

Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011

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INTRODUCTION

As in previous years, the consensus group to consider the use of biological agents in the treatment of rheumatic diseases met during the 13th Annual Workshop on Advances in Targeted Therapies in April, 2011. 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, B cell-specific agents, interleukin 1 (IL-1) antagonists, tocilizumab (TCZ) and tumour necrosis factor α blocking agents (TNF inhibitors), an update of the previous consensus statement is appropriate. To allow ease of updating, the 2010 (data from March 2009 to January 2010) updates are incorporated into the body of the article, while 2011 updates (February 2010–January 2011) are separated and highlighted. 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 appendix 1.¹ 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 abatacept and

rituximab (B cell-specific therapy) as well as IL-1 blocking agents, TCZ and TNF inhibitors. 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 (Food and Drug Administration) or EMA (European Medicines Agency) for clinical use. Extensive tables of the use of these agents in non-registered situations are included as appendices, to help experienced doctors to use these drugs in exceptional (‘off-label’) circumstances.

GENERAL STATEMENTS

The formatting of this document is arranged as follows: general introduction and general statements followed, in alphabetical order, by each biological agent arranged by generic name or general mechanism (when appropriate). Within each biological agent, the data are arranged by indication; the information is arranged according to clinical use, such as dosing, time to response, etc. Some combinations of indication occur when appropriate safety is included after clinical use, also in alphabetical order.

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 response to treatment is being measured or when patients are followed-up over time, validated quantitative measures for clinical trials can be used, such as Disease Activity

Score (DAS), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index, routine assessment of patient index data (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 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 (category A, B evidence).^{2–8} 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, enthesitis and dactylitis, global and pain response measures, functional indices and acute phase reactants, both as single measures and as part of composite measures, have been used.^{2,4,9}

For AS, measures such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) are used; they have been used in clinical trials, but have not been validated for routine clinical practice (category C evidence).⁵ In this disease, 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.

Pregnancy remains a controversial topic when using biological agents for rheumatic diseases. For all but the TNF inhibitors and IL-1 blocking agents, there are too few data to draw any conclusions. Since a lack of association is extremely difficult to prove, no biological agent can be assumed to be safe. In the absence of such data, this recommendation depends on the US FDA designation. Abatacept and TCZ have a category C designation, while TNF inhibitors and IL-1 blocking agents are designated as category B (see specific drugs).

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 the data regarding 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 can give informed consent for treatment. For ease of reference, the biological agents are listed in alphabetical order: abatacept; B cell therapy; IL-1 blocking agents; TCZ; TNF blocking agents.

ABATACEPT

One agent that modulates T cell activation (abatacept) has been approved in the USA and Europe.

Indications

Rheumatoid arthritis

Abatacept is recommended for treatment of active RA as monotherapy or with DMARDs in moderate to severe adult RA after an adequate trial of methotrexate (MTX) or another effective DMARD (in the USA). In early RA, abatacept has been approved in North America in MTX-naïve patients in combination with MTX (category A evidence^{6–8,10,11}). Abatacept had been approved by the EMA for moderate to severe active RA after an inadequate response to one or more DMARDs, including MTX, or a TNF inhibitor.¹²

Abatacept may be administered at the time when the next dose of the TNF inhibitor would normally be given (category C evidence).¹³ Abatacept has been used with MTX and other DMARDs (category A, B evidence).^{10,11,14–17}

Juvenile idiopathic arthritis

In the USA, abatacept is recommended for treatment of active polyarticular juvenile idiopathic arthritis (JIA) as monotherapy, or with DMARDs after an insufficient response of MTX in Europe.

In Europe, abatacept in combination with MTX is indicated for the treatment of moderate to severe polyarticular JIA in patients 6 years and older who have insufficient response to other DMARDs, including at least one TNF inhibitor (category A evidence).^{18,19}

Clinical use

Rheumatoid arthritis

Dosing

The adult dosing regimen is 750 mg or 1000 mg given at 0, 2 and 4 weeks then monthly, intravenously (product label) (category A evidence).²⁰

2011 UPDATE

Subcutaneous dosing has been approved by the FDA (category A evidence).²¹

Time to response

Some patients respond to abatacept, using the American College of Rheumatology (ACR) response criteria, within 2–4 weeks. Most adult patients respond within 12–16 weeks of starting therapy (it may take longer in children; see below (category A evidence).^{19,22} Patients continue to improve for up to 12 months (category A evidence).^{7,8,23} QoL and other patient-related outcomes such as sleep, fatigue and activity also improve (category A evidence).²⁴

Pharmacoeconomic and QoL

Abatacept appears to be cost-effective and comparable to other biological agents (category B effective^{15,25–27}; category D evidence^{28,29}).

Persistence

Some patients maintain response on abatacept for up to 3 (TNF-incomplete responders (TNF-IR)) to 5 (MTX-incomplete responders (MTX-IR)) years in long-term open-label extension studies (category C, D evidence).^{25,30,31}

Comparison with TNF inhibitors

In a controlled trial, the clinical efficacy of abatacept (10 mg/kg) was similar to low-dose infliximab (3 mg/kg); there were fewer serious adverse events in the abatacept-treated patients (category A evidence).³²

Switching to abatacept

It was effective after TNF inhibitor or rituximab (category D evidence).^{33,34}

2011 UPDATE

An indirect comparison, using 18 studies and one abstract, demonstrated no differences among abatacept, rituximab, TCZ and golimumab in TNF blocking agent incomplete responder RA patients. In MTX incomplete responders, TNF blocking agents were more effective than abatacept (category A evidence).³⁵

Structural changes

Abatacept in combination with MTX inhibits or reduces radiographic progression in RA in MTX-IR patients (category A, B and C evidence).^{25,36–38}

Clinical and epidemiological research

2011 UPDATE

A placebo comparison randomised controlled trial (RCT) of 12 months in seropositive patients with very early inflammatory arthritis showed that abatacept slowed radiographic progression (category A evidence).³⁹

Juvenile idiopathic arthritis**Dosing**

Abatacept is administered as intravenous infusions of 10 mg/kg for weight less than 75 kg, 750 mg for weight of 75–100 kg, and 1000 mg for weight over 100 kg. All regimens are given intravenously at 0, 2 and 4 weeks, then monthly (FDA product label) (category A evidence).¹⁹

Time to response

While most JIA patients respond within 16 weeks of starting therapy, maximal response in some children may require 3–6 months or longer before their maximal response is achieved (category B evidence).^{19 22}

Safety**Autoimmune disease**

No increased incidence of autoimmune diseases was noted in the abatacept clinical trial database (category D evidence).⁴⁰

Infections**Tuberculosis**

All patients in abatacept phase 3 trials were screened for tuberculosis (TB) with a tuberculin skin test (TST), but were still included if the screen was positive and they were treated for latent TB. To date, there have been seven cases of TB observed in the clinical trial program (rate 60/100 000 patient-years) (category C, D evidence).^{28 41} It is appropriate to screen patients considered for abatacept therapy for TB according to local practice.

Serious infections

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.

In comparison with placebo in clinical trials, the incidence of serious infections with abatacept was increased in trials at 12 months, but not in a meta-analysis pooling 6 and 12 month safety data (category A evidence).^{41 42} In a review of clinical trial data, the incidence of hospitalisations for infections remained stable for up to 5 years, and the incidence was not significantly different in the long-term extension compared with the blinded phase of clinical trials (3.0 vs 2.1/100 000 patient-years). As with the other such trials, the uncontrolled cohort design with observed data limits the generalisability of these data (category C evidence).⁴¹

2011 UPDATE

CORRONA database documented a 95% CI 0.48 to 0.96 serious infection risk ratio of 0.68 for abatacept compared with infliximab ($p < 0.05$), which was similar to other biological agents (adalimumab, etanercept and rituximab) (category B evidence).⁴³

In combination with other biological agents, the rate of serious infections is 4.4% (vs 1.5% in controls) (category C evidence).¹⁶ The use of abatacept with TNF inhibitor is not recommended, as an increased incidence of serious infections was noted when the combination was used (category A evidence).^{44 45} There are no data on the combination of abatacept and rituximab.

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 5/8 388 person-years), while an epidemiological overview showed no increase (category B, D evidence).^{40 46} Although this number is consistent with that expected from large RA cohorts, continuing surveillance is necessary. Comparing 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 evidence).⁴⁰ Epidemiological experience in six RA cohorts reveals no increased rate of solid malignancies compared with the RA cohorts (category D evidence),⁴⁶ although continued monitoring is necessary (category C evidence).⁴⁶

2011 UPDATE

Data from the abatacept clinical trials database and a French registry demonstrated no increased incidence of solid tumours in RA patients, including non-melanoma skin cancers or lung cancers. No unusual cancers were noted in patients with PsA.

Vaccinations

There was a decreased response to flu, tetanus and pneumococcal vaccinations when abatacept was used in healthy volunteers (category C evidence).⁴⁷ Flu and pneumococcal vaccinations in RA patients receiving abatacept were reduced, comparable to previous reports in RA patients receiving MTX (category D evidence).⁴⁸

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

Pregnancy

There have been too few cases of pregnancy when using abatacept for any solid conclusions to be drawn (see the general statement). According to the US FDA, this drug is considered category C, meaning 'No human studies and animal studies either show risk or are lacking. However, potential benefits may justify potential risks.'

2011 UPDATE

For PsA, a phase 2 trial of 170 patients assessed three different dosing regimens of abatacept compared with placebo. At 24 weeks, modest efficacy in joints and skin was demonstrated, which was superior in those not previously exposed to a TNF inhibitor⁴⁹ in 1997 for treatment of indolent CD20, B cell non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL).

A consensus statement on the use of rituximab in patients with RA has been published (category D evidence).⁵⁰

Rituximab 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 leukemia.

A consensus statement on the use of rituximab in patients with RA has been published (category D evidence 40).

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 inhibitor (category A, D evidence^{1–53}; FDA and EMA label; category

C and D evidence^{54–59}). It may also be used when TNF inhibitors are not suitable (category D evidence).^{51 60 61} Rituximab, in combination with MTX, has also been studied in MTX-naïve RA patients, where it resulted in significantly improved clinical outcomes as well as a reduction in the progression of radiographic joint damage (compared with MTX alone). Rituximab may therefore be considered for use in MTX-naïve RA patients.

A greater rate of ACR responses was seen with rituximab in rheumatoid factor/anticyclic citrullinated protein-positive patients who are DMARD non-responders (category B evidence).^{54 56} and in TNF inhibitor non-responders (category C evidence).^{54 60 62 63}

2011 UPDATE

An indirect meta-analytic comparison, using 18 studies and one abstract, demonstrated no differences among abatacept, rituximab, TCZ and golimumab in TNF blocking agent incomplete responder RA patients (category A evidence).³⁵

There has been great interest in identifying potential factors that might identify responses or non-response to rituximab by patients with RA, such as seropositivity, a genetic interferon type 1 signature and the number of B cells in the periphery. However, such data are not yet clinically useful (category C evidence).^{64–69}

Clinical use

Dosing

Rituximab is administered intravenously as two 1 g or two 500 mg infusions (given with 100 mg methylprednisolone or equivalent) separated by an interval of 2 weeks. These doses are relatively equivalent clinically, although higher doses appear to be associated with a numerically sooner response and greater ability to achieve higher levels of clinical response and also to retard radiographic progression than the lower dose (category A, D evidence).^{51–54 57–59 61 62 70–73}

Studies have shown that repeated treatment courses are effective in previously responsive patients with RA, and that treatment of patients with a partial response after 6 months can result in higher levels of response at week 48 (category B, C evidence).^{72–75} 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. Treatment with rituximab every 6 months showed better clinical efficacy than on-demand therapy with no significant increase in adverse events (category B evidence).⁷⁶

2011 UPDATE

It has been reported that a second course of rituximab may achieve a clinical response in patients that did not respond to a first course, and that this may relate to the extent of peripheral B cell depletion (category C evidence).⁶⁶

Time to response

In clinical trials, rituximab results in significant improvement in signs and symptoms and/or laboratory measures by 8–16 weeks (category A, D evidence).^{71 74 77–82}

Persistence

Rituximab is effective over up to 6 years 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, D evidence).^{51 71 75 76 80–83}

2011 UPDATE

An open-label trial in patients with PsA demonstrated a low degree of effectiveness in the arthritis component and little benefit in psoriatic skin lesions (category D evidence).⁸⁴

TNF switchers/degree of response

In a retrospective non-randomised open-label study,⁸⁵ and in an observational study comprising several thousand patients, patients who failed to respond to one or more TNF inhibitor appeared to have better clinical responses when switching to rituximab (RTX) as compared with another TNF inhibitor (category C evidence).^{86 87}

Improvement has also been demonstrated in patient-related outcomes such as HAQ-DI, patient global VAS, fatigue, disability and QoL (category A, evidence).^{88 89} RCTs show that the combination of rituximab with MTX yields better clinical efficacy for RA than monotherapy (category A evidence).^{51 52 56 80} Preliminary data from non-interventional studies suggest that combination with leflunomide (LEF) yields even higher responses than MTX (category D evidence).^{86 87}

Structural changes

Rituximab inhibits radiographic progression in both MTX-naïve patients and those who have had an inadequate response to one or more TNF inhibitors (category B evidence).^{81 90} In RA, at 1 year, in combination with MTX, the 1000 mg ×2 regimen reached the primary end point in protection against radiographic progression compared with MTX alone. This effect was maintained over 2 years (category B evidence).⁹¹

Safety

Hepatitis

Rituximab treatment is normally contraindicated in hepatitis B, since fatal hepatitis B re-activation has been reported in patients with NHL treated with rituximab. In the case of occult or latent hepatitis B virus (HBV), alanine transaminase should be measured regularly, and, if raised HBV DNA is found, should be checked with sensitive assays. Hepatitis B status should be assessed before treatment (category D evidence).^{92 93}

RTX has been used in hepatitis C virus (HCV)-associated cryoglobulinaemic vasculitis with both positive and negative results (category A, D evidence).⁹⁴

Infections (see also under 'Neurological syndromes' below)

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 radiograph 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 (category B evidence).^{95 96} There are insufficient data to make a determination about the necessity to screen for TB before the start of 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 TNF inhibitors and other biological agents, a small increase in serious bacterial infections was observed in patients receiving rituximab. There was no increase in the incidence of serious infectious events with up to nine courses of therapy (category A, B, D evidence).^{56 95 97–100} No increase in the rate of serious infections was seen in a cohort of 259 patients who received another biological agent after rituximab treatment compared with patients receiving RTX treatment before a biological agent (category D evidence).^{99 101}

