

Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2009

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Accepted 9 October 2009

As in previous years, the consensus group to consider the use of biological agents in the treatment of rheumatic diseases met during the 11th 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 to supply 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 abatacept,¹ B-cell-specific agents,² interleukin 1 receptor antagonists (IL1ra),³ tocilizumab (TCZ),⁴ and tumour necrosis factor α (TNF α) blocking agents,⁵ 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 the appendix.⁶ 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 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 abatacept¹ and rituximab (B-cell specific therapy),² as well as IL1 blocking agents,³ TCZ⁴ and TNF blocking agents. 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 on 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 unless disease-specific, 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^{2,7}). Validated quantitative measures such as the Disease Activity Score (DAS), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), RAPID 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 may all 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.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 (category C evidence⁸). 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 adverse effects, patients or their representatives should be provided with information about potential risks and benefits so that they may give informed consent for treatment.

ABATACEPT

One agent which modulates T-cell activation (abatacept) has been approved in the United States and Europe.

Indications

Rheumatoid arthritis

Abatacept is approved in North America for use alone or with background DMARDs for treatment of moderate to severe adult RA or polyarticular JIA.

Abatacept is recommended for treatment of active RA as monotherapy or with DMARDs after an adequate trial of methotrexate (MTX) or another effective DMARD (in the USA). Abatacept has been approved by the EMEA for active RA after an inadequate response to a non-biological DMARD and includes a failure of at least one TNF α blocking agent.

Abatacept may be administered at the time when the next dose of the TNF α blocking agent would normally be given (category C evidence⁹). Abatacept has been used with MTX and other DMARDs (category A evidence¹⁰⁻¹⁵).

Clinical use

Dosing and time to response

Abatacept is administered as intravenous infusions of approximately 8 or 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 and then monthly (FDA product label).

Abatacept decreases signs and symptoms of RA and improves physical function in adult patients with moderately 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^{10 11 16 17}).

2009 Update:

In MTX-naïve patients with early RA, MTX plus abatacept was better than MTX plus placebo (category B evidence¹⁸).

Some patients respond to abatacept, according to the ACR response criteria, within 2–4 weeks. Most patients respond within 12–16 weeks of starting treatment. Patients continue to improve for up to 12 months (category A evidence¹⁹⁻²¹). Quality of life and other patient-related outcomes such as sleep, fatigue and activity also improve (category A evidence²²⁻²⁷).

Persistence and degree of response

Some patients continue to respond to abatacept for up to 3 (TNF-incomplete responders (TNF-IR)) to 5 years (MTX-incomplete responders (MTX-IR)) in long-term, open-label extension studies (category C evidence^{12 14}).

Comparison with TNF α blocking agents

The efficacy of abatacept was similar to infliximab at 3 mg/kg with numerically fewer serious adverse events in the abatacept-treated patients (category A evidence²⁸).

Structural changes

Abatacept in combination with MTX slows radiographic progression in RA in MTX-IR (category A, B, C evidence^{14 25 29-31}).

Safety

Patients with chronic obstructive pulmonary disease (COPD) treated with abatacept had more serious lower respiratory tract infections than patients treated with placebo; therefore its use in patients with RA and COPD should be undertaken with caution.

Autoimmune disease

2009 Update:

No increased incidence of autoimmune diseases was noted in the abatacept clinical trial database (category D evidence³²).

Infections

Tuberculosis

All patients in abatacept phase 3 trials were screened for tuberculosis (TB) with a tuberculin skin test but were still included if the screen was positive and they were treated for latent TB. There are cases of TB observed in the clinical trial programme (category C, D evidence^{33 34}). The risk for reactivation of latent TB or for developing new TB when using abatacept is unknown. Until the risk is known, it is appropriate to screen patients considered for abatacept treatment for TB according to local practice.

Serious infections

In comparison with placebo in clinical trials the incidence of serious infections with abatacept was increased in one trial but not in a meta-analysis (category A evidence^{34 35}). In a review of clinical trial data, the incidence of hospitalisations for infections remained stable for up to 3 years and the incidence did not differ in the long-term extension as compared with the blinded phase of clinical trials. As with the other such trials, the uncontrolled cohort design with observed data limits the generalisability of these data (category C evidence³⁴).

In combination with other biological agents, the rate of serious infections is 4.4% (vs 1.5% in controls; category C evidence¹⁵) The use of abatacept with TNF blocking agents is not recommended, as an increased incidence of serious infections was noted when the combination was used (category A evidence^{36 37}). There are no data about the combination of abatacept and rituximab.

2009 Update:

There was a decreased response to influenza, tetanus and pneumococcal vaccinations when using abatacept in healthy volunteers (category C evidence³⁸). Influenza and pneumococcal vaccinations in patients with RA receiving

abatacept were reduced as in previous reports of patients with RA receiving MTX (category D evidence³⁹).

Owing to theoretical concerns, live vaccines should not be given while a patient is receiving abatacept or within 3 months of using abatacept.

Malignancies

There has been one case of a lymphoma occurring in a double-blind trial with abatacept versus none in the placebo group; four additional cases occurred in the open-label extension (cumulatively 5/4134 patient-years) while an epidemiological overview showed no increase (category B, D evidence⁴⁰⁻⁴¹). While this number is consistent with that expected from large RA cohorts, continuing surveillance is necessary.

2009 Update:

In a comparison of abatacept clinical trial data with national registries, no increased rates of lymphoma, lung, breast, colorectal or total malignancies were found, although the control populations were not completely comparable (category D evidence⁴⁰). Epidemiological experience in six RA cohorts shows no increased rate of solid malignancies compared with the RA cohorts (category D evidence⁴¹), but continued monitoring is necessary.

Summary

Abatacept is effective for the treatment of moderate to severe RA 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.

RITUXIMAB (RTX) B-CELL THERAPY

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) and chronic lymphocytic leukaemia. 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 evidence⁴²).

Indications

Rheumatoid arthritis

Rituximab has been approved by the FDA in the USA for the treatment of moderate-to-severe RA with MTX in patients who have had an inadequate response to at least one TNF α blocking agent (category A, D evidence⁴³⁻⁴⁵) (FDA and EMEA label; category C, D evidence⁴⁶⁻⁵¹). It may also be used when TNF inhibitors are not suitable (category D evidence⁵²⁻⁵⁴).

Current evidence on the efficacy of rituximab relates to rheumatoid factor-positive patients (category C evidence⁴⁶⁻⁴⁸). More robust ACR responses were seen with rituximab in rheumatoid factor/anti-CCP-positive patients, in DMARD non-responders (category C evidence⁴⁶⁻⁴⁸) and in TNF non-responders (category D evidence⁴⁶⁻⁵²⁻⁵⁵⁻⁵⁶).

Clinical use

Dosing and time to response

Rituximab is administered intravenously as two 1 g or two 500 mg (MTX-IR patients) rituximab infusions (given with 100 mg methylprednisolone or equivalent) separated by an interval of 2 weeks (category A evidence⁴⁶⁻⁵¹⁻⁵⁷⁻⁵⁸). In RA, it may be used alone or in combination with MTX (category A and D

evidence⁴³⁻⁴⁵⁻⁵⁴⁻⁵⁵⁻⁵⁸). The optimal treatment schedule is currently under investigation (category D evidence⁴³⁻⁴⁶⁻⁴⁸⁻⁵²⁻⁵⁵).

In clinical trials, rituximab results in significant improvement in signs and symptoms and/or laboratory measures by 8–16 weeks (category A, D evidence⁵⁸⁻⁶⁵).

Persistence and degree of response

Rituximab is effective in patients with an inadequate response to MTX for whom conventional DMARDs have failed or who have used one or more TNF inhibitors (category A, B evidence⁵⁷⁻⁵⁸⁻⁶⁴⁻⁶⁷). Improvement has also been demonstrated in patient-related outcomes such as HAQ-DI, patient global VAS, fatigue, disability and QoL (category A, evidence⁶⁸⁻⁶⁹). Evidence from randomised controlled trials shows that the combination of rituximab with MTX yields better clinical efficacy for RA than monotherapy (category A evidence⁴⁴⁻⁴⁸⁻⁵³⁻⁷⁰).

Studies have shown that repeated treatment courses are effective in previously responsive patients with RA (category C, D evidence⁶³⁻⁶⁶⁻⁷¹). Most of the patients who received subsequent courses did so 24 weeks or more after the previous course and none received repeated courses earlier than 16 weeks after the previous course (category D evidence⁷¹). There are conflicting data on the efficacy of retreatment of initial non-responders (category C evidence⁷³).

2009 Update:

In a retrospective non-randomised open-label study, patients for whom one or more TNF antagonists had been ineffective were switched to RTX and this drug was more effective than using another TNF inhibitor.⁷⁴

Repeat dosing studies revealed that in MTX-IR patients, escalation from 500 mg per infusion to 1000 mg in the second course was equivalent to two courses of 500 mg or 1000 mg (unpublished data) but in TNF-IR patients two courses of 1000 mg \times 2 appear to be more efficacious than two courses of 500 mg \times 2 (category C evidence⁷⁵).

