Introduction and objectives

Why do we need to update the RA biologics guidelines on the safety of anti-TNF therapies?

Inhibitors of TNF-α represent important treatment advances for a number of inflammatory conditions, including RA. TNF-α inhibitors offer a targeted strategy that contrasts with the non-specific immunosuppressive agents traditionally used to treat most forms of systemic inflammation. Information on who benefits from these agents and on their adverse effects continues to be collected through clinical studies, case series and reports and through national registries.

In 2001 and 2005, the British Society for Rheumatology (BSR) established and updated guidelines for the use of anti-TNF drugs in RA [1, 2]. These guidelines have indicated which adult patients with RA should be eligible for treatment with anti-TNF therapies, precautions that need to be taken in their use and action that should be taken in the event of adverse effects. The previous guidelines applied to the then-available anti-TNF therapies (etanercept and infliximab in 2001 [1], and etanercept, infliximab and adalimumab (first-generation anti-TNF agents) in 2005 [2]). Due to the large volume of information now available on these agents the BSR has, in 2010, produced separate guidelines on eligibility for anti-TNF treatment in RA (in press) These current guidelines cover the safety aspects of anti-TNF treatment in RA and apply to the first-generation products but also to the newly licensed second-generation anti-TNF drugs, certolizumab pegol and golimumab. There are relatively little safety data specifically for these second-generation agents but there are no data thus far to suggest that their side-effect profile would differ significantly from the first-generation agents. This is a rapidly changing field with new data emerging each month, so it is vital that clinicians keep up to date with this area of practice. These guidelines have
incorporated information that was available to the authors at the time of their completion (November 2009).

What are the objectives of these guidelines?
The scope for the guidelines was agreed by the BSR RA Biologics Guidelines Group (BSRBG) in 2007, with a view to producing recommendations on the safety aspects and the appropriate use of anti-TNF drugs in RA.

As a principle, the group also agreed to review other available guidelines (previous BSR [2], EULAR [3], ACR [4] and other international guidelines), and endorse these where appropriate. The group was mindful of the need not to reproduce the considerable work of other evidence-based guidelines, and to concentrate on those areas that were most relevant to patients and health-care professionals in clinical practice in the UK.

Who is the target audience for these guidelines?
These guidelines are directed at all UK health-care professionals who are involved in assessing patients for anti-TNF therapies and responsible for the monitoring of these drugs for efficacy and toxicity. They may also provide a model for other countries in their approach to managing anti-TNF safety issues.

Clinical situations covered by these guidelines
These guidelines provide a best-practice approach to the evidence-based use of anti-TNF therapies in RA.

What are the areas that the present guidelines do not cover?
These guidelines do not cover the use of anti-TNF drugs in other inflammatory arthropathies or diseases. They do not cover anti-TNF drugs that are still at an experimental stage of development.

How have the patients’ views been incorporated into the guidelines?
The National Rheumatoid Arthritis Society provided patient representation on the BSRBG. Final drafts of the guidelines have been circulated to patient representative bodies for comment, and feedback has been incorporated where appropriate. Drafts of the guidelines were also circulated at the BSR Annual General Meeting in Glasgow in April 2009, and feedback considered, and incorporated where appropriate.

What is the evidence to support these guidelines?
The guidelines are referenced throughout, and where new research has been performed to inform the guidelines this is included in detail in the text. Comprehensive literature searches were performed by T.D. and J.M.L., using relevant search terms to seek evidence to determine what changes to the previous BSR safety guidelines were required. Searches were conducted using primarily MEDLINE and PubMed. A manual search from the references cited by generated articles was also used. All searches were performed for literature up to October 2009. Abstracts were read for relevant evidence from the BSR, EULAR and ACR annual conferences up to October 2009. Evidence was graded according to the strength of literature to support each statement, using the grading suggested by the Royal College of Physicians of London (National Clinical Guidelines for Stroke by the Intercollegiate Stroke Working Party, June 2004 http://www.rcplondon.ac.uk/pubs/books/stroke/stroke_guidelines_2ed.pdf, 22 June 2010, date last accessed; Appendix I) and the document was prepared in accordance with the principles outlined in the Appraisal of Guidelines Research and Evaluation (AGREE) guidelines (www.agreecollaboration.org).

How will these guidelines be piloted and introduced?
These guidelines are an update of previous successful guidelines and will be published via the BSR.

How often will these guidelines be reviewed?
The guidelines will be revisited either in 3 years or sooner if major changes are required in the light of future published anti-TNF safety information.

How will these guidelines be publicized and implemented?
The full guidelines will be published on the BSR website, and sent to all BSR members and primary care trusts. A summary of the guidelines will be published in *Rheumatology*, with web links to the full guidelines.

Cost implications and conflicts of interest
No funding has been received to assist with the development of these guidelines. These guidelines have been developed with complete editorial independence. The conflicts of interest of contributors are listed at the end of this document.

Infection

Infection in general

Recommendation 1: anti-TNF therapy should not be initiated in the presence of serious active infections. (Level III evidence, Grade of recommendation B.)

Recommendation 2: anti-TNF therapy should be discontinued in the presence of serious infections, but can be recommenced once the infection has resolved clinically. (Level III evidence, Grade of recommendation B.)

Recommendation 3: use anti-TNF therapy with caution after discussing the relative risks (RRs) and benefits in the following circumstances:

- chronic infected leg ulcers;
- septic arthritis of a native joint within the last 12 months;
- sepsis of a prosthetic joint within the last 12 months, or indefinitely if the joint remains in situ;
- persistent or recurrent chest infections;
- indwelling urinary catheter;
- bronchiectasis; and
- hypogammaglobulinaemia.

(Level IV evidence, Grade of recommendation C.)

Serious infection (leading to hospital admission, i.v. antibiotics or death) is a major contributor to the increased mortality seen in RA patients—the risk is estimated to be twice that of the general population [5]. RA severity and extra-articular disease are also independently associated with infection [5]. Therefore, when deciding whether any drug raises infection risks, greater background infection rates in RA need to be taken into account. More severely affected patients are more likely to be on anti-TNF therapy while at the same time having an elevated background risk of infection.

Post-marketing surveillance and observational studies provided the first indications that TNF inhibitors are associated with an increased risk of serious infections [6, 7]. Data from individual randomized trials and observational studies were, however, inconsistent on this issue with reports of both increased risk [8–12] and of no increased risk [13–17]. The limitation of small numbers of patients in randomized controlled trials (RCTs) was addressed in a systemic review and meta-analysis of nine RCTs of infliximab and adalimumab that included 3493 patients who received TNF inhibitors and 1512 who received placebo [18]. The following observations were reported: pooled odds ratio (OR) for serious infections among patients treated with a TNF inhibitor was 2.0 (95% CI 1.3, 3.1) and for serious non-granulomatous infections was 1.9 (95% CI 1.2, 2.9) in RA patients receiving infliximab or adalimumab.

An increased risk of infection has also been noted in an observational study from a German registry. An RR of serious infections of 2.2 (95% CI 0.9, 5.4) for etanercept (64 per 1000 pyrs) and 2.1 (95% CI 0.8, 5.5) for infliximab (62 per 1000 pyrs) was found for 512 RA patients on etanercept and 346 on infliximab when compared with patients on DMARDs only (23 per 1000 pyrs) [19]. The registry data included viral and fungal infections, tuberculosis (TB) and bacterial infections. The Spanish registry also showed a 1.6-fold increase in rate of serious infection of 2868 pyrs for patients on anti-TNF drugs compared with 2433 pyrs for controls [20].

In contrast, the British Society for Rheumatology Biologics Registry (BSRBR) found no increase in serious infections in patients treated with anti-TNF therapies when compared with patients on conventional DMARDs [21]. This was an observational study of 7664 anti-TNF- and 1354 DMARD-treated RA patients. The incidence of serious infections in the anti-TNF group was 53.2 per 1000 person-years (pyrs) vs 41.2 in the control group. However, the frequency of serious skin and soft-tissue infections was increased in the anti-TNF-treated patients [incidence rate ratio (IRR) of 4.2]. Nineteen serious bacterial intracellular infections occurred, all in patients in the anti-TNF-treated cohort. Further analysis of the BSRBR data has, however, suggested that the way in which UK rheumatologists select patients for starting and discontinuing anti-TNF therapy may have influenced the lack of observed increased risk of infection in this study, and that important increases in true risk may exist, particularly in the early stages of treatment [22]. The most recent data presented from the BSRBR (2009) have shown that exposure to anti-TNF therapy is associated with an increased risk of septic arthritis, with incident rates of 5.0/1000 pyrs (95% CI 4.3, 5.8) in anti-TNF-treated RA patients compared with 1.9/1000 pyrs (95% CI 1.1, 3.0) in the DMARD control group [23].

In summary, although data from individual randomized clinical trials and the BSRBR failed to demonstrate a consistent increase in treatment-related infections, data from the meta-analysis of randomized clinical trials, the German and Spanish registries, and a re-analysis of BSRBR data, are consistent with the concept that TNF inhibitor use is associated with an approximate doubling of risk of serious infection, particularly early on in the course of therapy [22, 24].

Should infection develop in a patient treated with anti-TNF there is some evidence to suggest that infections may become more severe if patients continue with anti-TNF therapy [25]. Patients, therefore, need to be aware of the increased risk of infection, and that they should stop anti-TNF therapy until the infection has clinically resolved. Clinicians also need to be vigilant in assessing for infection, including joint infection, in patients treated with anti-TNF.