Clinical and epidemiological research

Baseline immunoglobulin levels were generally normal in patients entering clinical studies, and decreased levels of IgM, IgA and IgG have been seen with rituximab. 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, D evidence).^{57 62 98 102 103}

Following repeated courses of RTX, a proportion of patients develop IgG levels below the lower limit of normal. These patients have a numerical, but not statistical, increase in infections in open studies (category C evidence).⁹⁵ This increase has not been confirmed by open-label extension studies in patients with initial normal IgG levels. In contrast, IgM and IgA below the lower limit of normal before rituximab treatment identifies a patient group at highest risk (category C evidence).¹⁰⁰

B cell levels have been measured in clinical trials, but their importance in routine practice has not been proved. Depletion of the CD20+ B cell subpopulation by routine measures was not predictive of achieving or maintaining a clinical response in patients with RA (category C, D evidence).^{58 101 104–108} This suggests that the timing of re-treatment should be based on disease activity (category B evidence).⁷⁶

2011 UPDATE

Risk factors that have been identified that predispose to severe infections include chronic lung disease, chronic heart disease, extra-articular involvement of RA and low pretreatment IgG levels (category C evidence).¹⁰⁹

The contribution of biological agents is usually associated with serious infections event (SIE) (see under TNF inhibitor and IL-1ra). One very small (N=5) open, randomised study of rituximab plus abatacept or etanercept was not associated with more SIEs or increased clinical benefit over 6 months (category C evidence).¹⁰²

Infusion reactions

The most widespread adverse events are infusion reactions, which are most common with the first infusion of the first course (up to 35%) and are reduced with the second and subsequent infusion (about 5–10%). Intravenous corticosteroids have been shown to reduce the incidence and severity of infusion reactions by about 30% without changing efficacy (category A, C and D evidence).^{51 52 54 56 61 62 91 100 108} Rare anaphylactic reactions have occurred when rituximab was used (category D evidence).¹¹⁰

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, C evidence).^{95 100 108}

Neurological syndromes

Cases of progressive multifocal leucoencephalopathy (PML) have been seen in patients with systemic rheumatic diseases with and without rituximab treatment (FDA communication). Four cases reported to regulatory agencies of PML in patients with RA treated with rituximab have been reported. The causal relationship between PML and rituximab remains unclear (category C evidence).¹¹⁰

Pregnancy

Although more than 200 pregnancies have been reported among mothers exposed to rituximab, the data are too incomplete and also too confounded (eg, by the concomitant use of potentially

teratogenic drugs) to allow definitive conclusions (category C evidence).^{111–113} The antibody, as an IgG, may be excreted in mother's milk (category C evidence).¹¹³

See the general statement on p i3. According to the US FDA, this drug is considered category C, meaning 'No human studies and animal studies either show risk or are lacking. However, potential benefits may justify potential risks.'

Because of possible B cell depletion in the fetus after rituximab, it is recommended that rituximab be discontinued 1 year before a planned pregnancy, although these recommendations are not specifically data-driven (category C evidence).^{111–113}

Skin reactions

Rare reports of psoriasis, including severe cases, and rare instances of vasculitis¹¹⁴ have been reported in patients with RA, systemic lupus erythematosus and NHL after rituximab treatment (category D evidence).^{114–117} The causative role of rituximab in these circumstances remains unknown.

Vaccination

Rituximab significantly decreased the immune response to neoantigen (keyhole limpet haemocyanin) and pneumococcus as well as to flu vaccination, whereas delayed-type hypersensitivity responses and responses to tetanus were unchanged (category A, B evidence).¹¹⁸

Humoral responses to flu vaccination were modestly restored at 6–10 months after rituximab administration. Of note, patients with previous flu vaccination were more likely to develop protective titres to vaccination, arguing for yearly vaccination for all patients (category B evidence).¹¹⁸ No data are available on the success of vaccination against flu after several courses of rituximab.

Since rituximab causes B cell depletion, it is recommended that any vaccinations required by the patient, such as those to prevent pneumonia and flu, should be given before the start of treatment (category A evidence).¹⁰³ Until further data are available, the use of live attenuated vaccines should only be given before the use of rituximab.

IL-1-BLOCKING AGENTS

One IL-1-blocking agent, anakinra (IL-1 receptor antagonist), has been approved for use in RA. Two IL-1 inhibitors, rilonacept (IL-1 Trap) and canakinumab (anti-IL-1 β monoclonal) have been approved for use in cryopyrin-associated periodic syndromes (CAPS) (category A evidence).^{117 119–122}

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 evidence).^{123–125} 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^{120 121 126}; category C evidence¹²⁷). No trials of anakinra as the first DMARD for patients with early RA have been published.

Cryopyrin-associated periodic syndromes

Anti-IL-1 agents have prompt major and sustained clinical benefit in children and adults with CAPS, including severe familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome, familial

cold autoinflammatory syndrome/familial cold urticaria (category A, C evidence).^{128–130} These are all rare conditions due to mutations in the NALP3 gene, in which a major role for IL-1 has been shown. The efficacy of rilonacept and canakinumab has been shown in placebo-controlled randomised clinical trials (category A evidence).^{117 119} Canakinumab is indicated in the USA and Europe in adults, adolescents and children with CAPS aged 4 years and older with body weight above 15 kg. Rilonacept is indicated in the USA and Europe in adults and adolescents with CAPS aged 12 years and older (category A, C evidence).^{117 119 128 129}

Canakinumab is administered subcutaneously every 8 weeks at a dose of 150 mg for patients with body weight >40 kg and at 2 mg/kg for patients with body weight >15 and <40 kg. No dose adjustment is needed in patients with end-stage renal disease (category C evidence).¹³¹ Rilonacept is administered subcutaneously once a week at a dose of 160 mg for patients >18 years and at 2.2 mg/kg for patients between 12 and 18 years of age. There is no evidence that one agent is more effective than others in CAPS.

Juvenile idiopathic arthritis and adult-onset Still's disease

IL-1 blockade with anakinra is effective in a proportion of patients with systemic-onset JIA and adult-onset Still's disease (category B evidence)¹³² (see table in appendix for additional references)).

Clinical use

Time to response

Anakinra can lead to significant improvement in symptoms, signs and/or laboratory parameters of RA within 16 weeks, and can inhibit or induce slowing of radiographic progression (category A evidence).^{120 123 124 133} If improvement is not observed by 16 weeks, discontinuation of anakinra should be considered.

Comparison with TNF inhibitor

A recent meta-analysis demonstrates that anakinra is less effective than the TNF inhibitors in treating RA (category A evidence).^{134 135}

Safety

These agents have largely been established in RA patients receiving anakinra. Use of newer drugs (canakinumab or rilonacept) or use in non-approved indications may disclose other safety concerns (category A, C evidence).^{119 131}

Infections

Tuberculosis

To date, there is no indication that use of anakinra is associated with an increased incidence of TB (category D evidence).¹³⁶

Bacterial infections

Serious bacterial infections increased in frequency in patients receiving anakinra, and their incidence was higher than in patients with RA using non-biological DMARDs. The increased incidence of infection was greatest in patients who were also receiving corticosteroids or >100 mg/day anakinra (category A evidence).^{125 137} Patients should not start or continue anakinra if a serious infection is present (category A evidence).^{125 137 138} Treatment with anakinra in such patients should only be resumed if the infection has been adequately treated. Anakinra has been used to treat macrophage activation syndrome, which may be triggered by JIA or by infection (category D evidence).¹³⁹

When anakinra was used in combination with etanercept, there was no increase in efficacy. However, an increase in the incidence of serious infection was observed when compared with either compound used as monotherapy. Therefore the

combination of anakinra and etanercept should not be prescribed (category A evidence).¹²⁶

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 evidence).^{120 123 125 140}

Pregnancy

See general statement on page i3. According to the US FDA, this drug is considered category B (No evidence of risk in humans. If no adequate human studies are done, no animal studies have been done, or animal studies show risk but human studies do not).

Vaccinations

In one controlled trial, anakinra did not inhibit antitetanus antibody response (category D evidence).¹³³

TOCILIZUMAB

TCZ is a humanised monoclonal antibody to IL-6 receptor (category A, D evidence).^{141–147}

Indications

Rheumatoid arthritis

TCZ has been approved in the EU and a number of other countries in combination with MTX (category A, B, C evidence).^{148–152} It is approved as monotherapy for the treatment of moderate to severe active RA in adults who are incomplete responders (for adverse event or lack of response) to DMARDs or TNF inhibitors (category A, D evidence).^{141–143 145 146 153–159} The FDA has approved TCZ for use in patients with moderate to severe RA who are incomplete responders to TNF-antagonist agents (category D evidence).^{156–159} In Japan, TCZ is approved in RA patients who show insufficient response to one or more DMARDs (category A, D).^{143 159}

Juvenile idiopathic arthritis and other indications

In Japan and India, TCZ has also been approved for systemic JIA and multicentric Castleman's disease (category A evidence).^{153 160 161}

2011 UPDATE

Efficacy data from part of a phase 3 placebo controlled trial of 112 patients with JIA showed TCZ to be highly effective administered every 2 weeks at 12 mg/kg in children with body weight <30 kg, and at 8 mg/kg for children with body weight >30 kg. TCZ has been used in patients with adult-onset Still's disease.^{162–166}

Clinical use

TCZ reduces signs and symptoms of active RA in incomplete responders to DMARDs or TNF inhibitors (category A evidence).^{141 143–145} In many countries, TCZ can be used as monotherapy in DMARD/MTX-naïve patients (category A, D evidence).^{145 157 167} or DMARD inadequate responders (category A, D evidence).^{143 159}

2011 UPDATE

TCZ monotherapy was more effective than MTX monotherapy in a head-to-head comparison in early RA. An open-label RA clinical population-based study of TCZ in DMARD-IR patients demonstrated rapid improvement in signs and symptoms with a manageable safety profile.¹⁶⁸ Another open-label study

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demonstrated the effectiveness of TCZ in TNF inhibitor inadequate responders, but showed a higher rate of serious infections in this population compared with DMARD inadequate responders. Biochemical markers of bone balance were improved with TCZ in patients with an inadequate response to anti-TNF. Similar data were observed in an open-label randomised placebo controlled trial in DMARD-IR patients. Long-term efficacy data up to 3–5 years revealed good sustainability.

Cost-effective analysis based on UK standards (which may be different in other contexts) showed that TCZ was cost effective at the threshold commonly used in the UK (category B evidence).¹⁶⁹

Dosing

The dosing regimens recommended vary by indication and country so they are shown in table 1. It is administered intravenously monthly at a dose of 4 or 8 mg/kg. In general, 8 mg/kg has been found to be more effective than 4 mg/kg (table 1). 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 evidence).^{141–146 153} TCZ use and dosing have not yet been approved for use in children by the FDA or EMA.

Time to response

Onset of response can occur as early 2–4 weeks in some patients, but it may take 24 weeks or more in other patients (category A, D evidence).^{143 144 170 171} TCZ can be restarted after long-term withdrawal (category D evidence).¹⁷²

Comparison with TNF inhibitors

TCZ has not been compared directly with TNF inhibitors. It can be used after failure of one or more TNF inhibitors (category A, D evidence).^{144 173}

2011 UPDATE

A comparison of TCZ with other biological agents in DMARD-IR patients showed similar efficacy for ACR 20/50 responses, but statistically better response to TCZ than the other biological agents for ACR 70 responses (category A evidence).¹⁷⁴

An indirect, meta-analytical comparison, using 18 studies and one abstract, demonstrated no differences among abatacept, rituximab, TCZ and golimumab in TNF blocking agent incomplete responder RA patients. In MTX incomplete responders, TCZ was more effective than abatacept (category A evidence).³⁵

Structural changes

TCZ inhibits or reduces radiographic progression in patients who have had an inadequate response to MTX or other DMARDs (category A),^{175–177} and it also inhibits or reduces radiographic progression as monotherapy (category A evidence).^{154 178}

2011 UPDATE

Dose escalation of TCZ from 4 to 8 mg/kg resulted in a reduction in the annualised rate of radiographic progression (category D evidence).¹⁷⁹

Safety

Cardiovascular (CV) end points and lipid levels

The overall long-term effect of TCZ on CV outcomes is at present not known. In follow-up for up to 5 years (category D evidence),^{167 180–185} there was no apparent increase in cardiac event rates. Hypertension and cerebrovascular accidents have been observed (category A, D evidence).^{153 167 181 186–189} In follow-up with a median of 1.5 years, there is no increase in the rate of cerebrovascular accidents (category D evidence).¹⁸³

Increases in mean fasting plasma lipid levels were observed in 20–30% of TCZ-treated patients, including total cholesterol, low-density lipoprotein (LDL), triglycerides and high-density lipoprotein (HDL) (category A, D evidence).^{181 186 187 190 191} Lipid levels should be monitored 1–2 months after initiation of therapy and then every 6 months. It should be managed according to local recommendations. Initiation of statin therapy after administration of TCZ is effective in reducing lipids (category D evidence).¹⁹²

2011 UPDATE

Changes in subfractions of lipoproteins during the use of TCZ have been analysed, and it has been shown that TCZ increases chylomicrons, LDL and HDL while reducing C-reactive protein (CRP), lipoprotein (a) and fibrinogen, so effects on CV risk will require long-term observational studies to assess whether these lipid changes affect CV outcome (category D evidence).¹⁹³

Gastrointestinal

In 6-month controlled clinical trials, generalised peritonitis, lower gastrointestinal-perforation, fistulae and intra-abdominal abscesses have been reported (overall rate 0.26/100 patient-years compared with no events in the control arm). The concomitant use of corticosteroid and non-steroidal anti-inflammatory drugs may increase the risk of these events. TCZ should be used with caution in patients with a history of intestinal ulceration or diverticulitis (category D evidence).^{194 195}

Haematological

Neutropenia

In clinical trials, a higher proportion of patients treated with TCZ had a decrease in the absolute neutrophil count compared with placebo. A few patients showed a decrease in polymorphonuclear cells to less than 1000 and, rarely, below 500 cells/mm³ (grade 3 neutropenia). In one large clinical trial comparing TCZ with MTX, reversible grade 3 neutropenia associated with TCZ was 3.1% compared with 0.4% with MTX (category A evidence).¹⁴⁵

Table 1 Dosing information for tocilizumab

Disease	EMA area*	FDA area	Japan*
RA	8 mg/kg every 4 weeks	4 mg/kg every 4 weeks initially, with increase to 8 mg/kg every 4 weeks if clinically indicated	8 mg/kg every 4 weeks
Polyarticular JIA ¹⁶⁰	–	–	8 mg/kg every 4 weeks
Systemic onset JIA	–	–	8 mg/kg every 2 weeks (interval may be decreased to weekly)
Multicentric Castleman's disease ¹⁶¹	–	–	8 mg/kg every 2 weeks (interval may be decreased to weekly)

*In EMA area and Japan, it can also be used as monotherapy in patients with contraindications or intolerance to methotrexate.