Open-label extension studies of up to 6 years showed continued response (category D evidence⁷⁶). DMARDs other than methotrexate can be used with rituximab (category D, evidence⁷³).

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 blockers (category A evidence⁷⁷).

2009 Update:

Radiographic progression is slowed for up to 2 years within clinical trials (category A evidence⁷⁸).

Safety

Hepatitis

2009 Update:

Hepatitis B status should be assessed before treatment. Rituximab treatment is normally contraindicated in hepatitis B since fatal hepatitis B reactivation has been reported in patients with NHL treated with rituximab.

RTX has been used in HCV associated cryoglobulinaemic vasculitis (category A, D evidence⁷⁹⁻⁸⁰).

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. There is no evidence of an increased incidence of TB in patients with NHL treated with rituximab. 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.

Severe 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 evidence⁸¹).

2009 Update:

There is no increase in the incidence of serious infectious events with increasing numbers of rituximab courses (up to five courses; category A, D evidence^{48 76 82}).

No increase in the rate of serious infections was seen in a cohort of 185 patients who received another biologic after rituximab treatment compared with patients receiving RTX treatment before a biological agent (category D evidence⁸³).

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^{44 49 54 55 66}). 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^{49 55}).

2009 Update:

After repeat courses of RTX, a proportion of patients develop IgG levels below the lower limit of normal. The significance of these immunoglobulin decreases is unclear and further studies are required (category C, evidence^{76 82}).

B-cell levels have been measured in clinical trials but their importance in routine practice has not been proved. More complete depletion of peripheral levels of the CD20+ B-cell subpopulation was inconsistently predictive of achieving or maintaining a clinical response in patients with RA (category D evidence^{50 84-88}). 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 submaximal (category A evidence⁸⁹).

2009 Update:

In a controlled trial, rituximab significantly decreased the immune response to neoantigen, (KLH), and pneumococcus, whereas DTH responses and responses to tetanus were unchanged (category A evidence⁹⁰).

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 (up to 35%) and are reduced with the second and subsequent 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^{45 44 46 48 52-55 57}). Rare anaphylactoid reactions have occurred when rituximab is used (category C evidence⁹¹).

Malignancies

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 (category B evidence⁷⁶).

Neurological syndromes

Cases of progressive multifocal leucoencephalopathy (PML) have been seen in patients with systemic rheumatic diseases with and without rituximab treatment (FDA communication). Two cases of PML in patients with RA treated with rituximab have been reported. The causal relationship between PML and rituximab remains unclear.

Skin reactions

Rare reports of psoriasis, including severe cases, have been reported in patients with RA, SLE and NHL after rituximab treatment (category D evidence^{92 93}). 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 who have used 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.

IL1 BLOCKING AGENTS

One IL1 blocking agent, anakinra (IL1ra), has been approved for use in RA. A second IL1 inhibitor, rilonacept (IL1 Trap), has recently been approved for use in cryopyrin-associated periodic syndromes (CAPS; category A, C evidence⁹⁴⁻⁹⁶).

Indications

Rheumatoid arthritis

Anakinra may be used for the treatment of active RA, alone or in combination with MTX, at a dose of 100 mg/day subcutaneously (category A evidence⁹⁶⁻¹⁰¹). In Europe, the anakinra label requires prescription in combination with MTX. Anakinra is recommended for the treatment of active RA after an adequate trial of non-biological DMARDs or with other DMARDs (category A evidence^{98 99}; category C evidence¹⁰²). No trials of anakinra as the first DMARD prescribed for patients with early RA have been published.

Juvenile idiopathic arthritis (JIA) and adult-onset Still's disease

Anakinra is effective in a proportion of patients with systemic-onset JIA and adult-onset Still's disease (category D evidence^{103 104}).

2009 Update:**Cryopyrin-associated periodic syndromes**

Anakinra and rilonacept have clinical benefits in relatively small numbers of patients with CAPS, including familial cold autoinflammatory syndrome, Muckle–Wells syndrome and neonatal-onset multisystem inflammatory disease, which are characterised by mutations in the NALP3 gene (category A, C evidence^{95 102 104}). Successful treatment with anakinra in children with idiopathic recurrent pericarditis suggested that this disorder may be a previously unrecognised autoinflammatory syndrome (category D evidence¹⁰⁵). A placebo-controlled randomised clinical trial has highlighted the clinical efficacy of rilonacept in patients with CAPS⁷ (category A evidence⁹⁵).

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 (category A evidence^{96-98 100}). If improvement is not seen by 16 weeks, the continued use of anakinra should be reconsidered.

Comparison with TNF α blocking agents

Despite the lack of head-to-head comparisons, anakinra is considered to be less effective than TNF blocking agents (category B evidence¹⁰⁶). Clinical trials of patients for whom anti-TNF therapy has failed showed variable responses to anakinra (category C evidence¹⁰¹).

Infections**Tuberculosis**

To date, there is no indication that use of anakinra is associated with an increased incidence of TB (category D evidence¹⁰⁷).

Bacterial infections

The frequency of serious bacterial infections was increased in patients receiving anakinra, and its incidence is higher than in patients with RA using non-biological DMARDs. The increased incidence of infection was greatest in patients who were also receiving corticosteroids (category A evidence⁹⁹; category C evidence¹⁰⁷). Patients should not start or continue anakinra if a serious infection is present (category A evidence^{4 109-111}; category C evidence¹⁰⁷; category D evidence¹¹²). Treatment with anakinra in such patients should only be resumed if the infection has been adequately treated.

When anakinra was used in combination with etanercept, there was no increase in efficacy. However, an increase in the incidence of serious infection was seen in comparison with either compound used as monotherapy. Therefore, the combination of anakinra and etanercept should not be prescribed (category A evidence¹¹⁵).

Vaccinations**2009 Update:**

In one controlled trial, anakinra did not inhibit anti-tetanus antibody response (category D evidence¹¹⁴).

Injection site reactions

A dose-related incidence of injection site reactions, affecting up to 70% of patients, has been reported with the use of anakinra. These reactions often do not require treatment and seem to

moderate with continued use in most patients (category A evidence⁹⁶⁻⁹⁸).

Summary

Anakinra and rilonacept are effective in the treatment of CAPS. It is also effective in the treatment of JIA, adult Still's disease and RA, but its position in the therapeutic algorithm of RA is unclear.

Ankylosing spondylitis and psoriatic arthritis

Anakinra has been evaluated in two open-label studies of AS, but without consistent evidence of efficacy.^{115 116} Anakinra did not demonstrate clinical efficacy in PsA.⁴³

Crystal-associated arthropathies

There are anecdotal reports of clinical efficacy after treatment with anakinra in patients with intractable gout^{116a} and pseudogout^{116b}.

Other arthropathies

Treatment with intra-articular anakinra was evaluated in a randomised clinical trial of patients with osteoarthritis.¹¹⁷⁻¹³⁸ Treatment was well tolerated but no improvements were seen compared with placebo. There are anecdotal reports concerning the use of anakinra in patients with systemic lupus erythematosus, Behçet disease and relapsing polychondritis.

TOCILIZUMAB

Tocilizumab is a humanised anti-IL6 receptor monoclonal antibody (category A/D evidence¹³⁷⁻¹⁴²).

Indications

Tocilizumab has been approved in the European Union and a number of other countries in combination with MTX or as monotherapy for the treatment of moderate-to-severe active RA in adults who are incomplete responders (owing to adverse effects or lack of response) to DMARDs or TNF blocking agents (category A, D evidence^{137-142 144}).

In Japan and India tocilizumab has also been approved for polyarticular JIA, systemic-onset JIA and multicentric Castleman's disease (category A, D evidence¹⁴⁵⁻¹⁴⁸).

Clinical use

Tocilizumab reduces signs and symptoms of active RA in incomplete responders to DMARDs or TNF blocking agents (category A, D evidence¹³⁷). Tocilizumab can be used as monotherapy in DMARD/MTX-naïve patients (category A, D evidence¹⁴¹) or DMARD inadequate responders (category A, D^{137-140 142}).

Dosing

Tocilizumab is administered intravenously monthly in a dose of 4 or 8 mg/kg (category A, D¹³⁷⁻¹⁴²). In combination with MTX or other DMARDs it can be used at 4 or 8 mg/kg, although 4 mg/kg monotherapy was less effective in DMARD incomplete responders (category A, D evidence^{137-140 142}).

Timing of response

Onset of response occurs between 2–4 weeks in some patients but it may evolve for up to 24 weeks. (category A, D evidence³).

Juvenile idiopathic arthritis

Tocilizumab improves systemic signs and symptoms in patients with systemic-onset JIA in a dose of 8 mg/kg every 2 weeks (category A evidence¹⁴⁷) and in polyarticular JIA (category A, D evidence¹⁴⁴).