Anti-TNF therapies may also pose unacceptable additional infection risk to subgroups of RA patients with high background risk of infection (e.g. bronchiectasis). Unfortunately these risks have not been addressed adequately in the literature to date. This was highlighted by Lieberman-Maran et al. [26], when they reported on two RA patients who, having developed pneumonia while on infliximab or adalimumab, were diagnosed with bronchiectasis. Their literature review highlighted that data on any potential association between increased infection risk with anti-TNF and bronchiectasis were limited as many anti-TNF therapy trials have excluded patients with a history of bronchiectasis and most studies assessing infection risk have not included subgroup analysis for bronchiectasis.

Mycobacterial infections

Recommendation 4: prior to commencing treatment with anti-TNF therapy, all patients should be screened for mycobacterial infection in accordance with the latest National guidelines. Active mycobacterial infection needs to be adequately treated before anti-TNF therapy can be started. (Level IIb evidence, Grade of recommendation B.)

Recommendation 5: prior to commencing anti-TNF therapy, consideration of prophylactic anti-TB therapy (as directed by the latest National guidelines) should be given to patients with evidence of potential latent disease (past history of TB or abnormal chest X-ray). (Level IIb evidence, Grade of recommendation B.)

Recommendation 6: all patients commenced on anti-TNF therapies should be closely monitored for serious infection and bacteremia, as directed by the latest UK guidelines. (Level IIb evidence, Grade of recommendation B.)
mycobacterial infections. This should continue for at least 6 months after stopping treatment due to the prolonged elimination phase of the drug. (Level IV evidence, Grade of recommendation C.)

Recommendation 7: patients on anti-TNF therapy who develop symptoms suggestive of mycobacterial infections should receive full anti-mycobacterial chemotherapy, but may continue with their anti-TNF therapy if clinically indicated. (Level IV evidence, Grade of recommendation C.)

Most published studies have compared the incidence of TB in patients on TNF inhibitors with the baseline population risk but there is now a well-established increased risk of TB associated with anti-TNF therapy. The particularly high anti-TNF-associated TB case rates reported from the Spanish registry (1113 per 100,000 (post TB screening) for infliximab, [6]), Korea (2558 per 100,000 for infliximab, [27]), Japan (325 per 100,000 for infliximab, [28]) and Portugal (1500 per 100,000 for infliximab, [29]) are most likely to reflect the high incidence of latent TB infection in these countries; lower rates are reported in other countries such as the USA (61.9 per 100,000 for infliximab, [30]) and Sweden (145 per 100,000 for infliximab, [31]).

Important differences in the risk of latent TB reactivation exist among the first-generation drugs, with the risk being higher with infliximab and adalimumab than with etanercept [6, 7, 27, 31, 32]—a finding confirmed with recently published data from the French and British biologic registries [33, 34]. Data from the BSRBR have shown that the rate of TB was higher with the mAbs adalimumab (144 events/100,000 pyrs) and infliximab (136 events/100,000 pyrs) than with etanercept (39 events/100,000 pyrs). After adjustment, the IRR compared with etanercept-treated patients was 3.1 (95% CI 1.0, 9.5) for infliximab and 4.2 (95% CI 1.4, 12.4) for adalimumab [34]. The risk of TB reactivation from certolizumab pegol is uncertain, as experience with this newer drug is limited. Several cases of TB were reported in clinical trials of certolizumab pegol for the treatment of RA, whereas no cases occurred in the control arms [35, 36].

TB has been shown to occur sooner after starting infliximab than etanercept. Forty-three per cent of infliximab-associated cases occurred during the first 90 days of treatment, a pattern consistent with reactivation of latent infection. In contrast, etanercept-associated TB cases were distributed evenly throughout the reporting period, with only 10% occurring during the first 90 days of treatment [7].

TB occurring in association with TNF inhibitors has a higher likelihood of involving extrapulmonary sites and of being disseminated at presentation when compared with other TB cases. The majority of these cases have had a known history of previous TB, again suggesting reactivation of latent disease [37].

Appropriate screening for evidence of previous exposure or for latent TB, prior to commencing anti-TNF therapy can minimize the risk of developing TB. The efficacy of screening was demonstrated in the Spanish registry of patients with rheumatic disease treated with TNF inhibitors, Biobadaser. The impact of mandated recommendations, implemented in 2002, regarding screening for and treatment of latent TB infection [38] was investigated. A 78% reduction in TB case rates was noted following mandated screening but the risk still appeared to be higher than that of the general population. Furthermore, Gomez-Reino et al. have shown that failing to follow recommendations on screening is associated with a 7-fold increase in risk of TB [39].

New screening tests for latent TB (Quantiferon and the T-spot) have been developed over recent years but their role has not been fully validated in the rheumatoid population and they are not widely available to clinicians. However, they may have improved sensitivity in the immunosuppressed host (including patients with HIV infection) and might prove useful in those who have received Bacille Calmette-Guérin (BCG) immunization [40]. The cost of Quantiferon (£35/test) and T-spot (£100/test) screening of all UK patients prior to treatment with anti-TNF would prove prohibitive (personal communication: P. Ormerod, Blackburn Royal Infirmary). At the age of 50 years the annual incidence of active TB disease in the UK White Caucasian population is ~5/100,000 and the incidence of latent TB is approximately 10 times this level (50/100,000). Therefore, the number of tests needed to detect one case of latent infection would be 2000, at a cost of £70,000 with Quantiferon and £200,000 with the T-spot test. The economics improve slightly in older patients but are much worse (more than double the cost) for patients under the age of 35 years. The cost-effectiveness is better for patients from ethnic minorities known to be at higher risk of TB. For patients from South Asia, the incidence of TB is 120/100,000 and in black Africans it is 240/100,000, and this reduces the numbers needed to test to detect one positive case to 82 and 41, respectively. The true-negative predictive value of a negative test or the true-positive predictive value of a positive test is still not known, however, and these tests are currently therefore not recommended by the British Thoracic Society as TB-screening tools. National Institute for Clinical Excellence (NICE) are currently developing guidelines on the use of these IFN-γ tests for diagnosing latent TB with a planned publication date of November 2010.

Atypical mycobacterial infections

The numbers are too small to draw any significant conclusions but there are now many case reports of various atypical mycobacterium infections associated with all three first-generation anti-TNF drugs (Table 1). In a recent review of the US Food and Drug Administration (FDA) MedWatch database for reports of non-tuberculous mycobacteria (NTM) infections in patients receiving anti-TNF-α therapy, 239 reports were recorded. Of those reports, 105 (44%) met NTM disease criteria [41]. The median age of patients was 62 years; the majority of patients were females [66 (65%)] had RA [73 (70%)]. and were taking prednisolone [68 (65%)] or MTX [58 (55%)] concurrently. NTM infections were associated with infliximab (n = 73), etanercept (n = 25) and adalimumab (n = 7).
for RA infections reported in patients receiving anti-TNF therapy [42].

A previous review of US data on more than 233,000 patients treated with infliximab from 1998 to 2002, [7] showed that 30 patients developed unspecified mycobacterial species infection. Mycobacteria other than TB (MOTT) is rare and it remains difficult to determine whether cases associated with anti-TNF therapy are due to reactivation or primary infection. Cases of MOTT associated with TNF inhibitors may progress rapidly but have to date responded well to treatment and withdrawal of anti-TNF treatment [42].

Other opportunistic bacterial and fungal infections

Recommendation 8: patients on anti-TNF should be informed of appropriate food hygiene (see Arthritis Research Campaign patient information leaflets on etanercept [53], infliximab [54] and adalimumab [55]). (Level III evidence, Grade of recommendation B.)

Recommendation 9: health-care professionals managing patients on anti-TNF therapy should be aware of the risk of opportunistic infections in patients on anti-TNF therapy. They should have a high index of suspicion for atypical and opportunistic infections, and anti-TNF therapy should be promptly stopped in suspected cases and patients should have rapid access to specialist health care for consideration of early antibacterial/anti-fungal treatment. (Level III evidence, Grade of recommendation B.)

Food-borne infections from both *Listeria* and *Salmonella* have been reported with anti-TNF therapy. *Listeria* can be found in uncooked meat, vegetables, unpasteurized milk or foods prepared from raw milk. One report on 15 patients with *Listeria* infection while on anti-TNF therapy [56], indicated that 14 of the 15 cases were associated with infliximab with the remaining case occurring with etanercept. A further case of *Listeria* sepsis with infliximab [57], two cases of *Listeria* meningitis with etanercept [58] and infliximab [59] and a case of joint sepsis with adalimumab [21] have also been reported.

Wallis et al. [7] reported on data collected by the Adverse Event Reporting System (AERS) of the US FDA. Between January 1998 and September 2002, 323 cases of granulomatous infections were found in patients treated with infliximab or etanercept, including 38 cases with listeriosis (36 cases associated with infliximab and 2 with etanercept).

*Salmonella* can be spread through contaminated raw eggs, unpasteurized milk and undercooked meat. Wallis et al. [7] have identified 11 cases of anti-TNF-associated *Salmonella* infection (7 cases with infliximab and 4 cases with etanercept) from the FDA’s AERS. Two cases of *Salmonella* septic arthritis have been reported with etanercept and a further two have been reported with infliximab [57, 60]. Three cases of *Salmonella* septicaemia have been reported with anti-TNF therapy [61].