EMA, European Medicines Agency; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis.

This change usually occurs early after a dose and is transient. Complete blood counts should be monitored regularly according to local labels (usually every 4–8 weeks). In one study, there was an accompanying increase in infections, but this was not observed in most studies (category A, D evidence).^{196–199}

Vaccination

Safety and response to vaccinations were evaluated in patients with RA receiving TCZ. Most patients could be effectively immunised with flu and pneumococcal vaccine (category D evidence).²⁰⁰ As for the other biological agents, live vaccines should not be given while patients are receiving TCZ (category A, D evidence).^{153 181 197 201 202}

Increases in hepatic aminotransferases and bilirubin

Increases in alanine transaminase and aspartate aminotransferase occurred with similar frequency with TCZ monotherapy and MTX alone (category A evidence).^{203–205} In combination with DMARDs including MTX, increases are more common than with TCZ alone. Increases in bilirubin, mostly indirect and sometimes associated with Gilbert's syndrome, occur separately and are not associated with hepatic dysfunction. Liver function should be monitored regularly.

Recommendations for the management of TCZ-related laboratory abnormalities have been included in the EMA and FDA package, which are consistent with those for MTX. No instances of TCZ-induced hepatic failure or liver damage have been documented (category A, D evidence).^{141–145 153–155 167 175 181 186–188 196 197 200 203–205}

Infections

Bacterial infections

In two 6-month controlled clinical studies, the rate of serious infections in the 4 and 8 mg/kg arms were numerically higher in the TCZ than placebo+DMARD or placebo+MTX trials (1.470 vs 0.78) (category B evidence).^{197 206 207} The rates have been stable over time in open-label extensions of controlled trials (category D evidence).^{147 181 187 196 203} The downregulatory effect of TCZ on the acute-phase reactant, CRP, may limit the usefulness of CRP as a diagnostic indicator for infections. TCZ should not be given in the presence of serious or opportunistic infections (category D evidence).¹⁵³ As with other biological agents, careful observation for bacterial infections is necessary (category B, D evidence).^{181 186 197}

2011 UPDATE

A meta-analysis of six TCZ RCTs suggested that serious infections occurred more often than in the control group, but during longer term follow-up of up to 5 years, the rates of serious infections remained stable (category A evidence).²⁰⁸

Tuberculosis and opportunistic infections

Cases of TB and opportunistic infections have been observed in patients taking TCZ (EMA; category A, D evidence).^{134 197 209} Patients should be screened for (latent) TB before treatment. See TNF antagonist section for details of TB screening.

Viral infections

Cases of localised herpes zoster infection have occurred in clinical trials, but it is not clear whether herpes zoster is increased in association with TCZ (category D evidence).^{197 200 210}

2011 UPDATE

The safety of TCZ in patients with active hepatitis B or C is unknown, as patients with positive serologies were excluded from clinical trials.

Infusion-related events

Serious infusion reactions during/after treatment with TCZ are uncommon (category A, D).²¹¹

2011 UPDATE

Anaphylactic reactions have occurred (category D evidence).²¹² A fatal case of severe allergic reaction in a patient who was re-exposed to TCZ within a very short time period has been reported (digestive disease December 2010). A single case, however, requires discontinuation of TCZ treatment in patients with a history of severe allergic reactions.

Malignancies

There is no evidence that TCZ therapy is associated with an increased incidence of malignancies in patients with RA (category A, D evidence).^{141–145 167 175 181} Systematic safety surveillance should be performed during TCZ treatment similar to requirements for other biological agents.

2011 UPDATE

An analysis of pooled data from clinical trials and ongoing long-term extension studies of RA patients who received one or more doses of TCZ (N=4009; 10 994 patient-years) indicates that the overall malignancy rates remained stable with continued TCZ therapy and did not exceed reported malignancy rates from the SEER database (category B, D).^{7 8} Similarly, a systematic review and a meta-analysis of clinical trials reported no increased solid malignancies (breast, lung, colon, prostate) in patients treated with TCZ compared with those treated with placebo (category A).^{9 10} A trial using various background DMARDs with or without TCZ and another study following patients for 2 years showed no increases in solid malignancies (category A, D evidence).^{14 213}

Pregnancy

There have been too few cases of pregnancy during the use of TCZ for any conclusions to be drawn (category C evidence).¹¹³ According to the US FDA, this drug is considered category C, meaning 'No human studies and animal studies either show risk or are lacking. However, potential benefits may justify potential risks.'

Skin

Erythroderma has been ascribed to TCZ (category D evidence²¹⁴).

TNF BLOCKING AGENTS

TNF inhibitors 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 inhibitors are used in conjunction with another DMARD, usually MTX. TNF inhibitors have also been

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used successfully with other DMARDs, including sulfasalazine and LEF. TNF inhibitors are effective for the treatment of RA in MTX-naïve patients (category A, D evidence^{138 215–234}). They can be used as the first DMARD in some patients (category A evidence^{138 215–225 235}; category A, B evidence^{44 144 222 227 228 236–239}). They have been used successfully in combination with MTX for early RA. Adalimumab, certolizumab, etanercept and golimumab are 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^{240–242}). The combination of a TNF inhibitor and MTX yields better results for RA than monotherapy, particularly with respect to excellent clinical responses and radiological outcomes (category A evidence^{138 215–226 228–230 235 236 240–245}). Preliminary data indicate that a triple combination of traditional DMARDs is clinically as effective as a combination of MTX plus etanercept; their comparative effects on radiographic progression are being analysed (category A evidence²⁴⁶).

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, four TNF inhibitors (adalimumab, etanercept, golimumab and infliximab) have been widely approved for the treatment of patients with PsA with inadequate response to conventional treatments. Efficacy has been demonstrated both as monotherapy and with background MTX (category A, B evidence^{180 201 202 247–265}).

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 inhibitors 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^{237 266–274}). There is no evidence that combination therapy with conventional DMARDs is superior to monotherapy.

Juvenile idiopathic arthritis

Etanercept and adalimumab have been approved for JIA with a polyarticular course (FDA: 32 years for etanercept; 34 years for adalimumab; EMA: age 13–17 years for both) (category A, B evidence^{275–282}) (FDA and EMA approvals). Infliximab was beneficial at 6 mg/kg in polyarticular JIA (category B evidence^{275 276 281 282}).

Clinical use**Rheumatoid arthritis****Dosing**

Increasing the dose or reducing the dosing intervals of infliximab may provide additional benefit in RA, whereas increased doses of etanercept or certolizumab have no increased benefit on a group level (category A, B evidence^{135 238 275 283–285}). The addition or substitution of other DMARDs may increase efficacy in some patients.

2011 UPDATE

Increasing doses of golimumab confer no clinical benefit, but improve radiographic outcomes (category D evidence^{286 287}). Likewise, no effect of increasing certolizumab dosing from 200 to 400 mg monthly has been shown (category D evidence²⁸⁸). In clinical practice, 12–36% of patients have the dose of their

TNF blocking agent increased with only minor improvements, although the study was purely observational (category C evidence²⁸⁹).

Some patients using TNF blocking agents respond despite using lower MTX doses (≤ 8 mg/week) (category C evidence²⁹⁰; category C evidence²⁹¹).

LEF plus TNF blocking agents are equivalent to MTX plus TNF blocking agents for the treatment of RA (category B evidence²⁹²).

Time to response

TNF inhibitors when administered up to the maximum approved dosing regimens for RA and polyarticular JIA may elicit a response in 2–4 weeks in some patients. They usually lead to significant, documentable improvement in symptoms, signs and/or laboratory variables within 12–24 weeks (category A and B evidence^{138 215–230 232 235–237 242 243 245 265–268 274 275 282 285 293–300}). 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^{138 215 217–220 222–228 230 235–237 242 243 244 245 266–268 271 293–295 298 299}). For patients in remission or low disease activity (LDA), anecdotal studies indicate that lowering or even stopping the dose may be successful without loss of effect (category C evidence^{138 219 220 224 226 238 240–244 301}; category D evidence³⁰²).

If improvement occurs, treatment should be continued. If patients show no response to these agents, their continued use should be re-evaluated. Etanercept weekly dosing in children (0.8 mg/kg up to 50 mg weekly) also improves health-related QoL and results in reduced disease activity.³⁰³

2011 UPDATE

For certolizumab, the rapidity and degree of response at 6–12 weeks predicts the 1-year response. Some patients require longer than 12 weeks to respond, with about 35% of non-ACR 20 responders at 12 weeks responding by 24 weeks (category C evidence³⁰⁴).

Comparison of TNF inhibitors

There is no evidence that any one TNF inhibitor should be used before another one can be tried. There is also no evidence that any TNF inhibitor is more effective than any other in RA (category A and B evidence^{26 27 37 47 59 134 135 138 217 229 232–234 281 296}). A recent meta-analysis of RCTs demonstrated that etanercept, infliximab and adalimumab were more effective than anakinra for RA (category A evidence¹⁴³). A meta-analysis also contended that etanercept was safer than anakinra, adalimumab or infliximab (category A evidence^{134 135}).

2011 UPDATE

A registry followed patients for 8 years, and a meta-analysis indirectly comparing the TNF blocking agents generally concluded that the lowest rate and degree of response was to infliximab, while adalimumab and etanercept were more effective (category A, C evidence^{305 306}).

Because channelling bias may have occurred in the first study and the second study was an indirect comparison, these data will require well-performed prospective corroborative studies.

Persistence

In long-term observational studies, some patients continue to respond for up to 15 years (category C, D evidence^{134 307–310}).

Loss of response to a TNF inhibitor can occur. Failure to respond to one TNF inhibitor does not preclude response to another (category B and D evidence^{232–234 281 296}). Patients have been switched successfully from one TNF inhibitor to another. Several retrospective and observational studies suggest the efficacy of such switches. One recent RCT supports this regimen (category B and D evidence^{25 311–313}).

Data from some but not all observational data suggest the possibility that primary non-responding patients are less likely to respond to a second TNF inhibitor. Patients who have not tolerated one TNF inhibitor may respond to a second but are also less likely to tolerate a second TNF inhibitor (category C and D evidence^{296 314–318}). Patients who have responded to a TNF inhibitor but have lost response may respond to a second TNF inhibitor. The optimal treatment of patients not responding to TNF inhibitors remains to be determined (category C evidence^{167 217 220 225 242 267 275 319}).

Patients with high or moderate disease activity at baseline can respond well to TNF inhibitors (category C evidence^{319 320}).

Structural changes

TNF inhibitors inhibit or reduce radiographic progression in RA, even in some patients without a clinical response (category A evidence^{138 217 221 223 226 228 239 258 295 299 321–328}). Better clinical and radiological outcomes are achieved when TNF inhibitors are used in combination with a traditional DMARD (category A evidence³²⁹).

2011 UPDATE

Golimumab and etanercept slow radiographic progression in early RA.^{330 331} MRI is now being used to measure structural change and demonstrate response, but correlations with radiographs are weak (category C evidence^{332 333}).

Pharmacoeconomic and QoL data

TNF inhibitors may be cost effective from a societal perspective and improve QoL. The pharmacoeconomics evaluations are highly dependent on the specific circumstances of the analysis and the society in which the analysis is carried out (category B evidence^{141 218 334–343}).

2011 UPDATE

Recent data on societal participation, family participation and work have supported the effectiveness of TNF inhibitors.³⁴⁴

Juvenile idiopathic arthritis

Dose

TNF inhibitors, 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 variables. Etanercept weekly dosing in children (0.8 mg/kg up to 50 mg weekly) also improves health-related QoL and results in reduced disease activity (category B evidence³⁰³).

Comparison of TNF inhibitors in JIA

Etanercept appears less effective in patients with systemic-onset JIA than in patients with other forms of JIA (category C evidence^{277–279}). There are now ongoing 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. Except for systemic-onset JIA, there is no evidence that any one TNF inhibitor should be used before another one can be tried for the other JIA subtypes

(category C, D evidence^{277 345}). In JIA-associated uveitis, adalimumab and infliximab appear to be effective more often than etanercept (category C, D evidence^{346 347}).

2011 UPDATE

In an open trial, infliximab, 5 mg/kg up to every 6 weeks, was not as effective as adalimumab 24 mg/m² used every 14 days for uveitis (category C evidence³⁴⁸). However, others have suggested that a clinically effective dose of infliximab for uveitis may require up to 10–20 mg/kg as frequently as every 4 weeks (category D evidence³⁴⁶).

Switching TNF inhibitors

Anecdotal studies indicate that TNF inhibitors can be successfully switched in JIA (category D evidence^{280 281}).

Persistence

In one small open study, remission occurred in 24% of patients with systemic JIA, but 45–100% flared when the TNF inhibitor was stopped (category C evidence^{277 349}).

Structural changes

TNF inhibitors contribute to restoration of growth velocity in children whose JIA-associated inflammation is controlled (category B evidence³⁵⁰). Bone density improves after treatment with TNF inhibitors even in patients who have incomplete disease control (category C, D evidence^{277–280}).

Psoriatic arthritis

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 inhibitors (category D evidence²⁵⁵).

In addition to efficacy in joints and skin, efficacy has been demonstrated with TNF inhibitor therapy for enthesitis, dactylitis, function, QOL fatigue, productivity, work disability and inhibition of structural damage (category A, B, D evidence^{201 202 251 253 254 256–264 277 347 351–361}).

Dose and time to response

Improvement of signs and symptoms, function and QoL occurs within 12 weeks. Some patients continue to improve to week 24. For etanercept, 100 mg a week for 12 weeks followed by 50 mg a week, was more effective than 50 mg a week for skin but not arthritis, enthesitis or dactylitis (category D evidence³⁵⁸). In children, maximal response to etanercept may take longer than 3 months (category C evidence²⁷⁸).

Comparison of TNF inhibitors in PsA

A meta-analysis of randomised trial suggests that the efficacy of TNF inhibitor antibodies may be better than that of soluble receptor with respect to skin manifestations (category A evidence).³⁵⁵

2011 UPDATE

Recent data demonstrate that use of the dose of etanercept approved for psoriasis (ie, 50 mg twice weekly for 12 weeks followed by 50 mg weekly thereafter) yields responses in the skin comparable to those seen with TNF inhibitor antibodies (category A evidence^{358 361}).

Switching between TNF inhibitors 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 inhibitor, even if efficacy from a previous TNF inhibitor was never achieved (category C evidence^{356 362}).

