua) of Hallopeau which has failed to respond to standard systemic agents – refer to section 8.1: exceptional circumstances (*Strength of recommendation D; level of evidence 3*)
- TNF antagonists may be considered for patients with generalized pustular psoriasis (*Strength of recommendation D; level of evidence 3*)
- TNF antagonists (infliximab and etanercept) may be considered for patients with erythrodermic psoriasis (*Strength of recommendation D; level of evidence 3*)

14.0 Use of biologic therapy in combination with phototherapy

The rationale for using these two contrasting forms of treatment together is that both have differing mechanisms of action which may be synergistic when used together. However, trial data are limited to a single arm, open-label study, evaluating etanercept 50 mg twice weekly combined with narrowband UVB phototherapy given three times weekly (n = 86).[98] At week 12, 26% of patients achieved PASI 100, 58·1% achieved PASI 90, and 84·9% achieved PASI 75. It is unclear what effect each treatment had as this study failed to include a comparator group with either monotherapy or placebo.

There is currently insufficient evidence to recommend the combination of narrowband UVB phototherapy with etanercept, and no data at all on combined use of infliximab or adalimumab with phototherapy. An RCT is needed to establish whether combining UVB phototherapy with biologic therapies offers more rapid clearance of disease which is sustained when monotherapy continues with the biologic agent.

15.0 Adverse effects and toxicity

15.01 Methodological considerations

When considering the relative risks (and benefits) of biologic interventions, it is important to note that there are significant methodological limitations to published safety data. Trials are powered to detect efficacy, not adverse events, and there is therefore a high chance that low-frequency, drug-related adverse events will not be identified.[99] In addition, many of the data available in relation to psoriasis derive from clinical trials in which only the first 3 months have a comparable placebo group. Long-term extensions of these trials look at patients who remain on therapy and those lost from the cohorts may be lost because of adverse reactions (leading to under-reporting). Long-term data are also poorly reported.[100] Several high-quality meta-analyses of high-quality trials are limited by the sparsity of safety data within the original reports themselves.

Information accrued on TNF antagonist therapies used in other indications may not necessarily be applicable to the

population treated for psoriasis. This may be especially relevant in relation to assessment of skin cancer risk as patients with psoriasis may already have a higher risk of skin cancer due to prior phototherapy and immunosuppressive drugs. The demographics of different diseases are also likely to influence the toxicity profile of any intervention. For example, the higher incidence of RA in women has resulted in a female bias to safety data reported to the BSR biologics register (BSRBR). This underlines the importance of ensuring that all patients are registered with the BADBIR which will assess safety issues in the relevant population.

15.02 Overview of adverse effects for all interventions

A significant body of data is now available on the adverse effects and toxicity associated with biologic therapies. Comprehensive, detailed information is available in the SPC for each drug and is regularly updated by pharmaceutical companies (and approved by the drug regulatory authorities). The U.K. versions can be accessed at http://emc.medicines.org.uk/.

Schmitt *et al.*[101] recently reviewed tolerability of biologic and nonbiologic therapies in a meta-analysis. Tolerability assessed by withdrawals showed monthly withdrawal rates of 1·3% (range 0·5–1·6) for infliximab, 1·2% (0·6–1·9) for efalizumab, 0·4% (0·3–1·4) for etanercept and 0·3% for adalimumab. Additionally infusion reactions occurred in 2·1% of patients per month with infliximab. Serious adverse events occurred at a monthly rate of 1·1% with infliximab, 1·2% with efalizumab and 0·5% with adalimumab. Rates for etanercept could only be computed from the data for the 50 mg biweekly dose, and were 0·6%. Brimhall *et al.*[102] conducted a meta-analysis of adverse events of biologic therapies based on pooled short-term trial data. They expressed a relative risk of adverse events and severe adverse events, compared with placebo. Risks for efalizumab were 1·15 (adverse events) and 1·43 (serious adverse events); for etanercept 1·05 (adverse events) and 1·17 (serious adverse events); and for infliximab 1·18 (adverse events) and 1·26 (serious adverse events). Of these, only the relative risk of adverse events with infliximab and serious adverse events with efalizumab reached an increased level of statistical significance. Adalimumab was not included in the analysis.

15.1 Tumour necrosis factor antagonist therapies

15.11 Infections: bacterial, mycobacterial, viral

Data from clinical trials indicate that infections are common, but overall rates of infection are no greater than with placebo.

Rheumatology registry data do suggest an increased risk of skin and soft tissue infections [adjusted incidence rate ratio 4·28, 95% confidence interval (CI) 1·06–17·17] compared with standard disease-modifying antirheumatic drugs (DMARDs)[100] and although these are poorly characterized, they have included erysipelas, cellulitis, furunculosis, folliculitis, paronychia and wound infections. An increased risk of herpes zoster has also been reported in rheumatology patients on TNF monoclonal antibody therapy, but not etanercept, from the German rheumatology registry: crude incidence rate per 1000 patient-years 11·1 (95% CI 7·9–15·1) for the monoclonal antibodies, 8·9 (95% CI 5·6–13·3) for etanercept, and 5·6 (95% CI 3·6–8·3) for conventional DMARDs.[103] When rates were adjusted for age, RA severity and glucocorticoid use, a significantly increased risk was still observed for treatment with the monoclonal antibodies (hazard ratio 1·82, 95% CI 1·05–3·15), but not etanercept or TNF antagonist therapy as a class. These findings are supported by cohort and case–control studies using data from the U.K. general practice research database and a U.S. health plan claims database which showed increased risk of herpes zoster with biologic therapy (infliximab, etanercept and anakinra) compared with DMARDs in patients with RA.[104]

Serious infections, including opportunistic infections, have also been reported (see SPC and below for additional details).

15.12 Reactivation of tuberculosis

This is a major concern with all TNF antagonist therapies, as TNF plays a key role in host defence against mycobacterial infection, particularly in granuloma formation (and hence containment of mycobacteria) and inhibition of bacterial dissemination.[105,106] Early data (2003) from the BIOBADASER registry (Spanish Society of Rheumatology Database on Biologic Products) reported an estimated incidence of 1893 cases per 100 000 patient-years with infliximab[107] compared with 21 in the general population. This led to careful selection pretreatment and monitoring and greatly reduced the incidence in those complying with pretreatment testing and prophylaxis, although adherence to guidelines was poor.[108] The risk of tuberculosis may be greater with the monoclonal antibodies (infliximab and adalimumab) as compared with etanercept with incidences of tuberculosis in patients with RA reported to the BSRBR of 39 per 100 000 patient-years for etanercept, 103 per 100 000 patient-years for infliximab and 171 per 100 000 patient-years for adalimumab.[109,110] Even when latent tuberculosis is identified and treated prior to TNF antagonist therapy, patients may develop clinical evidence of infection. Thus a high index of suspicion throughout treatment is required. The clinical presentation of infection is often atypical, with at least 50% of cases associated with infliximab[111,112] and etanercept[113] being extrapulmonary. Late diagnosis, development of disseminated disease and concomitant immunosuppressive therapy may all contribute to high rates of morbidity, and associated mortality.[111,112] Onset of clinical infection varies according to the agent used, with median time between initiation of therapy and diagnosis of infection being 3 months,[111,112] 4–6 months[106] and 11·5 months[113] for infliximab, adalimumab and etanercept, respectively.

The mode of action of ustekinumab predicts that it would also facilitate reactivation of tuberculosis. All the trials conducted with this agent excluded patients with latent tuberculosis.

Although the levels of evidence and risk differ between agents the consensus of the guideline development group is to generalize the cautions and vigilance for latent or active tuberculosis to all biologic interventions.

Recommendations: Biologic therapy and infection risk

- Patients on biologic interventions should be monitored for early signs and symptoms of infection throughout treatment (*Strength of recommendation C; level of evidence* 2+)
- Patients on biologic interventions should be warned against risk factors for *Salmonella* and *Listeria* and should not consume raw or partially cooked dairy, fish or meat produce or unpasteurized milk or milk produce. Salads should be washed (*Strength of recommendation D (GPP); level of evidence* 4)
- All patients should be fully assessed for both active and latent tuberculosis before starting biologic therapy with special attention paid to those groups at high risk (*Strength of recommendation B; level of evidence* 2+)
- Patients with active or latent tuberculosis should receive treatment prior to initiating biologic therapy (*Strength of recommendation B; level of evidence* 2+)
- A high index of suspicion for tuberculosis should be maintained during therapy and for 6 months after discontinuation, with special emphasis on extrapulmonary, atypical and disseminated forms of the infection, and in those patients on additional immunosuppressant agents (*Strength of recommendation C; level of evidence* 2+)

See section 18.5 for recommendations on screening and monitoring for tuberculosis

Table 3 New York Heart Association classification of heart failure symptoms

Class	Symptoms[a]
I	No limitations. Ordinary 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, breathlessness, palpitation 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 out 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)

[a]Patients with heart failure may have a number of symptoms, the most common being breathlessness, fatigue, exercise intolerance and fluid retention.