Invasive fungal infections (IFIs) are also reported with anti-TNF therapy. A recent review by Tsiodras et al. [62] reported on MEDLINE and PubMed database searches for reports on IFIs associated with the three available anti-TNF therapies. Of the 281 cases of IFI associated with TNF-α inhibition, 226 (80%) were associated with infliximab, 44 (16%) with etanercept and 11 (4%) with adalimumab. The most prevalent IFIs were histoplasmosis [n = 84 (30%)], candidiasis [n = 64 (23%)], aspergillosis [n = 64 (23%)] and *Coccidioides* species [n = 29 (10%)]. Pneumonia was the most common pattern of infection.

*Pneumocystis jiroveci* pneumonia (formerly known as *Pneumocystis carinii* pneumonia (PCP)) is also reported with each of the anti-TNF agents. Eighty-four cases of PCP pneumonia with infliximab were reported from the FDA safety database; the majority of these patients were also on other immunosuppressants [63]. There are further case reports of PCP infection following infliximab [64–66], etanercept [67] and adalimumab [68] therapy. The risk of PCP has been reported to correlate with high-dose glucocorticoid use [69] but, to date, there are inadequate data to support the use of primary prophylaxis.

**TABLE 1** Mycobacteria other than TB (MOTT)-associated infections reported in patients receiving anti-TNF therapy for RA

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<thead>
<tr>
<th>MOTT infections</th>
<th>Anti-TNF therapy</th>
<th>References</th>
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<tbody>
<tr>
<td><em>Mycobacterium abscessus</em></td>
<td>Infliximab and</td>
<td>[43, 44]</td>
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<tr>
<td><em>Mycobacterium avium</em> complex</td>
<td>etanercept</td>
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<td><em>Mycobacterium chelonae</em></td>
<td>Infliximab</td>
<td>[42, 45, 46]</td>
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<td><em>Mycobacterium fortuitum</em></td>
<td>Etanercept</td>
<td>[47, 48]</td>
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<td><em>Mycobacterium mucogenericum</em></td>
<td>Etanercept</td>
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<td><em>Mycobacterium szulgai</em></td>
<td>Etanercept</td>
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<td><em>Mycobacterium xenopi</em></td>
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<td><em>Mycobacterium chelonae</em></td>
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<td><em>Mycobacterium fortuitum</em></td>
<td>Etanercept</td>
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**Varicella infections**

Recommendation 10: if a patient on anti-TNF treatment, or one of their household contacts, develops primary varicella (chickenpox), and if the risks from infection are perceived to be significant, the patient should be considered for varicella zoster immune globulin (VZIG). Shingles should be treated conventionally. (Level IIb evidence, Grade of recommendation B.)

Experience with primary varicella infection is limited as >90% of the adult population have evidence of serologic immunity and all bar a very few cases of varicella infection are due to reactivation [70]. Several case reports highlight risks from varicella zoster reactivation, in patients treated with anti-TNF therapy. Infliximab has had the highest rate of reports [71, 72] but cases have also been reported with etanercept [73] and adalimumab [74].

In a prospective study that included 5040 patients receiving a variety of DMARDs for RA, TNF-α inhibitors were associated with a moderately increased risk of herpes zoster [75]. There were 86 cases of herpes...
zoster among 82 patients. Fifteen patients had multidermatomal zoster, and four had herpes zoster ophthalmicus. Eighteen events were serious with 12 requiring hospitalization due to either severe multidermatomal disease \((n = 8)\), eye involvement \((n = 1)\) or other reasons \((n = 3)\). Complications were reported in three patients; post-herpetic neuralgia occurred in two patients (one while receiving etanercept and one while receiving adalimumab) and multidermatomal zoster with oesophagitis and pulmonary involvement occurred in one patient (while receiving infliximab). A statistically significant association between infliximab or adalimumab use and herpes zoster was observed after adjustment for age, disease severity and prednisolone use \([\text{hazard ratio (HR)} 1.82; 95\% \text{ CI 1.05, 3.15}]\). The risk was also increased with etanercept, although it did not achieve statistical significance.

Similarly, Smitten et al. \([76]\), analysed two large databases in the USA and UK and reported an increased risk of herpes zoster in patients receiving any disease-modifying treatment—the OR, when compared with RA patients not receiving DMARDs or glucocorticoids, was 1.54 \((95\% \text{ CI 1.04, 2.29})\) for patients receiving anti-TNF, 1.37 \((95\% \text{ CI 1.18, 1.59})\) for patients receiving conventional DMARDs alone and 2.51 \((95\% \text{ CI 2.05, 3.06})\) for patients receiving glucocorticoids.

In contrast to the studies described above, two large retrospective studies of patients with RA did not demonstrate an increased risk of herpes zoster in patients receiving TNF-\(\alpha\) inhibitors \([77, 78]\). Most of the reported cases of varicella zoster reactivation did well with conventional anti-viral treatment.

Little data are available on the effectiveness of VZIG in preventing infection in immunosuppressed patients. One study of immunosuppressed children who had household exposure to varicella \([79]\) demonstrated a moderate response to VZIG; however, 49 of 81 recipients of VZIG \((60\%)\), including some patients who had serological evidence of past varicella exposure, still developed varicella infection. The BSR has previously produced guidelines \((2002)\) on immunizations in immunosuppressed patients, which recommend the use of VZIG if contact with varicella is significant \([70]\). Until more data are available on anti-TNF-treated patients we feel it appropriate to recommend that VZIG is considered for such patients exposed to varicella infection in whom the risks of infection are perceived to be high.

**Hepatitis**

Small numbers of case reports and case series continue to be published on anti-TNF therapy in patients with hepatitis B and C.

**HBV**

Recommendation 11: screening for risk factors for HBV infection should be performed prior to commencing anti-TNF therapy and HBV tests should be performed in patients with risk factors. In patients who are HBV positive, a risk : benefit assessment should be undertaken, as anti-TNF treatment may be safe if appropriate anti-viral treatment is given. \((\text{Level IV evidence, Grade of recommendation C.)}\)

Recommendation 12: close monitoring of serum aminotransaminases and HBV DNA load during therapy should be considered in patients with HBV treated with anti-TNF therapy and concomitant anti-viral treatment would be recommended. \((\text{Level IV evidence, Grade of recommendation C.)}\)

Recommendation 13: patients with serological evidence of cleared past infection \([\text{HBsAg negative/core antibody (anti-HBcAb) positive}]\) should have their HBV serology monitored during therapy and may require concomitant anti-viral treatment if detrimental changes develop. \((\text{Level IV evidence, Grade of recommendation C.)}\)

When anti-TNF therapies have been used in HBV-infected patients who have also received concomitant anti-viral treatment the outcome from case reports has been good for infliximab, etanercept and adalimumab with no evidence of viral reactivation \([80–83]\). Serum aminotransaminases remained normal and there was no increase in viral load during treatment with each of the three anti-TNF agents. A further report on two HBV-infected RA patients and one HBV-infected SpA patient also indicated a good outcome of treatment with anti-TNF agents when concomitant lamivudine is used \([82]\).

The outcome from case reports of HBV-infected patients with RA and seronegative arthritis treated with anti-TNF therapy has been less favourable, however, when concomitant anti-viral treatment is not prescribed \([84–88]\). Reactivation of HBV infection in these cases was controlled with the introduction of lamivudine. Although there have been reports of a few patients doing well on anti-TNF without anti-viral prophylaxis \([89]\), the European Association for the Study of the Liver recommends that anti-viral therapy begins 2–4 weeks prior to the start of a TNF inhibitor in patients with inactive hepatitis B \([80]\). The duration of treatment required is currently unknown but may need to be life long.

There are some reports indicating that anti-TNF may be safe in patients with serological evidence of cleared past infection with hepatitis B \((i.e. \text{HBsAg-negative/anti-HBcAb-positive})\) without the need for anti-viral prophylaxis \([89]\). However, Charpin et al. \([90]\) have reported a significant decrease in anti-HBsAb titre in a proportion of patients treated with anti-TNF and recommended that HBV serology titres should be monitored in these patients, especially in those with a low anti-HBsAb titre at baseline.

**HCV**

Recommendation 14: screening for risk factors for HCV infection should be performed prior to commencing anti-TNF and HCV tests should be performed in patients with risk factors. Although studies to date suggest that anti-TNF therapies do not have a detrimental effect on HCV infection, anti-TNF should continue to be used with caution in such patients. \((\text{Level III evidence, Grade of recommendation B.)}\)

Recommendation 15: close monitoring of serum aminotransaminases and HCV RNA during therapy should be
performed in patients with HCV treated with anti-TNF therapy. (Level III evidence, Grade of recommendation B.)

There are a number of case reports and series demonstrating a good response to anti-TNF treatment, with no reactivation of HCV infection, regardless of whether concomitant anti-viral treatment is prescribed. Peterson et al. [92] reported no significant adverse events or significant changes in liver aminotransaminase levels among 24 patients with chronic HCV infection and RA who received infliximab or etanercept therapy. They also reported no change in HCV RNA viral load in six patients but some reduction in HCV RNA viral load in the remaining 16 patients.

Zein [93] reported on a small, randomized, placebo controlled trial (25 patients in each arm) of etanercept as adjuvant therapy to ribavirin in HCV-infected patients. More patients in the etanercept arm met the primary endpoints of normal alanine transaminase, absence of serum HCV RNA and absence of serious adverse side effects.