Clinical and epidemiological research

Persistence

Durability of clinical efficacy and radiographic data up to 2 years in PsA has been demonstrated with etanercept, infliximab and adalimumab and golimumab (category A, B, C evidence^{201 257 259 262 263 265}).

2011 UPDATE

Use of TNF blocking agents in an early PsA cohort suggests increased effectiveness when used early in the disease (category C evidence³⁶³). Clinical response has been demonstrated in the axial disease of PsA (category C evidence³⁶⁴). In the Danish registry, median drug survival was 2.9 years, and 1 and 2 year drug survival rates were 70% and 57%, respectively. Raised CRP at baseline was predictive of good treatment responses and continued treatment. In the British Registry, PsA patients treated with TNF blocking agents had a similar safety profile to a control cohort of seronegative arthritis patients receiving DMARD therapy (category B evidence³⁵⁷).

The GRAPPA group has established a measure of minimal disease activity as a target for therapy, which establishes a quantitative threshold for joint, skin, enthesial, and functional improvement (category D evidence³⁶⁵). In studies using the 1981 ACR remission criteria and the DAS 28 remission criteria, respectively, remission was more readily achieved and enduring in PsA than in RA patients (category B evidence³⁶⁶).

The GRAPPA group has also established a preliminary composite disease activity and responder index, based on international treatment recommendations, that addresses five clinical domains of PsA (joints, enthesitis, dactylitis, spine and skin).²⁵⁵ This composite index has shown responsiveness and discrimination ability in a clinical trial dataset (category B evidence³⁶⁷).

Indication**Ankylosing spondylitis**

In clinical trials in patients fulfilling the modified New York criteria for AS, improvement in signs and symptoms was seen after TNF inhibitors 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^{237 266–270 274 368–379}). Two recent placebo-controlled trials have shown significant efficacy in signs and symptoms in patients with non-radiographic axial spondyloarthritis (SpA) (category A, D evidence^{370 373}) according to the ASAS axial criteria for axial SpA (category A evidence³⁶⁹). The importance of adding regular physical therapy to TNF inhibitors has been highlighted in an observational trial (category C evidence³⁸⁰).

Clinical use

Two RCTs failed to demonstrate superiority of a combination of MTX with infliximab versus infliximab alone in the treatment of active AS over 1 year (category B evidence^{89 237 266}). Regular therapy with infliximab was more effective than 'on demand' therapy for treating AS (category A evidence^{381 382}). In a head-to-head comparison trial of a conventional DMARD (sulfasalazine) with a TNF inhibitor (etanercept), the latter was more effective (category A evidence^{295 383}).

There is evidence that the incidence of uveitis flares is reduced and anaemia improves when patients are treated with TNF inhibitors. TNF inhibitor antibodies decrease the frequency of uveitis episodes more than etanercept (category A evidence^{346 347 384}).

Antibodies directed against adalimumab or infliximab have been found to correlate with decreased clinical response in some

patients with AS. This was not found for etanercept (category C evidence^{385–389}). Acute phase reactions correlate with response (category B evidence^{390 391}).

Young patients with active AS and raised CRP levels responded better to TNF inhibitors than older patients without such markers (category A evidence^{237 372 374 390 391}). However, even in patients with advanced and severe AS, there is evidence that TNF inhibitors can be efficacious (category D evidence^{374 392}).

2011 UPDATE

Etanercept is effective in SpA patients with refractory heel enthesitis (HEEL study).

An observational study indicates that switching to a second TNF blocking agent may be effective, although the efficacy may be a little less with the second TNF blocker (category B evidence³⁹³).

Dosing

The approved doses of TNF inhibitors 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 and B evidence^{266–268 370 394}). No dose ranging studies have been performed with most of these drugs, except for golimumab, where no major differences in efficacy and safety between 50 mg and 100 mg doses were seen (category B evidence²⁵⁷).

Time to response

Although improvement may be seen more rapidly, 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 inhibitor (category A evidence^{274 381 383}).

Comparison of TNF inhibitors in AS

There is no evidence that any TNF inhibitor is more effective for musculoskeletal symptoms in AS than any other (category A, B, D evidence^{237 266–270 273 368–376}).

Persistence

TNF inhibitors (adalimumab, etanercept, infliximab) maintain efficacy for 2–7 years in open-label studies (category A, B, D evidence^{369 372 373 375 383}). The disease usually flares after discontinuation of TNF inhibitor (category C evidence^{369 372–375}). When TNF inhibitors are restarted, treatment response re-occurs in over 70% (category C evidence³⁷⁴).

Imaging changes

Several studies have shown that active inflammation of the sacroiliac joints and spine, as shown by MRI, is significantly reduced for up to 3 years by adalimumab, etanercept, infliximab and golimumab (category A, B, C evidence^{373 375 385 394} ESTHER study).

Patients with AS who received TNF inhibitors showed significant increases in bone mineral density scores (category C evidence^{368 369}).

Pharmacoeconomic data in AS

The use of TNF inhibitors may be cost effective in patients with active AS (category B evidence³⁹⁵).

2011 UPDATE

The Assessment of Spondylo-Arthritis International Society (ASAS) has updated its recommendations for the use of TNF inhibitors in AS (category C evidence^{274 368 369}).

Safety (arranged alphabetically) across indications

General reviews of TNF inhibitor safety have been published (category A, B evidence^{102 135 138 215 217 220 225 299 376 377 396}).

Autoimmune-like syndromes

Antiphospholipid and lupus-like syndromes have occurred in both adult and paediatric patients during treatment with TNF inhibitor. Autoantibody formation is common after TNF inhibitor therapy (eg, antinuclear antibodies), but clinical syndromes associated with these antibodies are rare (category C, D evidence^{325 397 398}).

2011 UPDATE

A case of dermatomyositis associated with the use of adalimumab has been reported (category D evidence³⁹⁹).

Cardiovascular

Treatment of non-RA patients with advanced chronic heart failure with TNF inhibitor 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 inhibitor therapy have shown inconsistent results (category B evidence^{314 315 396}).

On the other hand, several studies showed decreased CV events (myocardial infarction, stroke or transient ischaemic attack) (category D evidence^{314 400 401}).

A review (class C evidence^{315 402}) and multiple open studies of TNF inhibitors have been published (category C, D evidence^{402–406}). Reports on TNF inhibitors and lipids are somewhat conflicting, but infliximab, etanercept and golimumab report improving lipid and arthrogenic profiles, less arterial stiffness and decreased insulin resistance than controls. No long-term studies regarding cerebrovascular accident or death have appeared (class C, D evidence^{314 315 386 387 400 402 404–412}). One long-term study demonstrated that a reduction in myocardial infarctions was found (category C evidence^{400 412}). To date these profiles seem to reflect the degree to which inflammation is controlled. Better disease control was reflected in either unchanged or improved lipid profiles, while incomplete control was associated with worsening profiles. The clinical significance of these changes in CV symptoms is unknown, but recent studies suggest that the risk of CV events may be decreased in patients using these agents.⁴¹³

2011 UPDATE

A systematic review of TNF blocking agents, using observational data, documented increased lipid levels, although results are conflicting (category B, D evidence^{30 386–388 403 407–409 414}). In an analysis of about 10 000 patients who were treated with a TNF blocker in a North American Registry, there was a reduced risk of CV events (HR 0.39) compared with MTX users, whose risk was not reduced (HR 0.94). In contrast, prednisone use was associated with a dose-dependent increased risk. The risk reduction associated with TNF blockers was observed for both fatal and non-fatal CV events (category B evidence⁴¹⁵).

The only controlled study to date of lipid changes with TNF inhibitor therapy of golimumab in MTX-IR and TNF-IR reported that lipid levels (total cholesterol, LDL and HDL) were raised after TNF inhibitor therapy compared with controls. No significant changes in the ratios of total cholesterol/LDL, HDL/LDL or ApoA/ApoB were noted, and levels of very low density particles were reduced with a significant increase in LDL particle size.

Haematological

Rare instances of pancytopenia and aplastic anaemia have been reported (category C evidence²⁹⁴). If haematological adverse events occur, TNF inhibitors should be stopped and patients evaluated for evidence of other underlying diseases or association with concomitant drugs.

Transaminase elevation

Elevated liver function tests (LFTs) have been observed in patients treated with adalimumab and infliximab, with alanine transaminases/aspartate transaminase increased in 3.5–17.6% and increased more than twice the upper limit of normal in up to 2.1%. Mild increases in LFTs were more consistently observed with infliximab, less commonly with adalimumab and were not observed with etanercept in comparison with DMARDs (category B, C evidence, (Furst DE, 2008 1621 /id; Sokolove J, 2008 466 /id; Sokolove, 2010 42 /id)). Golimumab toxicity is associated with LFT increases (category A, C, D evidence^{416–421}). The use of concomitant drugs and other clinical conditions confound the interpretation of this observation (FDA; category B and C evidence^{352 422–427}). The follow-up and monitoring for increases in LFT should be governed by the patient's concomitant drugs, conditions and patient-related risk factors. Worsening of alcoholic hepatitis has been observed in patients receiving TNF inhibitors (category C evidence⁴²⁷).

2011 UPDATE

Two meta-analyses of safety of TNF blocker therapy across indications demonstrated the highest rates of serious infections in patients with RA compared with patients with PsA, AS and JIA. In these studies, RA patients were more likely to be receiving concomitant DMARD and corticosteroid therapy.^{401 428}

Infections**Tuberculosis**

An increased susceptibility to TB or re-activation of latent TB has been reported for all TNF inhibitors (category A, B, C evidence^{334 335 416 429–448}). The risk of TB is also increased by the use of corticosteroids. There appears to be a higher incidence of TB in patients using the monoclonal antibodies, infliximab and adalimumab, than in those using etanercept (category B, C, D evidence^{430 432–434}). While this difference may be due, in part, to differences in mechanism of action, biology or kinetics compared with the soluble receptor (category C, D evidence^{416 430–445}), it may also be, in part, due to the fact that populations treated with the various TNF inhibitors differ (eg, higher background rates of TB in some countries) and the data come from registries and voluntary reporting systems.

The clinical manifestations of active TB may be atypical in patients treated with TNF inhibitors (eg, miliary or extrapulmonary presentations), as has been seen with other immunocompromised patients (category C evidence^{438–440}).

In the USA, an area with low TB prevalence, the majority of mycobacterial infections among TNF inhibitor users were caused by non-tuberculous mycobacteria, with only 35% caused by *Mycobacterium tuberculosis*. *Mycobacterium 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 evidence⁴⁴¹).

Screening of patients about to start TNF inhibitor treatment has reduced the risk of re-activating latent TB for patients treated with these agents (category B evidence^{442 443}). Every patient should be evaluated for the possibility of latent TB, including

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a history that should comprise previous exposure, previous or active drug addiction, HIV infection, birth or extended living in a region of high TB prevalence, and working or living in TB high-risk settings such as jails, homeless shelters and drug rehabilitation centres (category B evidence^{334 438}).

In addition, physical examination and screening tests such as TSTs and/or interferon γ release assays, and chest radiographs should be carried out before TNF inhibitor therapy is started, according to local recommendations. In areas of high TB prevalence (ie, high-risk populations or in the event of potential TB exposure), repeat screening should be considered (category C evidence^{429 444 445}).

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 evidence³³⁵). The TST can also be falsely positive due to prior BCG vaccination. New blood-based diagnostic assays (interferon γ release assays) have been developed using TB-specific antigens. These tests (Quantiferon-Gold In-tube and T-Spot TB) have greater specificity for latent TB infection than does the TST and therefore provide a useful tool for evaluating people for latent TB (particularly those with a 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^{446 447}). The background rate of TB in the population should be considered in the interpretation of these tests, as it influences their positive predictive value.

The precise role of these tests in diagnosing latent TB in patients with rheumatoid disease remains under study (category C evidence⁴⁴¹).

Repeat screening should be performed in the event of TB exposure, and should be considered in patients who are at ongoing risk of TB exposure (eg, living or extended travel to endemic areas) (category C evidence⁴²⁹). Local screening guidelines should be followed.

Continued vigilance is required to detect re-activation of latent TB or acquisition of new cases.

In treating latent TB, the optimal time frame between starting preventive therapy for latent TB infection and starting TNF inhibitor therapy 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 re-activation (category C evidence^{335 442 443}). Before starting preventive anti-TB therapy in accordance with local guidelines, consultation with an infectious disease specialist should be considered. There are case reports of re-initiation of TNF inhibitor therapy after successful completion of a full course of antituberculosis therapy (category C evidence⁴⁴⁸).

2011 UPDATE

Two recent, large observational studies from the UK and France have documented the rates of TB re-activation in patients using adalimumab or infliximab to be significantly higher than in patients using etanercept (category C evidence^{433 434}).

TB risk data for golimumab and certolizumab are limited. Trials of golimumab excluded patients with active or latent TB, and cases of TB were uncommon (category B evidence⁴¹⁶). In trials of certolizumab, there was an increased incidence of TB relative to control, but TB screening procedures were not standardised among sites (category C evidence¹³⁴).

Other opportunistic infections

Other opportunistic infections have been reported in patients treated with TNF inhibitors (category C evidence^{138 215 320 449–453}). Particular vigilance is needed when considering infections whose containment is macrophage/granuloma dependent, such as listeriosis, non-tuberculous mycobacteria (category D evidence^{441 452}), coccidiomycosis and histoplasmosis (including re-activation of latent histoplasmosis) (category C and D evidence^{137 215 450 451 453}).

A British registry study found that the rate of intracellular infections among patients with RA treated with TNF inhibitors was 200/100 000 and significantly higher than in similar patients treated with DMARDs or corticosteroids (category C and D evidence^{437 449}).

2011 UPDATE

A French Registry analysed age- and sex-adjusted rates of opportunistic infections (excluding TB) of 152/100 000 among TNF blocking agent users. In case-control analysis, the risk of these infections was significantly more likely in those patients using monoclonal antibodies or steroids (>10 mg/day) than in those using etanercept (category C evidence⁴⁵⁴).

Bacterial infections

Serious bacterial infections (usually defined as bacterial infections requiring intravenous antibiotics or hospitalisation) have also been seen in patients receiving TNF inhibitors 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^{137 311–313 324 455}). Risk ratios of 1–3 were documented (category B, C evidence^{323 324}). TNF inhibitors should not be administered in the presence of active serious infections and/or opportunistic infections, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections and listeriosis (category C evidence^{137 323 329}).

Treatment with TNF inhibitors in such patients may be resumed if the infections have been treated adequately (category D evidence; FDA^{137 138 215 311–313 323}).

