



Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008

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Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008

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As in previous years, the consensus group to consider the use of biological agents in the treatment of rheumatic diseases met during the 10th Annual Workshop on Advances in Targeted Therapies. The group consisted of rheumatologists from a number of universities among the continents of Europe, North America, South America, Australia and Asia. Pharmaceutical industry support was obtained from a number of companies for the annual workshop itself but these companies had no part in the decisions about the specific programme or about the academic participants at this conference. Representatives of the supporting sponsors participated in the initial working groups with emphasis on supplying factual information. The sponsors did not participate in the drafting of the consensus statement.

This consensus was prepared from the perspective of the treating physician.

In view of the new data for tumour necrosis factor α (TNF α) blocking agents, B-cell-specific agents and interleukin 1 receptor antagonists (IL1ra), an update of the previous consensus statement is appropriate. The consensus statement is annotated to document the credibility of the data supporting it as much as possible. This annotation is that of Shekelle *et al* and is described in an appendix. We have modified the Shekelle annotation by designating *all* abstracts as “category D evidence”, whether they describe well-controlled trials or not, as details of the study were often not available in the abstracts. Further, the number of possible references has become so large, that reviews are sometimes included; if they contain category A references, they will be referred to as category A evidence.

The 162 rheumatologists and bioscientists who attended the consensus conference were from 23 countries, and were selected for their expertise in the use of biological agents for the treatment of rheumatic diseases. The number of attendees and participants was limited so that not everyone who might have been interested could be invited. All participants reviewed a draft document developed by the coauthors, based on a review of all relevant clinical published articles relating to TNF and IL1 blocking agents, as well as abatacept and rituximab. The draft was discussed in small working groups. The revisions suggested by each group were discussed by all participants in a final open session and this led to a final document, representing this updated consensus statement.

It is hoped that this statement, which is based on the best evidence available at this time, and is modified by expert opinion, will facilitate the optimal use of these agents for patients with conditions approved by the FDA or EMEA (European Medicines Agency) for clinical use. Extensive tables of the use of these agents in non-registered uses are included as appendices, to help experienced doctors to use these drugs in exceptional (“off-label”) circumstances.

GENERAL STATEMENTS

Individual patients differ in the clinical expression and aggressiveness of their disease, its concomitant structural damage, the effect of their disease on their quality of life (QoL) and the symptoms and signs engendered by their disease. They also differ in their risk for, and expression of, side effects to drugs. All these factors must be examined when considering biological treatment for a patient, as must the toxicity of previous and/or alternative disease-modifying antirheumatic drug (DMARD) use.

As increasing evidence has accumulated of the efficacy and clinical use of biological agents for the treatment of psoriatic arthritis (PsA) and ankylosing spondylitis (AS), these diseases will be discussed separately from rheumatoid arthritis (RA). Adverse reactions, however, will remain combined for all indications.

In general, in RA, when measuring response to treatment or when following up patients over time, the American College of Rheumatology (ACR) response criteria (as a combined index) should not be used in a clinical practice setting to monitor individual response, although some validated measure of response (such as those which follow) should be employed (category B evidence). Validated quantitative measures such as Disease Activity Score (DAS), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire disability index (HAQ-DI), visual analogue scales (VAS) or Likert scales of global response or pain by the patient or global response by the doctor, other validated measures of pain for individual patient care, joint tenderness and/or swelling counts, and laboratory data all may be used and may be appropriate measures for individual patients. The doctor should evaluate a patient's response using one of the above instruments to determine the patient's status and change.

For PsA, measures of response such as joint tenderness and swelling, global and pain response measures, functional indices and acute phase reactants have been used and appear responsive.^{1–3} For AS, measures such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Bath Ankylosing Spondylitis Functional Index (BASFI) have been used in clinical trials but have not been validated for routine clinical practice. Clinical measures such as joint tenderness and swelling, spinal motion, global and pain response measures, functional indices and acute phase reactants have been used and are validated.

The appropriate use of biological agents will require doctors experienced in the diagnosis, treatment and assessment of RA, PsA, AS and other rheumatic diseases who are aware of long-term observations of efficacy and toxicity, including cohort studies and data from registries. Because biological agents have toxicities, patients or their representatives should be provided with information about potential risks and benefits so that they may give informed consent for treatment.

TNF BLOCKING AGENTS

TNF α blocking agents differ in composition, precise mechanism of action, pharmacokinetics and biopharmaceutical properties, but this document emphasises areas of commonality. Studies that have clearly differentiated between compounds will be discussed, where appropriate.

Indications

Rheumatoid arthritis

In most patients, TNF α blockers are used in conjunction with another DMARD, usually methotrexate (MTX). TNF α blocking agents have also been used successfully with other DMARDs, including sulfasalazine and leflunomide. There is evidence that TNF α blocking agents are effective for the treatment of RA in MTX-naïve patients (category A evidence^{4–17}; category D evidence^{18–20}). TNF α blocking agents can be used as the first DMARD in some patients (category A evidence^{4–15 17 21 22}; category D evidence^{12 17 18 23}). Adalimumab and etanercept are both approved as monotherapy for RA. Infliximab is only approved for use with MTX in RA. However, observational data indicate that infliximab, too, is sometimes used as monotherapy (category C evidence^{24–26}). Evidence from randomised controlled trials show that the combination of a TNF α blocking agent and MTX yields better results for RA than monotherapy, particularly with respect to excellent clinical responses (ACR 70, remission) and radiological outcomes (category A evidence^{4–16 18–20 22–30}).

Psoriatic arthritis

Based on demonstration of control of signs and symptoms of joint and skin disease, improvement of function, QoL and inhibition of structural damage the three available TNF α blocking agents, adalimumab, etanercept and infliximab, have been approved widely for the treatment of patients with PsA with inadequate response to conventional treatments. Efficacy has been demonstrated both with monotherapy and with background MTX. (category A evidence^{31–43}).

Ankylosing spondylitis

Adalimumab, etanercept and infliximab have been approved widely for the treatment of active AS that is refractory to conventional treatments. In clinical trials, the efficacy of these TNF α blocking agents was shown to improve signs and

symptoms, function and QoL as monotherapy as well as with concomitant second-line agents, including sulfasalazine or MTX (category A^{44–54}).

Juvenile idiopathic arthritis

Etanercept and adalimumab have been approved for juvenile idiopathic arthritis (JIA) with a polyarticular course (etanercept category A evidence^{60–61}; FDA and EMEA). Infliximab was beneficial at 6 mg/kg in polyarticular JIA.

Appendix 1 provides evidence supporting the use of TNF α blocking agents in other rheumatic diseases or those with prominent rheumatic manifestations.

Clinical use

Rheumatoid arthritis

Dosing and time to response

Observations with infliximab suggest that increasing the dose or reducing the dosing intervals may provide additional benefit in RA, as may the addition or substitution of other DMARDs.

TNF α blocking agents, when administered up to the maximum approved dosing regimens for RA and polyarticular JIA, are expected to lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters within 12–24 weeks (category A and B evidence^{4–20 22 23 26–28 30 44–48 55–66}). Clinically significant important responses including patient-oriented measures (eg, HAQ-DI, patient's global VAS, Medical Outcome Survey Short Form 36 (SF-36)) and physical measures (eg, joint counts) should be demonstrated within 12–24 weeks for RA (category A evidence^{4 5 7–10 12–18 20 22 23 26–28 30 44–48 54–57 62 63}). If such improvement occurs, treatment should be continued. If patients show no response to these agents, their continued use should be re-evaluated. Raising the dose of etanercept does not seem to have an added benefit in 12- or 24-week studies in RA (category A evidence^{67 68}).

Comparing TNF α blocking agents

There is no evidence that any one TNF α blocking agent should be used before another one can be tried, just as there is no evidence that any TNF blocker is more effective than any other in RA (category A and B evidence^{4 7 19 58 60 64 69 70}).

Patients have been switched from one TNF blocking agent to another. But no double-blind, well-controlled switch trials have been fully published (category B and D evidence^{60 64 69–76}).

Persistence and degree of response

There is evidence that loss of response to a TNF blocking agent can occur and studies suggest that failure to respond to one TNF blocking agent does not preclude response to another (category B and D evidence^{58 60 64 69 70}).

Initial observational data suggest the possibility that primary non-responding patients are less likely to respond to a second anti-TNF agent. Patients who have not tolerated one TNF blocker may respond to a second but are also less likely to tolerate a second TNF blocking agent (category B and D evidence^{58 64 69 70}). The optimal treatment of patients not responding to TNF blockers remains to be determined. (category A evidence^{7 10 15 26}).