Further case reports/series for each of the anti-TNF agents have also reported good outcomes from anti-TNF treatment when used in HCV-infected patients with RA or seronegative arthropathies [81, 82, 88, 94–99]. There has been just one case report of HCV reactivation with etanercept [100].

HIV

Recommendation 16: risk factors for HIV infection should be documented prior to commencing anti-TNF therapy and, if present, an HIV test should be done. (Level III evidence, Grade of recommendation B.)

Recommendation 17: in considering anti-TNF use in HIV-positive patients, the following should influence decision-making, that a reasonable benefit to risk ratio exists for HIV patients if: (i) HIV infection is controlled and patients are not severely immunosuppressed (e.g. CD4 count >200 and HIV viral load <60 000 mm³); (ii) anti-TNF therapy is given in combination with highly active anti-retroviral therapy (HAART); and (iii) close monitoring of viral load and CD4 count is undertaken after anti-TNF therapy is started, and treatment changes are made in light of these results. (Level III evidence, Grade of recommendation B.)

There are several case reports describing the use of TNF inhibitors to treat RA or other inflammatory conditions in the setting of HIV infection [101–104]. In general, these reports suggest that TNF inhibition is well tolerated by HIV-infected patients, provided that HIV treatment is well established before initiation of TNF inhibitor therapy.

Cepeda et al. [101] reported recently on a retrospective open-label case series in the USA. Eight patients (two patients with RA, three with psoriatic arthritis, one with uSpA, one with ReA and one with AS) received treatment with etanercept and four of these eight patients went on to receive infliximab or adalimumab after not achieving a response with etanercept. All patients had a CD4 level >200 and a HIV viral load <60 000 mm³. Five patients were on HAART (three or more highly potent anti-HIV drugs, including reverse transcriptase inhibitors and protease inhibitors, used in combination) and three were not. Patients were followed up for 28 months (s.d. 20.9 months) and no significant clinical adverse effect was attributed to anti-TNF treatment (no disease progression related to HIV CD4 count and viral load, and no opportunistic infections).

There are also some individual case reports on the use of anti-TNF agents in HIV-infected patients with co-existent rheumatic disease; all patients treated with HAART had good clinical outcomes [94, 102–105].

Peri-operative infection

Recommendation 18: in RA patients on anti-TNF therapies, the potential benefit of preventing post-operative infections by stopping treatment (different surgical procedures pose different risks of infection and wound healing) should be balanced against the risk of a peri-operative flare in RA activity. (Level Ila evidence, Grade of recommendation B.)

Recommendation 19: if anti-TNF treatment is to be stopped prior to surgery, consideration should be given to stopping at a time three to five times the half-life for the relevant drug before surgery (infliximab 8–9.5 days, etanercept 100 h, adalimumab 15–19 days). (Level IV evidence, Grade of recommendation C.)

Recommendation 20: anti-TNF should not be restarted after surgery until there is good wound healing and no evidence of infection. (Level IV evidence, Grade of recommendation C.)

Current literature provides conflicting data with regard to the risk of infection peri-operatively in association with anti-TNF therapy. A retrospective study from The Netherlands [106], reported on 1219 surgical procedures in 768 RA patients. The study demonstrated that peri-operative continuation of anti-TNF therapy does not seem to be an important risk factor for surgical site infection. Similarly, a small prospective study by Bibbo and Goldberg [107] found that, in RA patients undergoing elective foot and ankle surgery, peri-operative use of anti-TNF agents was not associated with increased risk of infectious or healing complications.

However, several other studies have reported an increased risk of peri-operative infection rates with continued use of anti-TNF agents. One report showed that the continuation of anti-TNF therapy was associated with an increased risk of peri-operative infections (OR 4.4; 95% CI 1.10, 18.41) in a series of 91 RA patients who underwent orthopaedic procedures between 1999 and 2004 [108]. This association remained statistically significant after adjustment for age, sex and disease duration (OR 4.6; 95% CI 1.1, 20.0); prednisolone use, diabetes and serum RF status (OR 5.0; 95% CI 1.1, 21.9); and all six variables simultaneously (OR 5.3; 95% CI 1.1, 24.9). Ruyssen-Witrand et al. [109] reported on 770 patients treated with TNF blockers, of whom 92 underwent surgery (127 surgical procedures). Seventy-seven per cent of patients had RA and most of the surgical procedures
undertaken were orthopaedic (85%). The complication rates for orthopaedic procedures and for abdominal procedures were 13 and 43%, respectively—higher than the reported rates for surgery in RA patients [7% (orthopaedic) and 13% (abdominal)]. Dixon et al. [110] have analysed data from the BSRBR and found that the risk of serious post-operative infection is nearly 2-fold higher in patients who received anti-TNF therapy in the 28 days prior to surgery than in those who were not exposed.

Pappas and Giles [111] assessed peri-operative infection risks of anti-TNF therapy associated specifically with orthopaedic surgery. All studies assessed involved retrospective outcome data and the source populations differed greatly between studies making direct comparison difficult. Of the six published major studies, only one study [108] identified an increased risk associated with peri-operative anti-TNF exposure but the authors recommended that anti-TNF therapy should be stopped for a duration of three to five times their half-lives and restarted once the wound healing is deemed satisfactory (10–14 days).

Immunization

Recommendation 21: when considering primary immunizations and live attenuated immunizations in patients on anti-TNF therapy, it should be acknowledged that data on the effects of anti-TNF therapies are limited. Until further evidence is available, the BSR recommendations on the use of immunizations in patients on immunosuppressive therapy should be adhered to in patients on anti-TNF therapy [70]. (Level IV evidence, Grade of recommendation C.)

Recommendation 22: although there may be an attenuated response (particularly if MTX is being co-prescribed), patients on anti-TNF therapy should receive both influenza (including vaccines generated for specific flu outbreaks such as the recent Swine flu) and pneumococcal immunizations unless there are contraindications. (Level IV evidence, Grade of recommendation C.)

Recommendation 23: prior to commencing anti-TNF therapy, hepatitis B immunization should be considered for at-risk patients. (Level IV evidence, Grade of recommendation C.)

Patients receiving immunosuppressive therapy are advised to have both influenza and pneumococcal immunization. There have been only a few studies investigating the administration of vaccines in rheumatoid patients with assessments made on RA patients treated either with MTX alone or in combination with anti-TNF. A study [112] in SLE has shown that these patients had slightly lower response rates than expected for the healthy population but the disease itself could be an additional factor for decreased responsiveness. There are now some data, as detailed below, on the titre response to specific immunizations in patients receiving anti-TNF therapy. The effects of live attenuated vaccines in patients receiving anti-TNF agents remain unknown but these vaccines are not recommended in patients receiving anti-TNF treatment.

Influenza immunization

There is some evidence that there are differences between each of the first-generation anti-TNF agents in terms of response to influenza immunization. Adalimumab has been shown not to reduce responsiveness to immunization, whether used as monotherapy or in combination with MTX [113]. However, studies findings for etanercept and infliximab [114, 115] indicate that these drugs should be considered as factors that could lead to decreased response rates. A recent review [114] of influenza studies has indicated that this immunization is well tolerated and effective with or without the administration of MTX. However, a subset of patients may remain unprotected.

Pneumococcal immunization

MTX is associated with lower response rates to pneumococcal vaccines in most studies in patients with RA, SLE and other rheumatological diseases [113, 116–119]. In contrast, the use of etanercept or infliximab with MTX has not been associated with poor response [113, 116, 117, 119]. The theory that certain anti-TNF agents can lead to enhanced immune responses was put forward from one study [116], where patients with MTX had lowered responsiveness, but those with the combination of infliximab or etanercept with MTX had even better response rates than the healthy controls. The use of adalimumab alone has not been shown to affect antibody titre response to pneumococcal immunization, but the combination of MTX and adalimumab has resulted in decreased response rates when compared with MTX alone [113]. In order to increase the chance of developing protective antibody titres, it has been suggested that pneumococcal immunization should be considered before starting MTX in combination with adalimumab [118].

Hepatitis B immunization

There are limited data with regard to response to hepatitis B immunization in rheumatic patients on anti-TNF therapy. A study by Ravikumar et al. [120] suggests that TNF blockade with etanercept decreases responses to the hepatitis B vaccine. Patients with RA, who were treated with MTX, had very good response rates, whereas those treated with an MTX-etanercept combination or etanercept alone had poor response rates. Hepatitis B immunization is recommended for all unvaccinated adults at risk for HBV infection, ideally prior to starting anti-TNF treatment.

Duration of immunization response

Antibody levels in rheumatoid patients on DMARD therapy have been shown to decline faster than in those not on DMARD therapy and this raises the question of whether such patients should be revaccinated more frequently than standard recommendations [121]. No data to support specific recommendations are yet available on this issue for patients on anti-TNF therapy.
Malignancy

Recommendation 24: patients commencing anti-TNF therapy should be informed that overall there is no conclusive evidence for an increased risk of solid tumours or lymphoproliferative disease with the anti-TNF therapies above that which would be expected for the rest of the RA population, but ongoing vigilance is required. (Level Ia evidence, Grade of recommendation A.)