Comparison with TNF blocking agents

Tocilizumab has not been compared directly with TNF blocking agents. It can be used after failure of one or more TNF blocking agents (category A evidence¹⁴⁹).

Structural changes

Tocilizumab inhibits radiographic progression in patients who have had an inadequate response to MTX or other DMARDs (category A, D evidence^{140 142}), and it slows radiographic progression as monotherapy (category A evidence¹⁴⁴).

Safety

Cardiovascular end points and lipid levels

The overall long-term effect of TCZ on cardiovascular outcomes is at present not known. Increases in mean fasting plasma lipid levels were seen in TCZ-treated patients relative to controls, including total cholesterol, low-density lipoprotein and triglycerides with smaller increases in high-density lipoprotein (category A, D evidence^{150–153}).

2009 Update:

Initiation of statin therapy after receiving TCZ is effective in reducing lipids (category D evidence¹⁵⁴). In follow-up for a median of 1.5–5 years (category D evidence^{146 152}), there was no apparent increase in cardiovascular event rates. Hypertension and cerebrovascular accidents have been seen (category A, D evidence^{137–142 149–152}). In follow-up with a median of 1.5 years, there is no increase in the rate of cerebrovascular accidents (category D evidence¹⁴⁰).

Gastrointestinal

2009 Update:

During 6-month controlled trials, generalised peritonitis, lower gastrointestinal perforation, fistulae and intra-abdominal abscesses have been reported. Tocilizumab should be used with caution in patients with a history of intestinal ulceration or diverticulitis (category A, D evidence¹⁴⁰).

Haematological

Neutropenia: A higher proportion of patients treated with TCZ had a decrease in the absolute neutrophil count compared with placebo.

2009 Update:

A few patients had a decrease of polymorphonuclear cells to <1000 and/or 500 cells/mm³. This change usually occurs early after a dose and is transient. Complete blood counts should be monitored regularly. In one study, there was an accompanying increase in infections but this was not seen in most studies (category A, D evidence^{155 156}).

Increases in hepatic aminotransferase and bilirubin

Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred with similar frequency with TCZ monotherapy compared with MTX alone (category A evidence^{157–159}). In combination with MTX, increases are more common.

2009 Update:

Increases of bilirubin, mostly indirect, occur separately and are not associated with hepatic dysfunction. Liver function should be monitored regularly. Guidelines consistent with those for MTX for the management of TCZ-related laboratory abnormalities have been included in the EMEA package.¹⁴⁴ No instances of TCZ-induced hepatic failure or liver damage have been documented (category A, D evidence^{137–142 156 158}).

Infections

Bacterial Infections

The incidence of serious infection at rates up to 4.6/100 patient-years was stable in a median follow-up of 1.5 years (category D evidence¹⁵²). TCZ should not be given in the presence of serious or opportunistic infections (category D evidence¹⁴⁰). As with other biological agents careful observation for bacterial infections is necessary (category A, D evidence^{134–142 152 154 155}).

Tuberculosis and opportunistic infections

Patients with active tuberculosis and atypical mycobacterial infections were excluded in all studies, so there are insufficient data provide information about the need for TB screening before initiating TCZ treatment. Local practice for TB screening should be observed. Cases of TB have been seen in patients taking TCZ (EMA; category D evidence¹⁴⁰).

Viral infections

Cases of localised *H zoster* infection have occurred in clinical trials, but it is not clear whether *H zoster* is increased in association with TCZ (category D evidence^{139 140}).

Vaccination

Safety and response to vaccinations were evaluated in patients with RA receiving TCZ. Most patients could be effectively immunised with influenza vaccine (category D evidence¹⁵⁷). As for the other biological agents, live vaccines should not be given while patients are receiving TCZ (category A, D evidence^{140 156 157}).

Infusion-related events

Serious infusion reactions during/after treatment with TCZ are uncommon (category A, D¹⁶⁰).

Malignancies

There is no evidence that TCZ treatment is associated with an increased incidence of malignancies in patients with RA (category A, D evidence^{157–142 144–146 148 150}). Systematic safety surveillance should be performed during TCZ treatment, similar to requirements for other biological agents.

Summary

Tocilizumab is effective in patients with an inadequate response to MTX for whom conventional DMARDs have failed or who have had one or more TNF α inhibitors. It is also effective as monotherapy and in one study was better than MTX. The safety of TCZ requires further evaluation in long-term extension studies and surveillance databases.

Research agenda

- Studies are needed to determine whether immunisation with vaccinations should be carried out in adults before initiation of TCZ.

- ▶ Studies are needed with respect to the incidence of TB and opportunistic infections when using TCZ.
- ▶ Continued follow-up is necessary to ascertain relationships between TCZ and cardiovascular events, hepatic failure, viral illness (including *H zoster*) and malignancy.

TNF BLOCKING AGENTS

TNF 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 MTX. TNF α blocking agents have also been used successfully with other DMARDs, including sulfasalazine and leflunomide. They are effective for the treatment of RA in MTX-naïve patients (category A evidence^{109 112 115 116 161–167}; category D evidence¹⁶⁸). TNF α blocking agents can be used as the first DMARD in some patients (category A evidence¹¹⁰; category D evidence^{34 109 163 167}). 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^{169–171}). 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^{172–174}).

2009 Update:

Comparison of MTX + TNF blockers and combinations of traditional DMARDs plus steroids have been made for up to 2 years. Preliminary data indicate that combinations of traditional DMARDs, while effective in some patients, are less effective on a group level than combinations of MTX plus infliximab, MTX plus etanercept or MTX plus adalimumab (category A evidence¹⁷⁵).

Psoriatic arthritis

Based on the demonstration of control of signs and symptoms of joint and skin disease, improvement of function, QoL and inhibition of structural damage, the available TNF α blocking agents (adalimumab, etanercept, golimumab and infliximab) have been widely approved for the treatment of patients with PsA for whom conventional treatments have produced an inadequate response. Efficacy has been demonstrated both with monotherapy and with background MTX (category A evidence^{75 176–186}).

Ankylosing spondylitis

Adalimumab, etanercept, golimumab and infliximab have been widely approved for the treatment of active AS that is refractory to conventional treatments. In clinical trials, the efficacy of these TNF α blocking agents improved signs and symptoms, function and QoL as monotherapy as well as with concomitant second-line agents, including sulfasalazine or MTX (category A, B evidence^{187 187–193}; category D evidence¹⁹²). There is no evidence that combination therapy with conventional DMARDs is better than monotherapy with TNF blocking agents.

Juvenile idiopathic arthritis

Etanercept and adalimumab have been approved for JIA with a polyarticular course (FDA: ≥ 2 years for etanercept; ≥ 4 years for adalimumab; EMEA: age 13–17 years for both) (category A evidence^{111 194–196}; FDA and EMEA approvals). Infliximab was beneficial at 6 mg/kg in polyarticular JIA (category A evidence^{194 195}).

Appendix 3 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

Increasing the dose or reducing the dosing intervals of infliximab and adalimumab may provide additional benefit in RA, whereas increased doses of etanercept have increased benefit on a group level (category A evidence^{197 198}). The addition or substitution of other DMARDs may increase efficacy in some patients.

TNF α blocking agents, when administered up to the maximum approved dosing regimens for RA and polyarticular JIA may elicit response in 2–4 weeks in some patients. They usually lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters within 12–24 weeks (category A, B evidence^{117 199–206}). 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 34 109 112 115 116 161–167 170 171 173 199 204 205}). If such improvement occurs, treatment should be continued. If patients show no response to these agents, their continued use should be re-evaluated.

2009 Update:

For remission or low disease activity, anecdotal studies indicate that lowering the dose may be successful without loss of effect (category C evidence²⁰⁷).

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. There is also no evidence that any TNF blocking agent is more effective than any other in RA (category A and B evidence^{17 26 27 51}).

Persistence and degree of response

In long-term observational studies, some patients continue to respond for up to 10 years (category C evidence²⁰⁸).

Loss of response to a TNF blocking agent can occur. Failure to respond to one TNF blocking agent does not preclude response to another (category B, D evidence^{209 210}). Patients have been switched successfully from one TNF blocking agent to another.

2009 Update:

Several retrospective and observational studies suggest the efficacy of this switch of TNF blocking agents. One recent randomised controlled trial supports this regimen (category B, D evidence^{211–215}).

Observational data suggest the possibility that primary non-responding patients are less likely to respond to a second TNF blocking agent. Patients who have not tolerated one TNF blocking agent may respond to a second but are also less likely to tolerate a second TNF blocking agent (category B, D evidence^{200 208 209}). The optimal treatment of patients not responding to TNF blockers remains to be determined (category B evidence^{116 161 166 170}).

2009 Update:

Patients with high or moderate disease activity at baseline can respond well to TNF blocking agents (category C evidence^{216 217}).

Golimumab (approved in Canada and USA) has demonstrated similar efficacy in clinical trials as other anti-TNF agents in improving signs and symptoms of patients with RA.^{218 219} More extensive long-term safety data are needed to establish its place in the TNF blocking agent armamentarium.