Structural changes

There are data showing that TNF α blocking agents slow and/or inhibit radiographic progression in RA, even in some patients without a clinical response (category A evidence^{4 7 11 13 16 18 21 40 57 63 77 78}). Better clinical and radiological

Consensus statement

outcomes are achieved when TNF α blocking agents are used in combination with a traditional DMARD. Although some patients with RA without measurable clinical response have slowing of radiographic progression, the long-term clinical implications of these changes remain unknown.

Pharmacoeconomic data

Evidence has become available which shows that TNF blocking agents are cost effective from a societal perspective, although this is highly dependent upon the specific circumstances of the analysis and the society in which the analysis is done (category B evidence^{79–82}).

Juvenile idiopathic arthritis

Dosing and time to response

TNF α blocking agents, when given up to the maximum approved dosing regimens for polyarticular JIA, usually lead to an early significant, documentable improvement in symptoms, signs and/or laboratory parameters.

Comparing TNF α blocking agents

Etanercept appears less likely to be active in patients with systemic-onset JIA than in those patients with other forms of JIA. There are no prospective studies in children less than 4 years of age; however, some observational registry data suggest comparable efficacy and safety in JIA not of the systemic-onset subtype. As for other subtypes of JIA, there is no evidence that any one TNF α blocking agent should be used before another one can be tried, just as there is no evidence that any TNF blocker is more effective than any other. In JIA-associated uveitis adalimumab and infliximab appear to be effective more often than etanercept.

Structural changes

There is evidence that TNF α inhibition contributes both to restoration of growth velocity in children whose JIA-associated inflammation is controlled, and evidence that bone density improves after treatment with TNF α blocking agents in patients who improve clinically and even in those who have incomplete disease control on these agents.

Psoriatic arthritis

A systematic evidence-based review of the efficacy of TNF α blocking agents and other treatments with respect to the various domains of PsA (joints, enthesitis, dactylitis, spine and skin) has recently been published.^{83–91}

Timing of response

In addition to efficacy in joints and skin, efficacy has been demonstrated with TNF α blocking therapy in the treatment of enthesitis and dactylitis

Improvement of signs and symptoms, function and QoL occurs within 12 weeks.

Comparing TNF α blocking agents

Preliminary data suggest that one can achieve benefit for joint and skin signs and symptoms by switching to a different TNF α blocking agent, even if efficacy from a previous anti-TNF agent was never achieved.

Persistence of response and structural changes

Durability of clinical and radiographic data at 2 years in PsA has been demonstrated with etanercept, infliximab and adalimumab (category A evidence^{92–93}).

Pharmacoeconomic data

TNF α blocking agent therapy has reduced healthcare use, improved employment status, decreased time lost from work and increased productivity (category B evidence^{94–96}).

Ankylosing spondylitis

The Assessment of Spondyloarthritis International Society (ASAS) working group has published recommendations for the use of TNF α blocking agents in AS (category A evidence^{52–97}).

Dosing and time to response

The approved doses of TNF blockers for treatment of AS is 5 mg/kg infliximab intravenously every 6–8 weeks after induction, 25 mg twice a week or 50 mg once a week etanercept subcutaneously and 40 mg adalimumab subcutaneously every other week (category A and B evidence^{44–54 71 96 98 99}). No dose-ranging studies have been done with any of these drugs,

Generally, a reduction in signs and symptoms, and improvement in function and QoL will be seen by 6–12 weeks in response to treatment with a TNF α blocking agent. In clinical trials, improvement in signs and symptoms was assessed by patient-reported outcomes (BASDAI, BASFI, patient global VAS, SF-36), physical measures and laboratory parameters. There is also evidence of efficacy of TNF α blocking agent therapy in peripheral arthritis, dactylitis and enthesopathy.

Both infliximab and adalimumab have shown efficacy in active inflammatory bowel disease.

Two recent placebo-controlled trials have shown significant efficacy in signs and symptoms in patients with non-radiographic axial spondyloarthritis.¹⁰⁰

Comparing TNF α blocking agents

A recent randomised controlled trial demonstrated no superiority of a combination of MTX with infliximab versus infliximab alone in the treatment of active AS over 1 year.

There is no evidence that any TNF α blocking agent is more effective than any other for axial manifestations of AS. For non-musculoskeletal manifestations of AS, observational studies suggest that TNF α blocking therapy can reduce the incidence of uveitis flares with a trend favouring infliximab and adalimumab.¹⁰¹

Persistence

TNF α blocking agents maintain efficacy for at least 2–5 years in open-label studies (category B evidence^{53 102 103}).

Structural changes

Several studies have shown that active inflammation of the sacroiliac joints or spine, as shown by MRI, is significantly reduced by all three TNF α blocking agents (category A evidence^{53 99 102 104}). Inhibition of new bone formation when using TNF blocking agents has not been demonstrated (category B¹⁰⁵).

Pharmacoeconomic data

TNF α blocking agents used for AS may reduce economic resource use.

Appendix 1 provides a referenced listing of other conditions in which TNF α blocking agents have been used.

Safety (arranged alphabetically)

General reviews of TNF α blocking agent safety have been published.

Autoimmune-like syndromes

Antiphospholipid and lupus-like syndromes have occurred in patients during treatment with TNF α blocking agents. Autoantibody formation is common after TNF α blocking agent therapy (eg, antinuclear antibodies), but clinical syndromes associated with these antibodies are rare.

In children, infliximab concentration may drop more rapidly than in adults. This accounts for reports of decreased serum infliximab levels, increased infliximab antibodies and increased incidence of antinuclear antibodies at a dose of 3 mg/kg compared with a dose of 6 mg/kg administered at 8-week intervals after a standard loading phase.

Cardiovascular

Treatment of non-RA patients with advanced chronic heart failure with TNF α blocking therapy was associated with greater morbidity/mortality (infliximab) or lack of efficacy (etanercept). Studies that examined the risk of heart failure in patients with RA treated with TNF α blocking agent therapy have shown inconsistent results.^{106–109} Studies of the effect of TNF α inhibition on the risk of myocardial infarction and stroke are also inconsistent but some studies report a beneficial effect.^{110–111}

Congenital defects

There are conflicting results from databases as to the association of congenital malformations and TNF α blocking agents.^{112–113}

Haematological

Rare instances of pancytopenia and aplastic anaemia have been reported (category A and C evidence^{10–15–22–57–114–115}). If haematological adverse events occur, TNF α blocking agents should be stopped and patients evaluated for evidence of other underlying disease or association with concomitant drugs.

Hepatitis

Patients should be screened for viral hepatitis before TNF α blocking agent initiation, as the long-term safety of TNF α blocking agents in patients with chronic viral hepatitis (hepatitis B and C) is not known. In patients with hepatitis C and RA, several observational studies in infected patients have shown no increased incidence of toxicity (eg, raised liver function tests or viral load) associated with TNF α blocking agent therapy. Interestingly, one reported controlled trial of etanercept given adjunctively to standard anti-HCV therapy was associated with significant improvement in liver enzymes, viral load and symptoms (category C and D evidence^{116–125}).

In hepatitis B, patients treated with all three TNF α blocking agents have experienced increased symptoms, worsening of viral load and in some cases hepatic failure, especially after stopping the TNF α blocking agents (category C evidence¹²⁶; category D evidence^{127–134}). As a result, specific warnings about hepatitis B reactivation have been added to the US label by the FDA. TNF α blocking agents should not be used in patients with known hepatitis B infection; in the event that hepatitis B infection is discovered during use of TNF α blocking agents, prophylactic

antiviral therapy can be employed (category C evidence^{71–124–135–137}; Canadian Regulatory Authorities).

Rises in liver function tests have been seen in patients treated with adalimumab, infliximab or etanercept, with alanine transaminase-aspartate aminotransferase raised in 3.5–4.9% and increases of these liver enzymes more than twice the upper limit of normal in about 0.01%. The use of concomitant drugs and other clinical conditions confound the interpretation of this observation (FDA; category C evidence^{10–123–124–138–141}). The follow-up and monitoring for increases in liver function test should be governed by the patient's concomitant drugs, conditions and patient-related risk factors.

Infections

Tuberculosis (TB)

An increased susceptibility to TB or reactivation of latent TB has been reported for all TNF α blocking agents. The risk of TB is also increased by the use of corticosteroids.

The clinical manifestations of active TB may be atypical in patients treated with TNF α blocking agents (eg, miliary or extrapulmonary presentations) as has been seen with other immunocompromised patients (category C evidence^{114–128–131–142}). There have been more reported cases of reactivation of latent TB as a proportion of the total number treated in patients using infliximab and adalimumab than in those using etanercept (category C evidence^{127–134–142–143}). This may be due, in part, to differences in mechanism of action, biology or kinetics as compared with the soluble receptor (category D evidence^{128–131–135}) but may also be, in part, due to the fact that populations treated with the various TNF α blocking agents differ (eg, higher background rates of TB in some countries) and the data come from registries and voluntary reporting systems. No head-to-head comparisons among TNF blocking agents have been carried out and thus no definitive data on comparisons between these agents are available for the incidence of reactivation of latent TB.