15.13 Cardiovascular disease

The risks of TNF antagonist 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 3] were prematurely discontinued due to an excess mortality with high-dose infliximab; a similar trial of etanercept failed to show benefit.[114] Forty-seven spontaneous reports to the U.S. Food and Drug Administration (FDA) of new onset or worsening of pre-existing heart failure following either infliximab or etanercept have been reviewed in detail with the possibility of drug-induced pathology 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).[115] 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). Clinical trial data in psoriasis and other diseases[116] show no excess risk of heart failure although selection bias (i.e. exclusion of those at risk) may account for this.[117]

Recommendations: Cardiovascular disease and TNF antagonists

- TNF antagonist therapy should be avoided in patients with severe (NYHA class III and IV) cardiac failure (*Strength of recommendation D; level of evidence* 4)
- Patients with well-compensated (NYHA class I and II) cardiac failure should have a screening echocardiogram and those with an ejection fraction < 50% of normal should not be given TNF antagonist therapy (*Strength of recommendation D; level of evidence* 4)
- Treatment should be withdrawn at the onset of new symptoms or worsening of pre-existing heart failure (*Strength of recommendation D; level of evidence* 4)

15.14 Neurological disease

TNF antagonist therapy has been associated with the development of, or worsening of demyelinating disease although evidence for causality is inconclusive. 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. Cases of demyelination have been reported with all three TNF blockers available for psoriasis (SPC and in reference[118]). A detailed review of cases reported to the FDA in 2001 identified 17 due to etanercept and two due to infliximab, partial or complete resolution of symptoms on discontinuation and with recurrence of symptoms in at least one case following rechallenge.[118] Registry data in RA suggest that this risk is small.[119,120] Guidelines recently issued from the American Academy of Dermatology recommend that TNF antagonist therapy be avoided in patients with a personal history of, or a first-degree relative with a demyelinating disorder.[121]

Recommendations: Demyelination and TNF antagonists

- TNF antagonists should be avoided in patients with history of demyelinating disease and used with caution in those with a first-degree relative with such disease (*Strength of recommendation D; level of evidence* 3)
- If neurological symptoms suggestive of demyelination develop during TNF antagonist therapy, treatment should be withdrawn and specialist advice sought (*Strength of recommendation D; level of evidence* 4)

15.15 Paradoxical events

Certain diseases, including psoriasis, that are commonly responsive to TNF antagonist therapy, have 'paradoxically' been reported, rarely, to be triggered or exacerbated by TNF antagonist therapy. Various granulomatous reactions, particularly involving the lung and including some indistinguishable from sarcoid,[122] small vessel vasculitis (predominantly in the skin)[123] and uveitis[124] have been described in patients on TNF antagonists for mainly rheumatological indications. These data derive largely from spontaneous reports or case series so it is currently unclear as to the size of any risk, and whether it is relevant to patients using TNF antagonist therapy for psoriasis.

With respect to psoriasis, more than 120 sporadic cases of both new-onset and worsening psoriasis have been reported in patients using TNF antagonist therapy for a wide spectrum of predominantly rheumatological disorders although including some cases of psoriasis (reviewed[76,77]). This association is supported by data from the BSRBR indicating a significantly increased incidence of new-onset psoriasis with TNF antagonist therapy as compared with standard DMARDs in patients with RA.[125]

15.16 Malignancy

To date, there is no robust evidence of increased risk of malignancy with TNF antagonists in patients with psoriasis. Data from clinical trials are reassuring, and there is no indication from registry data in rheumatology populations of increased risk of solid tumours and lymphoma with TNF antagonist therapy as compared with standard DMARDs to date.[126] However, uncertainty and conflicting evidence remain around the possible increased risk of lymphoma, possibly because lymphomas are more common in patients with severe RA. Bongartz *et al.*[127] carried out a meta-analysis of nine trials of patients with RA treated with infliximab or adalimumab. The data included 3493 patients who received TNF antagonist treatment and 1512 patients who received placebo and demonstrated a pooled odds ratio for malignancy of 3·3 (95% CI 1·2–9·1). This paper raised a variety of methodological concerns[128–130] which included lack of adjustment for duration of exposure to TNF antagonist therapy, inclusion of open-label extension data for biologic therapy with no comparable placebo data, infliximab induction doses exceeding labelled dose in approximately 50% of patients and an unexpectedly low rate of malignancy in the control arms. In addition, both infliximab and adalimumab have been rarely associated with hepatosplenic T-cell lymphoma.[131] This rare, aggressive, and usually fatal tumour has occurred in adolescents and young adults with Crohn's disease who were also receiving treatment with azathioprine or mercaptopurine.[132–136] There are also reports of cases of early onset of lymphoma after introduction of TNF antagonist therapy[137,138] and regression of lymphoma following withdrawal of TNF antagonist therapy.[137,139]

With respect to skin cancer, data on TNF antagonists in RA are inconsistent. Pharmacovigilance data on 1440 patients with RA treated with etanercept from clinical trials (3530 person-years total exposure time) did not show any link between squamous cell carcinoma (SCC) development and etanercept.[140] Lebwohl *et al.*[141] carried out a retrospective analysis of 1442 patients with RA treated with etanercept for up to 5 years and similarly found no increased incidence of SCC (observed four SCCs, expected 5·9–13·1). However, an increased risk of nonmelanoma skin cancer (NMSC) (odds ratio 1·5, 95% CI 1·2–1·8) and a trend towards increased risk of melanoma (odds ratio 2·3, 95% CI 0·9–5·4) has recently been reported in a large (> 13 000 patients) observational study comparing rates of malignancy in patients with RA on biologic therapies with population rates (drug-specific data from this analysis are given in the relevant section below).[139]

Leonardi *et al.*[142] evaluated the incidence of malignancy in patients receiving efalizumab in 14 clinical trials (2980 patients). One case of malignant melanoma occurred in patients treated with efalizumab (incidence rate 0·04 per 100 patient-years, 95% CI 0·00–0·22), compared with no cases in the placebo cohort and an incidence of 0·02 per 100 patient-years derived for the general population. For NMSC, 51 tumours [basal cell carcinomas (BCCs); 30 SCCs] were reported in efalizumab-treated patients (i.e. 1·2% of all efalizumab-treated patients), compared with four tumours (two BCCs, two SCCs in two patients) in placebo-treated patients, giving incidence rates of 1·38 per 100 patient-years (95% CI 0·96–1·92) for efalizumab, 1·08 per 100 person-years (95% CI 0·13–3·89) for placebo, and 0·39 per 100 patient-years in external psoriasis cohorts on oral therapy or phototherapy. This increased incidence of NMSC in both efalizumab and placebo groups was suggested to be possibly related to ascertainment bias.

Long-term registry data collated from the pertinent population are essential to address properly the question of cancer risk in patients with severe psoriasis treated with biologic therapy.

Recommendations: Malignancy risk and biologic therapy

- It is very strongly recommended that all patients being treated with biologic therapy should be entered into the BADBIR (subject to patient consent) in order to establish whether biologic therapy is associated with any increased risk of important side-effects such as malignancy, compared with standard systemic therapy (*Strength of recommendation D (GPP); level of evidence* 4)
- All patients should be fully assessed prior to, and during treatment with, biologic therapy with respect to their past or current history of malignancy and/or any future risk of malignancy; the

risks and benefits of biologic therapy should be considered in this context (*Strength of recommendation D; level of evidence* 4)

- All patients should be encouraged to participate in national cancer screening programmes appropriate for their age and gender (*Strength of recommendation D (GPP); level of evidence* 4)
- Biologic therapy should be avoided in patients with a current or recent past history of malignancy *unless* the malignancy has been diagnosed and treated more than 5 years previously and/or where the likelihood of cure is high (this includes adequately treated NMSC) (*Strength of recommendation D; level of evidence* 4)
- Regular, comprehensive dermatological assessment for skin cancer, including melanoma, is recommended before and at regular intervals during therapy, especially in those patients at increased risk of skin cancer at baseline (*Strength of recommendation D; level of evidence* 4)
- Biologic therapy is relatively contraindicated in patients who have had prior therapy with > 200 PUVA and/or > 350 UVB treatments, especially when it has been followed by ciclosporin (*Strength of recommendation D; level of evidence* 4)

See Table 4 for summarized recommendations on screening and monitoring

15.2 Drug-specific details

15.21 Etanercept

The *commonest adverse events* reported are injection site reactions (14%),[143] allergic reactions, headache and upper respiratory tract infection.[102]

Injection site reactions, while common, diminish with ongoing therapy and do not relate to antibody development.