Structural changes

TNF α blocking agents slow and/or inhibit radiographic progression in RA, even in some patients without a clinical response (category A evidence^{220 221}). Better clinical and radiological outcomes are achieved when TNF α blocking agents are used in combination with a traditional DMARD (category A evidence²²²).

Pharmacoeconomic data

Evidence has become available 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^{106 223–226}).

Juvenile idiopathic arthritis (JIA)**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 in JIA

Etanercept appears less effective in patients with systemic-onset JIA than in 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 in JIA

TNF α inhibition contributes to restoration of growth velocity in children whose JIA-associated inflammation is controlled. Bone density improves after treatment with TNF α blocking agents even in patients who have incomplete disease control.

Psoriatic arthritis (PsA)

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has developed treatment recommendations for PsA based on a systematic evidence-based review of the efficacy of TNF blocking agents and other treatments for the various domains of PsA (joints, enthesitis, dactylitis, spine and skin).¹⁷⁷

2009 Update:

In addition to efficacy in joints and skin, efficacy has been demonstrated with TNF blocking therapy for enthesitis, dactylitis, function, QoL, fatigue, productivity,

work disability and inhibition of structural damage (category A, B, D evidence.^{75 177 183 184 227–234}).

No efficacy differences among TNF blocking agents were found when treating PsA (category A, C evidence^{226 231}). A recent meta-analysis of randomised trials suggests that the efficacy of TNF blocking antibodies may be better than that of soluble receptor with respect to skin manifestations (category C evidence²³⁵).

Dosing and time to response**2009 Update:**

Improvement of signs and symptoms, function and QoL occurs within 12 weeks. Some patients continue to improve to week 24. For etanercept, 100 mg/week was more effective than 50 mg/week for skin but not joint manifestations (category D evidence²³⁶).

Comparing TNF α blocking agents in PsA

Preliminary data suggest that one can sometimes achieve benefit for PsA-related 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 (category C evidence²³⁷).

Structural changes in PsA

Durability of clinical efficacy and radiographic data at 2 years in PsA has been demonstrated with etanercept, infliximab and adalimumab (category A, B, C evidence^{232 234 236}).

2009 Update:

Golimumab, a human TNF blocking therapy, is approved in Canada and the USA for PsA. It improves signs and symptoms in joints, skin, nails, enthesitis and dactylitis, as well as function and QoL at 24 and 52 weeks (category A, D evidence²³⁸) in both 50 and 100 mg monthly subcutaneous dosing regimens.

Ankylosing spondylitis (AS)

In clinical trials, improvement in signs and symptoms was seen after TNF blocking agents, using patient-reported outcomes (BASDAI, BASFI, patient global VAS, SF-36, spinal mobility measures, peripheral arthritis, enthesitis and acute phase reactants (category A, B, D evidence^{239–243}).

Both infliximab and adalimumab are efficacious in active inflammatory bowel disease, which can be associated with AS.

2009 Update:

Two recent placebo-controlled trials have shown significant efficacy in signs and symptoms in patients with non-radiographic axial spondyloarthritis (category A, D evidence^{238 242}) and according to the Assessment of Spondylo-Arthritis International Society (ASAS) axial criteria (category A evidence²⁴⁴).

There is evidence that the incidence of uveitis flares is reduced when patients are treated with TNF blocking agents (category B, C, D evidence^{245–247}).

Regular treatment with infliximab was more effective than “on demand” treatment for AS (category A evidence²⁴⁸). Observational studies indicate that switching to a second TNF blocking agent may be effective (category C, D evidence²³⁷).

There is no evidence that any TNF α blocking agent is more effective than any other. No dose-ranging studies have been done with any of these drugs.

The ASAS has published recommendations for the use of TNF α blocking agents in AS (category A evidence²⁴⁴).

Dosing

The approved doses of TNF blocking agents for treatment of AS are 5 mg/kg infliximab intravenously every 6–8 weeks after induction, subcutaneous etanercept, 25 mg twice a week or 50 mg once a week, 50 mg subcutaneous golimumab monthly and 40 mg adalimumab subcutaneously every other week (category A, B evidence^{249–251}; category D evidence^{214 217 218}).

Time to response

A reduction in signs and symptoms, and improvement in function and QoL will usually be seen by 6–12 weeks in response to treatment with a TNF α blocking agent. Response may be delayed for up to a year (category D evidence²⁵²).

Comparing TNF α blocking agents in AS

There is no evidence that any TNF blocking agent is more effective than any other (category A, B, D evidence^{186–193 259 240–242 243}).

Persistence in AS

2009 Update:

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 (category B evidence⁷¹).

Three TNF blocking agents (adalimumab, etanercept, infliximab) maintain efficacy for 2–7 years in open-label studies. Flare usually occurs after discontinuation of TNF blocking agents (category B, C evidence^{253–255}). When TNF blocking agents are restarted, recapture occurs in over 80% (category D evidence²⁵⁴).

Structural changes

Several studies have shown that active inflammation of the sacroiliac joints and spine, as shown by MRI or radiograph, is significantly reduced for up to 3 years by adalimumab, etanercept and infliximab (category A evidence^{240 242 250}; category D evidence²⁵¹).

Inhibition of new bone formation when using TNF blocking agents has not been demonstrated radiographically (category A, C evidence^{241 242}).

Pharmacoeconomic data in AS

The use of TNF blocking agents reduces the indirect costs of AS (category D evidence²⁵⁶).

Appendix 3 provides a reference 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 (category B, C evidence^{107 257–259}).

Autoimmune-like syndromes

Antiphospholipid and lupus-like syndromes have occurred in both adult and paediatric patients during treatment with TNF blocking agents. Autoantibody formation is common after TNF blocking agent therapy (eg, antinuclear antibodies), but clinical syndromes associated with these antibodies are rare (category C evidence^{260–262}).

Cardiovascular

Treatment of non-RA patients with advanced chronic heart failure with TNF 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 agents have shown inconsistent results (category B evidence^{263–265}).

2009 Update:

The effect of TNF blocking agents on lipids is controversial (category D evidence^{266–272}). Several studies showed decreased cardiovascular events (myocardial infarction, stroke or transient ischaemic attack) (category D evidence^{273 274}).

Haematological

Rare instances of pancytopenia and aplastic anaemia have been reported (category A, C evidence²⁷⁵). 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.

Transaminase elevation

Rises in liver function tests have been seen in patients treated with adalimumab, infliximab or etanercept, with ALT-AST raised in 3.5–17.6% and increases of these liver enzymes more than twice the upper limit of normal in up to 2.1% (category D evidence²⁷⁶). The use of concomitant drugs and other clinical conditions confound the interpretation of this observation (FDA; category B, C evidence^{277–285}). 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. Worsening of alcoholic hepatitis has been seen in patients receiving TNF blocking agents (category D evidence²⁷⁶).

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^{286–289}). 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^{290–293}). This may be due, in part, to differences in mechanism of action, biology or kinetics as compared with the soluble receptor (category D evidence^{287 289 292}) but may also be, in part, because 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.

2009 Update:

In a recent survey, done among infectious disease specialists in the United States (an area of low TB prevalence), only 35% of mycobacterial infections among TNF blocking agent users were *M tuberculosis*. *M avium*

was as frequently found as *M tuberculosis* and multiple other non-tuberculous mycobacterial infections accounted for the rest of the mycobacterial infections (category C evidence²⁹⁴).

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 evidence²⁹⁵⁻²⁹⁷). 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 evidence²⁹⁸; category D evidence²⁹⁹).

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, D evidence^{257 258 287 290 293 296 297}).

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 evidence³⁰⁰). The TST can also be falsely positive owing to prior BCG vaccination. 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. It should be noted that false-negative results and indeterminate results also occur with the interferon γ release assays (category C evidence^{301 302}).

The precise role of these tests in diagnosing latent TB in patients with rheumatoid disease continues to be studied (category C evidence³⁰²).

Continued vigilance is required to detect reactivation of latent TB or acquisition of new cases.

2009 Update:

In areas of high TB prevalence (ie, high-risk populations or in the event of potential TB exposure) repeat testing should be considered (category C evidence³⁰³⁻³⁰⁶).

In treating latent TB, the optimal time frame between starting preventive treatment 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 treatment and TNF blockade is unnecessary. While there are no prospective trials assessing this question, observational data from Spain suggest that initiating isoniazid treatment 1 month before TNF blockade substantially decreases the risk of latent TB reactivation (category C evidence^{296 306}).

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

2009 Update:

There are case reports of reinitiation of TNF blocking agents after successful completion of full course anti-tuberculosis treatment (category C evidence³⁰⁷).

Other opportunistic infections

Other opportunistic infections have been reported in patients treated with TNF α blocking agents (category C evidence³⁰⁸⁻³¹³). Particular vigilance is needed when considering patients

with infections whose containment is macrophage/granuloma dependent, such as those with listeriosis, non-tuberculous mycobacteria,¹⁸⁰ coccidiomycosis or histoplasmosis (including reactivation of latent histoplasmosis (category C, D evidence^{257-259 289 291 308-312})).