Recommendation 25: patients should be investigated for potential malignancy if clinically suspected, and anti-TNF treatment should be stopped if malignancy is confirmed. (Level III evidence, Grade of recommendation B.)

Recommendation 26: caution should be exercised in the use of anti-TNF therapies in patients with previous malignancy. (Level III evidence, Grade of recommendation B.)

Recommendation 27: the effect of anti-TNF therapies on pre-malignant conditions such as Barrett’s oesophagus, cervical dysplasia and large bowel polyps is unknown. Caution should be exercised in the use of anti-TNF therapies in such patients. (Level IV evidence, Grade of recommendation C.)

Recommendation 28: patients should be advised that there appears to be an increased risk of some skin cancers with anti-TNF therapy and on preventative skin care and skin surveillance. Patients should be encouraged to promptly report any new persistent skin lesions. (Level IIb evidence, Grade of recommendation B.)

Overall cancer rates

The possibility of an increase in the occurrence of cancer associated with anti-TNF therapy has been raised by some RCTs and a recent meta-analysis [18]. This meta-analysis of nine studies identified a 3-fold increase in the rate of malignancy with infliximab and adalimumab (OR 3.3; 95% CI 1.2, 9.1). High-dose therapy (defined as >6 mg/kg infliximab every 8 weeks or >40 mg adalimumab every other week) was associated with the greatest risk (OR 4.3; 95% CI 1.6, 11.8); there was no significant increased risk with lower doses (OR 1.4; 95% CI 0.3, 5.7). All nine clinical trials included in this meta-analysis excluded patients with pre-existing malignancies, and other factors could have lead to bias towards detection of malignancy in the anti-TNF arms of these studies.

In contrast, most observational studies have failed to confirm an increased overall risk of cancer among patients treated with TNF inhibitors. Setoguchi et al. [122] undertook a retrospective cohort study of US databases and controls and reported no increased risk of overall cancers [pooled adjusted HR for biologic users was 0.99 (95% CI 0.71, 1.36)]. Two reports from the Swedish registries [123, 124] indicated no increase in overall cancer risk in patients receiving anti-TNF therapy compared with those that are not [standardized incidence ratio (SIR) 1.1 (95% CI 0.6, 1.8); adjusted RR 0.93 (95% 0.76, 1.13)]. Cancer events from Spanish registries [20] are reported to be lower in anti-TNF-treated RA patients; the RR in RA patients not on anti-TNF therapy (n = 789) was 2.9 (95% CI 2.4, 3.5) when compared with RA patients treated with TNF blockers (n = 4459). The BSRBR [125] have reported no difference in the incidence of new malignancy in their anti-TNF cohort when compared with the DMARD cohort (adjusted IRR 0.7; 95% CI 0.4, 1.2). A large observational study from the USA [126] has recently also concluded that there is no increased overall risk of any malignancy for RA patients treated with anti-TNF therapy (SIR for all cancer was 1.0; 95% CI 1.0, 1.1).

Lymphoma

Patients with RA, irrespective of any treatments they receive, are known to have an increased incidence of lymphoma with reported risk ratios, compared with the general population, ranging from 1.9 to 2.7 [127, 133]. Post-marketing surveillance has identified patients who have developed lymphoma while being treated with anti-TNF therapies. A 2002 study based upon reports to the FDA noted 26 cases of lymphoma (mostly non-Hodgkin’s lymphoma) among patients treated with etanercept or infliximab [134]. Fifty-six per cent of the lymphomas were detected within 8 weeks of initiation of anti-TNF treatment and two patients had regression of their lymphoma when anti-TNF therapy was discontinued.

Clinical data on the risk of lymphoma potentially directly stemming from the use of TNF inhibitors are mixed. Evidence for an increased risk is provided by three main reports. A meta-analysis of nine RCTs [18] identified 10 lymphoma cases in anti-TNF-treated patients compared with no lymphomas in DMARD-treated patients. A retrospective cohort study from Sweden [123] reported an SIR for lymphoma of 11.5 (95% CI 3.7, 26.9) compared with that of 1.3 (95% CI 0.2, 4.5) for controls (DMARD users). The 5-fold increase of lymphoma incidence among RA patients exposed to anti-TNF agents may, in part, have been explained by confounding by indication and a low rate of lymphoma in the control population. An observational study from the USA [131] also reported a increased risk with an SIR for lymphoma in patients treated with biologics of 2.9 (95% CI 1.7, 4.9). However, no adjustment for baseline differences in disease duration and severity was made in this study.

Three main studies have reported no increase in lymphoma risk with anti-TNF therapies. A retrospective cohort study [122] reported a pooled HR for haematological malignancy, when compared with MTX users, of 1.37 (95% CI 0.71, 2.65). An observational study from Sweden [132] reported SIRs for lymphoma of 1.9 in the RA cohort vs 2.9 in the biologics user cohort. There was no significant increase in risk when compared with the control group (RR of 1.1; 95% CI 0.6, 2.1). A further observational study from the USA [135] showed no increase in risk [OR of 1.0 when compared with controls (95% CI 0.6, 1.8)].

Solid malignancy

There are also conflicting data on the risks of solid malignancy associated with anti-TNF therapy. An increased risk was reported from the meta-analysis of Bongartz et al. [18] with 15 solid malignancies identified among 29 malignancies in the TNF inhibitor group. In contrast, only
one solid malignancy was observed among the three malignancies seen in the comparison group. However, no increase in risk was found from the Swedish Early Arthritis Registry [132], where rates of solid malignancy among patients treated with anti-TNF therapy was no higher than expected for the underlying disease (SIR 0.9; 95% CI 0.7, 1.2).

**Non-melanoma and melanoma skin cancer**

There is evidence emerging for an increased risk of non-melanotic skin cancer (NMSC) and also for malignant melanomas (MMs) among patients treated with anti-TNF.

Wolfe and Michaud [126] reported increased rates of NMSC with biologic therapy (OR 1.5; 95% CI 1.2, 1.8) and a possible, but not statistically significant, higher risk for MM (OR 2.3; 95% CI 0.9, 5.4). Chakravarty et al. [136] have also reported an increased risk for developing NMSC from a large cohort study of RA patients treated with anti-TNF agents (HR 1.19; P = 0.042) and the Swedish Biologic Register has also reported a non-significant increased occurrence of NMSC in their RA cohort treated with anti-TNF therapy (RR 1.55; 95% CI 0.76, 3.15; n = 10) [124]. Many of the malignancies reported from the meta-analysis of Bongartz et al. [18] were NMSC (9 out of 35).

More recently, Amari et al. [137] reported an increased incidence of both NMSC and MM from a large retrospective cohort of RA patients (16,829 RA patients, of whom 3,096 were on anti-TNF treatment). The incidence of NMSC was 25.9 per 1000 pyrs in patients on TNF antagonists and 19.6 per 1000 pyrs in those on non-biologic DMARDs. Patients on anti-TNF agents had a higher risk of developing NMSC than those on non-biologic DMARDs with an HR of 1.34 (95% CI 1.15, 1.58; P = 0.0001). Factors that increased the risk of NMSC included older age, male gender, glucocorticoid use, a history of prior malignancies and duration of anti-TNF therapy. The incidence of MM was also increased at 3.7 per 1000 pyrs in patients on TNF antagonists, compared with 2.6 per 1000 pyrs in those on non-biologic DMARDs. Patients on anti-TNF agents had a higher risk of MM with an HR of 1.5 (95% CI 1.01, 2.24; P < 0.05).

The BSRBR also published its data on the risk of NMSC in 2009 [138]. Among 11,757 consecutive anti-TNF-treated patients with RA, compared with 35,155 biologic-naive subjects with active RA receiving traditional DMARD, there was a non-significant but 70% increased risk of NMSC. Infliximab was associated with the highest risk of NMSC in this group (an almost 3-fold increase in risk). This data has resulted in recommendation that vigilance for NMSC should be maintained in all patients with RA, but especially in those treated with anti-TNF therapy.

**Previous history of malignancy**

Little data are available on the risks of anti-TNF therapies in patients with a past history of malignancy but caution has generally been advised on the basis of theoretical risk. Watson et al. [125] (BSRBR) compared a group of 154 patients with RA and previous cancer [65 (42%) of these patients had had their malignancy within 10 years of starting anti-TNF therapy] with a group of 9844 patients with RA but no previous malignancy. Six patients (4%) who had previous malignancy developed a new cancer, compared with 158 patients (1.6%) without previous malignancy [IRR 2.5 (95% CI 1.2, 5.8)]. Three of these cancers (50%) occurred in patients with a previous malignancy that had developed <10 years before starting anti-TNF (one case was local recurrence/metastasis).

More recent data from the BSRBR [139] compared 177 RA patients on anti-TNF with 118 DMARD-treated RA patients, all of whom had a prior history of malignancy. There was a lower crude rate for new malignancies among the anti-TNF-treated cohort [25.3 events/1000 pyrs (95% CI 13.4, 43.2)] when compared with the DMARD-treated cohort [41.9 events/1000 pyrs (95% CI 20.1, 77.1)] with an age- and gender-adjusted IRR of 0.53 (95% CI 0.22, 1.26) for anti-TNF-treated patient compared with DMARD-treated patients. Three out of 11 anti-TNF patients with a prior history of malignancy who developed a new malignancy had a past history of melanoma. The time from melanoma to starting anti-TNF therapy was <10 years for all three patients (2.9, 3.5 and 7.5 years). None of the 10 patients with an earlier the-then incident malignancy in the DMARD cohort had prior melanoma.