Infections constituted 21% of FDA reports of adverse effects in 2001.[144] In a short-term evaluation of 1347 patients with psoriasis these included sinusitis, upper respiratory tract infections and influenza, and were of similar rates to placebo. Skin infections occurred in 14% of patients.[145] Serious infections were rare (0·4%) and comparable with placebo rates.[143]

Aside from tuberculosis (discussed above), opportunistic infections may occur including listeriosis,[146,147] streptococcal pneumonia, aspergillosis, histoplasmosis,[148] cryptococcosis, *pneumocystis* pneumonia, *Legionella* and *Salmonella*.[144,147]

Malignancy. A long-term 3-year open-label etanercept study of 1498 patients not treated with other disease-modifying drugs revealed no change in the rate of malignancy (or severe infections) over time and malignancies were fewer than expected in the normal population.[119] An increased risk of NMSC of 1·2 (95% CI 1·0–1·5) and melanoma 2·4 (95% CI 1·0–5·8) has been reported in those patients treated with etanercept for RA.[139] Combining the results of placebo- and active comparator-controlled clinical trials of etanercept, more cases of NMSC were observed in patients receiving etanercept compared with control patients, particularly in patients with psoriasis (SPC). Other data in relation to malignancy are summarized in section 15.16.

Lupus-like syndrome with positive antibodies is reported but is rare and affected patients have not experienced systemic features.

Aplastic anaemias and pancytopenia have been reported rarely following etanercept and a neutropenia occurred in one of the long-term trials over 12 months.[144]

15.22 Infliximab

The commonest side-effects are upper respiratory tract infection, headache, increased hepatic enzymes and infection.

Acute infusion-related reactions with diverse symptoms occur in 3–22% of patients with psoriasis,[149] including, rarely, anaphylactic shock and delayed hypersensitivity. Antibodies to infliximab can develop which can increase the risk of immunological reactions and reduce the efficacy of therapy. Detailed information on management of infusion reactions is available in a recent comprehensive review.[149]

Hepatoxicity in the form of elevation in liver transaminases is well recognized to occur with infliximab therapy.[53] In general, these elevations are transient and asymptomatic but rare cases of severe hepatitis and acute liver failure resulting in transplantation or death have been reported.

Infections. Soft tissue infections, sepsis, candidiasis, fungal infections, pharyngitis, sinusitis and rhinitis are uncommonly reported. Serious infections have included pneumonia, bronchitis, peritonitis, septicaemia, pyelonephritis, cellulitis, systemic fungal infection and herpes zoster. Aside from tuberculosis (discussed above), opportunistic infections are also of concern and include atypical mycobacteria, histoplasmosis, coccidioidomycosis, *Pneumocystis* pneumonia, candidosis and aspergillosis.[145]

Malignancy. There is no indication from registry data of increased malignancy risk with infliximab. In a clinical trial investigating efficacy of infliximab in chronic obstructive pulmonary disease, nine of 157 patients in the active arm developed a malignancy as compared with one of 77 with placebo,[150] although this finding was not statistically significant. An increased risk of skin cancer has been reported in patients treated with infliximab: NMSC 1.7 (95% CI 1·3–2·2) and melanoma 2·6 (95% CI 1·0–6·7).[139] Other data in relation to malignancy are summarized in section 15.16.

Other adverse effects. As with etanercept, there are reports of lupus-like reactions and demyelination, but these are rare.

15.23 Adalimumab

The commonest adverse events reported are injection site reactions, viral, candidal and bacterial infections, dizziness, headaches, vertigo, gastrointestinal upset, musculoskeletal pain, rash, asthenia and malaise (SPC).

Injection site reactions occur in 15% of patients treated (compared with 9% of patients receiving placebo or active control) but generally do not result in discontinuing therapy.

Table 4 Recommended pretreatment and monitoring investigations

	Pretreatment[a]	Monitoring[a]	Grade of evidence; strength of recommendation[b]
BADBIR	Yes	6-monthly	D; 4
Disease severity assessment			
Skin: PASI (or BSA affected if PASI not applicable), DLQI	Yes	To establish disease response; 6-monthly thereafter	A; 1+
Joints: follow recommended BSR guidelines for psoriatic arthritis	Yes	To establish disease response; 6-monthly thereafter	A; 1+
Identification of contraindications to therapy and/or development of therapy-induced toxicity			
Thorough history, symptom enquiry, clinical examination (including full skin check; assessment for lymphadenopathy, hepatosplenomegaly)	Yes	At 3- to 6-monthly intervals	D (GPP)
Cardiovascular assessment[c]			
Echocardiogram if well-compensated NYHA class I and II	Yes	Clinical assessment at 3- to 6-monthly intervals	D; 4
Neurological assessment			
Exclude demyelination[c]	Yes	At 3- to 6-monthly intervals	D; 4
Infection			
Consider risk factors for tuberculosis; sexual history; drug abuse; history of blood transfusions; any past or current chronic infection	Yes	At 3- to 6-monthly intervals	GPP
Malignancy			
Ensure concordant with national cancer screening programmes; gynaecological review of patients with history of cervical dysplasia; any past or current malignancy	Yes	At 3- to 6-monthly intervals	GPP
Assessment for latent tuberculosis			
See Figure 1	Yes	Annually (IGRA)	A; 2+
Blood tests			
Full blood count	Yes	At 3 months, then every 6 months	A; 1+
Creatinine, urea, electrolytes	Yes	At 3 months, then every 6 months	GPP
Liver function tests	Yes	At 3 months, then every 6 months	A; 1+
Hepatitis B	Yes	Periodically in those at risk	D; 4
Hepatitis C	Yes[a]	Periodic assessment of hepatitis C viral load if positive	D; 4
Human immunodeficiency virus	Yes[d]	Periodically in those at risk	D; 4
Autoantibodies (antinuclear antibodies, antinuclear double-stranded DNA antibodies	Yes	Only if symptoms suggest development of autoimmune phenomena, e.g. abnormal liver function tests	D; 4
Urine			
Urine analysis	Yes	Not routinely	
Urine pregnancy test	Yes	Periodically in those at risk	
Radiology			
Chest X-ray	Yes	Only if clinically indicated	

BADBIR, British Association of Dermatologists Biologic Interventions Register; PASI, Psoriasis Area and Severity Index; BSA, body surface area; DLQI, Dermatology Life Quality Index; BSR, British Society for Rheumatology; NYHA, New York Heart Association; IGRA, interferon gamma release assay. [a]Additional assessment and monitoring may be required in patients on concomitant therapy or in certain clinical circumstances. [b]See Appendix 1. [c]Applies to tumour necrosis factor blockers only. [d]In those with risk factors.

Infections. A composite of clinical trials involving 12 506 patient-years and postmarketing surveillance was reported for adalimumab in 2006.[151] The rate of serious infection was 5·1 per 100 patient-years and was not increased above those published in RA untreated with biologic therapy. Four cases of histoplasmosis occurred in endemic areas. Post-tuberculin screening, the rate of tuberculosis was 330 per 100 000 patient-years in Europe and 80 per 100 000 in

North America and 0·6% of patients receiving tuberculosis prophylaxis acquired tuberculosis. Postmarketing surveillance has revealed further cases of tuberculosis and opportunistic infections.

Malignancy. In the same analysis outlined above,[151] a standardized incidence ratio of 3·19 was reported for the rate of lymphomas but such increases are observed in severe RA without biologic interventions. A further analysis of an open-label study (REACT) with 6610 patients was published in 2007 and included patients with other concomitant disease-modifying drugs.[152] Results were similar to those in the original report,[151] with the exception of malignancy, where the standardized incidence ratio for malignancies (including lymphoma but excluding BCCs and carcinoma *in situ*) was 0·71 (95% CI 0·49–1·0). The observed number of lymphoma cases was significantly greater than the expected number only in the RA trials (standardized incidence rate 2·98; 95% CI 1·89–4·47). Other data in relation to malignancy are summarized in section 15·16.

Other adverse effects associated with TNF antagonists have also been reported with adalimumab, with incidence rates of 0·08 per 100 patient-years for demyelinating disorders, 0.1 per 100 patient-years for lupus-like syndromes and 0·28 per 100 patient-years for congestive cardiac failure.[151]

15.3 Safety and efalizumab

Safety data for efalizumab are more limited compared with TNF antagonist therapy as therapy has largely been confined to patients with psoriasis, with approximately 47 000 patient-years exposed to date. Several studies have examined safety in clinical trials with extended open observation of patients for up to 3 years[153–157] and all give a similar incidence of adverse events.

Very recently, three cases of confirmed PML have been reported in patients on efalizumab with consequent withdrawal of the European marketing licence by the European Medicines Agency. PML is a rare, progressive, demyelinating disorder of the central nervous system, associated with reactivation of John Cunningham virus (JCV) in immunosuppressed individuals. It leads to death or severe disability, and there are no known medical interventions that can reliably prevent or treat the disorder. All three of the reported cases occurred in patients on efalizumab monotherapy for 3 years or more. The occurrence of this usually fatal adverse event is of significant concern particularly given that if PML is particularly associated with protracted use of efalizumab, estimates suggest that as many as 1500 patients have been exposed to treatment for as long as 3 years. It also highlights the risk of unexpected serious adverse events that follows the introduction of any new drugs into clinical practice.