A 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, D evidence^{289 291 293}).

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 evidence³¹⁴⁻³¹⁶). Risk ratios of 1–3 were documented. 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 5 161 205 257-259 308-312 314-316 318}).

Treatment with TNF α blocking agents in such patients may be resumed if the infections have been treated adequately (category D evidence; FDA^{259 287-289 298 319}).

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 and possibly increased further in elderly patients. (category C evidence³¹⁵; category D evidence³²⁰).

The possible contribution of previous or concomitant corticosteroids to increasing the risk of infection should always be considered (category B evidence^{207 315 316}).

2009 Update:

Biological agents and high-dose corticosteroid affect acute phase reactions (eg, erythrocyte sedimentation rate, C-reactive protein) irrespective of the cause of the inflammation. Therefore care needs to be exercised to help diagnose infection in the presence of these agents (category C evidence^{321 322}).

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 evidence³¹⁴).

The incidence of serious infections is approximately doubled when IL1ra or abatacept is used with any of the TNF α blockers in combination (category A evidence; FDA^{36 37 113 258 259}).

The use of two biological agents in combination is not recommended.

Viral infections

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, D evidence^{278 279 285}). 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, D evidence^{277 285}). 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 evidence³²³).

2009 Update:

A recent observational study reported a small increase risk of *H zoster* with monoclonal antibodies, while other studies did not report an increased risk (category B, D evidence^{217 219 321}).

Vaccinations

TNF α blocking agents do not usually adversely effect the development of protective antibodies after vaccination with influenza or polysaccharide pneumococcal vaccine, although there is a small decrease in the prevalence of adequate protection and a decrease in the titre of response, especially in combination with MTX (category A, B evidence^{324–326}). 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^{4 109–112 115 116 160–162 166 167 190 257}). One study indicates that human anti-chimeric antibodies against infliximab were associated with decreased response and increased infusion reactions (category C evidence³²⁷).

Acute reactions after infliximab or adalimumab administration are uncommon and are usually mild to moderate, but may, rarely, be serious (category A evidence^{4 110 161 166 193 219 226}; category B, C evidence³²⁸). In most instances, infusion reactions can be treated by the use of corticosteroids or antihistamines, or by slowing the infusion rate (category B, C evidence^{322 327}).

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^{329 330}). In most studies the risk for lymphoma (especially non-Hodgkin's lymphoma) is increased two- to fivefold in patients with RA as compared with the general population (category B evidence^{331–335}). A similar risk is seen in patients with RA who have received TNF α blocking agent therapy (category B, C evidence^{259 329 333 334}). It is unclear if the risk is increased (category A, B evidence^{336 337}).

While two meta-analyses of anti-TNF therapies (with infliximab and adalimumab) report a higher rate of solid malignancies, including skin, (category A, C evidence^{338 339}) several other large observational databases and a case-control study did not demonstrate an increased incidence of solid tumours in patients receiving TNF α blocking agent compared with matched controls (category B, C evidence^{340–344}).

2009 Update:

Further studies found no increased risk of solid tumours in analyses of the same data wherein positive associations

were previously found (category A, B, C evidence^{345 346}). Neither the duration of treatment nor the duration of follow-up were associated with an increased risk of cancer during the first 5 years of treatment (category B evidence^{335 345}).

The evidence for an increased incidence of non-melanotic skin cancers associated with TNF blocking agents is conflicting (category B evidence³⁴⁵).

In patients at risk for malignancies (eg, smokers) or in patients with 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^{341 342}). Lung cancer seems to be increased in RA, although whether this is owing to disease activity or confounding factors is not known (category C evidence^{341 342}). 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 evidence³⁴³).

The concomitant use of azathioprine with infliximab in adolescents has been associated with the occurrence of rare hepatosplenic lymphomas (category C evidence, FDA). It is not currently known if TNF blockade worsens an underlying malignancy or increases the risk of recurrence (category B evidence^{344 346}).

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 including Guillain-Barré syndrome have been reported in patients using TNF α blocking agents (category C evidence³⁴⁷). 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 (category D evidence^{348–352}).

Risks during pregnancy

2009 Update:

The safety of anti-TNF therapy during pregnancy is unknown. Experts disagree about whether TNF blocking agents should be stopped when pregnancy is being considered or whether they can be continued throughout pregnancy. Some studies found no increased fetal loss or miscarriages when using TNF blocking agents, while one recent study did find an increased rate of miscarriages (category D evidence^{353–355}).

A rare combination of congenital abnormalities (VACTERL—vertebral abnormalities, anal atresia, cardiac defect, tracheo-oesophageal, renal and limb abnormalities) and partial VACTERL defect have been reported rarely although the risk and causality is unclear (category C evidence³⁵⁶).

Pulmonary

Rare instances of acute, severe and sometimes fatal interstitial lung disease have been reported in patients using TNF α blocking agents (category C evidence³⁵⁷).

Skin disease

2009 Update:

Cases of psoriasis, psoriaform lesions or exacerbation of psoriasis have been reported when using all TNF blocking agents. In some cases, switching TNF blocking agents allowed continuation of treatment without recrudescence of skin lesions (category D evidence^{358–361}). Additionally rare cases of Stevens–Johnson syndrome, digital vasculitis, erythema multiforme, toxic epidermal necrolysis granulomatous reactions in skin and lungs have been noted (category D evidence^{362–364}).

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. 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.

OTHER BIOLOGICAL AGENTS

Alefacet (approved in the USA for psoriasis but not PsA) is a fully human fusion protein that blocks interaction between LFA-3 on antigen-presenting cells and CD2 on T cells, leading to decreased T-cell activation and deletion of certain T-cell clones. It is approved for the treatment of psoriasis in the USA. A phase 2 trial in PsA demonstrated modest efficacy in joints and skin at 24 weeks. A second course (each course is 12 weekly intramuscular injections followed by 12 weeks without injections) during an open-label extension demonstrated sustained articular efficacy (category A evidence³⁶⁵).

Efalizumab is a humanised monoclonal antibody to the CD11 subunit of LFA-1. It has been removed from the market after cases of progressive multifocal leukoencephalopathy.

Ustekinumab is an inhibitor of IL12 and 23 which acts in both the TH17 and TH1 pathways of inflammation and is approved for the treatment of psoriasis, and is given at 0, 4 and then every 12 weeks subcutaneously (category A evidence³⁶⁶). A phase 2 study of patients with PsA, dosed weekly for 4 weeks, showed improvement in the signs and symptoms of PsA at the 12-week primary end point (category A evidence³⁶⁷).

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.

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.

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Competing interests: None.

Provenance and peer review: Commissioned; not externally peer reviewed.

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APPENDIX 1 RITUXIMAB SYNOPSIS

Table A1 ANCA-associated vasculitis

Disease	Author, reference no	No
WG	Keogh <i>et al</i> ⁶⁶⁸	10: Effective
WG/MPA	Stasi <i>et al</i> ⁶⁶⁹	10: 8 WG/2 MPA: Effective
WG/MPA	Eriksson <i>et al</i> ⁶⁷⁰	9: 7 WG/2 MPA: Effective
WG/MPA	Keogh <i>et al</i> ⁶⁷¹	11: 10 WG/1 MPA: Effective
WG/MPA/CSS	Smith <i>et al</i> ⁶⁷²	11: 5 WG/5 MPA/1 CSS: Effective
WG	Aries <i>et al</i> ⁶⁷³	8: Granulomatous manifestations: Effective in 3; no response in 3; ineffective 2
WG	Brihaye <i>et al</i> ⁶⁷⁴	8: Refractory/relapsing: Effective
WG	Henes <i>et al</i> ⁶⁷⁵	6: Refractory: Effective
WG	Golbin <i>et al</i> ⁶⁷⁶	28: Refractory: Effective
WG	Sailler <i>et al</i> ⁶⁷⁷	37: 3 WG; 19 autoimmune cytopenia; 5 autoimmune coagulation disorder; 7 cryoglobulinaemia; 2 pemphigus; 1 SLE Effective: increased incidence of SAE
ANCA vasculitis	Lovric <i>et al</i> ⁶⁷⁸	15: Refractory ANCA associated vasculitis: Effective
WG	Seo <i>et al</i> ⁶⁷⁹	8: Effective
ANCA associated	Roccatello <i>et al</i> ^{680 381}	7: Effective
WG	Martinez Del Pero <i>et al</i> ⁶⁸²	34: Effective
WG	Guillevin <i>et al</i> ⁶⁸³	21: As effective as infliximab
WG	Ramos-Casals <i>et al</i> ⁶⁸⁴	8: Effective
WG	Palm <i>et al</i> ⁶⁸⁵	9: Effective: suppressing inflammation not airway stenosis
Refractory WG	Cohen <i>et al</i> ⁶⁸⁶	22: As effective as infliximab

ANCA, antineutrophil cytoplasmic antibodies; CSS, Churg–Strauss syndrome; MPA, microscopic polyangiitis; SAE, serious adverse event; SLE, systemic lupus erythematosus; WG, Wegener's granulomatosis.