**Patients at risk of developing malignancy**

In patients at risk for malignancies (for example, smokers) or in patients with chronic obstructive pulmonary disease (COPD), there may be an increased risk of lung cancers. In a trial of patients with COPD (all smokers/ex-smokers) assigned to infliximab vs placebo, nine infliximab-treated patients developed lung cancers during the trial and another four lung cancers were found during open-label follow-up. [140]. There continues to be no data on any increased risk of developing malignancy in pre-malignant conditions such as Barrett’s oesophagus, cervical dysplasia and colonic polyps.

**Autoimmune diseases**

Recommendation 29: if a lupus-like syndrome or other significant autoimmune disease develops while on anti-TNF therapies, treatment should be discontinued and appropriate interventions should be initiated. Re-challenging with anti-TNF therapy should only be undertaken with caution. (Level III evidence, Grade of recommendation C.)

Reports of the development of auto-antibodies, autoimmune disease and vasculitis in patients treated with each of the anti-TNF agents continue. The formation of ANAs and antibodies to dsDNA have previously been reported in response to all first-generation TNF inhibitors, but may be more common with infliximab [141–144]. While anti-TNF-induced autoantibodies have been reported to occur quite commonly, the incidence of ‘full-blown’ anti-TNF-induced lupus or vasculitis is rare [145].

The BSRBR has reported on 11,394 anti-TNF patients followed for a total of 26,927 pyrs, as well as a control
group receiving only DMARD therapy. Of these, 40 anti-TNF-treated patients have developed a new lupus event, compared with only one of the DMARD-treated patients (adjusted IRR 3.17; 95% CI 0.38, 26.26). Although the number of events was small, there was a trend towards an increased incidence of lupus events in those receiving anti-TNF therapies. The most common lupus symptom was skin rash; lupus nephritis or neuropsychiatric symptoms were not reported [146].

Ramos-Casals et al. [147] assessed all cases of autoimmune diseases induced by anti-TNF therapies reported in the literature through to December 2006 (233 cases). One hundred and thirteen cases of vasculitis were identified in association with anti-TNF therapy (59 cases with etanercept, 47 with infliximab, 5 with adalimumab). Ninety-eight (87%) of the patients with vasculitis had cutaneous involvement including palpable purpura [55 patients (57%)], erythematous papules/macules/punctate lesions [11 patients (11%)], ulcers [9 patients (9%)] and nodules [9 patients (9%)]. Visceral involvement of the peripheral nerves and kidneys were reported in 18 (16%) and 15 (13%) patients, respectively. Eighty-three of the 113 vasculitis cases were confirmed histopathologically. Among these, leucocytoclastic vasculitis was reported in 52 patients (63%), necrotizing vasculitis in 14 (17%), lymphocytic vasculitis in 5 (6%) and other findings in 12 (14%). Ninety-two of the cases of vasculitis resolved following the discontinuation of anti-TNF therapy. Among the 16 patients re-challenged with a TNF inhibitor, vasculitis recurred in 12 (75%). Ninety-two cases of lupus following anti-TNF therapy (40 cases with infliximab, 37 with etanercept, 15 with adalimumab) were also reported. Nearly half the cases fulfilled four or more ACR classification criteria for SLE; this proportion fell to one-third after discarding cases with pre-existing lupus-like features. The symptoms and signs of SLE resolved following the discontinuation of the TNF inhibitor in 71 of the 72 patients on whom information regarding disease outcome was available.

In summary, and as highlighted from these reports, the clinical features of anti-TNF-induced lupus appear distinct from classical drug-induced lupus (DIL) with a phenotype more similar to idiopathic SLE [145], albeit a mild form. It is associated with more cerebral and renal involvement than classical DIL. Withdrawal of anti-TNF therapy usually leads to resolution of symptoms. Steroids and/or immunosuppressive therapy may be required in severe cases.

**Demyelination**

Recommendation 30: anti-TNF therapy should not be given when there is a clear history of multiple sclerosis and should be used with caution with other demyelinating diseases. (Level III evidence, Grade of recommendation B.)

Recommendation 31: anti-TNF therapy should be withdrawn if demyelination occurs and the patient should be referred for specialist investigation. (Level III evidence, Grade of recommendation B.)

Stubgen et al. [148] have recently reviewed ongoing case histories and series reports and highlighted the association between anti-TNF treatment and various disorders of peripheral nerves such as Guillain–Barré syndrome, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex and axonal sensorimotor polyneuropathies. Cases were reported for all three first-generation anti-TNF agents with symptoms developing over a wide range of time intervals from starting anti-TNF treatment (8 h to 2 years). Withdrawal of anti-TNF resulted in slow resolution of symptoms in many cases; however, additional treatment with i.v. steroid, with or without IVIG or cyclophosphamide, or plasmapheresis was required for others. With these interventions symptoms resolved in the vast majority of cases over time periods ranging from 3 weeks to 35 months. A small minority of patients, however, never achieved symptom resolution. There were some reports of successful re-challenge with anti-TNF without recurrence of neurological symptoms, but there are also reports of worsening symptoms or recurrence on re-challenge, and re-challenge is therefore not recommended but may be considered on an individual case basis. Additional case reports reinforce the risks of neurological complications from anti-TNF therapies.

**CNS demyelination**

There are further reports implicating all three first-generation anti-TNF agents in new cases of demyelination with the highest rate reported with etanercept [149–152], followed by infliximab [153, 154] and then adalimumab [155].

**Optic neuritis**

Simsek et al. [156] have reported 15 patients who developed optic neuritis while on anti-TNF therapy—8 of these patients had received infliximab, 5 had received etanercept and 2 patients had received adalimumab. On stopping anti-TNF treatment, nine patients experienced complete resolution and two patients had partial resolution of their symptoms while four patients continued to have symptoms.

**Demyelinating peripheral nervous system disease**

There are also further reports implicating all three first-generation anti-TNF agents in the development of peripheral nerve demyelination [157]. Shin et al. [158] report one incident case from the authors themselves and 15 patients identified from the FDA database, in whom Guillain–Barre syndrome developed following anti-TNF therapy. Guillain–Barre syndrome developed following infliximab therapy in 10 patients, following etanercept therapy in 5 patients and following adalimumab therapy in 1 patient. Among the 13 patients for whom follow-up data were available, 1 patient experienced no resolution, 9 patients had partial resolution and 3 patients had complete resolution of Guillain–Barre syndrome following therapy.
Cardiac failure and ischaemic heart disease

Recommendation 32: anti-TNF therapy should not be initiated in patients with New York Heart Association (NYHA) Grade 3 or 4 cardiac failure (CF) (Table 2) and should be used with caution in patients with mild (NYHA Grade 1 or 2) CF. (Level Ib evidence, Grade of recommendation A.)

Recommendation 33: anti-TNF therapy should be discontinued if CF develops or worsens while on treatment. (Level IV evidence, Grade of recommendation C.)

CF

Concern about the possible adverse effect of CF associated with anti-TNF therapy stems from randomized clinical trials of TNF inhibitors when used as a potential therapy for CF. (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial [159], Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction (RECOVER) trial [160], Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial [161]). Because of the adverse experiences reported with etanercept and infliximab with CF, no treatment trials of adalimumab in CF have ever been attempted. Data from trials specifically assessing the risk of CF with the use of anti-TNF therapy at the licensed RA doses are inconclusive [162]. Interpretation of the results from these trials is hampered by issues relating to potential confounding by indication or contraindication and by lack of control for confounding conditions or severity of RA. Most studies and case reports, however, have been generally reassuring with regard to the risks of CF as a complication of anti-TNF therapy.

Post-marketing surveillance data gathered by the FDA identified 47 cases of CF associated with etanercept or infliximab reported to the AERS through to January 2002 [163]. Thirty-eight of these patients developed new-onset CF and nine experienced an exacerbation of their CF.

Bernatsky et al. [164] reported a beneficial effect for anti-TNF therapies on the rate of hospitalization for CF (RR 0.5; 95% CI 0.2, 0.9). As the study only considered hospitalized patients, no information is available for milder degrees of CF. Cole et al. [165], however, found no difference in the number of admissions for CF between veterans with RA treated with TNF inhibitors (n = 103), RA patients not treated with TNF inhibitors (n = 100) and non-RA patients (n = 100). Listing et al. [166] also reported no significant difference in the HR for developing new-onset CF or worsening CF in patients treated with anti-TNF therapy (n = 2757) when compared with those treated with conventional DMARDs (n = 1491). Curtis et al. [167] reported a non-significant increased risk of CF in patients <50 years of age treated with anti-TNF therapy. A lower CF event rate (0.05 per 100 pyrs) was noted in an analysis of US post-marketing safety of adalimumab with 55,384 pyrs of exposure from 2002 to 2004 [168].

Myocardial infarction

Interpretation of trial results has again been hampered by issues relating to potential confounding by indication or contraindication and by lack of control for confounding conditions or severity of RA. Data available to date have shown no detrimental effects of anti-TNF therapy on the frequency of MI and, with good response to treatment there may be a reduction in the incidence of MI.

Suissa et al. [169] reported on a nested case-control study including patients registered in an insurance database. Five hundred and fifty-eight patients with RA and acute MI were matched with 5580 RA controls. No change in the RR of hospitalization for acute MI was found for patients currently taking biologic agents (RR 1.30; 95% CI 0.92, 1.83).