The commonest adverse events were headaches (36%), chills (11%), fever (9%), asthenia (6%) or influenza-like symptoms (9·8%), back pain (6%), diarrhoea (6%) and myalgia (6%). These commonly occur during the first few weeks of treatment but tend to resolve with continued therapy.[155]

Thrombocytopenia occurs uncommonly (between one in 500 and one in 1000 patients), so platelet counts should be monitored. Lymphocytosis and leucocytosis (up to 3·5 × upper limit of normal) is a regular finding with efalizumab therapy due to its effect of blocking their migration out of the bloodstream, and may be used to confirm patient concordance.

A transient, acute, pruritic eruption occurs commonly in previously uninvolved sites (7%).[156] 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 be mistaken for a psoriasis flare. Flares of psoriasis are uncommon (2%), and tend to occur in low or nonresponders.[156]

Arthralgia and *exacerbation of psoriatic arthritis* have been reported in association with efalizumab. A pooled review of RCT data reported no increased incidence of joint symptoms or development of psoriatic arthritis in those patients receiving efalizumab compared with placebo.[154] However, in a 2-year follow-up study of 555 patients, the rate of arthralgia and arthritis increased over time from 1·6% to 5·6% at the end of the study with most of the affected patients having a prior history of psoriatic arthritis.[158] In addition, a multicentre, retrospective case cohort review of all patients treated with efalizumab in France identified 16 patients with new-onset, severe psoriatic arthritis, with a median time to onset of 11 weeks, and evidence of improvement in symptoms on drug withdrawal.[159]

Infection rates. There is no direct evidence of increased rates of infection with efalizumab. We are not aware of reported cases of tuberculosis. *Candida* colitis and cytomegalovirus (CMV) have been reported. However, the SPC has special warnings for infection including tuberculosis, opportunistic infection, pyelonephritis, septic arthritis and septicaemia. Opportunistic infections are reported as uncommon in the SPC.

Malignancy. There have not been increased reports of malignancy, with the overall incidence reported as 1.7 per 100 patient-years in a systematic review of safety data published in 2006.[144] Leonardi *et al.*[142] pooled data from clinical trials and reported no significant increase in solid malignancies or lymphoproliferative disease. However, as summarized in section 15.16, an increase in NMSC was noted.[142]

15.4 Safety and ustekinumab

Safety of ustekinumab in psoriasis has been evaluated in two phase III trials.[71,72] Five hundred and ten patients received up to 76 weeks of treatment in one study reported by Leonardi *et al.*[71] and 1212 received treatment for up to 52 weeks in the study reported by Papp *et al.*[72] Overall rates of adverse events were similar to placebo, and there was no consistent evidence for a relationship between dose or frequency of dosing, and the occurrence of adverse events. An RCT comparing ustekinumab and etanercept in psoriasis reported comparable rates of adverse events with both drugs through 12 weeks of

therapy, with the exception of injection site reactions which were more common with etanercept.[74] Further, limited data on adverse events are available in each of three phase II studies evaluating ustekinumab in psoriatic arthritis,[73] Crohn's disease[160] and multiple sclerosis,[161] respectively, where the pattern and rates of adverse events were similar in active and placebo groups. No exacerbation of demyelinating events was reported in the study evaluating ustekinumab in multiple sclerosis ($n = 150$ receiving active drug).[161]

Common adverse events in both studies included upper respiratory tract infection, nasopharyngitis, arthralgia, cough and headache.

Injection site reactions were uncommon (1·5%), perhaps because of the infrequency of drug administration. Antibodies (neutralizing) develop in approximately 5% of patients and are associated with poorer responses to therapy, but do not correlate with injection site reactions.

Infection. In the study by Leonardi *et al.*[71] the incidence of serious infections was 0·4–0·8% in the different subgroups and similar to the placebo phase. There were three incident cases of noncutaneous cancers and four cutaneous cancers. Laboratory abnormalities were low in rate and were similar between treated patients and the placebo group.[71] In the study reported by Papp *et al.*,[72] serious infection occurred in 0–0·5%, similar to placebo. There were seven cutaneous cancers and one other (noncutaneous) cancer on therapy, with similar rates in the placebo arm.

No cases of tuberculosis, demyelination or lymphoma were identified. However, as discussed in section 15.1, the mode of action of ustekinumab would be expected to facilitate reactivation of tuberculosis.

16.0 How to determine the optimal choice and sequence of therapy

Given the proven efficacy of TNF antagonists in psoriasis, the substantial body of available clinical safety data (albeit not confined to patients with psoriasis) and the high proportion of patients with associated psoriatic arthropathy, TNF antagonists should be considered the first-line biologic intervention. Multiple factors will determine which of the three available TNF antagonists should be used first in a particular patient. This includes those related to the drug itself and how they relate to the clinical circumstance, patient preferences (e.g. mode of administration) and access, the latter being determined largely by local funding arrangements. In the short term, the monoclonal antibodies (infliximab and adalimumab) have a quicker onset of action, and are more effective than etanercept, although by 1 year the proportion of patients maintaining a PASI 75 may be comparable (Table 2). With respect to safety, systematic review of RCT data from short-term studies suggests that the risk of adverse events may be slightly higher with infliximab compared with etanercept[101,102] and adalimumab[101] while registry data indicate that risks of reactivation of tuberculosis and herpes zoster may be greater with adalimumab and infliximab as compared with etanercept.[103,109,110]

Ustekinumab is more effective than etanercept in the short term (based on a large RCT directly comparing the two agents)[74] and is probably of comparable efficacy to adalimumab and infliximab, but safety data are very limited. Ustekinumab should therefore be reserved for patients who have failed or cannot use TNF antagonists.

There are only limited efficacy data on use of a second biologic therapy in patients with psoriasis where the first has failed. Mechanisms underlying primary failure (i.e. inadequate response following initiation of treatment) or secondary failure (i.e. loss of response over time) are poorly understood,[24] although in the case of TNF antagonists, development of anti-drug antibodies with consequent reduction in circulating drug levels is well described with both infliximab and adalimumab.[53,63] Further, while infliximab, adalimumab and etanercept all act to block TNF, they are pharmacologically distinct (see reference[24] for a detailed review). Thus failure to respond to one TNF antagonist may not preclude response to a second. This is supported by findings in a small open-label study[69] and retrospective case cohort review[162] which demonstrate efficacy of adalimumab following etanercept failure.

Of note, approximately a third of patients entered into ustekinumab RCTs had been previously treated with biologic therapy (predominantly TNF antagonists), and this did not influence therapeutic outcome.

Recommendations: How to determine the optimal choice and sequence of therapy

- TNF antagonists are recommended as first-line intervention for patients fulfilling criteria for treatment with biologic therapy – refer to section 8.0 (*Strength of recommendation B; level of evidence 1+*)
- The choice of which of the three TNF antagonists **to use first** should be based on clinical need and requires a careful assessment of risks and benefits of each agent in the context of the individual patient. With this proviso, the following additional recommendations are made:
- For patients with stable chronic plaque psoriasis, etanercept or adalimumab may be considered first choice based on the favourable risk/benefit profile and ease of administration (*Strength of recommendation D; level of evidence 4*)
- For patients requiring rapid disease control, adalimumab or infliximab may be considered first choice due to the early onset of action, and high chance of achieving PASI 75 by 3 months (*Strength of recommendation A; level of evidence 1+*)
- For patients with unstable or generalized pustular psoriasis, limited evidence indicates that infliximab is effective in these clinical situations, and may therefore be considered first choice (*Strength of recommendation D; level of evidence 3*)
- For patients who do not respond to a TNF antagonist (either primary or secondary failure), a second TNF antagonist may be considered (*Strength of recommendation D; level of evidence 3*)
- Due to the lack of patient-years exposure and long-term safety data limited to 1 year, ustekinumab should be reserved for use as a second-line biologic agent where TNF therapy has failed or cannot be used (*Strength of recommendation B; level of evidence 1+*)

17.0 How to use biologic therapy in special circumstances

17.1 Use of biologic therapy in children

One RCT[163] indicates that etanercept is effective in chronic plaque psoriasis in children. Among 106 patients aged 4–17 years (median 14 years) who received etanercept 0.8 mg kg^{-1} (up to maximum dose of 50 mg) by weekly subcutaneous injection, 57% achieved a PASI 75 at 12 weeks as against 11% in the placebo arm. Subjects had psoriasis with a baseline PASI of 12 or more and had disease that was poorly controlled with topical therapy or had prior treatment with phototherapy or systemic therapy. Improvement was noted by 4 weeks of treatment and was maintained during an open-label extension to week 36. There was no significant difference in response when the results were analysed separately for those under the age of 12 years as compared with those over the age of 12 years.

In the RCT the frequency of exposure-adjusted adverse events was low and similar to the placebo arm. Three serious infections were reported in the open-label phase in patients receiving etanercept. Longer-term safety data are needed in this patient group.

17.11 Quality of evidence

The patient cohort in the cited RCTs may not be representative of patients likely to be treated in clinical practice, in that not all patients were required to have failed or be contraindicated to systemic therapy.