Other studies indicate that serious infections in certain sites are more common when TNF inhibitors are used, such as the skin, soft tissues and joints, and the risk may be highest during the first 6 months of treatment.

2011 UPDATE

Among JIA patients in an open study, the rate of serious infections was not different among MTX, etanercept and etanercept plus MTX groups (category C evidence²²). Further, in a large cohort study in the UK, discontinuations for infections in JIA patients were only about 1% (category B evidence⁴⁵⁴).

Rates of serious infection are 1.5–2-fold higher in older patients than in young adults (category D evidence³²⁹; category C evidence³¹³).

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 when these measures are used to help diagnose infection in the presence of these agents (category C evidence^{336 337}; category B evidence^{312 313 457}).

The incidence of other bacterial infections (not designated as serious) may be increased by TNF inhibitor treatment (relative risk 2.3–3.0, 95% CI 1.4 to 5.1) (category C evidence^{137 311–313 323}).

The incidence of serious infections is approximately doubled when IL-1 receptor antagonist or abatacept is used with any of

the TNF inhibitors in combination (category A evidence; FDA 44 45 241 377).

The use of TNF inhibitor plus IL-1 blocking agents or abatacept in combination is not recommended.

2011 UPDATE

A recent analysis from a British registry confirmed a small but significant overall risk of serious infections in patients treated with a TNF blocker. Incidence rates for TNF blockers were 42/1000 vs 32/1000 patient-years of follow-up in patients treated with non-biological DMARDs, resulting in an adjusted HR of 1.2 (category C evidence⁴⁵⁵).

Viral infections

Hepatitis

Patients should be screened for viral hepatitis before TNF inhibitor initiation, as the long-term safety of TNF inhibitors in patients with chronic active 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 LFTs or viral load) associated with TNF inhibitor therapy (category C, D evidence^{338 352 381 423-425 458}). 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 evidence⁴⁵⁹). Patients with hepatitis B treated with adalimumab, etanercept and infliximab have experienced worsening of their symptoms, increased viral load, and, in some cases, hepatic failure (especially after stopping the TNF inhibitor) (category C, D evidence^{352 423 424 426 458 460}).

Although specific warnings about hepatitis B re-activation have been added to the US label by the FDA, TNF inhibitors have been used in patients with known persistent hepatitis B infection, with concomitant hepatitis B treatment (category D evidence⁴⁶¹). In the event that hepatitis B infection is discovered during use of TNF inhibitors, prophylactic antiviral therapy can be employed (category C evidence⁴⁵⁹).

Small case series have been reported in which TNF inhibitors were used in patients with evidence of previous hepatitis B (hepatitis B surface antibody positive, hepatitis B surface antigen (HBsAg) and HBV DNA negative) with only transient increases in transaminases and no change in viral load (category D evidence⁴²⁴).

2011 UPDATE

In a cohort (n=67) study of TNF blocking agent-using patients with evidence of prior hepatitis B (hepatitis B core antigen positive, HBsAg negative and HBV DNA negative), no patients developed hepatitis B re-activation during a mean follow-up of 42 months. In contrast, another case series documented an increased risk of hepatitis B (category C, D evidence^{462 463}). The hepatitis B viral load should be carefully monitored if TNF blocking agents are used in patients with previous hepatitis B. A recent observational study reported a small increased risk of herpes zoster with monoclonal antibodies, while another observational study found no increase in risk with anti-TNF therapy as a whole, and reported significantly lower risks for etanercept and adalimumab than for infliximab (category D and B evidence^{336 464}). Overall, vaccination for herpes zoster before starting a TNF blocking agent was advised (category D evidence⁴⁶⁵).

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 inhibitors than with placebo (category A, B, C evidence^{138 215 217 239 320 376 396}). One study indicates that human antichimeric antibodies against infliximab were associated with decreased response and increased infusion reactions (category C evidence³²⁸).

Acute reactions after adalimumab, golimumab or administration are uncommon and are usually mild to moderate, but may, rarely, be serious (category A, B evidence^{138 216 224 269 466}). 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^{328 337 467}).

2011 UPDATE

A survey indicates that administration reactions after certolizumab or golimumab may be more common than previously thought, occurring in >50% of patients; only 13% of the reactions were moderate to severe (category C evidence).⁴⁶⁸

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).^{392 468} In most studies the risk of lymphoma (especially NCL) is increased 2–5-fold in patients with RA compared with the general population (category B, D evidence).⁴⁷⁰⁻⁴⁷⁵ A similar risk is seen in patients with RA who have received TNF inhibitor therapy (category A, B, C evidence).^{293 392 396 469-476} It is unclear if the risk of lymphoma is increased.

While two meta-analyses (with infliximab and adalimumab) report a higher rate of solid malignancies, including skin (category A evidence),^{477 478} several other large observational databases and a case-control study did not show an increased incidence of solid tumours in patients receiving TNF inhibitors compared with matched controls (category B, C evidence).^{392 471-475 479-485}

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).^{483 484} 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 therapy (category B evidence).⁴⁸¹

The evidence regarding an increased incidence of non-melanotic skin cancers associated with TNF inhibitor therapy is conflicting (category B evidence).⁴⁷⁰

In patients with COPD, there may be an increased risk of lung cancers associated with TNF inhibitor treatment. 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).^{485 486} Lung cancer appears to be increased in RA, although whether this is due to disease activity or confounding factors is not known (category C evidence).^{485 488} 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 evidence).⁴⁸²

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).^{473 483}

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Vigilance for the occurrence of lymphomas and other malignancies (including recurrence of solid tumours) remains appropriate in patients treated with TNF inhibitors.

2011 UPDATE

Three meta-analyses including RCTs, extension studies and registries of patients receiving etanercept, infliximab, adalimumab, golimumab or certolizumab for the treatment of plaque psoriasis and PsA demonstrated no statistically significant increased risk of cancer with short-term use of TNF inhibitors (category A, B evidence).^{487–489} Other open-label studies and registries supported this conclusion (category C, D evidence).^{19 22 490} One publication on etanercept, including RCTs and registries, showed a 2–4-fold increased risk of lymphoma in RA patients, supported by a study of certolizumab (category B evidence).⁴⁸⁹ However, given that the risk of lymphoma in biological agent-naïve and -exposed RA patients was similar, the authors of the etanercept study conclude that there is no additional risk for lymphoma patients receiving etanercept over the existing increased risk of lymphoma in RA patients (category D evidence).¹⁸

A literature review of skin malignancies in patients with RA, PsA and AS suggests an increased frequency of skin cancers, possibly due to both underlying disease and immunomodulatory treatment. Consideration should be given to screening patients for cutaneous malignancy before initiation of biological agents and monitoring during therapy.

After TNF inhibitor treatment is started, cancer risk does not increase with time (category B evidence).⁴⁸¹

Although malignancies in JIA have been reported, recent data did not show an increased frequency of malignancy in JIA patients treated with TNF blocking agents compared with JIA patients per se (category C evidence, FDA letter^{278 491 492}).

Neurological diseases

Rare instances of central and peripheral demyelinating syndromes including multiple sclerosis, optic neuritis and Guillain-Barré syndrome have been reported in patients using TNF inhibitors (category C evidence).^{493–502} In some cases, but not all, these syndromes have improved after withdrawal of TNF inhibitor therapy and steroids were given. Accordingly, TNF inhibitor therapy should not be given to patients with a history of demyelinating disease, multiple sclerosis or optic neuritis (category C, D evidence).^{493–502}

The demyelinating events tend to occur within the first 5–8 months of use (category C evidence).^{495 501}

2011 UPDATE

A recent analysis of 21 425 patient-years of TNF blocker exposure from a Spanish registry could not clearly demonstrate an increase in the incidence of demyelinating diseases in patients with rheumatic disease (category C evidence).⁵⁰³

Risks during pregnancy

The safety of anti-TNF therapy during pregnancy is unknown. Experts disagree about whether TNF inhibitors should be stopped when pregnancy is being considered or whether they can be continued throughout pregnancy. Some studies found no increased fetal loss or spontaneous abortions during the use of TNF inhibitors, but one recent study did find an increased rate of spontaneous abortions (category C, D evidence).^{504–507}

A rare combination of congenital abnormalities (VACTERL (vertebral abnormalities, anal atresia, cardiac defect, tracheo-esophageal, renal and limb abnormalities)) and partial VACTERL defect have been reported rarely, although the risk and causality is unclear (category C evidence).⁵⁰⁶

According to the US FDA, this drug class is considered category B, meaning no evidence of risk in humans (if no adequate human studies have been done, no animal studies have been done, or animal studies show risk but human studies do not). A systematic review of 667 pregnancies came to the conclusion that, to date, no definite harm to pregnancy can be ascribed to TNF inhibitors (FDA category B evidence).¹¹³

A single patient study examined maternal serum, placenta, breast milk and infant etanercept levels, finding an ~3% transfer of etanercept from serum to placenta and no transfer of etanercept in breast milk (category D evidence).⁵⁰⁷

2011 UPDATE

Eighty-eight live births in a total of 130 pregnancies were reported in patients treated with TNF blockers from a British biological agent register. The rate of spontaneous abortion was highest among patients exposed to anti-TNF at the time of conception: in 33% with anti-TNF plus MTX/LEF and in 24% if treated with anti-TNF without other DMARD. This was higher than the 17% spontaneous abortions in those with prior exposure to anti-TNF and to 10% in the control group. Confounding drugs (MTX/LEF) were problematic, and no established differences were found between TNF blockers and control.

Male sexual function

In limited data, sperm volume and function were not different from normal. Men using TNF inhibitors are able to father normal children, and sexual function seems either unaffected or improved (category C evidence).⁵⁰⁸

2011 UPDATE

In a small study of 26 male patients, sperm concentration and morphology were similar in patients with spondyloarthritis treated or not with TNF blockers, but the sperm of the anti-TNF-treated patients showed significantly more motility (category B evidence).⁵⁰⁸

Rare instances of acute, severe and sometimes fatal interstitial lung disease (ILD) have been reported in patients using TNF inhibitors (category C evidence).⁵⁰⁹

2011 UPDATE

Case reports of interstitial pneumonia after TNF blocker use continue to appear.^{510 511} However, in an analysis from a British registry, the mortality of RA patients with ILD following treatment with TNF blockers was not higher than with traditional DMARD therapy (23% vs 21%), despite probable channelling bias toward more use of TNF blockers in those with underlying ILD or organising pneumonia (category C evidence).⁵¹²

Sarcoidosis can occur, rarely, when TNF blocking agents are used (category D evidence⁵¹³; category C evidence⁵¹⁴).

Skin disease

More than 200 cases of psoriasis, psoriaform lesions or exacerbation of psoriasis have been reported with the use of all TNF inhibitors. In some cases, switching TNF inhibitor allowed continuation of therapy without recrudescence of skin lesions (category D evidence).^{515–519} In addition, rare cases of Henoch-Schönlein purpura, Stevens-Johnson syndrome, digital vasculitis, erythema multiforme, toxic epidermal necrolysis granulomatous reactions in skin and lungs have been noted (category D evidence).^{467 493 520–525} Hypersensitivity reactions to TNF inhibitor treatment were not associated with the atopic status of the patients, in one small study.

Vaccinations

Appropriate vaccinations should be carried out before initiation of TNF inhibitor therapy, according to national guidelines. This includes herpes zoster.⁴⁶⁵

TNF inhibitors do not usually adversely affect the development of protective antibodies after vaccination with flu 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).^{327 339 340 526} Vaccination with live attenuated vaccines (eg, nasal flu vaccine, BCG, yellow fever, herpes zoster) is not recommended, although the incidence of dissemination (especially herpes zoster) is very low.⁴⁶⁵

Measles, mumps, rubella (MMR) vaccination with appropriate secondary response has been reported in JIA patients treated with etanercept and MTX even though, in clinical practice, live attenuated vaccines are not generally recommended in children with JIA treated with MTX (category D evidence⁵²⁷).

2011 UPDATE

In some patients whose flu titres do not rise with an initial vaccination, repeat vaccination may be effective (category D evidence).⁵²⁸

Other biological agents

Alefacept (approved in the USA for psoriasis but not PsA)

Alefacept 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 (category B evidence).⁵²⁹ A second course (each course is 12 weekly intramuscular injections followed by 12 weeks off) during an open-label extension demonstrated sustained articular efficacy (category A evidence).⁵²⁹

Efalizumab is a humanised monoclonal antibody to the CD11 subunit of LFA-1. Efalizumab has been removed from the market following cases of PML.

Ustekinumab

Ustekinumab is an inhibitor of IL-12 and IL-23 which acts in both the TH17 and TH1 pathways of inflammation and is approved for the treatment of psoriasis, dosed at 0, 4 and then every 12 weeks subcutaneously (category B evidence).⁵³⁰ For skin, it was slightly more cost effective than etanercept in one study, although local conditions can drastically alter cost-effectiveness estimates (category C evidence).⁵³¹ Modest efficacy has been demonstrated in a phase 2 trial in PsA.^{532 533}

Apremilast, a phosphodiesterase 4 inhibitor, has shown modest efficacy in a phase 2 PsA study.⁵³⁴

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 QoL 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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APPENDIX 1 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 2 ABATACEPT

- ▶ JIA-associated uveitis may improve with abatacept therapy (category C evidence).¹⁷
- ▶ A placebo controlled RCT of abatacept demonstrated no effects on the primary or most secondary outcomes (flares) but showed that abatacept improved SF-36 physical component summary, sleep and fatigue (category A evidence).⁵³⁶
- ▶ Abatacept was effective in an RCT of undifferentiated inflammatory arthritis (category A evidence).³⁹

Disease	Author (reference)	Patients (n)	Outcome
Ankylosing spondylitis	Olivieri <i>et al</i> ⁵³⁶	1	Positive
	Berner <i>et al</i> ⁵³⁷	3	One positive; two negative
Autoimmune thrombocytopenia	Kloepfer <i>et al</i> ⁵³⁸	1	Positive
Gout	Puszczewicz <i>et al</i> ⁵³⁹	1	Positive
Hepatitis C	Mahajan <i>et al</i> ⁵⁴⁰	2	Two positive
PsA	Mease <i>et al</i> ⁵⁴¹	1	Positive
Relapsing polychondritis	Moulis <i>et al</i> ⁵⁴²	1	Positive
SLE	Merrill <i>et al</i> ⁵⁴³	2	One negative; One positive
Uveitis JIA	Simonini <i>et al</i> ⁵⁴⁴	2	Four positive
Uveitis JIA	Zulian <i>et al</i> ⁴⁸⁸	6	Positive

JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; SLE, systemic lupus erythematosus