Screening of patients about to start TNF α blocking agents has reduced the risk of reactivating latent TB for patients treated with these agents (category B evidence^{114–128–134–142–144–146}). Every patient should be evaluated for the possibility of latent TB, including a history that should comprise seeking a history of prior exposure, prior drug addiction or active drug addiction, HIV infection, birth or extended living in a region of high TB prevalence and a history of working or living in TB high-risk settings such as jails, homeless shelters and drug rehabilitation centres (category B evidence^{71–114–131–152–134–143–147}; category D evidence¹⁴⁸).

In addition, physical examination and screening tests such as tuberculin skin tests (TSTs) and chest radiographs should be carried out before TNF α blocking agent therapy is started, according to local recommendations (category B, C and D evidence^{114–127–128–134–142–145–146}).

The TST is a diagnostic aid, and false-negative results can occur in the setting of immune suppression (eg, HIV, renal dialysis, corticosteroid use and RA) (category C evidence¹⁴⁹). The TST can also be falsely positive due to prior BCG vaccination.² New blood-based diagnostic assays (interferon γ release assays) have been developed using TB-specific antigens. These tests (Quantiferon-Gold and T-Spot TB) have greater specificity for latent TB infection than does the TST, and therefore might provide a useful tool in evaluating people for latent TB, particularly those with history of BCG vaccination.^{3–32} It should be noted that false-negative results and indeterminate results also occur with the interferon γ release assays owing to

Consensus statement

immunosuppressant(s) therapy.³³ The precise role of these tests in diagnosing latent TB in patients with rheumatoid disease remains under study.¹⁵⁰

Continued vigilance is required to detect reactivation of latent TB or acquisition of new cases. The role of repeated or serial tuberculin skin testing during anti-TNF therapy is unclear.

In treating latent TB, the optimal time frame between starting preventive therapy for latent TB infection and starting TNF α blocking agents is unknown. Given the low numbers of bacilli present in latent TB infection, it is likely that waiting long time periods between initiating preventive therapy and TNF blockade is unnecessary. While there are no prospective trials assessing this question, observational data from Spain suggest that initiating isoniazid therapy 1 month before TNF blockade substantially decreases the risk of latent TB reactivation.

Before starting preventive anti-TB therapy in accordance with local guidelines, consultation with an infectious disease specialist should be considered.

Other opportunistic infections

Other opportunistic infections have been reported in patients treated with TNF α blocking agents (category C evidence^{4 5 7-11 18-20 27 63 77 142 143 151}). Particular vigilance is needed when considering those infections whose containment is macrophage/granuloma dependent, such as patients with listeriosis, non-tuberculous mycobacteria,³⁶ coccidiomycosis or histoplasmosis (including reactivation of latent histoplasmosis) (category C and D evidence^{114 131 132 142 143 152-156}), but the incidence of opportunistic infections is low. A recent British registry study found that the rate of intracellular infections among patients with RA treated with TNF α blocking agents was 200/100 000, and significantly higher than in similar patients treated with DMARDs or corticosteroids (category C and D evidence^{131 132 134}).

Bacterial infections

Serious bacterial infections (usually defined as bacterial infections requiring intravenous antibiotics or hospitalisation) have also been seen in patients receiving TNF α blocking agents at rates between 0.07 and 0.09/patient-year compared with 0.01–0.06/patient-year in controls using other DMARDs (category C evidence^{114 142 143 157 158}). Risk ratios of 1–3 were documented. Other studies indicate that serious infections in certain sites are more common when using TNF α blocking agents, such as the skin, soft tissues and joints, and the risk may be highest during the first 6 months of treatment. The possible contribution of previous or concomitant corticosteroids to increasing the risk of infection should always be considered.

The incidence of other bacterial infections (not designated as serious) may be increased when using TNF α blocking agents (relative risk 2.3–3.0, 95% confidence interval (CI) 1.4 to 5.1) (category C evidence¹⁵⁹). The incidence of serious infections is higher when IL1ra and etanercept or abatacept with any of the TNF α blockers are used in combination (category A evidence; FDA^{114 142 143 160-162}). Therefore, the use of two biological agents in combinations is not recommended. TNF α blocking agents should not be administered when serious infections and/or opportunistic infections occur, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections and listeriosis (category C evidence^{4 5 7-9 11 18-20 22 27 63 77 114 131 143 147 151-156 163 164}).

Treatment with TNF α blocking agents in such patients may be resumed if the infections have been treated adequately (category D evidence; FDA^{128-131 143 147 152-156 164}).

Vaccinations

TNF α blocking agents do not significantly influence the development of protective antibodies after vaccination, although there is a small decrease in the prevalence of adequate protection and titre of response, especially in combination with MTX (category B evidence^{165 166}). Vaccination with live attenuated vaccines (eg, nasal flu vaccine, BCG, yellow fever, herpes zoster) is not recommended.

Injection site/infusion reactions

In placebo-controlled trials, injection site reactions, most of which were mild to moderate (but some of which resulted in drug discontinuation) were more common with subcutaneously administered TNF α blocking agents than with placebo (category B evidence^{4-10 15 19-22 30 48 57 62 114 167}). One study indicates that human anti-chimeric antibodies against infliximab were associated with decreased response and increased infusion reactions (category C evidence¹⁶⁸).

Acute reactions after infliximab or adalimumab administration are uncommon and are usually mild to moderate, but may, rarely, be serious (category A evidence^{4 7 15 19-21 57 62 77 114 169}; category B and C evidence^{10 11 63 170}). In most instances, infusion reactions can be treated by the use of corticosteroids or antihistamines, or by slowing the infusion rate (category B and C evidence^{168 171}).

The data suggest that a better safety profile for infusion reactions may be obtained using 6 mg/kg rather than 3 mg/kg of infliximab in children.

Malignancies

The incidence of lymphoma is increased in chronic inflammatory diseases such as RA. This increase is associated with high disease activity (category C evidence^{172 173}). The risk for lymphoma (especially non-Hodgkin's lymphoma) is increased two- to fivefold in patients with RA as compared with the general population.

A similar risk is seen in patients with RA who have received TNF α blocking agent therapy (category C evidence^{143 172 174}).

There are conflicting data about whether there is an increased risk for lymphoma and solid malignancies with TNF α blocking agent therapies for RA. Several large observational databases and a case-control study did not demonstrate an increased incidence of solid tumours in patients receiving TNF α blocking agents compared with matched controls, while two meta-analyses of anti-TNF therapies (with infliximab and adalimumab) reported a higher rate of solid malignancies including skin cancers (category A and C evidence¹⁷³⁻¹⁷⁸). One population-based study showed that the incidence of both melanoma and non-melanoma skin cancer was slightly increased when TNF α blocking agents were used (R1\; 1.4–2.0; category C evidence¹⁷⁷). In patients at risk for malignancies (eg, 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 assigned to infliximab versus placebo, nine developed lung cancers during the trial and another four lung cancers were found during open-label follow-up (category A evidence^{179 180}). Lung cancer appears to be increased in RA, although whether this is owing to disease activity or confounding factors is not known (category C evidence¹⁸⁰). In a study of Wegener's

granulomatosis, the use of etanercept with cyclophosphamide was associated with six solid malignancies versus none in the cyclophosphamide placebo group (category A evidence¹⁸¹).

The concomitant use of azathioprine with infliximab in adolescents has been associated with the occurrence of rare hepatosplenic lymphomas (FDA).

There is limited information about the risk of developing a future malignancy in patients receiving TNF α blocking agent therapy who had a previous malignancy (category D evidence¹⁸²). Vigilance for the occurrence of lymphomas and other malignancies (including recurrence of solid tumours) remains appropriate in patients treated with TNF α blocking agents

Neurological diseases

Rare instances of central and peripheral demyelinating syndromes have been reported in patients using TNF α blocking agents.^{183 184} In some cases, but not all, these syndromes have improved after withdrawal of TNF α blocking therapy and steroids were given. Accordingly, TNF α blocking therapy should not be given to patients with a history of demyelinating disease or optic neuritis.

Pregnancy

There are insufficient data on the use of TNF α blocking therapy, IL1ra therapy, abatacept or rituximab at the time of conception, during pregnancy and during lactation for specific advice.^{113 185}

Pulmonary

Rare instances of acute, severe and sometimes fatal interstitial lung disease have been reported in patients using TNF α blocking agents (category C evidence¹⁸⁶; category D evidence^{76 186}). In addition, rare cases of sarcoid-like granulomatous lung disease have been reported.