17.12 Licensed indications and existing NICE guidance (Table 1)

Etanercept is licensed for treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. NICE is currently considering a proposal for Single Technology Assessment. Etanercept is also licensed for treating juvenile idiopathic arthritis (JIA), a term which encompasses paediatric psoriatic arthritis. NICE has approved the use of etanercept in children aged 4–17 years with five or more inflamed joints who have failed to respond to methotrexate. The long-term safety of etanercept in JIA has been demonstrated up to 8 years.[164]

Recommendations: Use of biologic therapy in children

- Etanercept is recommended for the treatment of severe psoriasis in children from the age of 8 years who fulfil the stated disease severity criteria – refer to section 8.0 (*Strength of recommendation A; level of evidence* 1++)
- Etanercept therapy should be initiated at a dose of 0·8 mg kg^{-1} weekly and disease response assessed at 3–4 months (*Strength of recommendation A; level of evidence* 1++)
- In patients who respond, treatment may be continued according to clinical need, although long-term data on efficacy are limited to 1 year (*Strength of recommendation A; level of evidence* 1+)

17.2 Use of biologic therapy in women planning pregnancy or who are pregnant

The overall question relates to the safety of biologic therapy in women who are pregnant. In practical terms this can be broken down to four main scenarios. Firstly, is it safe for women planning pregnancy or for women who are pregnant to continue with biologic therapy for psoriasis or should women established in biologic therapy come off biologic therapy prior to planning pregnancy? Secondly, is it safe for women who are pregnant and experience a flare of psoriasis during pregnancy to be initiated on biologic therapy? Thirdly, what action should women who are established on biologic therapy for psoriasis take if they discover that they are pregnant? Fourthly, is it safe for women to initiate or continue biologic therapy while breast feeding?

There are no prospective or retrospective studies that have addressed treatment of psoriasis during pregnancy with TNF antagonists. However, there are several publications concerning the outcome of pregnancy following exposure to TNF antagonists in a number of other diseases (principally Crohn's disease and arthritis) although these patients, in contrast to patients with psoriasis, are more likely to have been exposed to combination therapy.

17.21 Surveys and retrospective series: tumour necrosis factor antagonists

Mahadevan *et al.*[165] describe the first intentional use of infliximab during pregnancy in a retrospective review of 10 patients with Crohn's disease. Eight patients received maintenance therapy during the whole of pregnancy, one received infliximab during the first trimester and one during the third trimester. Concomitant medication included 6-mercaptopurine in five women and systemic steroids in four women. Eight of the 10 women had caesarean sections. There were no fetal congenital abnormalities; three infants were premature and one had low birth weight but these were not thought to be secondary to infliximab therapy.

Databases for monitoring safety set up by Centocor (pharmaceutical company that markets infliximab) include TREAT[166] and the Infliximab Safety Database[167] (which may in part overlap) and report 66 and 146 pregnancies,[166,167] respectively, in which exposure to infliximab occurred. No fetal abnormalities were reported in the TREAT study and rates of miscarriage and neonatal complications were not increased compared with control groups in either study. One preterm death at 24 weeks and four infants born with complications are reported in the Infliximab Safety Database[167] including one Fallot's tetralogy and one neonatal sepsis.

A report of the BSRBR includes information on 23 pregnancies in which exposure to TNF antagonists occurred at the time of conception resulting in 14 live births with no major fetal abnormalities.[168,169] There were six first-trimester spontaneous abortions and three elective first-trimester abortions.

In a retrospective study of 442 patients treated with TNF antagonists[170] three women with RA became pregnant. One patient opted for elective abortion while two patients exposed to either adalimumab or etanercept proceeded to deliver healthy infants although one was premature. Perinatal complications included neonatal jaundice, neonatal urinary *Escherichia coli* infection and adrenal congenital hyperplasia of probable hereditary origin.

Four further patients with severe arthritis were maintained on anti-TNF therapy (one etanercept, three infliximab) during pregnancy and all gave birth to healthy infants with no complications.[171]

As TNF has been hypothesized to be involved in the pathogenesis of spontaneous abortions, a recent study compared anticoagulants (group I), anticoagulants plus intravenous immunoglobulins (IVIG) (group II) or anticoagulants plus IVIG plus etanercept or adalimumab (group III; 17 patients) as treatment for women with recurrent spontaneous abortion.[172] Anti-TNF agents were administered 30 days prior to a cycle of conception and continued until fetal cardiac activity was demonstrated by ultrasound. Significant improvement in pregnancy outcome was observed in groups II and III compared with group I. No birth defects were observed in any of the babies in group III who had been exposed to anti-TNF agents.

A recent publication describes the outcome of pregnancy of 15 women receiving anti-TNF therapy (infliximab, $n = 3$; adalimumab, $n = 2$; etanercept, $n = 10$) at the time of conception or during pregnancy reported by French rheumatologists, through a web-based structured questionnaire.[173] The women had received anti-TNF therapy for a median of 8 months before pregnancy (range 1–48 months). Two miscarriages were reported and one woman who was also taking methotrexate opted for elective abortion. The median length of exposure to anti-TNF therapy during the 12 successful pregnancies was 6 weeks (range 3–38 weeks) with 12 of 12 women receiving anti-TNF therapy during the first trimester compared with four of 12 women during the third trimester. No complications, prematurity, malformations or neonatal illnesses were described.

In contrast to the reports above, congenital abnormalities have been associated with TNF antagonists in a recent review of the FDA database; a total of 61 congenital anomalies occurred in 41 children born to mothers taking a TNF antagonist (22 took etanercept, 19 took infliximab) in the period 1999–2005. In 24 of 41 cases, the mother was on no other medication. The most common reported congenital anomaly was some form of heart defect. Twenty-four of the 41 (59%) children had one or more congenital anomalies forming part of VACTERL (vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities). The rate of specific anomalies was significantly higher than historical controls implicating a causal role for TNF antagonists.[174]

A survey returned by 150 American rheumatologists indicated that they were more concerned about the risks of methotrexate in pregnancy than anti-TNF biologic agents.[175] Three congenital abnormalities reported in the survey were all associated with methotrexate usage alone.

17.22 Case reports: tumour necrosis factor antagonists

A patient with psoriasis and psoriatic arthritis who continued etanercept 50 mg subcutaneously twice weekly throughout her pregnancy gave birth to a child with fetal anomalies of the VATER association (including renal dysplasia, skeletal defects and tracheoesophageal fistula).[176]

The successful use of etanercept (and IVIG) during pregnancy for flare of systemic lupus erythematosus and RA has been reported and healthy babies with no complications ensued.[177,178]

There are limited data on outcomes of pregnancies following exposure to adalimumab. There are three case reports of women with Crohn's disease who received adalimumab during pregnancy and gave birth to healthy babies with no complications.[169,179,180] A patient with Takayasu's arthritis continued adalimumab (and leflunomide) during pregnancy and delivered a healthy baby with no complications.[181]

17.23 Infliximab crosses the placenta and has a long half-life but is not detected in breast milk

High infliximab levels were detected in the serum of an infant born to a mother with refractory Crohn's disease who continued to receive infliximab ($10\ mg\ kg^{-1}$) during her pregnancy.[182] The last infusion was given 2 weeks prior to labour. Infant infliximab levels were high at 6 weeks ($39{\cdot}5\ \mu g\ mL^{-1}$) and remained elevated up to 6 months of age. Infliximab was not detected in breast milk, suggesting that placental transfer results in neonatal exposure and that the half-life of infliximab is prolonged in infants.

A recent case report describes a successful pregnancy with no infant abnormalities in a mother with refractory Crohn's disease who continued to receive infliximab ($10\ mg\ kg^{-1}$) during her pregnancy and while breast feeding.[183] Analysis of breast milk revealed no evidence of infliximab over 30 days.

A recent report in abstract form of a prospective study of five women receiving infliximab indicates that infliximab was detectable in infants up to 2–6 months of age depending on the date of the last infusion in relation to birth,[184] suggesting further caution over the use of infliximab in the later stages of pregnancy.

17.24 Licensing guidance and summary

Manufacturers of etanercept, infliximab and adalimumab advise avoidance during pregnancy. Although no toxicity or teratogenicity has been reported in animal studies of etanercept, caution

should be exercised when considering the use of TNF antagonists during pregnancy. There are surveys and reports of successful and complication-free use of biologic therapy during pregnancy but these are limited and there are also some reports of perinatal complications including premature birth together with recent data associating VACTERL with TNF antagonists. Risk assessment is therefore difficult.

Also, these drugs may be used in combination with methotrexate which is contraindicated in pregnancy because of well-documented associations with spontaneous miscarriage, cleft palate and skeletal abnormalities.[185–187]

17.25 Use of biologic therapy in men and conception

There are very few publications that have addressed whether TNF or TNF antagonists may affect spermatogenesis, number or quality of sperm. It is therefore difficult to draw definitive conclusions. As TNF levels are elevated in infertile women with endometriosis, Eisermann *et al.*[188] evaluated the effects of TNF on sperm mobility and found a dose-dependent decrease that was reversed by anti-TNF antibody. On the other hand, La Montagna *et al.*[189] found reduced sperm mobility (although this was not quantified) in two of three patients evaluated with ankylosing spondylitis who were receiving infliximab. These data suggest that TNF/TNF antagonists may have some biological effect on sperm motility but the clinical relevance of this is presently unclear.