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APPENDIX 3 ANECTODAL STUDIES USING RITUXIMAB

Rituximab synopsis

ANCA-associated vasculitis

Disease	Author (reference)	N
ANCA associated	Roccatello <i>et al</i> ^{545 546}	7: Effective
ANCA-associated renal vasculitis	Jones <i>et al</i> ⁸	44: Effective
ANCA-associated vasculitis	Rhee <i>et al</i> ⁵⁴⁷	39: Effective
ANCA vasculitis	Lovric <i>et al</i> ⁵⁴⁸	15: Refractory ANCA-associated vasculitis: effective
ANCA vasculitis	Brito-Zeron <i>et al</i> ⁵⁴⁹	19: Effective
Churg–Strauss	Cartin-Ceba <i>et al</i> ⁵⁵⁰	3: Effective
Hepatitis C-related vasculitis	Terrier <i>et al</i> ⁸⁴	32: Effective
Refractory WG	Cohen <i>et al</i> ⁵⁵¹	22: As effective as infliximab
Refractory WG – meningitis	Sharma <i>et al</i> ⁵⁵²	1: Effective
Systemic vasculitis	Diaz-Legarest <i>et al</i> ⁵⁵³	45: Effective
WG	Aries <i>et al</i> ⁵⁵⁴	8: Granulomatous manifestations: effective in 3; no response in 3; ineffective in 2
WG	Brihay <i>et al</i> ⁵⁵⁵	8: Refractory/relapsing: effective
WG	Henes <i>et al</i> ⁵⁵⁶	6: Refractory: effective
WG	Golbin <i>et al</i> ⁵⁵⁷	28: Refractory: effective
WG	Guillevin <i>et al</i> ⁵⁵⁸	21: As effective as infliximab
WG	Keogh <i>et al</i> ⁵⁵⁹	10: Effective
WG	Martinez Del Pero <i>et al</i> ⁵⁶⁰	34: Effective
WG	Palm <i>et al</i> ⁵⁶¹	9: Effective: suppressing inflammation not airway stenosis
WG	Ramos-Casals <i>et al</i> ⁵⁶²	8: Effective
WG	Sailer <i>et al</i> ⁵⁶³	37: WG (3); autoimmune cytopenia (19); autoimmune coagulation disorder (5); cryoglobulinaemia (7); pemphigus (2); SLE (1) effective: increased incidence of SAE
WG	Seo <i>et al</i> ⁵⁶⁴	8: Effective
WG	Taylor <i>et al</i> ⁵⁶⁵	10: Effective
WG/CNS involvement	Sharma <i>et al</i> ⁵⁵²	1: Effective
WG/MPA	Stasi <i>et al</i> ⁵⁶⁶	10: 8WG/2MPA: effective
WG/MPA	Eriksson <i>et al</i> ⁵⁶⁷	9: 7WG/2MPA: effective
WG/MPA	Keogh <i>et al</i> ⁵⁶⁸	11: 10WG/1MPA: effective
WG/MPA/CSS	Smith <i>et al</i> ⁵⁶⁹	11: 5WG/5MPA/1CSS: effective
	Stone <i>et al</i> ⁵⁷⁰	197: Effective (similar to cytoan)

ANCA, antineutrophil cytoplasmic antibody; CNS, central nervous system; CSS, Churg–Strauss syndrome; MPA, microscopic polyangiitis; SAE, serious adverse event; SLE, systemic lupus erythematosus; WG, Wegener’s granulomatosis.

Cryoglobulinaemia

Disease	Author (reference)	N
HCV related	Pietrogrande <i>et al</i> ⁵⁷¹	Consensus statement
Mixed cryoglobulinaemia	De Vita <i>et al</i> ⁵⁷²	59: Effective
HCV mixed cryoglobulin	Saadoun <i>et al</i> ⁵⁷³	38: Effective
HCV-related mixed cryo	Ferri <i>et al</i> ⁵⁷⁴	80: Effective
Mixed	Quartuccio <i>et al</i> ⁵⁷⁵	5: Effective
Mixed	Petrarca <i>et al</i> ⁵⁷⁶	19: Effective
HCV related	Dammacco <i>et al</i> ⁵⁷⁷	22: Effective
Type II HCV-associated	Sene <i>et al</i> ⁵⁷⁸	6: Ineffective
Type II and III	Sansonno <i>et al</i> ⁵⁷⁹	20: Effective
Type II	Zaja <i>et al</i> ⁵⁸⁰	15: 12 HCV: effective
Type II HCV-associated	Quartuccio <i>et al</i> ⁵⁸¹	5: Effective
Type III	Basse <i>et al</i> ⁵⁸²	7: Renal transplant patients: 5 HCV: effective
Type II	Bryce <i>et al</i> ⁵⁸³	8: Essential 1; HCV/SS/LPD 7: effective
Type II HCV-associated	Saadoun <i>et al</i> ⁵⁸⁴	16: Effective
Type II	Cavallo <i>et al</i> ⁵⁸⁵	13: Effective
Type II HCV-associated	Ramos-Casals <i>et al</i> ⁵⁸⁶	8: Effective
Type II HCV-associated	Roccatello <i>et al</i> ⁵⁴⁵	12: Effective
Type II HCV-associated	Visentini <i>et al</i> ⁵⁸⁷	6: Effective

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Type II HCV-associated	Roccatello <i>et al</i> ⁵⁸⁸	6 HCV: 5 had GN: effective
Type II	Brito-Zeron <i>et al</i> ⁵⁴⁹	9: Effective
Mixed	Saadoun <i>et al</i> ⁵⁸⁹	38: Effective
Non-viral vasculitis	Terrier <i>et al</i> ⁵⁹⁰	23: Effective

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

Henoch–Schonlein purpura

	Donnithorne <i>et al</i> ⁵⁹¹	3: Effective
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Sjögren's syndrome

Disease	Author (Reference)	N
	Meiners <i>et al</i> ⁵⁹²	37: Effective
	Mekinian <i>et al</i> ⁵⁹³	17: Effective
	Voulgarelis <i>et al</i> ⁵⁹⁴	6: Effective
	Dass <i>et al</i> ⁵⁹⁵	17: Effective for fatigue
	Pijpe <i>et al</i> ⁵⁹⁶	15: 8 SS and 7 SS/MALT: effective
	Devauchelle-Pensec <i>et al</i> ⁵⁹⁷	16: SS: effective
	Seror <i>et al</i> ⁵⁹⁸	16 SS/NHL: effective
	Gottenberg <i>et al</i> ⁵⁹⁹	6: 4 SS and 2 SS/MALT: effective
	Galarza <i>et al</i> ⁶⁰⁰	8: Effective
	Meijer <i>et al</i> ⁶⁰¹	8: SS/7 MALT: effective
	St Clair <i>et al</i> ⁶⁰²	12: SS: effective
	Ramos-Casals <i>et al</i> ⁵⁶²	10: Effective
	Meijer <i>et al</i> ⁶⁰³	30: Effective
	Vivino <i>et al</i> ⁶⁰⁴	6: Effective
	Ramos-Casals <i>et al</i> ⁵⁸⁶	24: Effective
	Tsirogianni <i>et al</i> ⁶⁰⁵	11: Effective
	Vasilyev <i>et al</i> ⁶⁰⁶	11: Effective
	Pijpe <i>et al</i> ⁶⁰⁷	5: Effective
	Brito-Zeron ⁵⁴⁹	15: Effective
	Gottenberg <i>et al</i> ⁶⁰⁸	43: Effective

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

Juvenile idiopathic arthritis

Disease	Author (reference)	N
Juvenile autoimmune disease	El-Hallak <i>et al</i> ⁶⁰⁹	10: Effective
TNF non-responders	Salmoso <i>et al</i> ⁶¹⁰	14: Effective
Juvenile idiopathic arthritis	Alexeeva <i>et al</i> ⁶¹¹	50: Effective
Juvenile autoimmune disease	Jansson <i>et al</i> ⁶¹²	65: Effective

Systemic lupus erythematosus

Disease	Author (reference)	N
SLE	Merrill <i>et al</i> ⁵⁴³	257: Ineffective
Refractory SLE	Diaz-Lagares <i>et al</i> ⁶¹³	128: Effective
Refractory SLE	van Vollenhoven <i>et al</i> ⁶¹⁴	80: Effective
Refractory SLE	Marenco <i>et al</i> ⁶¹⁵	125: Effective
Refractory SLE	Garcia-Carrasco <i>et al</i> ⁶¹⁶	52: Effective
SLE	Galarza-Maldonado <i>et al</i> ⁶¹⁷	46: Effective
SLE	Terrier <i>et al</i> ⁶¹⁸	136: Effective
Newly diagnosed SLE	Ezeonyejì <i>et al</i> ⁶¹⁹	9: Effective
SLE nephritis	Jonsdottir <i>et al</i> ⁶²⁰	43: Effective
Refractory SLE	Lateef <i>et al</i> ⁶²¹	10: Effective
SLE	Catapano <i>et al</i> ⁶²²	31: Effective
Refractory SLE	Tanaka <i>et al</i> ⁶²³	15: Partially effective
SLE haemolytic anaemia	Gormond-Mennesson <i>et al</i> ⁶²⁴	26: Effective
Paediatric SLE/LN	Hadded <i>et al</i> ⁶²⁵	11: Effective
Paediatric SLE	MacDermott <i>et al</i> ^{626 627}	7: Effective
Paediatric SLE/LN	Marks <i>et al</i> ⁶²⁷	7: Effective
SLE	Ng <i>et al</i> ⁶²⁸	7: Refractory: effective 4/7

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Refractory SLE	Tokunaga <i>et al</i> ⁶²⁹	7: Effective
SLE	Leandro <i>et al</i> ⁶³⁰	6: Effective
SLE	Leandro <i>et al</i> ⁶³¹	24: Effective
SLE	Looney <i>et al</i> ⁶³²	17: Effective
SLE	Tokunga <i>et al</i> ⁶³³	5: Effective
SLE	Ng <i>et al</i> ⁶³⁴	41: Effective
SLE	Tanaka <i>et al</i> ⁶³⁵	19: Effective
SLE	Amoura <i>et al</i> ⁶³⁶	22: Effective
SLE	Welin-Henriksson <i>et al</i> ⁶³⁷	20: Effective
SLE	Cambridge <i>et al</i> ⁷⁰	25: Effective
SLE	Gillis <i>et al</i> ⁶³⁸	6: Effective
SLE	Nwobi <i>et al</i> ⁶³⁹	18: Effective
SLE	Albert D <i>et al</i> ⁶⁴⁰	18: Effective
SLE	Boletis <i>et al</i> ⁶⁴¹	10: Effective
SLE	Jonsdottir <i>et al</i> ^{642 643}	16: Effective
SLE	Lindholm <i>et al</i> ⁶⁴⁴	31: Effective
SLE: thrombocytopenia and haemolytic anaemia	Lindholm <i>et al</i> ⁶⁴⁵	19: Effective
SLE	Melander <i>et al</i> ⁶⁴⁶	20: Effective
SLE	Reynolds <i>et al</i> ⁶⁴⁷	11: Effective
SLE	Tanaka <i>et al</i> ⁶⁴⁸	15: Effective
SLE	Podolskaya <i>et al</i> ⁶⁴⁹	19: Effective
SLE	Ramos-Casals <i>et al</i> ⁶⁵²	27: Effective
SLE	Ramos-Casals <i>et al</i> ⁶⁵²	27: Effective
SLE	Lu <i>et al</i> ⁶⁵⁰	45: 19 achieved remission; 21 achieved partial remission
Paediatric SLE with autoimmune thrombocytopenia and/or haemolytic anaemia	Kumar <i>et al</i> ⁶⁵¹	9: Effective
SLE	Garcia-Carrasco <i>et al</i> ⁶¹⁶	52: Effective
SLE	Brito-Zeron ⁵⁴⁹	107: Effective
Refractory SLE	Gilboe <i>et al</i> ⁶⁵²	16: Effective
SLE	Terrier <i>et al</i> ⁶⁵³	86: Effective
	Karpouzas <i>et al</i> ⁶⁵⁴	30: Effective
Refractory SLE	Garcia <i>et al</i> ⁶⁵⁵	52: Effective
SLE	Karpouzas <i>et al</i> ⁶⁵⁶	35: Effective
SLE+Sjorgrens	Logvinenko <i>et al</i> ⁶⁵⁷	48: Effective

LN, lupus nephritis; SLE, systemic lupus erythematosus.

Lupus nephritis

Disease	Author (reference)	N
Proliferative LN	Furie <i>et al</i> ⁶⁵⁸	144: Ineffective (questionable study design)
LN	Guzman <i>et al</i> ⁶⁵⁹	35: Effective
LN	Jónsdóttir <i>et al</i> ⁶⁶⁰	25: Effective
LN	Ramos-Casals <i>et al</i> ⁶⁶¹	106: Effective
Paediatric LN	Pusongchai <i>et al</i> ⁶⁶²	19: Effective
LN	Sangle <i>et al</i> ⁶⁶³	16: Effective except in rapidly progressive crescentic lupus nephritis
LN	Sfikakis <i>et al</i> ⁶⁶⁴	7: Effective
LN	Jónsdóttir <i>et al</i> ⁶⁴³	18: Effective
Refractory LN	Arce-Salinas <i>et al</i> ⁶⁶⁵	8: Effective
LN	Pepper <i>et al</i> ⁶⁶⁶	18: Effective
LUNAR	Furie <i>et al</i> ⁶⁶⁷	144: Ineffective
Refractory juvenile-onset LN	Olmos <i>et al</i> ⁶⁶⁸	12: Effective
LN	Jónsdóttir <i>et al</i> ⁶²²	58: Effective

LN, lupus nephritis.

Idiopathic and inflammatory myopathy/myositis

Disease	Author (reference)	N
Refractory PM, DM juvenile DM	Oddis <i>et al</i> ⁶⁶⁹	200: Ineffective (questionable study design)
DM	Levine ⁶⁷⁰	6: Effective
Inflammatory myopathy	Couderc <i>et al</i> ⁶⁷¹	30: Effective
Polymyositis	Mahler <i>et al</i> ⁶⁷²	13: Effective
DM	Specker <i>et al</i> ⁶⁷³	26: Effective

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Myopathy associated with anti-SRP antibodies	Valiyi <i>et al</i> ⁶⁷⁴	8: Effective
Juvenile DM	Bader-Meunier <i>et al</i> ⁶⁷⁵	8: Effective
DM	Haroon <i>et al</i> ⁶⁷⁶	1: Effective
DM	Chung <i>et al</i> ⁶⁷⁷	8: (partial response)
PM	Ramos-Casals <i>et al</i> ⁶⁸²	3: Effective
Idiopathic inflammatory myopathy	Sultan ⁶⁷⁸	8: Effective in DM only
DM	Rios-Fernandez <i>et al</i> ⁶⁷⁹	4: Effective
PM	Majmudar <i>et al</i> ⁶⁸⁰	3: Effective
PM	Fikha <i>et al</i> ⁶⁸¹	2: Effective
DM	Sanchez-Ramon <i>et al</i> ⁶⁸²	1: Effective
	Brito-Zeron ⁵⁴⁹	20: Effective
Anti-SRP myopathy	Valiyil <i>et al</i> ⁶⁸³	8: Effective

DM, dermatomyositis; PM, polymyositis; SRP, signal recognition particle.