Skin disease

Some cases of new-onset psoriatic skin lesions or exacerbations of pre-existing psoriasis have been reported in patients who used TNF α blocking agents. (category C evidence¹⁸⁷). In addition, safety reviews of TNF α blocking agents have disclosed rare cases of erythema multiforme, Steven–Johnson's syndrome and toxic epidermal necrolysis.

Summary

TNF α blocking agents are effective DMARDs and are a major advance in the treatment of RA, PsA, AS, JIA and anterior uveitis complicating JIA. Their use is expanding to other rheumatic diseases. Studies in selected areas of efficacy, toxicity and general use of TNF α blocking agents are needed to help define further the most appropriate use of these agents. Further considerations when using TNF α blocking agents in these diseases are the balancing of efficacy, toxicity and cost issues. It is hoped that this statement, based on the best evidence available at this time, and modified by expert opinion, will facilitate the optimal use of these agents.

IL1 BLOCKING AGENTS

Only one IL1 blocking agent (anakinra) has been approved for use in RA and the discussion below refers to this agent. A second one, riloncept, has recently been approved for cryopyrin associated autoinflammatory syndromes.^{188 189}

Indications

Rheumatoid arthritis

Anakinra may be used for treatment of active RA, alone or with MTX, at a dose of 100 mg a day subcutaneously (category A evidence^{190–195}). In Europe, the anakinra label requires its use with MTX. Anakinra is recommended for the treatment of active RA after an adequate trial of another conventional DMARD, of which MTX is a common example. The safety of anakinra has also been studied with other DMARDs (category A evidence^{192 193}).

The use of anakinra as the first DMARD for the treatment of RA should, at present, be limited because no trials in early RA have been published.

Anakinra has been investigated in two open-label studies in AS with no clear efficacy (see section on IU receptor blockade).^{196 197}

Cryopyrin-associated periodic syndrome

Anakinra demonstrates significant efficacy in cryopyrin-associated periodic syndrome caused by mutations in the cryopyrin gene such as familial cold-induced urticaria, Muckle–Wells syndrome (see Appendix 2) and neonatal-onset multisystem inflammatory disease (NOMID). Therapeutic responses have also been reported in anecdotal cases of other periodic fever syndromes (see Appendix 2)

Juvenile idiopathic arthritis

Anakinra is active in a proportion of the patients with systemic-onset JIA and adult-onset Still's disease. It has been used in osteoarthritis (category D evidence^{198 199}), systemic lupus erythematosus (SLE) (category D evidence^{200 201}) and crystal-induced disease (category C evidence^{202–204}).

Psoriatic arthritis

Anakinra did not show effectiveness in PsA or AS.

Clinical use

Timing of response

Anakinra can lead to significant improvement in symptoms, signs and/or laboratory parameters of RA within 16 weeks, and can slow the rate of radiographic progression in this disease (category A evidence^{190–192 194}). If improvement is not seen by 16 weeks, the continued use of anakinra should be re-evaluated.

Comparisons with TNF α blocking agents

Despite lack of head-to-head comparisons anakinra is considered less effective than TNF blocking agents (category B evidence⁸²).

Trials of patients for whom TNF blocking agents have failed demonstrate mixed responses (category C evidence¹⁹⁵). Anakinra did not inhibit antitetanus antibody response in a controlled trial (category A evidence²⁰⁵).

Structural changes

Anakinra can slow the rate of radiological progression in RA.

Appendix 2 provides a referenced listing of other conditions in which anakinra has been used.

Safety

Infections

Tuberculosis

To date, there is no indication that use of anakinra is associated with an increased incidence of TB.

Consensus statement

Bacterial infections

Serious bacterial infections increased in patients receiving anakinra, and its incidence is higher than in patients with RA using other DMARDs. This increased incidence was magnified by corticosteroid use (category A evidence¹⁹³). Anakinra should not be started, or should be discontinued, when serious infections occur (category A evidence^{4 17 21 167}; category D evidence¹⁶⁰). Treatment with anakinra in such patients should only be resumed if the infection(s) have been adequately treated.

When anakinra was used in combination with etanercept, there was no increased efficacy, but an increased rate of serious infections was noted compared with either agent used as monotherapy. Therefore, the combination should not be used (category A evidence¹⁶⁰).

Injection site reactions

A dose-related incidence of injection site reactions, affecting up to 70% of patients, has occurred with the use of anakinra. These reactions often do not require treatment and seem to moderate with continued use in some patients (category A evidence^{190–192}).

Summary

Anakinra is effective for the treatment of rheumatoid arthritis and cryopyrin-associated diseases but its specific place (eg, before or after TNF α blocking agents) in the rheumatological armamentarium is not yet defined. It is hoped that this statement, based on the best evidence available at this time, and modified by expert opinion, will facilitate the optimal use of these agents.

ABATACEPT

One agent which modulates T-cell activation (abatacept) has been approved, and references are therefore to this product.

Indications

Rheumatoid arthritis

Abatacept is approved in North America for use alone or with background DMARDs for treatment of active RA. Abatacept is recommended for treatment of active RA as follows: after an adequate trial of MTX or another effective DMARD (in the USA); abatacept has been approved by the EMEA for active RA after an inadequate response to another non-biological DMARD and includes a failure of at least one TNF α blocking agent. Monotherapy is only approved in the USA in patients for whom one or more TNF α blocking agent has produced an inadequate response. Abatacept may be administered at the time when the next dose of the TNF α blocking agent, would normally be given (category C evidence²⁰⁶). Abatacept has been used with MTX and other DMARDs.

Juvenile idiopathic arthritis

Abatacept is under review for approval and has been approved by the FDA for polyarticular JIA (category D evidence^{207 208}).

A randomised controlled trial has been published in multiple sclerosis²⁰⁹ and controlled trials are underway in SLE, vasculitis, inflammatory myositis and Sjögren's syndrome.

Clinical use

Dosing and time to response

Abatacept is administered as intravenous infusions of approximately 10 mg/kg (500 mg for weights less than 60 kg; 750 mg

for weights of 60–100 kg and 1000 mg for weights over 100 kg) at 0, 2, 4 weeks then monthly (FDA product label).

Abatacept has been shown to decrease signs and symptoms and improve physical function in adult patients with moderate to severely active RA who have had an inadequate response to one or more DMARDs such as MTX or TNF blocking agents (category A evidence^{210 211}). Improvement usually occurs within 16 weeks, although additional improvement can occur for up to 3 years (category D evidence^{212 213}). If clinical improvement occurs, treatment should be continued. If no meaningful improvement occurs within 16 weeks the continued use of abatacept should be re-evaluated.

Structural changes

Abatacept in combination with MTX inhibits radiographic progression in RA (category A evidence^{11 212}).

Pharmacoeconomic data

A study of abatacept in patients with RA for whom TNF blocker therapy has failed concludes that cost effectiveness is within the currently acceptable range.²¹⁴

Safety

Patients with COPD treated with abatacept had more adverse events than patients treated with placebo; therefore its use in patients with RA with COPD should be undertaken with caution.

Infections

Tuberculosis

All patients in abatacept phase 3 trials were screened for TB and excluded if the screen was positive. Patients were included in a large trial who were purified protein derivative positive but treated for latent TB with no reactivation of TB. The risk for reactivation of latent TB or for developing new TB when using abatacept is unknown. Until the risk is known, it is prudent to screen patients considered for abatacept therapy for TB according to local practice.

Bacterial infections

Abatacept is associated with an increased risk of serious bacterial infections in comparison with placebo (category A evidence;²³ EULAR 07). In combination with other biological agents, the rate of serious infections is 4.4% (vs 1.5% in controls).²¹⁵

The use of abatacept with TNF α blocking agents is not recommended as an increased incidence of serious infections was noted when the combination was used (category A evidence^{161 162}). There are no data about the combination of abatacept and rituximab.

Vaccinations

Abatacept did reduce antibody response titres but did not significantly inhibit the ability of healthy subjects or patients with RA to develop an immune response.

Based on theoretical concerns, live vaccines should not be given while the patient is receiving abatacept or within 3 months of using abatacept.

Malignancies

An increased number of cases of lung cancer were seen in the placebo-controlled trials (4 abatacept, 0 controls). An additional nine cases were reported during open-label extension studies

(cumulatively 13 cases/4134 patients). The epidemiology of the overall incidence of lung cancer was 0.24 in the double-blind period and 0.15 in the cumulative period.²¹⁶ Although this was higher than in the general population, it was equal to that in the RA population. There has been one case of lymphoma occurring in the double-blind period with abatacept versus none in the placebo group and four additional cases in the open-label extension (cumulatively 5/4134 patient-years) (category B evidence²¹⁷). While this number is consistent with that expected from large RA cohorts, continuing surveillance is necessary. In addition, there has been one case of acute lymphocytic leukaemia during open-label treatment in patients with JIA.