Table A2 Cryoglobulinaemia

Disease	Author, reference no	Number
Type II HCV-associated	Sene <i>et al</i> ⁶⁸⁷	6: Ineffective
Type II and III	Sansonno <i>et al</i> ⁶⁸⁸	20: Effective
Type II	Zaja <i>et al</i> ⁶⁸⁹	15: 12 HCV: Effective
Type II HCV-associated	Quartuccio <i>et al</i> ⁶⁹⁰	5: Effective
Type III	Basse <i>et al</i> ⁶⁹¹	7: Renal transplant patients: 5 HCV: Effective
Type II	Bryce <i>et al</i> ⁶⁹²	8: Essential 1; 7 HCV/SS/LPD: Effective
Type II HCV-associated	Saadoun <i>et al</i> ⁶⁹³	16: Effective
Type II	Cavallo <i>et al</i> ⁶⁹⁴	13: Effective
Type II HCV-associated	Ramos-Casals <i>et al</i> ⁶⁹⁴	8: Effective
Type II HCV-associated	Roccatello <i>et al</i> ⁶⁹⁰	12: Effective
Type II HCV-associated	Visentini <i>et al</i> ⁶⁹⁵	6: Effective
Type II HCV-associated	Roccatello <i>et al</i> ⁶⁹⁶	6 HCV: 5 had GN: Effective

GN, glomerulonephritis; HCV, hepatitis C virus; LPD, lymphoproliferative disease; SS, Sjögren's syndrome.

Table A3 Sjögren's syndrome

Author, reference no	Number
Voulgarelis <i>et al</i> ⁶⁹⁷	6: Effective
Dass <i>et al</i> ⁶⁹⁸	17: Effective for fatigue
Pijpe <i>et al</i> ⁶⁹⁹	15: 8 SS and 7 SS/MALT: Effective
Devauchelle-Pensec <i>et al</i> ¹⁰⁰	16: SS: Effective
Seror <i>et al</i> ¹⁰¹	16: SS/NHL: Effective
Gottenberg <i>et al</i> ¹⁰²	6: 4 SS; 2 SS/MALT: Effective
Galarza <i>et al</i> ¹⁰³	8: Effective
Meijer <i>et al</i> ¹⁰⁴	15: 8 SS/7 MALT: Effective
St Clair <i>et al</i> ¹⁰⁵	12: SS: Effective
Ramos-Casals <i>et al</i> ¹⁰⁴	10: Effective
Meijer <i>et al</i> ¹⁰⁶	30: Effective
Vivino <i>et al</i> ¹⁰⁷	6: Effective
Ramos-Casals <i>et al</i> ¹⁰⁸	24: Effective
Tsirogianni <i>et al</i> ¹⁰⁹	11: Effective
Vasilyev <i>et al</i> ¹¹⁰	11: Effective

MALT, mucosa associated lymphoid tissue lymphoma; NHL, non-Hodgkin's lymphoma; SS, Sjögren's syndrome.

Table A4 Juvenile idiopathic arthritis

Disease	Author, reference no	Number
Juvenile autoimmune disease	El-Hallak <i>et al</i> ¹¹¹	10: Effective

Table A5 Systemic lupus erythematosus

Disease	Author, reference no	Number
SLE	Merrill <i>et al</i> ¹¹²	257: Ineffective
Refractory SLE	Tanaka <i>et al</i> ¹¹³	15: Partially effective
SLE: Haemolytic anaemia	Gomardd-Mennesson <i>et al</i> ¹¹⁴	26: Effective
Paediatric SLE/LN	Willems <i>et al</i> ¹¹⁵	11: Effective
Paediatric SLE	MacDermott <i>et al</i> ¹¹⁶	7: Effective
Pediatric SLE/LN	Marks <i>et al</i> ¹¹⁷	7: Effective
SLE	Ng <i>et al</i> ¹¹⁸	7 Refractory: Effective 4/7
Refractory SLE	Tokunaga <i>et al</i> ¹¹⁹	7: Effective
SLE	Leandro <i>et al</i> ¹²⁰	6: Effective
SLE	Leandro <i>et al</i> ¹²¹	24: Effective
SLE	Looney <i>et al</i> ¹²²	17: Effective
SLE	Tokunga <i>et al</i> ¹²³	5: Effective
SLE	Ng <i>et al</i> ¹²⁴	41: Effective
SLE	Tanaka <i>et al</i> ¹²⁵	19: Effective
SLE	Amoura <i>et al</i> ¹²⁶	22: Effective
SLE	Welin-Henriksson <i>et al</i> ¹²⁷	20: Effective
SLE	Cambridge <i>et al</i> ¹²⁸	25: Effective
SLE	Gillis <i>et al</i> ¹²⁹	6: Effective
SLE	Nwobi <i>et al</i> ¹³⁰	18: Effective
SLE	Albert <i>et al</i> ¹³¹	18: Effective
SLE	Boletis <i>et al</i> ¹³²	10: Effective
SLE	Jonsdottir <i>et al</i> ^{133 434}	16: Effective
SLE	Lindholm <i>et al</i> ¹³⁵	31: Effective
SLE:	Lindholm <i>et al</i> ¹³⁶	19: Effective
Thrombocytopenia and haemolytic anaemia		
SLE	Melander <i>et al</i> ¹³⁷	20: Effective
SLE	Reynolds <i>et al</i> ¹³⁸	11: Effective
SLE	Tanaka <i>et al</i> ¹³⁹	15: Effective
SLE	Podolskaya <i>et al</i> ¹⁴⁰	19: Effective
SLE	Ramos-Casals <i>et al</i> ¹³⁸⁴	27: Effective
SLE	Lu <i>et al</i> ¹⁴²	45: 19 Achieved remission; 21 achieved partial remission
Paediatric SLE with autoimmune thrombocytopenia and/or haemolytic anaemia	Kumar <i>et al</i> ¹⁴³	9: Effective

LN, lupus nephritis; SLE, systemic lupus erythematosus.

Table A6 Lupus nephritis

Disease	Author, reference no	Number
LN	Guzman <i>et al</i> ¹⁴⁴	35: Effective
LN	Sangle <i>et al</i> ¹⁴⁵	16: Effective except in rapidly progressive crescentic lupus nephritis
LN	Vigna <i>et al</i> ¹⁴⁶	22: Effective
LN	Smith <i>et al</i> ¹⁴⁷	6: Effective
LN	Sfikakis <i>et al</i> ¹⁴⁷	7: Effective
LN	Jónsdóttir <i>et al</i> ¹³⁴	18: Effective
Refractory LN	Arce-Salinas <i>et al</i> ¹⁴⁸	8: Effective

LN, lupus nephritis.

Table A7 Idiopathic and inflammatory myopathy/myositis

Disease	Author, reference no	Number
DM	Levine ⁴⁴⁹	6: Effective
DM	Chung L <i>et al</i> ⁴⁵⁰	8:(partial response)
PM	Ramos-Casals <i>et al</i> ¹³⁸⁴	3: Effective
Idiopathic inflammatory myopathy	Sultan <i>et al</i> ⁴⁵¹	8: Effective in DM only

DM, dermatomyositis; PM, polymyositis.

Table A8 Behçet's disease

Disease	Author	Number
Retinal vasculitis	Sadreddini, <i>et al</i> ⁴⁵²	1: Effective
Severe ocular lesions	Davatchi <i>et al</i> ⁴⁵³	10: Effective

Table A9 Polyneuropathy

Disease	Author, reference no	Number
IgM antibody associated polyneuropathy	Pestronk <i>et al</i> ⁴⁵⁴	21: Effective
Anti-MAG antibodies associated with polyneuropathy	Renaud <i>et al</i> ⁴⁴¹	9: Effective
IgM antibody associated polyneuropathy	Levine <i>et al</i> ⁴⁵⁵	5: Effective
Anti-MAG antibodies associated with polyneuropathy	Benedetti <i>et al</i> ⁴⁵⁶	13: Effective
Anti-MAG antibodies associated with polyneuropathy	Benedetti <i>et al</i> ⁴⁵⁷	10: Effective
Anti-MAG antibodies associated with polyneuropathy	Dalakas <i>et al</i> ⁴⁵⁸	13: Effective in 4

MAG, myelin-associated glycoprotein.

Table A10 Demyelinating diseases of the central nervous system

Disease	Author, reference no	Number
Neuromyelitis optica	Cree <i>et al</i> ⁴⁵⁹	8: Effective
Relapsing-remitting MS	Hauser <i>et al</i> ⁴⁶⁰	69: Effective
Relapsing-remitting MS	Bar-Or <i>et al</i> ⁴⁶¹	26: Effective
Neuromyelitis optica	Jacob <i>et al</i> ⁴⁶²	24: Effective
Neuromyelitis optica	Genain <i>et al</i> ⁴⁶³	9: Effective
Neuromyelitis optica	Jacob <i>et al</i> ⁴⁶⁴	25: Effective

MS, multiple sclerosis.