Recommendations: Use of biologic therapy in women planning pregnancy or who are pregnant

- Pregnancy should be avoided in patients with psoriasis receiving biologic therapy and effective contraception is strongly recommended to prevent pregnancy in women of child-bearing potential (*Strength of recommendation D; level of evidence* 3)
- In patients who are planning a pregnancy, biologic agents should be avoided (and/or stopped in advance) so the fetus is drug free during the critical developmental period of the first 12 weeks (*Strength of recommendation D; level of evidence* 3)
- If patients who are established on biologic agents discover they are pregnant, they should be referred to a specialist fetal medicine unit for further assessment and consideration should be given to stopping biologic therapy (*Strength of recommendation D; level of evidence* 4)
- Notwithstanding recommendations above, patients should be assessed on a case-by-case basis and the risks to the mother of stopping biologic therapy should be balanced against any potential harm to the fetus/infant (*Strength of recommendation D; level of evidence* 4)
- For those patients receiving infliximab during pregnancy, infusions should be avoided after 30 weeks if at all possible in view of its relatively long half-life and evidence that it crosses the placenta and may persist for several months in the fetal circulation (*Strength of recommendation D; level of evidence* 3)
- Breast feeding should be avoided in patients receiving biologic therapy although limited evidence indicates that infliximab is not excreted in breast milk (*Strength of recommendation D; level of evidence* 4)

17.3 Use of biologic therapy in the perioperative period for elective surgery

There are no prospective randomized trials comparing continuous vs. interrupted biologic therapy for patients on TNF antagonists undertaking surgery. Most published evidence comes from retrospective studies of orthopaedic procedures in RA[190–195] that have been the subject of detailed review.[196] One study found an increase in serious postoperative infection rate associated with prior TNF antagonist use,[192] whereas the other five studies did not show significant differences. However, in the largest of the latter studies[195] there was a trend towards increased early and late surgical site infection in the group who continued TNF antagonist therapy perioperatively (8·7%) vs. those who had TNF antagonist therapy interrupted perioperatively, although this did not reach significance. There was also a greater frequency of wound dehiscence in the group who continued TNF antagonist therapy (9·8%) vs. interrupted therapy (0·9%) compared with those who were TNF antagonist therapy naive (4·4%).

In a retrospective study of patients with Crohn's disease treated by intestinal resection, 40 patients on infliximab prior to surgery had no greater postoperative complication rate or prolonged hospital stay than a control group of 39 patients corrected for age, gender and type of surgery who were not exposed to infliximab.[197]

As a general rule it takes five half-lives for a product to be completely eliminated from the body. Some studies have used four half-lives to determine the interval prior to surgery for interrupting therapy. There may be additional uncertainly about tissue bioavailability. The approximate half-lives of etanercept, adalimumab, infliximab, efalizumab and ustekinumab are 3–5 days, 14–19 days, 8–9 days, 5–10 days and 21 days, respectively (in reference[196] and SPCs).

It is beyond the scope of these guidelines to address the risk of concomitant agents such as immunosuppressive drugs used with biologic therapy during surgery. However, in a well-designed randomized prospective nonblinded study, perioperative use of methotrexate was not associated with an increased risk of adverse outcomes following joint replacement.[198]

17.31 Quality of evidence

Most of the studies have been retrospective and underpowered to detect less than major risks of postoperative complications. It is also difficult to compare studies because of differences in source population, indications for surgery and underlying risk of infection due to the condition itself. From the studies available the two most robust reported[192,195] would yield grade 2+ evidence.

17.32 Existing guidance

The BSR guidelines for RA recommend that TNF antagonists (etanercept, adalimumab and infliximab) should be withheld

2–4 weeks prior to major surgical procedures and treatment restarted postoperatively if there is no evidence of infection and wound healing is satisfactory.[199] Guidelines from the Dutch Society for Rheumatology (http://www.nvr.nl/) and the French Society for Rheumatology[200] are similar and use four drug half-lives as the cut-off.

Recommendations: Use of biologic therapy in the perioperative period for elective surgery

- Until there is more evidence available concerning the risk of perioperative use of biologic therapies in psoriasis and/or psoriatic arthritis, BSR guideline recommendations on discontinuation of TNF antagonists in RA should be applied, i.e. TNF antagonists should be discontinued at least four half-lives prior to major surgery (2 weeks for etanercept, 6–8 weeks for adalimumab, 4–6 weeks for infliximab)
- Although there is no evidence for ustekinumab we would recommend ustekinumab is discontinued 12 weeks prior to major surgery (i.e. four half-lives prior to surgery) (*Strength of recommendation D (GPP); level of evidence* 4)
- Biologic therapy can be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory (*Strength of recommendation D; level of evidence* 3)

17.4 Use of biologic therapy in patients with chronic viral infections (including hepatitis B and C and human immunodeficiency virus)

Patients with potentially harmful chronic viral infections have been exposed to biologic therapy either coincident to treatment for psoriasis (or other inflammatory indication) or as part of intentional adjuvant therapy, as is the case with TNF antagonist therapy in patients with hepatitis C and human immunodeficiency virus (HIV) infections. The limited data available, mainly small case series and case reports, have been subject to a recent, comprehensive review, and guidelines on screening and monitoring provided.[201]

17.41 Hepatitis C

TNF plays a role in hepatitis C-induced hepatocyte injury and treatment resistance to interferon alfa-2b. The role of TNF blockade has therefore been investigated in a phase II, randomized, placebo-controlled study, where etanercept (24 weeks, n = 19) was used as adjuvant therapy to ribavirin and interferon in treatment-naive patients.[202] Etanercept improved viral clearance rates with no significant increase in adverse events. Data from small case series and case reports[203–206] also report successful use of TNF antagonist therapy for rheumatological disease in hepatitis C virus-positive patients, with no increased rate of hepatotoxicity or viral replication.

17.42 Hepatitis B

In contrast to hepatitis C, TNF may play a role in clearing and controlling hepatitis B virus. Cases of severe (and sometimes fatal) reactivation of occult hepatitis B infections have been reported (summarized[201]).

17.43 Human immunodeficiency virus

The safety of biologic therapy in the context of HIV infection is unknown but particular caution should be exercised in this group given the risks of infection. Paradoxically, perhaps, TNF has been implicated in HIV disease progression in HIV-associated tuberculosis, and therefore the benefit of etanercept as adjunctive therapy for this indication has been investigated in a phase I study (25 mg twice weekly for 4 weeks, n = 16).[207] There was a tendency towards improved outcome in the etanercept arm and, more importantly, no increased toxicity compared with standard antituberculous therapy (n = 47). There are several case reports of successful use of TNF antagonist therapy for rheumatological indications in patients who are HIV positive.[201]

17.44 Herpesviruses

The risks of reactivation of latent herpesviruses in patients with psoriasis are unknown, although there are sporadic case reports of severe disseminated infections with both CMV and varicella-zoster[201] in the context of TNF antagonists. Registry data also indicate an increased risk of herpes zoster with adalimumab and infliximab in patients with rheumatological disease (see section 15.1).[103]

In a short-term (14-week) evaluation of 60 consecutive patients with Crohn's disease treated with infliximab, no evidence for reactivation of JCV, Epstein–Barr virus (EBV), human herpesvirus (HHV)-6, HHV-7, HHV-8 or CMV was identified in serum using polymerase chain reaction (PCR).[208] A similar study prospectively measured viral DNA in plasma and peripheral blood mononuclear cells in patients with RA (n = 15) during the first 6 weeks of infliximab treatment, and reported no evidence of reactivation of EBV, CMV or HHV-6. A further longer-term study evaluated EBV alone (measured in peripheral blood mononuclear cells using PCR) in patients with RA over a period of up to 5 years, and reported stable levels in patients using etanercept (n = 48) and infliximab (n = 68).[209]

Risks of herpes reactivation in the context of efalizumab and ustekinumab are unknown. However, with respect to efalizumab, recent reports of PML indicate that JCV reactivation can occur.

Recommendations: Use of biologic therapy in patients with chronic viral infections

- There is insufficient evidence to recommend treatment with biologic therapy in patients with known chronic, potentially harmful, viral infections and clinicians should seek specialist advice on a case-by-case basis (*Strength of recommendation D; level of evidence* 4)
- In patients who are hepatitis C carriers, there is limited evidence to support the use of etanercept provided they are appro-

priately evaluated and monitored during therapy (*Strength of recommendation D, level of evidence* 4)

- TNF antagonist therapy should be avoided in chronic carriers of hepatitis B because of the risk of reactivation (*Strength of recommendation D; level of evidence* 4).