Summary

Abatacept is effective for the treatment of moderate to severe rheumatoid arthritis in patients who have had an inadequate response to MTX or to at least one TNF α blocking agent. The safety of abatacept is still being defined, although caution is advised when using abatacept in the presence of COPD. It is hoped that this statement, based on the best evidence available at this time, and modified by expert opinion, will facilitate the optimal use of this agent.

RITUXIMAB

Rituximab is a chimeric anti-CD20 monoclonal antibody, which was approved in 1997 for treatment of indolent CD20, B-cell non-Hodgkin's lymphoma (NHL). More than 1 000 000 patient exposures (usually four infusions per patient) have been documented over 9 years in postmarketing surveillance of these patients with NHL. A consensus statement on the use of rituximab in patients with RA has been published (category D evidence²¹⁸).

Indications

Rheumatoid arthritis

Rituximab has been approved by the FDA in the USA for the treatment of moderate-to-severe RA in patients who have had an inadequate response to at least one TNF α blocking agent (category A and D evidence²¹⁹⁻²²¹) (FDA and EMEA label; category C and D evidence²²²⁻²²⁸). It may also be used when TNF inhibitors are not suitable (category D evidence^{221 229 230}). In RA, it may be used alone or in combination with MTX (category A and D evidence^{219-221 229 231}). Patients should have at least moderate disease activity despite MTX therapy.

Current evidence on the efficacy of rituximab relates to rheumatoid factor-positive patients (category D evidence²²²). Divergent ACR responses were seen with rituximab in rheumatoid factor-negative patients, in TNF α blocking agent non-responders, in DMARD non-responders (category D evidence^{222 225} and in TNF non-responders (category D evidence²³⁰⁻²³²).

Clinical use

Dosing and time to response

Rituximab is administered intravenously as two 1 g rituximab infusions (given with 100 mg methylprednisolone or equivalent) separated by an interval of 2 weeks; two 500 mg doses can also be used with little decrease in efficacy (category A evidence^{222 224-228 233}). The optimal treatment schedule is currently under investigation (category D evidence^{219 222 223 230 231}). Appropriate supportive equipment should be available when rituximab is used in case of rare anaphylactoid reactions.

In clinical trials, rituximab results in significant improvement in signs and symptoms and/or laboratory measures by 8–16 weeks (category D evidence²³⁴⁻²⁴¹).

Persistence and degree of response

Rituximab is effective in patients with an inadequate response to MTX for whom conventional DMARDs have failed or have one or more TNF inhibitors (category A evidence^{233 242}). Improvement has also been demonstrated in patient-related outcomes such as HAQ-DI, patient global VAS, fatigue, disability and QoL.

Evidence from randomised controlled trials shows that the combination of rituximab with MTX yields better clinical efficacy for RA than monotherapy (category A evidence^{220 222 225 242}).

Studies have shown that repeat treatment courses are effective in previously responsive patients with RA (category D evidence²⁴³). Most of the patients who received subsequent courses did so 24 weeks after the previous course and none received repeated courses earlier than 16 weeks after the previous course (category D evidence²⁴³). No data are available on repeated treatment in patients who failed to respond to the initial course.

Structural changes

There are data indicating that rituximab can slow radiographic progression in patients who have had an inadequate response to one or more TNF inhibitors (category A evidence²⁴⁴).

Appendix 3 provides a referenced listing of conditions in which rituximab has been used.

Safety

Hepatitis

Hepatitis B status should be assessed before treatment, and rituximab treatment should be used with caution in hepatitis B-positive patients since hepatitis B reactivation has been reported in patients with NHL treated with rituximab.

Infections

Tuberculosis

In general, patients who did not respond to TNF inhibitors will also have been prescreened for the presence of active or latent TB. In the RA clinical trials of rituximab in TNF inhibitor non-responders, patients with active TB were excluded. Others were screened by chest x ray examination, but were not screened for latent TB by purified protein derivative testing. Moreover, there is no evidence of an increased incidence of TB in patients with NHL treated with rituximab. Based on the evidence from clinical trials where many patients were prescreened on the basis of prior anti-TNF studies, there are insufficient data to make a determination about the necessity to screen for TB before starting treatment. Thus, the clinician should be vigilant for the occurrence of TB during treatment.

Rituximab should not be given in the presence of serious or opportunistic infections.

Bacterial infections

Similar to the TNF α blocking agents and the other biological agents, a small increase in serious infections (not intracellular infections) in patients receiving rituximab 2 \times 1000 mg compared with placebo has been reported (category A evidence²⁴⁵). An increase in the rate of serious infections was seen in a cohort of

Consensus statement

78 patients who received a TNF α blocking agent after rituximab treatment.

Since baseline immunoglobulin levels were generally normal in patients entering clinical studies, and decreased levels of immunoglobulin M, A and G have been seen with rituximab, it may be useful to determine baseline immunoglobulin levels (category D evidence^{220 226 229 231}). In clinical trials no increase in serious infections has been reported in the patients with reduced levels of IgM after rituximab treatment compared with their previously normal IgM levels (category B evidence^{226 231}). B-cell levels have been measured in clinical trials but their importance in routine practice has not been proved. Depletion of peripheral levels of the CD20+ B-cell subpopulation was not found to be predictive of achieving or maintaining a clinical response in patients with RA (category D evidence²²⁷). This suggests that the timing of re-treatment should be based on disease activity rather than repletion of peripheral B-cell levels.

Vaccination

Since rituximab causes B-cell depletion, it is recommended that any vaccinations required by the patient, such as those to prevent pneumonia and influenza, should be given before starting treatment. While receiving treatment, appropriate vaccination (such as against influenza) should be given when indicated, although the responses have been shown to be suboptimal (category D evidence²⁴⁶). Until further data are available, the use of live attenuated vaccines should only be given before the use of rituximab.

Infusion reactions

The most widespread adverse events are infusion reactions, which are most common with the first infusion of each course (about 35%) and are reduced with the second infusion (about 10%). Intravenous corticosteroids were shown to reduce the incidence and severity of infusion reactions by about 30% without changing efficacy (category A, C and D evidence^{219 220 222 225 229–231 233}).

Neurological syndromes

Three cases of progressive multifocal leucoencephalopathy (PML) have been seen in patients receiving rituximab for non-approved indications (FDA communication). Two cases were patients with severe SLE, one was a patient with cryoglobulinaemic vasculitis. All three had received prior extensive immunosuppressive therapy. A recent review identified 37 cases of PML in patients with rheumatic diseases who had not received rituximab (two-thirds SLE, one case in a patient with RA). Roughly 40% of the SLE patients did receive extensive treatment before PML manifestation.^{246 247} Twenty-seven cases of PML are known in NHL reports. The causal relationship between PML and rituximab (Rituxan) remains unclear.

There is no evidence that rituximab is associated with an increased incidence of solid tumours in RA. Nevertheless, vigilance for the occurrence of solid malignancies remains warranted during treatment with rituximab.

Skin reactions

Rare reports of psoriasis or psoriatic arthritis, including severe cases have been reported in patients with RA, SLE and NHL after rituximab treatment (category D evidence^{248 249}). The causative role of rituximab in this circumstance remains unknown.

Summary

Rituximab is effective in patients with an inadequate response to MTX for whom conventional DMARDs have failed or have one or more TNF α blocking agents. The safety of rituximab is still being defined. It is hoped that this statement, based on the best evidence available at this time, and modified by expert opinion, will facilitate the optimal use of these agents

CONCLUSION

The treatment of RA and other rheumatic diseases and conditions of altered immunoreactivity has changed dramatically for the better since the introduction of biological agents into the armamentarium of the treating physician. It is hoped that this consensus statement will provide guidance to the clinician in his/her efforts to improve the quality of life of patients with these conditions. In addition, this consensus statement should provide evidence-based support for the selection of agents and justification for their use.

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Consensus statement

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Consensus statement

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Consensus statement

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Consensus statement

APPENDICES: CATEGORIES OF EVIDENCE

- ▶ **Category A evidence:** based on evidence from at least one randomised controlled trial or meta-analyses of randomised controlled trials. Also includes reviews if these contain category A references.
- ▶ **Category B evidence:** based on evidence from at least one controlled trial without randomisation or at least one other type of experimental study, or on extrapolated recommendations from randomised controlled trials or meta-analyses.

- ▶ **Category C evidence:** based on non-experimental descriptive studies such as comparative studies, correlational studies and case-control studies which are extrapolated from randomised controlled trials, non-randomised controlled studies or other experimental studies.
- ▶ **Category D evidence:** based on expert committee reports or opinions or clinical experience of respected authorities or both, or extrapolated recommendations from randomised controlled trials, meta-analyses, non-randomised controlled trials, experimental studies or non-experimental descriptive studies. Also includes all abstracts.