Dixon et al. [170] reported data from the BSRBR. There was no significant difference in the incidence of first MI between RA patients taking TNF inhibitors (4.6/1000, n = 8670) and control active RA patients treated with traditional DMARDs (5.9/1000, n = 2170). The incidence of MI was, however, lower in patients who achieved a good or moderate EULAR response at 6 months (3.5/1000 events in responders compared with 9.4/1000 events in non-responders).

Cardiovascular (CV) events

Issues relating to potential confounding by indication or contraindication and the lack of control for confounding conditions or severity of RA have also been factors in studies assessing risk of CV events in association with anti-TNF therapies. Data available to date suggest a potential beneficial effect of anti-TNF therapy on CV events but further data are required before firm conclusions can be drawn.

Jacobsson et al. [171] compared a cohort of RA patients treated with anti-TNF therapy (n = 531) with patients in a historical cohort (to time of publication, n = 452) not

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**Table 2** New York Heart Association (NYHA) grading of heart failure

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<th>Class</th>
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Jacobsson et al. [171] compared a cohort of RA patients treated with anti-TNF therapy (n = 531) with patients in a historical cohort (to time of publication, n = 452) not
exposed to TNF inhibitors. The rate of first CV event (not clearly defined) was lower in patients treated with TNF inhibitors (14.0/1000 pyrs at risk; 95% CI 5.7, 22.4) compared with those not exposed (35.4/1000 pyrs at risk; 95% CI 16.5, 54.4).

Solomon et al. [172] undertook a nested case–control study comparing 946 elderly patients (mean age 82 years) with RA and a history of hospitalization with MI or stroke with age- and gender-matched controls without a CV event. MTX monotherapy was used as the reference group. There was no beneficial or detrimental effect of biologic use (with and without MTX) compared with MTX monotherapy. The use of biologics was associated with a decreased risk of MI or stroke when compared with the use of other immunosuppressant agents (AZA, cyclosporin and LEF) and glucocorticoids without concomitant use of MTX.

Carmona et al. [20] reported on two cohorts of patients; the first treated with TNF inhibitors (n = 4459) and the second not treated with TNF inhibitors (n = 789). There were significant reductions in the risk of ischaemic heart disease, CF and stroke in those treated with TNF inhibitors. The standardized mortality ratios for CV disease were not significantly different between the groups (mortality rate ratio 0.58; 95% CI 0.24, 1.41).

**Haematological complications**

Recommendation 34: for all patients on anti-TNF therapy including those not on concomitant DMARDs, full blood counts should be monitored regularly. (Level III evidence, Grade of recommendation B.)

Cases of haematological abnormality have continued to be reported in patients treated with each of the three first-generation anti-TNF agents but in many cases there have been other co-prescribed medications that may have been responsible for these changes. One case series reports neutropenia (<2.0 × 10⁹/l) in 14.3% of 133 RA patients on anti-TNF therapy [173]. The main predictors of neutropaenia were a history of previous neutropenia on DMARD therapy (OR 7.78; 95% CI 4.37, 13.85) and a low baseline neutrophil count (RR 3.79; 95% CI 2.56, 5.45). Significant rates of anti-TNF-induced neutropenia [11 out of 130 patients (8%) and 40 out of 290 patients (14%)] have also been described in two other studies [174, 175]. Most anti-TNF therapy-induced neutropenia in these studies was mild, did not result in any significant clinical complications, and did not require modification in anti-TNF therapy. Reports of anti-TNF-associated pancytopenia and aplastic anaemia are rare but in some cases have been fatal [176, 177].

**Pregnancy and lactation**

The safety of the anti-TNF therapies has not been established through pregnancy or lactation.

Recommendation 35: precautions against pregnancy should be exercised in both female and male patients treated with anti-TNF (or their partners). Continuation of anti-TNF therapy could be considered in patients wishing to conceive/father a child if the risks of stopping treatment are perceived to be high. *(Level IV evidence, Grade of recommendation C.)*

Recommendation 36: consideration should be given to stopping anti-TNF in a woman who becomes pregnant on treatment but continuation of anti-TNF therapy could be considered if the risks of stopping treatment are perceived to be high. (Level IV evidence, Grade of recommendation C.)

Recommendation 37: the pros and cons of breastfeeding in patients treated with anti-TNF therapies should be considered on an individual basis. (Level IV evidence, Grade of recommendation C.)

*Current data sheet recommendations are that infliximab should be discontinued for 6 months and that adalimumab should be discontinued for 5 months before a female patient becomes pregnant. No specific data sheet guidance is currently available on the duration that female patients should be off etanercept prior to becoming pregnant or on male patients treated with any of the anti-TNF agents who wish to father a child.*

**Pregnancy**

There are few new data addressing the potential impact of TNF inhibitors on pregnancy. Although some small case series have failed to demonstrate convincing evidence of teratogenicity associated with targeted TNF inhibition, much remains unknown about the possible effects of TNF antagonists on pregnancy. In 2006, concerns were raised about the possibility of a VACTERL association with TNF inhibitors. A VACTERL is a non-random association of birth defects that occurs in approximately 1.6/10 000 live births (V, vertebral anomalies; A, anal atresia; C, cardiovascular anomalies; T, tracheoesophageal fistula; E, esophageal atresia; R, renal and/or radial anomalies; and L, limb defects) [178]. Carter et al. [178] examined the FDA database using the keyword ‘congenital anomaly’ as a search tool and reported a number of congenital abnormalities among 41 children born to mothers taking a TNF antagonist. Twenty-two of the mothers took etanercept at some point during their pregnancy and 19 took infliximab. There were no reports of congenital abnormality in women on adalimumab. Fifteen (37%) of the children had more than one congenital anomaly. Twenty-four children (59%) had one or more VACTERL-associated congenital anomalies; in these cases, the mother was on no medication other than etanercept (n = 14) or infliximab (n = 10).

Roux et al. in 2007 [179] reported on 3 women with RA (from a group of 442 patients treated with anti-TNF therapy) who unexpectedly became pregnant. One patient (treated with etanercept) chose a therapeutic termination at 2.5 months, despite no demonstrable abnormality and satisfactory fetal growth on ultrasound. The other two patients (one with adalimumab exposure and one with etanercept exposure) delivered healthy infants.

Roux et al.’s [179] review of the existing literature identified 70 RA cases exposed to etanercept during pregnancy with 32 resultant live births, 10 miscarriages,
7 therapeutic terminations and 1 miscarriage (with malformation secondary to trisomy 18). There were 4 live births, 3 miscarriages, 1 therapeutic termination and 1 malformation (intestinal malrotation) among 20 cases exposed to infliximab and 1 therapeutic termination with no miscarriages among 5 patients exposed to adalimumab.

Outcome data from a post-marketing safety database were reported by Katz et al. [180] for 96 of 131 patients with Crohn’s disease or RA who had exposure to infliximab during pregnancy. Sixty-seven per cent of the pregnancies resulted in live births, 15% in spontaneous abortions and 19% in terminations. Among the live births there were five cases of varying fetal complications.

A recent abstract from the BSRBR reported on 99 pregnancies and suggested a possible increase in miscarriage rate in pregnancies conceived while taking anti-TNF. However, other confounders (other DMARDs/unplanned pregnancy factors) may also have played a role in these miscarriages [181]. TNF is important during early pregnancy, hence the possible explanation for the effect of anti-TNF therapy in increasing the risk of miscarriage [182, 183].

In addition to these reports of pregnancy complications and congenital abnormalities associated with anti-TNF therapy, there are, however, reports of successful pregnancy outcomes despite treatment with anti-TNF. Rosner et al. in 2007 [184] reported on four women with severe intractable arthritis who successfully conceived and maintained their pregnancies to full term while under continuous anti-TNF therapy. In all cases, the newborn babies were entirely well and remained so after 6 months to 2 years of follow-up. A recent publication by Berthelot et al. [185] is also reassuring, with a good reported outcome for 15 pregnancies in women treated with anti-TNF drugs. This publication also included a literature review [185].

Most other reports on anti-TNF agents and pregnancy to date have focused on inflammatory bowel disease but at least two ongoing registries for rheumatic disease patients also suggest their apparent safety [186, 187]. The number of reported pregnancies associated with anti-TNF treatment now exceeds 300, but only 29 women were treated during their whole pregnancy. The rate of congenital malformations observed so far for women exposed to anti-TNF only at the time of conception appear reassuring when comparison is made with the general population. However, there are too few reports of exposure during pregnancy to allow any firm conclusion about the safety of TNF blockers in pregnancy. Adalimumab and infliximab are IgG antibodies and as such cannot cross the placenta in the first trimester [188]. Therefore, it would appear to be entirely safe to administer them to the mother during this time [189]. Long-term follow-up of children born to parents exposed to anti-TNF at conception or through pregnancy to identify any potential minor forms of VACTERL association, overlooked at birth, would be desirable.

Accordingly, anti-TNF drugs are still classified by the FDA as ‘pregnancy risk category B’, as human studies are still insufficient to guarantee their safety for the fetus. No adverse effects have been observed in animal pregnancies thus far.

**Fathering children**

There remains no data to provide guidance on the safety of fathering children while taking anti-TNF therapy or on how long before conception patients should be recommended to discontinue anti-TNF therapy. Viktil et al. [190] suggests that there were no obvious problems for the 28 fathers taking a biologic drug.