See Table 4 for recommendations on screening for occult viral infections

17.5 Use of biologic therapy and vaccination

Live and live attenuated vaccinations can cause severe or fatal infections in immunosuppressed individuals due to the extensive replication of the vaccine strain and therefore are contraindicated in patients on biologic therapy.[210] Current live vaccinations available in the U.K. include bacille Calmette–Guérin (BCG), measles, mumps, rubella, yellow fever, oral polio and oral typhoid. There is no evidence available to provide recommendations on the safe time-frame from administration of a live vaccine to starting or recommencing a biologic therapy. Drug-specific advice is given only in the SPC for ustekinumab (i.e. withhold ustekinumab for 15 weeks before and 2 weeks after live vaccination). The UK's Department of Health[210] gives comprehensive guidance on vaccination, and also indications for use of human normal immunoglobulin and human varicella-zoster, for patients on immunosuppressive therapy [including cytokine inhibitors (*sic*)] and states that live vaccinations should not be administered until 6 months have elapsed from the withdrawal of immunosuppressive treatment.[210]

No data are available on risks for patients on biologic therapy who come into contact with individuals who have received a live vaccine (i.e. secondary transmission of infection by live vaccines) although current Department of Health guidance states that vaccination is not contraindicated in siblings/close relatives of patients who are immunosuppressed.[210]

Inactivated vaccines are safe to give to patients receiving a biologic therapy.[210] Several studies attempt to address the equally important question as to whether vaccination provides adequate protection from infection, using antibody response as a surrogate marker. Most of the evidence relates to TNF antagonists in rheumatological disease and findings differ depending on the vaccine. With respect to pneumococcal vaccination, there is no evidence to indicate that monotherapy with infliximab, etanercept or adalimumab significantly impairs humoral responses[211–215] although data on adalimumab are confined to measurement of vaccination responses following only 1 week of therapy.[215] However, in a well-designed RCT in psoriatic arthritis, methotrexate led to a significant reduction in humoral responses to pneumococcal vaccine when compared with etanercept or placebo control.[213] Findings in this study are supported by further cohort studies where methotrexate alone, or in combination with any of the three TNF antagonists, was associated with reduced antibody formation, and appeared to be a strong predictor of poor response.[211,212] Findings in relation to influenza vaccination are slightly different, in that humoral responses were found to be reduced in patients on any of infliximab, etanercept or adalimumab[216–218] although antibody levels were still at levels predictive of clinical protection in most patients. Normal responses to influenza have also been reported in a large RCT involving adalimumab (compared with placebo) although, as outlined above, this possibly reflects the fact that vaccination occurred after only 1 week of treatment.[215]

There is little evidence available on what time period should elapse from drug discontinuation to administration of inactivated vaccines to yield an optimal immunological response.

Recommendations: Use of biologic therapy and vaccination

- Vaccination requirements should be reviewed and brought up to date prior to initiation of biologic therapy with reference to Department of Health Guidance (*Strength of recommendation D (GGP); level of evidence* 4)
- Patients should not receive live or live attenuated vaccinations < 2 weeks before, during, and for 6 months after discontinuation of, biologic therapy (*Strength of recommendation D; level of evidence* 4)
- Inactivated vaccines are safe to administer concurrently with a biologic therapy (*Strength of recommendation B; level of evidence* 2++)
- Where possible, inactivated vaccines should be administered 2 weeks before starting therapy to ensure optimal immune responses (*Strength of recommendation D (GGP); level of evidence* 4)
- Clinicians should be aware that TNF antagonist monotherapy may lead to reduced antibody responses to influenza vaccine and that TNF antagonists in combination with methotrexate (only) may lead to reduced antibody responses to pneumococcal vaccine (*Strength of recommendation B; level of evidence* 2++)
- Patients should be advised to receive the pneumococcal vaccine and annual influenza vaccine while on biologic therapy (*Strength of recommendation D; level of evidence* 4)

18.0 How to prescribe therapy

18.1 Who should prescribe biologic therapy?

These treatments should be made available to all those patients fulfilling the currently recommended eligibility criteria.

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.

In the UK, supervising consultants are responsible for ensuring that all patients receiving biologic therapies are registered with the BADBIR throughout the treatment period.

18.2 Role of the specialist nurse

The specialist nurse is a key member of the multidisciplinary team delivering a biologic therapies service. With additional

training a nurse may take responsibility for a number of the tasks outlined in the patient pathway including screening, disease assessments, treatment administration, patient education, prescription coordination, patient support, patient monitoring and data collection for the BADBIR. Competencies for nurses involved in the delivery of biologic therapies are in development by the British Dermatological Nursing Group, along the lines of those already developed by the Royal College of Nursing Rheumatology Forum.[219]

Recommendations: Prescribing biologic therapy

- The specialist nurse is a key member of the multidisciplinary team delivering biologic therapy, and acts to facilitate all aspects of the patient pathway (*Strength of recommendation D (GGP); level of evidence 4*)
- In clearly defined clinical situations, suitably experienced and qualified nurse prescribers who have an expertise in the use of biologic therapies may prescribe biologic therapies under the direct supervision of a consultant dermatologist (*Strength of recommendation D (GGP); level of evidence 4*)

18.3 Patient information and consent

Patients should be fully informed of the risks and benefits of biologic therapies through detailed, collaborative discussion with the supervising consultant and clinical nurse specialist.[17] Written information should be provided (available on the BAD website) and patients given adequate time to consider their decision. Where therapies are being used outside their licensed indications, written consent should be obtained.

18.4 British Association of Dermatologists Biologic Interventions Registry

Short-term clinical trials in selected subjects do not adequately evaluate real world safety in long-term clinical usage of a drug. The potential for any new drug to result in delayed but important unexpected serious adverse effects is highlighted by recent experience with efalizumab. Voluntary reporting schemes lack the benefits of prospective follow up of a known denominator of patients in whom safety data are specifically collected. The BADBIR is now established, and collects vital long-term safety data throughout the U.K. with the intention that all patients on biologic interventions for psoriasis be registered and followed up for 5 years together with 4000 control subjects on conventional second-line drugs for psoriasis. Original NICE guidance on biologic therapies for psoriasis indicates registry participation as an important part of normal clinical care. The guideline development group very strongly recommends (above) that patients be registered in this way (see http://www.badbir.org/).

18.5 Pretreatment assessment and monitoring

All patients should undergo a full clinical history, physical examination and further investigations as indicated in recommendations above, and also based on the toxicity profile of the relevant drug. Recommended pretreatment and monitoring assessments (Table 4) are summarized.

Assessment for risk of tuberculosis in patients considered for TNF antagonist therapy is outlined in Figure 1, and is based on the British Thoracic Society guideline which specifically addresses this question.[220] The British Thoracic Society guideline did not address the role of the now increasingly available *in vitro* interferon gamma release assay (IGRA) tests. The tests [QuantiFERON®-TB Gold (Cellestis Ltd, Carnegie, Vic., Australia) and T-SPOT®.TB (Oxford Immunotec, Abingdon, U.K.)] are both *in vitro* tests, based on release of interferon gamma following stimulation by *Mycobacterium tuberculosis*-specific antigens (ESAT-6, CFP-10, TB7.7). QuantiFERON is cheaper to perform than the T-SPOT.TB and can be done in batches, but may be less sensitive. These tests have some advantages in being more specific in that there is no cross-reactivity with either BCG or most (but not all) clinically relevant atypical mycobacteria. They have proven utility in identifying latent tuberculosis but their place in screening low-risk individuals is still unclear. Repeated tuberculin skin testing may lead to a boosting of the *in vitro* interferon gamma release, and result in a false-positive result.

The Health Protection Agency has issued an interim position statement (pending publication of the NICE Health Technology Assessment which is expected in 2010) and has provisionally approved the tests[221] in certain clinical circumstances, while also discussing the lack of evidence on which to base recommendations. It recommends that the tests may be a suitable alternative to tuberculin skin testing for screening in BCG-vaccinated individuals and also for assessment of patients who are immunosuppressed in whom tuberculin skin testing is unreliable. However, the positive predictive value and negative predictive value in these situations are unknown.