Table A11 Pemphigus, pemphigoid, epidermolysis bullosa and other dermatological diseases

Disease	Author, reference no	Number
BP, PV	Schmidt <i>et al</i> ⁴⁶⁵	7: Effective
PV	Goh <i>et al</i> ⁴⁶⁶	5: Partially effective
PV	Cianchini <i>et al</i> ⁴⁶⁷	12: Effective
Pemphigus	Joly <i>et al</i> ⁴⁶⁸	21: Effective
Pemphigus	Marzano <i>et al</i> ⁴⁶⁹	6: Effective
PV	Allen <i>et al</i> ⁴⁷⁰	42: Effective
PV	Antonucci <i>et al</i> ⁴⁷¹	5: Effective
Atopic eczema	Simon <i>et al</i> ⁴⁷²	6: Effective
Pemphigus	Shimanovich <i>et al</i> ⁴⁷³	7: Effective

BP, bullous pemphigoid; PV, pemphigus vulgaris.

Table A12 Scleroderma

Disease	Author, reference no	Number
Scleroderma ILD	McGonagle <i>et al</i> ⁴⁷⁴	1: Effective
Scleroderma	Lafyatis <i>et al</i> ⁴⁷⁵	15: Not effective
Scleroderma skin	Lombardi <i>et al</i> ⁴⁷²	6: Effective

ILD, interstitial lung disease.

Table A13 Antiphospholipid syndrome

Disease	Author, reference no	Number
Relapsing catastrophic antiphospholipid syndrome	Asherson <i>et al</i> ⁴⁷⁶	3: Effective
Relapsing catastrophic antiphospholipid syndrome	Manner <i>et al</i> ⁴⁷⁷	1: Effective

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

Table A14 Anecdotal studies of IL1ra

Disease	Author(s)	Patients (n)
Acute stroke	Emsley <i>et al</i> ⁴⁷⁸	34
		22
Adult-onset Still's disease	Rudinskaya <i>et al</i> ⁴³⁶	2
	Quartier <i>et al</i> ⁴⁷⁹	15
	Aelion <i>et al</i> ⁴⁸⁰	2
	Haraoui <i>et al</i> ⁴⁸¹	3
	Kallioliis <i>et al</i> ⁴⁸²	2
	Nordstrom <i>et al</i> ⁴⁸³	3
	Kallioliis <i>et al</i> ⁴⁸²	3
	Fitzgerald <i>et al</i> ⁴⁸⁴	4
	Vasques Godinho <i>et al</i> ⁴⁸⁵	1
	Tan <i>et al</i> ⁴⁸⁶	1
Bone marrow transplant	Antin <i>et al</i> ⁴⁹⁷	186
Consider intra-articular use of anakinra	Birmingham <i>et al</i> ⁴⁸⁸	7
Cytophagic histiocytic panniculitis	Behrens <i>et al</i> ⁴⁸⁹	1
FCAS	Hoffman <i>et al</i> ⁴⁹⁰	2
	Metzys <i>et al</i> ⁴⁹¹	1
Diabetes mellitus	Larsen <i>et al</i> ⁴⁹²	?
GVHD	Antin <i>et al</i> ⁴⁹⁷	8
Hyper-IgD and periodic fever syndrome	Bodar <i>et al</i> ⁴⁹³	3
		Rigante <i>et al</i> ⁴⁹⁴
Osteoarthritis	Chevalier <i>et al</i> ¹⁰³	?
Osteoarthritis (intra-articular)	Church <i>et al</i> ¹⁰⁴	14
		1
Psoriatic arthritis	Jung <i>et al</i> ⁴⁹⁵	20
		Gibbs <i>et al</i> ⁴⁹⁶
Relapsing polychondritis	Vounotrypdis <i>et al</i> ⁴⁹⁷	1
Schnitzer's syndrome	Martinez-Taboada <i>et al</i> ⁴⁹⁸	1
Systemic lupus erythematosus	Moosig <i>et al</i> ⁴⁹⁹	3
		Ostendorf <i>et al</i> ⁵⁰⁰

FCAS, familial cold autoinflammatory syndrome; GVHD, graft versus host disease.

APPENDIX 3 ANECDOTAL STUDIES OF ANTI-TUMOUR NECROSIS FACTOR AGENTS

Table A15 Anecdotal studies of antitumour necrosis factor agents

Disease	Author(s)	Drugs	Patients (n)
Adult Still's disease	Huffstutter <i>et al</i> ⁶⁰¹	Infliximab	2
	Kraetsch <i>et al</i> ⁶⁰²	Infliximab	6
	Weinblatt <i>et al</i> ⁶⁰³	Etanercept	12
Amyloidosis	Fernandez-Nebro ⁶⁰⁴	Etanercept	3
	Elkayam <i>et al</i> ⁶⁰⁵	Infliximab	1
	Gottenberg <i>et al</i> ⁶⁰⁶	Etanercept/infliximab	15
	Ortiz-Santamaria <i>et al</i> ⁶⁰⁷	Infliximab	6
	Tomero <i>et al</i> ⁶⁰⁸	Infliximab	12
	Smith <i>et al</i> ⁶⁰⁹	Etanercept	1
	Robinson and Guitart ⁶¹⁰	Etanercept	1
Apthous stomatitis	Vujevich and Zirwas ⁶¹¹	Adalimumab	
	Atzeni <i>et al</i> ⁶¹²	Etanercept	1
	Sakellariou <i>et al</i> ⁶¹³	Infliximab	1
Back pain (including sciatica)	Genevay <i>et al</i> ⁶¹⁴	Etanercept	10
	Estrach <i>et al</i> ⁶¹⁵	Infliximab/adalimumab	7
Behçet's disease	Gulli <i>et al</i> ⁶¹⁶	Infliximab	1
	Hassard <i>et al</i> ⁶¹⁷	Infliximab	1
	Licata <i>et al</i> ⁶¹⁸	Infliximab	1
	Magliocco and Gottlieb ⁶¹⁹	Etanercept	20
	Morillas-Arques <i>et al</i> ⁶²⁰	Adalimumab/etanercept	
	Rozenbaum <i>et al</i> ⁶²¹	Anti-TNF	
	Saulsbury and Mann ⁶²²	Infliximab	
	Sangle <i>et al</i> ⁶²³	Infliximab	1
	Sfikakis <i>et al</i> ⁶²⁴	Infliximab	5
	Sfikakis ⁶²⁵	Infliximab	11
	Ribi <i>et al</i> ⁶²⁶	Infliximab	1
	Sweiss <i>et al</i> ⁶²⁷	Infliximab	3
	van Laar <i>et al</i> ⁶²⁸	Adalimumab	6
	Cortot <i>et al</i> ⁶²⁹	Etanercept	1
	Cirrhosis and alcoholic hepatitis	Naveau <i>et al</i> ⁶³⁰	Infliximab
Spahr <i>et al</i> ⁶³¹		Infliximab	20
Wendling <i>et al</i> ⁶³²		Infliximab	1
Menon <i>et al</i> ⁶³²		Etanercept	13
Anker <i>et al</i> ⁶³²		Infliximab/etanercept	150
Congestive heart failure	Tsimberidou <i>et al</i> ⁶³³	Etanercept	13
Cutaneous T-cell lymphoma	Bongartz <i>et al</i> ⁶³⁹	Infliximab	
	Cortis <i>et al</i> ⁶³⁴	Etanercept	
	Cummins <i>et al</i> ⁶³⁵	Etanercept	
	Zeichner <i>et al</i> ⁶³⁶	Adalimumab	1
	Cusak and Buckley ⁶³⁷	Etanercept	6
Dermatomyositis	Hengstman <i>et al</i> ⁶³⁸	Infliximab	2
	Miller <i>et al</i> ⁶³⁹	Etanercept	10
	Sprott <i>et al</i> ⁶⁴⁰	Etanercept	1
	Nzeusseu <i>et al</i> ⁶⁴¹	Infliximab	1
	Saadeyh ⁶⁴²	Etanercept	4
	Norman <i>et al</i> ⁶⁴³	Etanercept	2
	Ortego-Centeno <i>et al</i> ¹²⁰	Adalimumab	1
Erythema nodosum	Takada <i>et al</i> ¹²²	Etanercept	2
	Ozgoçmen <i>et al</i> ¹²⁵	Etanercept	1
Familial Mediterranean fever	Ghavami <i>et al</i> ¹²⁸	Etanercept	1
Felty's syndrome	Andonopoulos <i>et al</i> ¹²⁶	Infliximab	2
Giant cell arteritis	Cantini <i>et al</i> ¹²⁷	Infliximab	4
	Tan <i>et al</i> ¹³⁵	Etanercept	1
	Ahmed <i>et al</i> ¹³³	Adalimumab	1
	Wolff <i>et al</i> ⁶⁴⁴	Etanercept	21
	Uberti <i>et al</i> ⁶⁴⁵	Etanercept	20
Graft vs host disease (acute)	Kennedy <i>et al</i> ⁶⁴⁶	Etanercept	20
	Chiang <i>et al</i> ⁶⁴⁷	Etanercept	8
	Pavletic <i>et al</i> ⁶⁴⁸	Etanercept	4