**Lactation**

There remains insufficient data to address the issue of the safety of each of the anti-TNF drugs for infants during lactation. Ostensen and Eigenmann [191] report an etanercept concentration in breast milk of 75 ng/ml in a lactating mother; a level that was ~4% of the maternal serum concentration (2058 ng/ml). However, it is highly unlikely that oral administration of anti-TNF therapy via breast milk is likely to have any effect on the child [192].

**Interstitial lung disease**

Recommendation 38: patients with pre-existing interstitial lung disease (ILD) should have monitoring of their lung function if treated with anti-TNF therapies, and consideration should be given to stopping anti-TNF therapy in patients with worsening, or new features of ILD. (Level III evidence, Grade of recommendation B.)

The 2005 BSR guidelines made no recommendations on anti-TNF therapy and pre-existing lung disease. Data have since emerged on ILD in particular, but also on bronchiectasis (as reported under ‘infection’ section).

There are reported cases of ILD associated with each of the first-generation anti-TNF therapies. The majority of cases have been reported in patients with RA but such patients are known to have an increased risk of ILD, and confounding by indication may therefore be a factor in these cases.

Ramos-Casals et al. [147] analysed autoimmune diseases reported to have been induced by anti-TNF therapies (233 cases in 226 patients). Twenty-four cases of ILD associated with anti-TNF therapy were reported within this group and further details on the cases highlighted the poor prognosis of ILD in these patients, despite cessation of anti-TNF therapy. There was a reported outcome for only 19 cases but over half showed no resolution of their ILD after stopping anti-TNF therapy and one-third of the patients died; most of these patients had known pulmonary disease prior to commencing anti-TNF treatment. The possible adjuvant role of concomitant MTX therapy, however, may also have been a factor in these cases, overall, half the patients who developed ILD had also received MTX.

Dixon et al. [193] have presented data from the BSRBR showing that baseline ILD is a strong predictor of increased all-cause mortality in RA patients (mortality OR 2.12; 95% CI 1.52, 2.95), but that this risk is irrespective of the use or not of anti-TNF treatment.
It is important to note that data thus far indicate that ILD can be severe and life threatening in RA patients, regardless of the treatment received. Some data suggest that anti-TNF therapy may worsen both all-cause and ILD-specific mortality in RA patients with baseline ILD but no data are required before any firm conclusions can be drawn on the risks specifically linked to anti-TNF therapies.

Psoriasis

Recommendation 39: if psoriasis develops on anti-TNF therapy patients should receive conventional psoriasis treatment and consideration should be given to stopping anti-TNF therapy if the skin lesions persist despite specialist dermatology treatment and advice or are particularly severe. (Level III evidence, Grade of recommendation B.)

A significant number of reports of psoriasis developing in patients treated with all three first-generation anti-TNF agents have emerged in recent years, despite NICE now having approved the use of anti-TNF therapies for the treatment of psoriasis [194–196].

Harrison et al. [197] reported data from the BSRBR suggesting the incidence of psoriasis is increased in patients treated with anti-TNF therapy. A total of 9826 anti-TNF-treated and 2880 DMARD-treated RA patients with new-onset psoriasis as an adverse event were recorded on the BSRBR. Twenty-five incident cases were reported in patients receiving anti-TNF therapy and none in the comparison cohort. The crude incidence rate of psoriasis in those treated with anti-TNF therapy was elevated at 1.04 (95% CI 0.67, 1.54) per 1000 pyrs compared with the rate of 0 (upper 97.5% CI 0.71) per 1000 pyrs in the DMARD-treated patients. Adalimumab-treated patients had a significantly higher rate of incident psoriasis compared with etanercept-treated (IRR 4.6; 95% CI 1.7, 12.1) and infliximab-treated (IRR 3.5; 95% CI 1.3, 9.3) patients. Thirteen patients developed psoriasis within the first 6 months of anti-TNF therapy; eight of these patients were receiving adalimumab, three had had infliximab and two had had etanercept. Of these 13 patients, 4 stopped anti-TNF therapy due to their psoriasis and reported improvement in their psoriasis after stopping treatment. No information on the course of skin disease in patients who did not stop treatment due to psoriasis was available.

In a literature review, Collamer et al. [198] reported on the incidence of new or worsening psoriasis in patients treated with TNF inhibitors. Nearly 50% of patients were treated for RA and similar rates of occurrence of psoriasis were reported for each of the anti-TNF therapies (infliximab 37%, etanercept 31%, adalimumab 32%). New-onset psoriasis was found to occur at any time after initiation of TNF antagonist therapy, to often present with an uncommon morphology, and to usually respond to psoriasis treatments. Seventy-nine per cent of patients were able to continue with anti-TNF therapy (the original agent or an alternative).

Ko et al. [199] undertook a further Ovid MEDLINE and PubMed literature search for cases of psoriasis in patients receiving TNF-blocking agents published between January 1990 and September 2007. Several reports of new-onset and worsening psoriasis in association with TNF blockade therapy were found. A series of 127 cases (from 1990 to 2007; 70 on infliximab, 35 on etanercept and 22 on adalimumab) showed a prevalence of psoriasis in anti-TNF-treated patients ranging from 0.6 to 5.3%, with a range of time to onset after starting treatment of a few days to 4 years. Among these 127 reports there was a disproportionately higher representation of the primary conditions of AS (in 16.1% of the cases) and Behçet’s disease (in 1.5%). While psoriasis classically presents as thick, erythematous plaques with an adherent silvery scale on the extensor surfaces of extremities (with >80% of psoriasis patients having plaque type), psoriasis occurring during TNF blockade has been mostly reported as the pustular type occurring on the palms and soles (pustular, palmer/plantar type in >40% of the cases, compared with plaque-type psoriasis in just 33% of the cases). Various treatment approaches were employed for the psoriasis with mixed results. Topical corticosteroids were used in 55% of cases but when used alone, led to resolution of the psoriasis in only 25%. Thirteen patients had their TNF inhibitor switched to an alternative but this led to resolution of the psoriasis in just 15% of the cases. Stopping TNF blockade alone improved psoriasis in 50% of patients. Stopping TNF inhibitors and starting systemic therapy was the most effective treatment approach from this review, resulting in resolution of the psoriasis in >64% of the cases.

Uveitis

Recommendation 40: if patients develop uveitis while on anti-TNF, a trial of an alternative anti-TNF agent could be considered. (Level III evidence, Grade of recommendation B.)

Recommendation 41: anti-TNF should be used with caution in patients with a history of previous uveitis and the RRAs of the available anti-TNF agents should be reviewed prior to selecting which treatment to use. (Level III evidence, Grade of recommendation B.)

There are now several case reports of uveitis developing in patients treated with anti-TNF therapy despite the fact that anti-TNF therapy has also been reported to successfully treat patients with resistant uveitis. Most cases of anti-TNF therapy-associated uveitis have been reported with etanercept [200, 201]. Most reports of successful treatment of resistant uveitis with anti-TNF therapy have been with infliximab [202–205].

Lim et al. [206] reported on a registry-based study that collected data on spontaneous reports of uveitis during the period 1 January 1998 through 1 January 2006. Forty-three cases of uveitis were recorded in patients who were receiving anti-TNF therapy. Seventeen patients were known to have diseases that are associated with an increased risk of uveitis (i.e. AS, Crohn’s disease or JIA). RA patients were included in the remaining 26 cases in which no known condition predisposing to uveitis was identified; the number taking etanercept, infliximab or...
adalimumab in this group was 20, 4 and 2, respectively. The authors highlighted that etanercept therapy was associated with a significantly greater number of reported uveitis cases in comparison with infliximab (P < 0.001) but also conceded that there were several limitations to this study; in particular, there was limited information on the clinical diagnoses available to the authors [206]. More data are therefore required on uveitis associated with each of the available anti-TNF agents before further conclusions can be drawn on the RR associated with individual agents.

Summary and conclusions

Inhibitors of TNF-α represent important treatment advances in RA. The use of anti-TNF drugs in RA has been increasing significantly over the past few years and information on the safety of these agents continues to be collected. Data are particularly scarce for the second-generation anti-TNF agents but there are no data thus far to suggest that safety guidance for these agents should differ from those provided for the first-generation agents.

Data from post-marketing surveillance, observational studies, individual randomized trials and from national registries (in a number of different countries) have been used as sources of evidence for these guidelines on anti-TNF safety in RA. Many questions remain unanswered, however, and ongoing studies and data collection will be essential to further clarify the answers to these questions.

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Appendix I

Rating the strength of evidence for recommendations

For each final recommendation, the strength of evidence was assigned using the grading suggested by the Royal College of Physicians of London (National Clinical Guidelines for Stroke by the Intercollegiate Stroke Working Party, June 2004 http://www.rcplondon.ac.uk/pubs/books/stroke/stroke_guidelines_2ed.pdf, table 1.1; 22 June 2010, date last accessed).

The data supporting recommendations on safety aspects of anti-TNF therapy were derived primarily from observational studies, and to a lesser degree from evidence from RCTs. Many of these studies might have addressed the general topic under discussion but did not specifically address the questions of relevance. Therefore, the recommendations could not be derived directly from the evidence but required synthesis of the data from studies plus extrapolation to the specific clinical scenarios under consideration. As a result, many of the recommendations were graded as Level C.