Behcet's disease

Disease	Author (reference)	N
Retinal vasculitis	Sadreddini <i>et al</i> ⁶⁸⁴	1: Effective
Severe ocular lesions	Davatchi <i>et al</i> ⁶⁸⁵	10: Effective
Ocular inflammatory disease	Kurz <i>et al</i> ⁶⁸⁶	4: Effective

Polyneuropathy

Disease	Author (reference)	N
IgM antibody-associated polyneuropathy	Pestronk <i>et al</i> ⁶⁸⁷	21: Effective
Demyelinating neuropath and Sjogren's syndrome	Botez <i>et al</i> ⁶⁸⁸	1: Effective
Anti-MAG antibodies associated with polyneuropathy	Renaud <i>et al</i> ⁶⁸⁹	9: Effective
Anti-MAG antibodies associated with polyneuropathy	Renaud <i>et al</i> ⁶⁸⁹	8: Effective
IgM antibody-associated polyneuropathy	Levine <i>et al</i> ⁶⁹⁰	5: Effective
Anti-MAG antibodies associated with polyneuropathy	Benedetti <i>et al</i> ⁶⁹¹	13: Effective
Anti-MAG antibodies associated with polyneuropathy	Benedetti <i>et al</i> ⁶⁹²	10: Effective
Anti-MAG antibodies associated with polyneuropathy	Dalakas <i>et al</i> ⁶⁹³	13: Effective in 4

MAG, myelin-associated glycoprotein.

Demyelinating diseases of the central nervous system

Disease	Author (reference)	N
Neuromyelitis optica	Cree <i>et al</i> ⁶⁹⁴	8: Effective
Relapsing-remitting multiple sclerosis	Hauser <i>et al</i> ⁶⁹⁵	69: Effective
Relapsing-remitting multiple sclerosis	Bar-Or <i>et al</i> ⁶⁹⁶	26: Effective
Neuromyelitis optica	Genain <i>et al</i> ⁶⁹⁷	9: Effective
Neuromyelitis optica	Jacob <i>et al</i> ⁶⁹⁸	25: Effective
Multiple sclerosis (primary progressive)	Hawker <i>et al</i> ⁶⁹⁹	439: Ineffective

Pemphigus, pemphigoid, epidermolysis bullosa and other dermatological diseases

Disease	Author (reference)	N
BP, PV	Schmidt <i>et al</i> ⁷⁰⁰	7: Effective
PV	Goh <i>et al</i> ⁷⁰¹	5: Partially effective
PV	Cianchini <i>et al</i> ⁷⁰²	12: Effective
Pemphigus	Joly <i>et al</i> ⁷⁰³	21: Effective
Pemphigus	Marzano <i>et al</i> ⁷⁰⁴	6: Effective
PV	Allen <i>et al</i> ⁷⁰⁵	42: Effective
PV	Antonucci ⁷⁰⁶	5: Effective
Atopic eczema	Simon <i>et al</i> ⁷⁰⁷	6: Effective
Pemphigus	Shimanovich <i>et al</i> ⁷⁰⁸	7: Effective
Pemphigus (ocular)	Foster <i>et al</i> ⁷⁰⁹	12: Effective
Pemphigus	Schmidt <i>et al</i> ⁷¹⁰	136: Effective
Pemphigus	Pfütze <i>et al</i> ⁷¹¹	5: Effective
Psoriatic arthritis	Mease <i>et al</i> ⁴⁰¹	20: Marginally effective

BP, bullous pemphigoid; PV pemphigus vulgaris.

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Scleroderma		
Disease	Author (reference)	N
Scleroderma ILD	McGonagle <i>et al</i> ⁷¹²	1: Effective
Scleroderma ILD	Daoussis <i>et al</i> ⁷¹³	14: Effective
Cutaneous scleroderma	Smith <i>et al</i> ⁷¹⁴	8: Effective
Scleroderma	Bosello <i>et al</i> ⁷¹⁵	9: Effective
Scleroderma ILD	Yoo <i>et al</i> ⁷¹⁶	15: Not effective
Scleroderma	Lafyatis <i>et al</i> ⁷¹⁷	15: Not effective
Scleroderma skin	Smith <i>et al</i> ⁷¹⁴	8: Effective
Scleroderma pulmonary/skin ILD, interstitial lung disease.	Daoussis <i>et al</i> ⁷¹³	14: Effective
Antiphospholipid syndrome		
Disease	Author (reference)	N
Relapsing catastrophic antiphospholipid syndrome	Asherson <i>et al</i> ⁷¹⁸	3: Effective
Relapsing catastrophic antiphospholipid syndrome	Manner <i>et al</i> ⁷¹⁹	1: Effective
Paediatric catastrophic antiphospholipid syndrome	Nageswara <i>et al</i> ⁷²⁰	1: Effective
	Brito-Zeron ⁵⁴⁹	5: Effective
Cutaneous necrosis	Costa <i>et al</i> ⁷²¹	1: Effective
	Kumar <i>et al</i> ⁷²²	21: Effective
Autoimmune pulmonary alveolar proteinosis		
	Borie <i>et al</i> ⁷²³	1: Effective
Relapsing polychondritis		
	Leroux <i>et al</i> ⁷²⁴	9: Ineffective
Mixed connective tissue disease		
	Ben Abdelghani <i>et al</i> ⁷²⁵	5: Effective
Ankylosing spondylitis		
	Nocturne <i>et al</i> ⁷²⁶	8: Ineffective
	Song <i>et al</i> ⁷²⁷	20: Effective

APPENDIX 4

Anecdotal studies of interleukin 1 receptor antagonist (anakinra): a placebo-controlled randomised clinical trial has highlighted the clinical efficacy of rilonacept in patients with CAPS (category A evidence).¹¹⁷ Anakinra has been used with effect in CAPS, FME, TRAPS, DIRA and Schnitzler syndrome.

Ankylosing spondylitis and psoriatic arthritis: anakinra has been evaluated in two open-label studies of AS, but without consistent evidence of efficacy.^{728 729} Anakinra did not demonstrate clinical efficacy in PsA.⁷³⁰

Crystal-associated arthropathies: there are anecdotal reports of clinical efficacy following treatment with anakinra in patients with intractable gout⁷³¹ and pseudogout.⁷³²

Other arthropathies: treatment with intra-articular anakinra was evaluated in a randomised clinical trial of patients with osteoarthritis (category A evidence).⁷³³ Treatment was well tolerated, but no improvements were observed compared with placebo.

APPENDIX 5 ANECDOTAL STUDIES USING INTERLEUKIN 1 INHIBITORS

Disease	Author (reference)	Patients (n)
Acute stroke	Emsley <i>et al</i> ⁷³⁴	34
Adult-onset Still's disease	Rudinskaya <i>et al</i> ⁷³⁵	1
	Lequerre <i>et al</i> ⁷³⁶	15
	Aelion <i>et al</i> ⁷³⁷	2
	Haraoui <i>et al</i> ⁷³⁸	3
	Kalliolias <i>et al</i> ⁷³⁹	2
	Nordstrom <i>et al</i> ⁷⁴⁰	3
	Kalliolias <i>et al</i> ⁷³⁹	3
	Fitzgerald <i>et al</i> ⁷⁴¹	4
	Vasques Godinho <i>et al</i> ⁷⁴²	1
Behcet's disease	Botsios <i>et al</i> ⁷⁴³	1
	Tan <i>et al</i> ⁷²⁹	1
Consider intra-articular use of anakinra	Birmingham <i>et al</i> ⁷⁴⁴	7
Cytophagic histiocytic panniculitis	Behrens <i>et al</i> ⁷⁴⁵	1
Diabetes type 2	Larsen <i>et al</i> ⁷⁴⁶	70
	Larsen <i>et al</i> ⁷⁴⁷	67
Familial Mediterranean Fever	Bilginer <i>et al</i> ⁷⁴⁸	1
	Mitroulis <i>et al</i> ⁷⁴⁹	1
	Moser <i>et al</i> ⁷⁵⁰	1
	Roldan <i>et al</i> ⁷⁵¹	1
	Gattringer <i>et al</i> ⁷⁵²	2
	Kuijk <i>et al</i> ⁷⁵³	1
	Calligaris <i>et al</i> ⁷⁵⁴	1
	Belkhir <i>et al</i> ⁷⁵⁵	1
	So <i>et al</i> ⁷⁵⁶	10
Gout	Gratton <i>et al</i> ⁷⁵⁷	1
	McGonagle ⁷³¹	1
	Singh <i>et al</i> ⁷⁵⁸	1
	Antin <i>et al</i> ⁷⁵⁹	186
Hyper-IgD syndrome	Bodar <i>et al</i> ⁷⁶⁰	3
	Rigante <i>et al</i> ⁷⁶¹	
	Cailliez <i>et al</i> ⁷⁶²	1
Macrophage activation syndrome	Kelly <i>et al</i> ⁷⁶³	1
Psoriatic arthritis	Jung <i>et al</i> ⁷⁶⁴	20
	Gibbs <i>et al</i> ⁷⁶⁵	12
Recurrent pericarditis	Picco <i>et al</i> ⁷⁶⁶	3
Relapsing polychondritis	Vounotrypidis <i>et al</i> ⁷⁶⁷	1
	Wendling <i>et al</i> ⁷⁶⁸	1
	Buonuomo <i>et al</i> ⁷⁶⁹	1
	Besada <i>et al</i> ⁷⁷⁰	24
Schnitzer's syndrome	Moosig <i>et al</i> ⁷⁷¹	3
Systemic lupus erythematosus	Ostendorf <i>et al</i> ⁷⁷²	4
	Gattorno <i>et al</i> ⁷⁷³	4
TNF receptor-associated	Sacr� <i>et al</i> ⁷⁷⁴	1
Periodic syndrome (TRAPS)	Simon <i>et al</i> ⁷⁷⁵	1
	Gattorno <i>et al</i> ⁷⁷⁶ , Lequerr� <i>et al</i> ⁷³⁶	

GVHD, graft versus host disease; TNF, tumour necrosis factor; TRAPS, TNF-receptor associated periodic syndrome.

Clinical and epidemiological research

APPENDIX 6 ANECDOTAL STUDIES USING TUMOUR NECROSIS FACTOR BLOCKING AGENTS

Disease	Author (reference)	Drugs	Patients (n)
Adult Still's disease	Huffstutter and Sienknechet ⁷⁷⁷	Infliximab	2
	Kraetsch <i>et al</i> ⁷⁷⁸	Infliximab	6
	Weinblatt <i>et al</i> ⁷⁷⁹	Etanercept	12
	Fernandez-Nebro ⁷⁸⁰	Etanercept	3
Amyloidosis	Elkayam <i>et al</i> ⁷⁸¹	Infliximab	1
	Gottenberg <i>et al</i> ⁷⁸²	Etanercept/infliximab	15
	Ortiz-Santamaria <i>et al</i> ⁷⁸³	Infliximab	6
	Tomero <i>et al</i> ⁷⁸⁴	Infliximab	12
	Kallinick <i>et al</i>	Etanercept	1
	Ravindran <i>et al</i>	Etanercept	1
	Smith <i>et al</i> ⁷⁸⁵	Etanercept	1
Aphthous stomatitis	Robinson and Guitart ⁷⁸⁶	Etanercept	1
	Vujevich and Zirwas ⁷⁸⁷	Adalimumab	
	Atzeni <i>et al</i> ⁷⁸⁸	Etanercept	1
Asthma		Various TNF blocking agents	12
Back pain (including sciatica)	Sakellariou <i>et al</i> ⁷⁸⁹	Infliximab	1
	Genevay <i>et al</i> ⁷⁹⁰	Etanercept	10
	Estrach <i>et al</i> ⁷⁹¹	Infliximab/adalimumab	7
Behcet's disease	Gulli <i>et al</i> ⁷⁹²	Infliximab	1
	Hassard <i>et al</i> ⁷⁹³	Infliximab	1
	Licata <i>et al</i> ⁷⁹⁴	Infliximab	1
	Magliocco and Gottlieb ⁷⁹⁵	Etanercept	20
	Morillas-Arques <i>et al</i> ⁷⁹⁶	Adalimumab/etanercept	
	Rozenbaum <i>et al</i> ⁷⁹⁷	Anti-TNF	
	Saulsbury and Mann ⁷⁹⁸	Infliximab	
	Sangle <i>et al</i> ⁷⁹⁹	Infliximab	1
	Sfikakis <i>et al</i> ⁸⁰⁰	Infliximab	5
	Sfikakis ⁸⁰⁰	Infliximab	11
	Ribi <i>et al</i> ⁸⁰¹	Infliximab	1
	Sweiss <i>et al</i> ⁸⁰²	Infliximab	3
	Van Laar <i>et al</i> ⁸⁰³	Adalimumab	6
Bronchiolitis, cirrhosis and alcoholic hepatitis	Cortot <i>et al</i> ⁸⁰⁴	Etanercept	1
	Naveau <i>et al</i> ⁸⁰⁵	Infliximab	36
	Spahr <i>et al</i> ⁸⁰⁶	Infliximab	20
	Wendling <i>et al</i> ⁸²⁶	Infliximab	1
	Menon <i>et al</i> ⁸⁰⁷	Etanercept	13
	Tsimberidou <i>et al</i> ⁸⁰⁸	Etanercept	13
Cutaneous T-cell lymphoma		Infliximab	3
Complex regional pain syndrome (A2)			
Dermatitis, hidradenitis, miscellaneous	Bongartz <i>et al</i> ⁴⁷⁷	Infliximab	
	Cortis <i>et al</i> ⁸⁰⁹	Etanercept	
	Cummins <i>et al</i> ⁸¹⁰	Etanercept	
	Zeichner <i>et al</i> ⁸¹¹	Adalimumab	1
	Cusack and Buckley ⁸¹²	Etanercept	6
Dermatomyositis	Hengstman <i>et al</i> ⁸¹³	Infliximab	2
	Miller <i>et al</i> ⁸¹⁴	Etanercept	10
	Sprott <i>et al</i> ⁸¹⁵	Etanercept	1
	Nzeusseu <i>et al</i> ⁸¹⁶	Infliximab	1
	Saadeyh ⁸¹⁷	Etanercept	4
	Norman <i>et al</i> ⁸¹⁸	Etanercept	2
Diabetic macular oedema	Sfikakis <i>et al</i> ⁸¹⁹	Infliximab	14
	Wu <i>et al</i> ⁸²⁰	Infliximab/adalimumab	39 Ineffective
Erythema nodosum	Ortego-Centeno <i>et al</i> ⁸²¹	Adalimumab	1
Familial Mediterranean fever	Takada <i>et al</i> ⁸²²	Etanercept	2
	Ozgocmen <i>et al</i> ⁸²³	Etanercept	1
Felty's syndrome	Ghavami <i>et al</i> ⁸²⁴	Etanercept	1
Gastric cancer	Zhao <i>et al</i> ⁸²⁵	Infliximab	19