Continued

Table A15 Continued

Disease	Author(s)	Drugs	Patients (n)
Graves ophthalmopathy Hepatitis C	Andolina <i>et al</i> ⁵⁴⁹	Etanercept	1
	Paridaens <i>et al</i> ⁵⁵⁰	Etanercept	10
	Cacoub <i>et al</i> ⁵⁵¹	Interferon	27
	McMinn <i>et al</i> ⁵⁵²	Etanercept	3
	Peterson <i>et al</i> ⁵⁵³	Infliximab/etanercept	24
	Pritchard ⁵⁵⁴	Etanercept	1
	Ince <i>et al</i> ⁵⁵⁵	Etanercept	12
	Moreno <i>et al</i> ⁵⁵⁶	Etanercept	5
	Allen and Wolverton ⁴⁷⁰	Etanercept	2
	Marotte <i>et al</i> ⁵⁵⁷	Etanercept	9
	Rokhsar <i>et al</i> ⁵⁵⁸	Etanercept	1
	Magliocco and Gottlieb ⁵¹⁹	Etanercept	3
	HIV	Wallis <i>et al</i> ⁵⁵⁹	Etanercept
Immunodeficiency (common variable)	Smith and Skelton ⁵⁶⁰	Etanercept	1
	Lin <i>et al</i> ⁵⁶¹	Etanercept	1
	Cepeda <i>et al</i> ⁵⁶²	Etanercept	7
Inclusion body myositis	Barohn <i>et al</i> ⁵⁶³	Etanercept	9 (ineffective)
	Singh <i>et al</i> ⁵⁶⁴	Etanercept	1
Juvenile-onset HLA-B27- associated severe and refractory heel enthesitis	Olivieri <i>et al</i> ⁵⁶⁵	Adalimumab	1
Kawasaki's disease	Weiss <i>et al</i> ⁵⁶⁶	Infliximab	1
	Burns <i>et al</i> ⁵⁶⁷	Infliximab	16
Multicentric histiocytosis	Lovelace <i>et al</i> ¹⁰⁸	Etanercept	1
	Matejicka <i>et al</i> ¹⁴³	Etanercept	1
	Kovach <i>et al</i> ⁵⁶⁸	Etanercept	1
Myelodysplasia	Birnbaum and Gentile ⁵⁶⁹	Etanercept	1
	Deeg <i>et al</i> ⁵⁷⁰	Etanercept	14
	Rosenfeld and Bedell ⁵⁷¹	Etanercept	19 (ineffective)
	Raza <i>et al</i> ⁵⁷²	Etanercept	26
	Maciejewski ⁵⁷³	Etanercept	16
Osteoarthritis (erosive)	Magnano <i>et al</i> ⁵⁷⁴	Adalimumab	12
Periodic fever (children)	Athreya <i>et al</i> ⁵⁷⁵	Etanercept	3
Pigmented villonodular synovitis	Kroot <i>et al</i> ⁵⁷⁶	TNF	
Polychondritis	Carter ⁵⁷⁸	Infliximab	1
	Ehresman ⁵⁷⁹	Etanercept	5
Polymyositis	Hengstman <i>et al</i> ⁵³⁸	Infliximab	2
	Sprott <i>et al</i> ⁵⁴⁰	Etanercept	1
	Adams <i>et al</i> ⁵⁷⁷	Adalimumab	2
Pyoderma gangrenosum	Fonder <i>et al</i> ⁵⁸⁰	Adalimumab	1
	Heffernan <i>et al</i> ⁵⁸¹	Adalimumab	1
SAPHO syndrome	Wagner <i>et al</i> ¹³¹	Etanercept	2
Sarcoidosis	Moul and Korman ¹³²	Adalimumab	1
	Khanna <i>et al</i> ¹²⁹	Etanercept	1
	Utz <i>et al</i> ¹³⁰	Etanercept	17
	Heffernan <i>et al</i> ¹³⁴	Adalimumab	1
	Callejas-Rubio <i>et al</i> ⁵⁸⁴	Adalimumab	1
	Thumbfart ³¹⁷	Infliximab	1
Soiatica	Sweiss <i>et al</i> ⁵⁸³	Infliximab	3
	Hobbs ⁵⁸⁶	Etanercept	1
	Korhonen <i>et al</i> ¹¹⁸	Infliximab	12
Scleroderma	Korhonen <i>et al</i> ¹¹⁹	Infliximab	40
	Tobinick and Davoodifar ¹²⁴	Etanercept	43
	Ellman <i>et al</i> ⁵⁸⁷	Etanercept	8
	Bosello <i>et al</i> ⁵⁸⁸	Etanercept	
Silicone granulomas	Lam <i>et al</i> ¹²¹	Infliximab	18
	Pasternack <i>et al</i> ¹²³	Etanercept	4
Sjögren's syndrome	Zandbelt <i>et al</i> ⁵⁸⁹	Etanercept	15 (ineffective)
	Sankar <i>et al</i> ²¹²	Etanercept	14 (ineffective)
	Pessler <i>et al</i> ⁵⁹⁰	Etanercept	1
	Still's disease (includes adult onset)	Fautrel <i>et al</i> ⁵⁹¹	Etanercept
Stern <i>et al</i> ⁵⁹²		Etanercept	1 (worsening)
Asherson <i>et al</i> ⁵⁹³		Etanercept	1
Kumari and Uppal ⁵⁹⁴		Etanercept	1

Continued

Table A15 Continued

Disease	Author(s)	Drugs	Patients (n)	
Sweet's syndrome	Gindi <i>et al</i> ⁶⁹⁵	Etanercept	1	
	Yamauchi <i>et al</i> ⁶⁹⁶	Etanercept	24	
Systemic lupus erythematosus	Aringer <i>et al</i> ⁶⁹⁷	Infliximab	6	
	Fautrel <i>et al</i> ⁶⁹¹	Etanercept	1 (SCLE)	
	Lurati <i>et al</i> ⁶⁹⁸	Etanercept	1	
	Norman <i>et al</i> ⁶⁴³	Etanercept	1 (SCLE)	
	Hernandez-Ibarra <i>et al</i> ⁶⁹⁹	N/A	–	
	Principi <i>et al</i> ⁶⁰⁰	Infliximab	1	
Takayasu's arteritis	Hoffman <i>et al</i> ⁶⁰¹	Anti-TNF	15	
	Della Rossa <i>et al</i> ⁶⁰²	Infliximab	2	
	Tato <i>et al</i> ⁶⁰³	Adalimumab	1	
TRAPS	Hull <i>et al</i> ⁶⁰⁴	Etanercept	>50	
	Lamprecht <i>et al</i> ⁶⁰⁵	Etanercept	2	
	Drewe <i>et al</i> ⁶⁰⁶	Etanercept	1	
	Estrach <i>et al</i> ⁶⁰⁷	Infliximab/adalimumab	7	
	Joseph <i>et al</i> ⁶⁰⁷	Infliximab	5	
	Smith <i>et al</i> ⁶⁰⁸	Etanercept	7	
	Braun <i>et al</i> ⁶⁰⁹	Etanercept/infliximab	717 (uveitis in AS)	
	Foster <i>et al</i> ⁶¹⁰	Etanercept	20 (ineffective)	
	Biestler <i>et al</i> ⁶¹¹	Adalimumab	18	
	Foeldvari <i>et al</i> ⁶¹²	Anti-TNF α	47	
	Vazquez-Cobian <i>et al</i> ⁶¹³	Adalimumab	14	
	Reiff <i>et al</i> ⁶¹⁴	Etanercept	10	
	Schmeling and Horneff ⁶¹⁵	Etanercept	20 (ineffective)	
	Vasculitis*	Booth <i>et al</i> ⁶¹⁶	Infliximab	32
		Feinstein and Arroyo ⁶¹⁷	Etanercept	1
van der Bijl <i>et al</i> ⁶¹⁸		Infliximab	11	
Saji and Kimmotsu ⁶¹⁹		Infliximab	1 (Kawasaki's disease)	
Sangle <i>et al</i> ⁶²³		Infliximab	1 (Churg–Strauss)	
Arbach <i>et al</i> ⁶²⁰		Etanercept/infliximab	3	
Wegener's granulomatosis	Gause <i>et al</i> ⁶²¹	Infliximab	10	
	Sangle <i>et al</i> ⁶²³	Infliximab	3	

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

AS, ankylosing spondylitis; SCLE, subacute cutaneous lupus erythematosus.