In the U.S.A., the Centers for Disease Control and Prevention advocate tuberculin skin testing in all patients irrespective of whether or not they are on immunosuppressant therapy and this is reflected in the American Academy of Dermatology guidelines on tuberculosis screening for patients considered for TNF antagonist therapy.[121]

18.51 Monitoring

Clinicians should maintain a high index of suspicion for tuberculosis throughout treatment, and for 6 months after discontinuation. Those at particular risk include recent immigrants from high-prevalence countries, injection drug users residents and employees of high-risk congregate settings (e.g. prisons, homeless shelters), mycobacteriology laboratory personnel, and persons with high-risk medical conditions (diabetes mellitus, chronic renal failure, some haematological conditions, conditions requiring prolonged high-dose corticosteroid or other immunosuppressive therapy, mastectomy/jejunoileal bypass).[222] Annual tuberculin skin testing has been recommended in the U.S.A. for both dermatology[121] and rheumatology practice,[223] although only 21–37% of U.S. rheumatologists surveyed concord with this

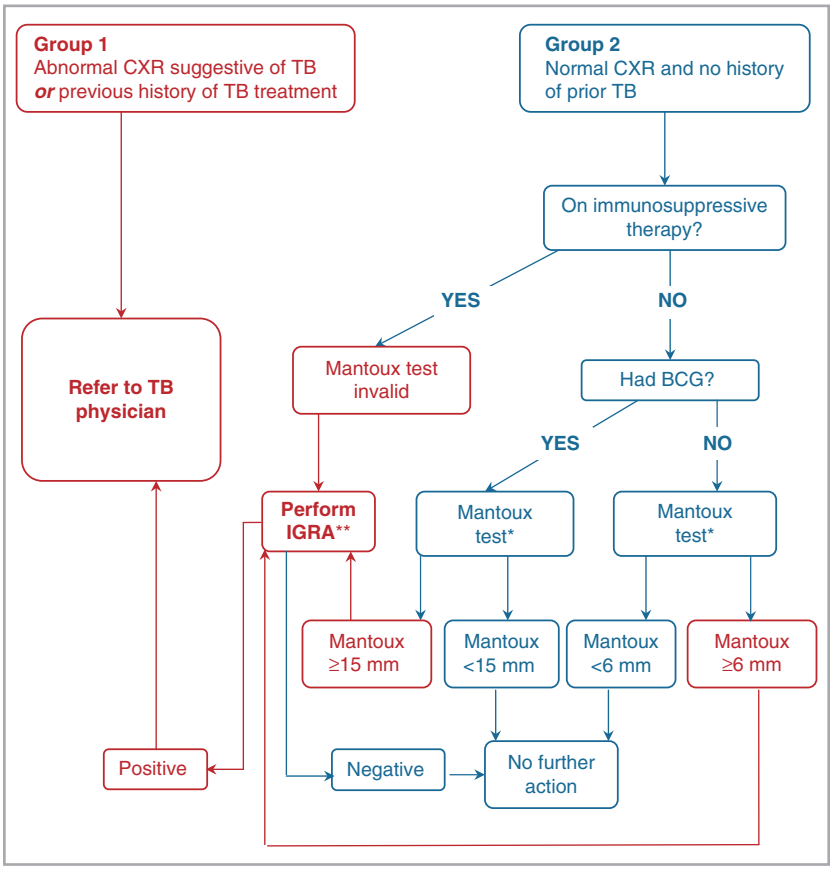

Fig 1. Algorithm for assessment and management of tuberculosis (TB) in patients scheduled for biologic therapy. Adapted from guidelines issued by the Joint Tuberculosis Committee of the British Thoracic Society.[220] CXR, chest X-ray; BCG, bacille Calmette–Guérin. *Interferon gamma release assay (IGRA) may be used in place of Mantoux testing if available. **Seek advice if uncertain how to interpret the result.

advice, and the validity of skin testing in the context of biologic therapy is unproven. Where there is a low incidence of tuberculosis in the community annual testing is unnecessary but in patients with risk factors annual checks for conversion of IGRA may be useful.

Recommendations: Assessment and monitoring for tuberculosis (Fig. 1)

- A pretreatment chest X-ray and Mantoux skin test currently remain the preferred screening tests in patients not on immunosuppression (*Strength of recommendation D; level of evidence 4*)
- Tuberculin testing is not valid in patients already established on immunosuppressive therapy (e.g. methotrexate). IGRA tests may have a role in this group and can be used if practicable, although the positive and negative predictive values are unknown. The T-SPOT.TB test may be more sensitive in patients on immunosuppressive drugs (*Strength of recommendation D; level of evidence 4*)
- Patients with signs to suggest tuberculosis or a history of previous treatment for tuberculosis should be referred to a tuberculosis physician (*Strength of recommendation D; level of evidence 4*)
- Patients with test(s) to support latent tuberculosis should be stratified for risk and considered for prophylactic antituberculous therapy; further advice should be sought from a tuberculosis physician when necessary (*Strength of recommendation D; level of evidence 4*)
- When antituberculous therapy is indicated, patients should complete 2 months of treatment before commencing biologic therapy with either isoniazid (total treatment course 6 months) or rifampicin plus isoniazid (total treatment course 3 months) or rifampicin alone (total treatment course at least 4 months) (*Strength of recommendation D; level of evidence 4*)
- During treatment, and for 6 months following discontinuation, a high index of suspicion for tuberculosis should be maintained, especially in those at high risk (*Strength of recommendation D; level of evidence 4*)
- For patients on biologic therapies longer than 1 year who have negative screening tests for tuberculosis on initiation of therapy, annual assessment for tuberculosis may be considered in high-risk patients using whichever IGRA is locally available (*Strength of recommendation D; level of evidence 4*)

18.6 How should patients be transitioned from one therapy to another?

Patients may need to be transitioned from standard systemic therapy to biologic therapy, from one biologic therapy to another (either the same or different class) or from biologic

therapy to standard systemic therapy. Ideally, there should be a washout period (the length of which is discussed below) between one drug and another so that pretreatment assessments occur off therapy (e.g. baseline disease severity, tuberculin skin tests) and so that the immunosuppressive 'burden' is minimized. However, more commonly, the transition period involves either sequential use of therapy without a 'washout' or a period of overlap between one drug and another, particularly where suddenly stopping therapy is associated with a risk of unstable disease (either treatment- or disease-related).

All the RCTs cited required patients to discontinue standard systemic therapy for at least 4 weeks, and biologic therapy (for the ustekinumab trials) for 3 months, prior to initiating biologic therapies. Given that in the short term, overall, serious adverse events were no greater than placebo, this provides evidence to support 'ideal' washout periods.

In situations where a 'washout' period is not feasible, it should be noted that safety data relating to TNF antagonists indicate additional risks of infection with concomitant use of immunosuppressive therapy. Also, even in the context of apparent treatment failure, loss of a drug's efficacy in psoriasis may not equate to loss of all pharmacological activity. This may be especially pertinent when switching from one biologic therapy to another, given that although these treatments are 'targeted', subsequent immunological events 'downstream' are complex. Standard therapies should be rationalized wherever possible and stopped (or the dose reduced) once response to the biologic treatment is achieved. Methotrexate is not associated with increased toxicity when prescribed with TNF antagonists, and limited data on combined therapy with etanercept and acitretin show no excess toxicity.

When switching from biologic therapy to biologic therapy, given the absence of data, overlap should be avoided. Traditionally, the time taken for a drug to be cleared from the body equates to four times a drug's terminal half-life and is therefore the recommended interval between therapies. Disease flares associated with discontinuation of efalizumab in low or nonresponders respond to standard systemic therapy.[224–226]

Recommendations: Transitioning from one therapy to another

- Standard systemic therapy (with the exception of methotrexate) should be discontinued for 4 weeks prior to initiation of biologic therapy whenever possible to minimize risk of infection and establish baseline disease severity. When necessary, methotrexate cotherapy may be continued at the minimal required dose (*Strength of recommendation B; level of evidence 1+*)
- Where discontinuing standard systemic therapy is associated with risk of severe or unstable disease, use of concomitant systemic therapy should be rationalized during the transition period and stopped as soon as therapeutic efficacy of the biologic therapy is established (*Strength of recommendation D; level of evidence 4*)
- When switching from one biologic therapy to another biologic therapy, overlap should be avoided with the recommended interval being four times the drug half-life (*Strength of recommendation D; level of evidence 4*)

18.7 What are the indications for stopping therapy?

Therapy should be discontinued when patients fail to achieve an adequate response following treatment initiation or when treatment response is not maintained (see section 9.0 for definition of adequate treatment response).

Withdrawal of therapy is also indicated due to the following events:

(i) a serious adverse event. Serious adverse events which may justify the withdrawal of treatment include malignancy (excluding NMSC), severe drug-related toxicity, severe intercurrent infection (temporary withdrawal)

(ii) pregnancy (temporary withdrawal)

(iii) elective surgical procedures (see section 17.3)

19.0 Recommended audit points

Dermatology teams involved in prescribing biologic interventions should use audit as a tool to monitor their service against national guidelines of care. The aim should be to ensure that the service is high in quality, safe and cost-effective. Possible topics for audit might include one or more of the following:

(i) Compliance with NICE guidance for patient selection criteria for prescribing of biologic therapies in psoriasis.

(ii) Compliance with pretreatment assessment of patients referred for biologic therapies.

(iii) Compliance with recommendation that all U.K. patients initiating biologic therapy should be registered with the BADBIR.

(iv) Compliance with withdrawal recommendations for biologic therapies in patients who fail to respond adequately or develop significant adverse events.

(v) Patient satisfaction survey of biologic therapies care.

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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 Institute for Health and 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[a]
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 signifi cant risk that the relationship is not causal[a]
3	Nonanalytical studies (e.g. case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

Strength of recommendation

Class	Evidence
A	• At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, **or** • 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 • Evidence drawn from a NICE technology appraisal
B	• A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, **or** • Extrapolated evidence from studies rated as 1++ or 1+
C	• A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, **or** • Extrapolated evidence from studies rated as 2++
D	• Evidence level 3 or 4, **or** • Extrapolated evidence from studies rated as 2+, **or** • Formal consensus
D (GPP)	• A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT, randomized controlled trial.