Continued

APPENDIX 6 Continued

Disease	Author (reference)	Drugs	Patients (n)
Giant cell arteritis	Andonopoulos <i>et al</i> ⁸²⁶	Infliximab	2
	Cantini <i>et al</i> ⁸²⁷	Infliximab	4
	Tan <i>et al</i> ⁸²⁸	Etanercept	1
	Ahmed <i>et al</i> ⁸²⁹		1
Graft versus host disease (acute)	Wolff <i>et al</i> ⁸³⁰	Etanercept	21
	Uberti <i>et al</i> ⁸³¹	Etanercept	20
	Kennedy <i>et al</i> ⁸³²	Etanercept	20
	Chiang <i>et al</i> ⁸³³	Etanercept	8
	Pavletic <i>et al</i> ⁸³⁴	Etanercept	4
	Andolina <i>et al</i> ⁸³⁵	Etanercept	1
Graves' ophthalmopathy	Paridaens <i>et al</i> ⁸³⁶	Etanercept	10
Hearing loss	Ada-9 033111	Adalimumab	1
Hepatitis C	Cacoub <i>et al</i> ⁸³⁷	Interferon	27
	McMinn <i>et al</i> ⁸³⁸	Etanercept	3
	Peterson <i>et al</i> ⁸³⁹	Infliximab/etanercept	24
	Pritchard ⁸⁴⁰	Etanercept	1
	Ince <i>et al</i> ⁸⁴¹	Etanercept	12
	Allen and Wolverton ⁷⁰⁵	Etanercept	2
	Marotte <i>et al</i> ⁸⁴²	Etanercept	9
	Rokhsar ⁸⁴³	Etanercept	1
	Magliocco and Gottlieb ⁷⁹⁵	Etanercept	3
Hidradenitis suppurativa	Grant <i>et al</i> ⁸⁴⁴	Infliximab	15
HIV	Wallis <i>et al</i> ⁸⁴⁵	Etanercept	16
Immunodeficiency (common variable)	Smith and Skelton ⁸⁴⁶	Etanercept	1
	Lin <i>et al</i> ⁸⁴⁷	Etanercept	1
	Cepeda <i>et al</i> ⁸⁴⁸	Etanercept	7
Inclusion body myositis	Barohn <i>et al</i> ⁸⁴⁹	Etanercept	9 (ineffective)
	Singh <i>et al</i> ⁸⁵⁰	Etanercept	1
Juvenile-onset HLA-B27-associated severe and refractory heel enthesitis	Olivieri <i>et al</i> ⁸⁵¹	Adalimumab	1
Kawasaki's disease	Weiss <i>et al</i> ⁸⁵²	Infliximab	1
	Burns <i>et al</i> ⁸⁵³	Infliximab	16
Lung cancer (non-small cell)	Jatoi <i>et al</i> ⁸⁵⁴	Infliximab	6 (ineffective)
Multicentric histiocytosis	Lovelace <i>et al</i> ⁸⁵⁵	Etanercept	1
	Matejicka <i>et al</i> ⁸⁵⁶	Etanercept	1
	Kovach <i>et al</i> ⁸⁵⁷	Etanercept	1
Myelodysplasia	Birnbaum and Gentile ⁸⁵⁸	Etanercept	1
	Deeg <i>et al</i> ⁸⁵⁹	Etanercept	14
	Rosenfeld and Bedell ⁸⁶⁰	Etanercept	19 (Ineffective)
	Raza <i>et al</i> ⁸⁶¹	Etanercept	26
	Maciejewski ⁸⁶²	Etanercept	16
Osteoarthritis (erosive)	Magnano <i>et al</i> ⁸⁶³	Adalimumab	12
Periodic fever (children)	Athreya <i>et al</i> ⁸⁶⁴	Etanercept	3
Pigmented villonodular synovitis	Kroot <i>et al</i> ⁸⁶⁵	TNF	
Polymyositis	Hengstman <i>et al</i> ⁸¹³	Infliximab	2
	Sprott <i>et al</i> ⁸¹⁵	Etanercept	1
	Adams <i>et al</i> ⁸⁶⁶	Adalimumab	2
Polychondritis	Carter ⁸⁶⁷	Infliximab	1
	Ehresman ⁸⁶⁸	Etanercept	5
Polymyalgia rheumatica	Karampetsou (A9)	Infliximab	Ineffective
Pyoderma gangrenosum	Fonder <i>et al</i> ⁸⁶⁹	Adalimumab	1
Renal cell carcinoma	Larkin <i>et al</i> ⁸⁷⁰	Infliximab	16 (ineffective)
Sacroiliitis AS		Infliximab	
	Heffernan <i>et al</i> ⁸⁷¹	Adalimumab	1
SAPHO syndrome	Anker and Coats ⁸⁷²	Infliximab/etanercept	150
	Sweiss <i>et al</i> ⁸⁰²	Infliximab	3
	Callejas-Rubio <i>et al</i> ⁸⁷³	Adalimumab	1

Continued

Clinical and epidemiological research

APPENDIX 6 Continued

Disease	Author (reference)	Drugs	Patients (n)
Sarcoidosis	Korhonen <i>et al</i> ⁸⁷⁴	Infliximab	12
	Korhonen <i>et al</i> ⁸⁷⁵	Infliximab	40
	Lam <i>et al</i> ⁸⁷⁶	Infliximab	18
	Pasternack <i>et al</i> ⁸⁷⁷	Etanercept	4
	Tobinick and Davoodifar ⁸⁷⁸	Etanercept	43
	Khanna <i>et al</i> ⁸⁷⁹	Etanercept	1
	Utz <i>et al</i> ⁸⁸⁰	Etanercept	17
	Wagner <i>et al</i> ⁸⁸¹	Etanercept	2
	Moul <i>et al</i> ⁸⁸²	Adalimumab	1
	Khanna <i>et al</i> ⁸⁷⁹	Etanercept	1
	Utz <i>et al</i> ⁸⁸⁰	Etanercept	1
	Heffernan <i>et al</i> ⁸⁸³	Adalimumab	1
	Callejas-Rubio ⁸⁷³	Adalimumab	1
	Querfeld ⁸⁸⁴	Etanercept	1
	Sweiss <i>et al</i> ⁸⁰²	Etanercept	1
Scleritis	Hobbs ⁸⁸⁵	Etanercept	1
	Karampetsou <i>et al</i> ⁸⁸⁶	Infliximab	1 (ineffective)
Scleroderma	ADA-46 033111	Adalimumab	1
	Ellman <i>et al</i> ⁸⁸⁷	Etanercept	8
Silicone granulomas	Bosello <i>et al</i> ⁸⁸⁸	Etanercept	
	Pasternack <i>et al</i> ⁸⁷⁷	Etanercept	4
Sjogren's syndrome	Zandbelt <i>et al</i> ⁸⁸⁹	Etanercept	15 (ineffective)
	Sankar <i>et al</i> ⁸⁹⁰	Etanercept	14 (ineffective)
Still's disease (includes adult onset)	Pessler <i>et al</i> ⁸⁹¹	Etanercept	1
	Karampetsou <i>et al</i> ⁸⁸⁶	Infliximab	Ineffective
	Fautrel <i>et al</i> ⁸⁹²	Etanercept	20 (ineffective)
	Stern <i>et al</i> ⁸⁹³	Etanercept	1 (worsening)
	Asherson <i>et al</i> ⁸⁹⁴	Etanercept	1
	Kumari and Uppal ⁸⁹⁵	Etanercept	1
	Gindi <i>et al</i> ⁸⁹⁶	Etanercept	1
Sweet's syndrome	Yamauchi <i>et al</i> ⁸⁹⁷	Etanercept	24
	Aringer <i>et al</i> ⁸⁹⁸	Infliximab	6
Systemic lupus erythematosus	Fautrel <i>et al</i> ⁸⁹²	Etanercept	1 (SCLE)
	Lurati <i>et al</i> ⁸⁹⁹	Etanercept	1
	Norman <i>et al</i> ⁹¹⁸	Etanercept	1 (SCLE)
	Hernandez-Ibarra <i>et al</i> ⁹⁰⁰	N/A	—
	Principi <i>et al</i> ⁹⁰¹	Infliximab	1
	Hoffman <i>et al</i> ⁹⁰²	Anti-TNF	15
	Della Rossa <i>et al</i> ⁹⁰³	Infliximab	2
TRAPS	Tato <i>et al</i> ⁹⁰⁴	Adalimumab	1
	Hull <i>et al</i> ⁹⁰⁵	Etanercept	> 50
	Lamprecht <i>et al</i> ⁹⁰⁶	Etanercept	2
	Drewe <i>et al</i> ⁹⁰⁷	Etanercept	1
	Estrach <i>et al</i> ⁷⁹¹	Infliximab/adalimumab	7
	Joseph <i>et al</i> ⁹⁰⁸	Infliximab	5
	Smith <i>et al</i> ⁹⁰⁹	Etanercept	7
	Braun <i>et al</i> ⁹¹⁰	Etanercept/infliximab	717 (uveitis in AS)
	Foster <i>et al</i> ⁹¹¹	Etanercept	20 (ineffective)
	Biester <i>et al</i> ⁹¹²	Adalimumab	18
	Foeldvari <i>et al</i> ⁹⁴⁶	Anti-TNF	47
	Vazquez-Cobian <i>et al</i> ⁹¹³	Adalimumab	14
	Reiff <i>et al</i> ⁹¹⁴	Etanercept	10
	Schmeling and Horneff ⁹¹⁵	Etanercept	20 (ineffective)
	Guignard <i>et al</i> ⁹¹⁶	Adalimumab	8
Vasculitis*	Krelenbaum <i>et al</i> ⁹¹⁷	Infliximab	1
	Booth <i>et al</i> ⁹¹⁸	Infliximab	32
	Feinstein and Arroyo ⁹¹⁹	Etanercept	1
	van der Bijl ⁹²⁰	Infliximab	11

Continued

APPENDIX 6 Continued

Disease	Author (reference)	Drugs	Patients (n)
Wegener's granulomatosis	Saji <i>et al</i> ⁹²¹	Infliximab	1 (Kawasaki's disease)
	Sangle <i>et al</i> ⁷⁹⁹	Infliximab	1 (Churg–Strauss)
	Arbach <i>et al</i> ⁹²²	Etanercept/infliximab	3
	Gause <i>et al</i> ⁹²³	Infliximab	10
	Sangle <i>et al</i> ⁷⁹⁹	Infliximab	3
	Karampetsou ⁸⁸⁶	Etanercept	Ineffective

A recent randomised controlled trial demonstrated no superiority of a combination of methotrexate with infliximab versus infliximab alone in the treatment of active AS over 1 year (category B evidence).⁹²⁴

AS, ankylosing spondylitis; TNF, tumour necrosis factor; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis.

APPENDIX 7 ANECDOTAL STUDIES USING TOCILIZUMAB

Disease	Author (reference)	Patients (n)	Outcome
Acquired haemophilia A complicated by GVHD	Nishida <i>et al</i> ⁹²⁵	1	Positive on acquired haemophilia A
Adult-onset Still's syndrome	Perdan-Pitkmaier <i>et al</i> ¹⁶³	1	Positive
	Iwamoto <i>et al</i> ⁹²⁶	1	Positive
	Thonhofer <i>et al</i> ¹⁶²	7	Positive
	Naniwa <i>et al</i> ⁹²⁷	1	Positive
	M de Brandt ²⁷⁴	1	Positive
	Cunha <i>et al</i> ⁹²⁸	2	Positive
	Puechal <i>et al</i> ¹⁶⁵	14	11 Positive reports
	With associated aseptic meningitis	1	Positive
	Sabnis ⁹²⁹	1	Positive
	Kishida <i>et al</i> ⁹³⁰	One with DIC	Positive
Adult-onset Still's syndrome with thrombotic thrombocytopenic purpura	Matsumoto <i>et al</i> ⁹³¹		
	Sumida <i>et al</i> ⁹³²	1	Positive
Amyloidosis	Nishida <i>et al</i> ⁹³³	1	Positive
	Henes <i>et al</i> ¹⁶⁴	1	Clinical improvement but not in MRI
	Sato <i>et al</i> ⁹³⁴	1	Positive
	Sato <i>et al</i> ⁹³⁴	1	Positive
AS	Shima <i>et al</i> ⁹³⁵	1	Positive
Crohn's disease and AS refractory to TNF	Brulhart <i>et al</i> ⁹³⁶	1	Positive
Polymyalgia rheumatica	Hagihara <i>et al</i> ⁹³⁷	1	Positive
Reactive arthritis	Tanaka <i>et al</i> ⁹³⁸	1	Positive
Relapsing polychondritis	Kawai <i>et al</i> ⁹³⁹	2	Positive, also on lung disease
RS3PE syndrome	Tanaka <i>et al</i> ⁹⁴⁰	1	Positive
Severe GVHD	Gergis <i>et al</i> ⁹⁴¹	1	Positive
SLE	Illei <i>et al</i> ⁹⁴²	16	Dose ranging study, positive with caution on neutropenia
Systemic sclerosis	Shima <i>et al</i> ⁹⁴³	2	Positive on skin softening
Takayasu's arteritis	Nishimoto ⁹⁴⁴	1	Positive

Tocilizumab to include iritis (JIA) in a dose of 8 mg/kg every 2 weeks (category A evidence)¹⁵⁵ and in polyarticular JIA (category A, D evidence).¹⁵³

AS, ankylosing spondylitis; GVHD, graft versus host disease; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor; DIC, disseminated intravascular coagulopathy.



Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011

D E Furst, E C Keystone, J Braun, et al.

Ann Rheum Dis 2012 71: i2-i45

doi: 10.1136/annrheumdis-2011-201036

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