APPENDIX 1 ANECDOTAL STUDIES OF ANTI-TUMOUR NECROSIS FACTOR AGENTS

Table A1 Anecdotal studies of antitumour necrosis factor agents

Disease	Author(s)	Drugs	Patients (n)
Adult Still's disease	Huffstutter and Sienknechet ²⁵⁴	Infliximab	2
	Kraetsch <i>et al</i> ²¹⁸	Infliximab	6
	Weinblatt <i>et al</i> ²⁵⁷	Etanercept	12
Amyloidosis	Fernandez-Nebro ²⁵⁹	Etanercept	3
	Elkayam <i>et al</i> ²⁶¹	Infliximab	1
	Gottenberg <i>et al</i> ²⁶³	Etanercept/ infliximab	15
	Ortiz-Santamaria <i>et al</i> ²⁶⁵	Infliximab	6
	Tomero <i>et al</i> ²⁶⁷	Infliximab	12
	Kallinick <i>et al</i>	Etanercept	1
	Ravindran <i>et al</i>	Etanercept	1
Aphthous stomatitis	Smith <i>et al</i> ²⁷¹	Etanercept	1
	Robinson and Guitart ²⁷³	Etanercept	1
Back pain (including sciatica)	Vujevich and Zirwas ²⁷⁵	Adalimumab	
	Atzeni <i>et al</i> ²⁷⁷	Etanercept	1
Behçet's disease	Sakellariou <i>et al</i> ²⁷⁸	Infliximab	1
	Genevay <i>et al</i> ²⁸⁰	Etanercept	10
Behçet's disease	Estrach <i>et al</i> ²⁸²	Infliximab/ adalimumab	7
	Gulli <i>et al</i> ²⁸⁵	Infliximab	1
	Hassard <i>et al</i> ²⁸⁷	Infliximab	1
	Licata <i>et al</i> ²⁸⁸	Infliximab	1
	Magliocco and Gottlieb ²⁷⁴	Etanercept	20
	Morillas-Arques <i>et al</i> ²⁸⁹	Adalimumab/ etanercept	
	Rozenbaum <i>et al</i> ²⁹¹	Anti-TNF	

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Table A1 Continued

Disease	Author(s)	Drugs	Patients (n)	
Bronchiolitis	Saulsbury and Mann ²⁹⁴	Infliximab		
	Sangle <i>et al</i> ²⁹⁶	Infliximab	1	
	Sfikakis <i>et al</i> ²⁹⁸	Infliximab	5	
	Sfikakis ²⁹⁹	Infliximab	11	
	Ribi <i>et al</i> ³⁰¹	Infliximab	1	
	Sweiss <i>et al</i> ³⁰³	Infliximab	3	
	Van Laar <i>et al</i> ³⁰⁵	Adalimumab	6	
	Cortot <i>et al</i> ³⁰⁶	Etanercept	1	
	Cirrhosis and alcoholic hepatitis	Naveau <i>et al</i> ²²³	Infliximab	36
		Spahr <i>et al</i> ³⁰⁹	Infliximab	20
Cutaneous T-cell lymphoma	Wendling <i>et al</i> ¹³⁶	Infliximab	1	
	Menon <i>et al</i> ³¹¹	Etanercept	13	
Dermatitis, hidradenitis, miscellaneous	Tsimberidou <i>et al</i> ³¹³	Etanercept	13	
	Bongartz <i>et al</i> ¹⁷⁵	Infliximab		
Dermatomyositis	Cortis <i>et al</i> ³¹⁵	Etanercept		
	Cummins <i>et al</i> ³¹⁷	Etanercept		
	Massarotti and Sabell'ao ³¹⁹	Etanercept		
	Zeichner <i>et al</i> ³²²	Adalimumab	1	
	Cusak and Buckley ³¹⁹	Etanercept	6	
	Jurgens-Meyer <i>et al</i>	Etanercept	1	
	Hengstman <i>et al</i> ³¹⁴	Infliximab	2	
	Miller <i>et al</i> ³²⁶	Etanercept	10	
	Sprott <i>et al</i> ³¹⁶	Etanercept	1	
	Nzeusseu <i>et al</i> ³²⁹	Infliximab	1	
Dermatomyositis	Saadeyh ³³¹	Etanercept	4	
	Norman <i>et al</i> ³³²	Etanercept	2	

Continued

Table A1 Continued

Disease	Author(s)	Drugs	Patients (n)
Erythema nodosum	Ortego-Centeno <i>et al</i> ⁹³⁵	Adalimumab	1
Familial Mediterranean fever	Takada <i>et al</i> ⁹³⁸	Etanercept	2
Felty's syndrome	Ozgcimen <i>et al</i> ⁹⁴⁰	Etanercept	1
Giant cell arteritis	Ghavami <i>et al</i> ⁹⁴²	Etanercept	1
	Andonopoulos <i>et al</i> ⁹⁴⁵	Infliximab	2
	Cantini <i>et al</i> ⁹⁴⁷	Infliximab	4
	Tan <i>et al</i> ⁹⁴⁹	Etanercept	1
	Ahmed <i>et al</i> ⁹⁵⁰	Etanercept	1
Graft vs host disease (acute)	Wolff <i>et al</i> ⁹⁵⁰	Etanercept	21
	Uberti <i>et al</i> ⁹⁵¹	Etanercept	20
	Kennedy <i>et al</i> ⁹⁵²	Etanercept	20
	Chiang <i>et al</i> ⁹⁵³	Etanercept	8
	Pavletic <i>et al</i> ⁹⁵⁵	Etanercept	4
	Andolina <i>et al</i> ⁹⁵⁶	Etanercept	1
Graves ophthalmopathy	Paridaens <i>et al</i> ⁹⁵⁸	Etanercept	10
Hepatitis C	Cacoub <i>et al</i> ⁹⁶⁰	Interferon α	27
	McMinn <i>et al</i> ⁹⁶²	Etanercept	3
	Peterson <i>et al</i> ⁹⁶⁴	Infliximab/ etanercept	24
	Pritchard ⁹⁶⁵	Etanercept	1
	Ince <i>et al</i> ⁹¹⁶	Etanercept	12
	Moreno <i>et al</i> ⁹⁶⁸	Etanercept	5
	Allen and Wolverson ⁹⁶⁹	Etanercept	2
	Marotte <i>et al</i> ⁹⁷⁰	Etanercept	9
	Rokhsar ⁹⁷²	Etanercept	1
	Magliocco and Gottlieb ⁹⁷⁴	Etanercept	3
HIV	Wallis <i>et al</i> ⁹⁷⁶	Etanercept	16
Immunodeficiency (common variable)	Smith and Skelton ¹²⁵	Etanercept	1
	Lin <i>et al</i> ⁹⁷⁹	Etanercept	1
	Cepeda <i>et al</i> ⁹⁸¹	Etanercept	7
Inclusion body myositis	Barohn <i>et al</i> ⁹⁸³	Etanercept	9 (ineffective)
	Singh <i>et al</i> ⁹⁸⁴	Etanercept	1
Juvenile-onset HLA-B27-associated severe and refractory heel enthesitis	Olivieri <i>et al</i> ⁹⁸⁶	Adalimumab	1
Kawasaki's disease	Weiss <i>et al</i> ⁹⁹⁰	Infliximab	1
	Burns <i>et al</i> ⁹⁹²	Infliximab	16
Multicentric histiocytosis	Lovelace <i>et al</i> ⁹⁹³	Etanercept	1
	Matejicka <i>et al</i> ⁹⁹⁵	Etanercept	1

Continued

Table A1 Continued

Disease	Author(s)	Drugs	Patients (n)
	Kovach <i>et al</i> ⁹⁹⁷	Etanercept	1
Myelodysplasia	Birnbaum and Gentile ³⁰⁰	Etanercept	1
	Deeg <i>et al</i> ³⁰²	Etanercept	14
	Rosenfeld and Bedell ³⁰⁴	Etanercept	19 (ineffective)
	Raza <i>et al</i> ³⁰⁷	Etanercept	26
	Maciejewski ³⁰⁸	Etanercept	16
Osteoarthritis (erosive)	Magnano <i>et al</i> ³²⁵	Adalimumab	12
Periodic fever (children)	Athreya <i>et al</i> ³¹⁰	Etanercept	3
Pigmented villonodular synovitis	Kroot <i>et al</i> ³¹²	TNF	
Polymyositis	Hengstman <i>et al</i> ³¹⁴	Infliximab	2
	Sprott <i>et al</i> ³¹⁶	Etanercept	1
	Adams <i>et al</i> ³¹⁸	Adalimumab	2
Polychondritis	Carter ^{320 321}	Infliximab	1
	Ehresman ³²¹	Etanercept	5
Pyoderma gangrenosum	Fonder <i>et al</i> ³²³	Adalimumab	1
	Heffernan <i>et al</i> ³²⁴	Adalimumab	1
SAPHO syndrome	Anker and Coats ³²⁸	Infliximab/ etanercept	150
	Sweiss <i>et al</i> ³³⁰	Infliximab	3
	Callejas-Rubio <i>et al</i> ³³³	Adalimumab	1
	Korhonen <i>et al</i> ³³⁴	Infliximab	12
	Korhonen <i>et al</i> ³³⁶	Infliximab	40
	Lam <i>et al</i> ³³⁷	Infliximab	18
	Pasternack <i>et al</i> ³³⁹	Etanercept	4
	Tobinick and Davoodifar ³⁴¹	Etanercept	43
	Khanna <i>et al</i> ³⁴³	Etanercept	1
	Utz <i>et al</i> ³⁴⁴	Etanercept	17
	Wagner <i>et al</i> ³⁴⁶	Etanercept	2
	Moul <i>et al</i> ³⁴⁸	Adalimumab	1
Sarcoidosis	Khanna <i>et al</i> ³⁴³	Etanercept	1
	Utz <i>et al</i> ³⁴⁴	Etanercept	1
	Heffernan <i>et al</i> ³⁵²	Adalimumab	1
	Callejas-Rubio ³³³	Adalimumab	1
	Querfeld ³⁵⁵	Etanercept	1
	Sweiss <i>et al</i> ³⁰³	Etanercept	1
	Hobbs ³⁵⁸	Etanercept	1
Scleroderma	Ellman <i>et al</i> ³⁶⁰	Etanercept	8
	Bosello <i>et al</i> ³⁶¹	Etanercept	
Silicone granulomas	Pasternack <i>et al</i> ³³⁹	Etanercept	4
Sjögren's syndrome	Zandbelt <i>et al</i> ³⁶⁴	Etanercept	15 (ineffective)
	Sankar <i>et al</i> ⁷²	Etanercept	14 (ineffective)
	Pessler <i>et al</i> ³⁶⁶	Etanercept	1

Continued

Consensus statement

Table A1 Continued

Disease	Author(s)	Drugs	Patients (n)
Still's disease (includes adult onset)	Fautrel <i>et al</i> ⁶⁸⁸	Etanercept	20 (ineffective)
	Stern <i>et al</i> ⁶⁷⁰	Etanercept	1 (worsening)
	Asherson <i>et al</i> ⁶⁷²	Etanercept	1
Sweet's syndrome	Kumari and Uppal ³⁷⁴	Etanercept	1
	Gindi <i>et al</i> ⁶⁷⁵	Etanercept	1
Systemic lupus erythematosus	Yamauchi <i>et al</i> ⁶⁷⁶	Etanercept	24
	Aringer <i>et al</i> ⁶⁷⁸	Infliximab	6
	Fantrel <i>et al</i> ⁶⁸⁸	Etanercept	1 (SCLE)
	Lurati <i>et al</i> ⁶⁸⁰	Etanercept	1
	Jackson <i>et al</i>	Etanercept	1 (SCLE)
	Norman <i>et al</i> ⁶³²	Etanercept	1 (SCLE)
	Hernandez-Ibarra <i>et al</i> ⁶⁸¹	N?A	—
	Principi <i>et al</i> ⁶⁸²	Infliximab	1
	Hoffman <i>et al</i> ⁶⁸³	Anti-TNF	15
	Takayasu's arteritis	Della Rossa <i>et al</i> ⁶⁸⁴	Infliximab
Tato <i>et al</i> ⁶⁸⁵		Adalimumab	1
TRAPS	Hull <i>et al</i> ⁶⁸⁶	Etanercept	>50
	Lamprecht <i>et al</i> ⁶⁸⁷	Etanercept	2
	Drewe <i>et al</i> ⁶⁸⁸	Etanercept	1
	Estrach <i>et al</i> ⁶⁸²	Infliximab/adalimumab	7
	Joseph <i>et al</i> ⁶⁸⁹	Infliximab	5
	Smith <i>et al</i> ⁶⁹⁰	Etanercept	7
	Braun <i>et al</i> ⁶⁹¹	Etanercept/infliximab	717 (uveitis in AS)
	Foster <i>et al</i> ⁶⁹²	Etanercept	20 (ineffective)
	Biester <i>et al</i> ⁶⁹³	Adalimumab	18
	Foeldvari <i>et al</i> ⁶⁹⁴	Anti-TNF	47
	Vazquez-Cobian <i>et al</i> ⁶⁹⁵	Adalimumab	14
	Reiff <i>et al</i> ⁶⁹⁶	Etanercept	10
	Schmeling and Horneff ⁶⁹⁷	Etanercept	20 (ineffective)
	Guignard <i>et al</i> ¹⁰¹	Adalimumab	8
	Vasculitis*	Booth <i>et al</i> ⁶⁹⁸	Infliximab
Feinstein and Arroyo ⁶⁹⁹		Etanercept	1
van der Bijl ⁴⁰¹		Infliximab	11
Saji <i>et al</i> ⁴⁰²		Infliximab	1 (Kawasaki's disease)
Sangle <i>et al</i> ²⁹⁶		Infliximab	1 (Churg—Strauss)
Arbach <i>et al</i> ⁴⁰⁵		Etanercept/infliximab	3
Wegener's granulomatosis		Gause <i>et al</i> ⁴⁰⁶	Infliximab
	Sangle <i>et al</i> ²⁹⁶	Infliximab	3

APPENDIX 2 ANECDOTAL STUDIES OF INTERLEUKIN 1 RECEPTOR ANTAGONIST (ANAKINRA)

Table A2 Anecdotal studies of IL-1ra

Disease	Author(s)	Patients (n)
Acute stroke	Emsley <i>et al</i> ¹²²	34
		22
Adult-onset Still's disease	Rudinskaya <i>et al</i> ⁶⁵¹	2
	Quartier <i>et al</i> ⁶⁵³	15
	Aelion <i>et al</i> ⁶⁵⁴	2
	Haraoui B <i>et al</i> ⁶⁵⁶	3
	Kalliolias <i>et al</i> ⁶⁵⁷	2
	Nordstrom <i>et al</i> ⁶⁵⁹	3
	Kalliolias <i>et al</i> ⁶⁵⁷	3
	Fitzgerald <i>et al</i> ⁶⁶²	4
	Vasques Godinho <i>et al</i> ⁶⁶³	1
	Haibel <i>et al</i>	1
Tan <i>et al</i> ¹⁹⁷	1	
Bone marrow transplant	Antin <i>et al</i> ⁶⁶⁵	186
Consider intra-articular use of anakinra	Birmingham <i>et al</i> ⁶⁶⁷	7
Cytophagic histiocytic panniculitis	Behrens <i>et al</i> ⁶⁶⁹	1
FCAS	Hoffman <i>et al</i> ⁶⁷¹	2
	Metys <i>et al</i> ⁶⁷³	1
Diabetes mellitus	Larsen <i>et al</i> ^{673a}	?
GVHD	Antin <i>et al</i> ⁶⁶⁵	8
Hyper-IgD and periodic fever syndrome	Bodar <i>et al</i> ⁶⁷⁷	3
	Rigante <i>et al</i> ⁶⁷⁹	1
Osteoarthritis	Chevalier <i>et al</i> ¹⁹⁸	?
Osteoarthritis (intra-articular)	Chevalier <i>et al</i> ¹⁹⁹	14
		1
Psoriatic arthritis	Jung <i>et al</i> ⁴⁰⁰	20
	Gibbs <i>et al</i> ^{400a}	12
Relapsing polychondritis	Vounotrypidis <i>et al</i> ⁴⁰³	1
Schnitzer's syndrome	Martinez-Taboada <i>et al</i> ⁴⁰⁴	1
Systemic lupus erythematosus	Moosig <i>et al</i> ²⁰⁰	3
	Ostendorf <i>et al</i> ²⁰¹	4

*See also Behçet's disease, giant cell arteritis, Takayasu's arteritis, Wegener's granulomatosis.

AS, ankylosing spondylitis; CINCA, chronic infantile neurological cutaneous and articular syndrome; FCAS, familial cold autoinflammatory syndrome; GVHD, graft versus host disease; NOMID, neonatal-onset multisystem inflammatory disease; SCLE, subacute cutaneous lupus erythematosus.

APPENDIX 3 ANECDOTAL STUDIES OF RITUXIMAB

Table A3 ANCA-associated vasculitis

Disease	Author(s)	Patients (n)
WG	Keogh <i>et al</i> ⁴⁰⁷	10
WG/MPA	Stasi <i>et al</i> ⁴⁰⁸	10
WG/MPA	Eriksson <i>et al</i> ⁴⁰⁹	9
WG/MPA	Keogh <i>et al</i> ⁴¹⁰	11
WG/MPA/CSS	Smith <i>et al</i> ⁴¹¹	11
WG	Aries <i>et al</i> ⁴¹²	8
WG	Brihaye <i>et al</i> ⁴¹³	8
WG	Henes <i>et al</i> ⁴¹⁴	6
WG	Golbin <i>et al</i> ⁴¹⁵	28

ANCA, antineutrophil cytoplasmic antibodies; CSS, Churg–Strauss syndrome; MPA, microscopic polyangiitis; WG, Wegener's granulomatosis.

Table A4 Cryoglobulinaemia

Disease type	Author(s)	Patients (n)
II and III	Sansonno <i>et al</i> ⁴¹⁶	20
II	Zaja <i>et al</i> ⁴¹⁷	15
II	Roccatello <i>et al</i> ⁴²⁴	12
II	Bryce <i>et al</i> ⁴²⁰	11
II	Bryce <i>et al</i> ⁴²¹	8
II HCV-associated	Roccatello <i>et al</i> ⁴²²	6
HCV-associated	Petrarca <i>et al</i> ⁴²³	14
II HCV-associated	Quartuccio <i>et al</i> ⁴¹⁸	5
HCV-associated	Saadoun <i>et al</i> ⁴²⁵	15
HCV-associated	Sansonno <i>et al</i> ⁴²⁶	20
HCV-associated	Visentini <i>et al</i> ⁴²⁷	6
HCV-associated	Petrarca <i>et al</i> ⁴²⁸	14
III	Basse <i>et al</i> ⁴¹⁹	7

GN, glomerulonephritis; HCV, hepatitis C virus; IFN, interferon; LPD, lymphoproliferative disease; NHL, non-Hodgkin's lymphoma; SS, Sjögren's syndrome.

Table A5 Sjögren's syndrome (SS)

Disease	Author(s)	Patients (n)
SS	Voulgarelis <i>et al</i> ⁴²⁹	6
SS	Gottenberg <i>et al</i> ⁴³⁰	6
SS	Dass <i>et al</i> ⁴³¹	18
SS	Devauchelle-Pensec <i>et al</i> ⁴³²	16
SS	Ihrler <i>et al</i> ⁴³³	8
SS	St Clair <i>et al</i> ⁴³⁴	12
SS	Levesque <i>et al</i> ⁴³⁵	12
SS	Seror <i>et al</i> ⁴³⁶	16
SS	Ramos-Casals <i>et al</i> ⁴³⁷	216
SS	Lavie <i>et al</i> ⁴³⁸	5

Table A6 Juvenile idiopathic arthritis and other juvenile rheumatic disease

Disease	Author(s)	Patients (n)
Refractory paediatric autoimmune diseases	El-Hallak <i>et al</i> ⁴³⁹	10

Consensus statement

Table A7 Systemic lupus erythematosus

Disease	Author(s)	Patients (n)
SLE-associated haemolytic anaemia	Gomard-Mennesson <i>et al</i> ⁴⁴⁰	26
SLE/LN (Paediatric)	Haddad <i>et al</i> ⁴⁴¹	11
SLE (Paediatric)	MacDermott and Lehman ⁴⁴²	7
SLE/LN (Paediatric)	Marks and Tullus ⁴⁴³	7
SLE	Ng <i>et al</i> ⁴⁴⁴	7
SLE and ANCA-associated vasculitis	Smith <i>et al</i> ⁴¹¹	11
SLE (Neuropsychiatric)	Tokunaga <i>et al</i> ⁴⁴⁵	10
SLE	Leandro <i>et al</i> ^{446, 447}	24
SLE	Anolik <i>et al</i> ^{448, 449} , Looney ⁴⁵⁰	17
SLE	Tokunaga <i>et al</i> ⁴⁵¹	5
SLE	Ng <i>et al</i> ⁴⁴⁴	24
SLE	Ng <i>et al</i> ⁴⁵²	41
SLE	Tanaka Y, <i>et al</i> ⁴⁵³	19
Severe SLE	Jonsdottir T, <i>et al</i> ⁴⁵⁴	16
Refractory SLE	Tanaka Y, <i>et al</i> ⁴⁵⁵	15
SLE	Ramos-Casals, <i>et al</i> ⁴³⁷	328
SLE	Amoura <i>et al</i> ⁴⁵⁶	22
SLE	Welin-Henriksson <i>et al</i> ⁴⁵⁷	20
SLE	Cambridge <i>et al</i> ⁴⁵⁹	25
SLE	Gillis <i>et al</i> ⁴⁶⁰	6
SLE (Paediatric)	Kumar <i>et al</i> ⁴⁵⁸	7
SLE (Paediatric)	Nwobi <i>et al</i> ⁴⁶¹	18

ANCA, antineutrophil cytoplasmic antibodies; LN, lupus nephritis; SLE, systemic lupus erythematosus.

Table A8 Lupus nephritis (LN)

Disease	Author(s)	Patients (n)
LN	Vigna <i>et al</i> ⁴⁶²	22
LN	Smith ⁴¹¹	6
LN	Guzman <i>et al</i> ⁴⁶³	24
LN	Sangle <i>et al</i> ⁴⁶⁴	16
LN	Sfikakis <i>et al</i> ⁴⁶⁵	7

Table A9 Solid organ transplant rejection

Disease	Author(s)	Patients (n)
Renal allograft	Stegall <i>et al</i> ⁴⁶⁶	32
Cardiac transplant	Garrett <i>et al</i> ^{467, 468}	8
Kidney/pancreas transplant/post-transplant lymphoproliferative disease	Sharma <i>et al</i> ⁴⁶⁹	5
ABO-incompatible kidney transplant	Tyden <i>et al</i> ⁴⁷⁰	60
ABO-incompatible liver transplant	Egawa <i>et al</i> ⁴⁷¹	13

Table A10 Idiopathic and inflammatory myopathies/myositis

Disease	Author(s)	Patient (n)
DM	Chung <i>et al</i> ⁴⁷²	8
DM	Levine ⁴⁷³	7
DM	Chung <i>et al</i> ⁴⁷⁴	8

DM, dermatomyositis.

Table A11 Nephropathies

Disease	Author(s)	Patients (n)
IMN	Remuzzi <i>et al</i> ⁴⁷⁵	8
IMN	Ruggenenti <i>et al</i> ⁴⁷⁶	8
IMN	Cravedi <i>et al</i> ⁴⁷⁸	12
IMN	Fervenza <i>et al</i> ⁴⁷⁹	15
Nephrotic syndrome	Bagga <i>et al</i> ⁴⁷⁷	5

IMN, idiopathic membranous nephropathy.

Table A12 Polyneuropathies

Disease	Author(s)	Patients (n)
IgM antibody-associated neuropathy	Pestronk <i>et al</i> ¹⁸⁰	21
Anti-MAG antibody associated polyneuropathy	Renaud <i>et al</i> ¹⁸¹	9
Anti-GM1 ganglioside or anti-MAG antibody-associated polyneuropathies	Levine and Pestronk ¹⁸²	5
Polyneuropathy	Benedetti <i>et al</i> ¹⁸³	13

MAG, myelin-associated glycoprotein.

Table A13 Demyelinating diseases of the central nervous system

Disease	Author(s)	Patients (n)
NMO	Jacob <i>et al</i> ¹⁸⁷	22
NMO	Genain <i>et al</i> ¹⁸⁸	9
NMO	Cree <i>et al</i> ¹⁸⁴	8
RRMS	Hauser <i>et al</i> ¹⁸⁵	104
RRMS	Bar-Or <i>et al</i> ¹⁸⁶	26

NMO, neuromyelitis optica; RRMS, relapsing and remitting multiple sclerosis.

Table A14 Graves' disease

Disease	Author(s)	Patients (n)
GD and TAO	Salvi <i>et al</i> ¹⁸⁹	9
Graves' ophthalmology	Nielsen <i>et al</i> ¹⁹⁰	10

GD, Graves' disease; TAO, thyroid-associated ophthalmopathy.

Table A15 Pemphigus, pemphigoid and epidermolysis bullosa acquisita

Disease	Author(s)	Patients (n)
BP, PV	Schmidt <i>et al</i> ¹⁹²	7
PV	Goh <i>et al</i> ¹⁹³	5
PV	Cianchini <i>et al</i> ¹⁹¹	12
Pemphigus	Joly <i>et al</i> ¹⁹⁴	21
Pemphigus	Marzano <i>et al</i> ¹⁹⁵	6
PV	Allen <i>et al</i> ²⁶⁹	42
PV	Antonucci <i>et al</i> ¹⁹⁶	5

BP, bullous pemphigoid; PV, pemphigus vulgaris.