CONSENSUS STATEMENT

Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007

D E Furst, F C Breedveld, J R Kalden, J S Smolen, G R Burmester, J Sieper, P Emery, E C Keystone, M H Schiff, P Mease, P L C M van Riel, R Fleischmann, M H Weisman, M E Weinblatt

Ann Rheum Dis 2007;**66**(Suppl III):iii2–iii22. doi: 10.1136/ard.2007.081430

As in previous years, the consensus group to consider the use of biological agents was constituted by rheumatologists from the universities of Erlangen, Leiden and Vienna in Europe in cooperation with other universities in the USA, Canada and Europe. Pharmaceutical industry support was obtained from a number of companies, but these companies had no part in the decisions regarding the specific programme or about the academic participants at this conference. These sponsors participated in the initial small breakout groups with emphasis on supplying factual information. The companies, on the other hand, had no part in the larger, final consensus group or in the final consensus statement.

The perspective of this consensus is from the treating physician's point of view.

The 160 rheumatologists and bioscientists who attended the consensus conference were chosen from a worldwide group of physicians and other scientists from 21 countries, with 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.

Based on the new data regarding TNF blocking agents, B cell-specific agents & IL1rα, an update of the previous consensus statement is appropriate.[1] The consensus statement is annotated to document the credibility of the data supporting it as much as possible. This annotation is that of Shekelle *et al.* and is described in an appendix.[2] We have modified the Shekelle annotation by designating all abstracts as ''Category D evidence'', whether they describe well-controlled trials or not, based on a need to be able to describe details of the studies and results. As the number of possible references has become so large, reviews are sometimes used and, if they contain Category A references, will be referred to as Category A evidence. All participants reviewed relevant clinical published articles relating to tumour necrosis factor (TNF) and interleukin (IL) 1 blocking agents, and abatacept and rituximab. They were given a draft consensus statement and were asked to revise the document in small discussion groups; open discussion of the revisions led to a final document, representing this updated consensus statement.

GENERAL STATEMENTS

Individual patients differ in the aggressiveness of their disease and its concomitant structural damage, the effect of their disease on their quality of life, and the symptoms and signs engendered by their disease. They also differ in their susceptibility to, 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 for treating psoriatic arthritis (PsA) and ankylosing spondylitis (AS) with biological agents, efficacy and clinical use for these diseases will be treated separately from rheumatoid arthritis (RA). Adverse reactions, however, will remain combined for all indications. In general, in RA, when measuring response to therapy or when following patients over time, the American College of Rheumatology (ACR) response criteria (as a combined index) should not be used in a clinical practice setting to monitor individual response, although some validated measure of response (such as those which follow) should be employed (Category B evidence[3]). Validated quantitative measures such as Disease Activity Score (DAS), Simple Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire disability index (HAQ-DI), visual analogue scales (VAS) or Likert scales of global response or pain by the patient or global response by the physician, other validated measures of pain for individual patient care, joint tenderness and/or swelling counts, and laboratory data all may be used and may be the most appropriate measures for individual patients (Category B evidence[3 4]). The physician should evaluate a patient's response using the above measures to determine the patient's status and improvement.

For PsA, measures of response such as joint tenderness and swelling, global and pain response measures, functional indices and acute phase reactants have been used and appear responsive (Category A evidence[5]). For AS, measures such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Bath Ankylosing Spondylitis Functional Index (BASFI) have been used in a clinical trial setting but have not been validated for the routine clinical practice setting. 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 (Category A evidence[6–10]).

The use of biological agents will require physicians experienced in the diagnosis, treatment and assessment of RA, PsA, AS and other rheumatic diseases. These physicians will need to make long-term observations for efficacy and toxicity, including cohorts, registries and so on. Because these agents have toxicities, patients or their representatives should be provided with information about potential risks and benefits so that they may give informed consent for treatment.

Abbreviations: abs, abstract; ACR, American College of Rheumatology; ANA, antinuclear antibody, AS, ankylosing spondylitis; ASCVD, atherosclerotic cardiovascular disease; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CDAI, Clinical Disease Activity Index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; FDA, Food and Drug Administration; HAQ-DI, Health Assessment Questionnaire disability index; MTX, methotrexate; PPD, purified protein derivative; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index; TB, tuberculosis; VAS, visual analogue scale

TNF BLOCKING AGENTS

TNF blocking agents differ in composition, precise mechanism of action, pharmacokinetics, biopharmaceutical properties and so on, but this document emphasises areas of commonality. Data that clearly have differentiated compounds will be discussed if such areas can be identified.

Indications

Rheumatoid arthritis

In most patients, TNF blockers are used in conjunction with another DMARD, usually methotrexate (MTX). TNFα blocking agents have also been used successfully with other DMARDs, including sulfasalazine and leflunomide (Category A/B evidence[11–37]). There is evidence that TNF blockers are effective for the treatment of RA in MTX-naive patients (Category A evidence,[12–17 21 22 26 27 31 34 36] Category D evidence[19 24 25]). TNF blocking agents can be used as the first DMARD in some patients (Category A evidence,[12–18 22 26–28 31 33 36] Category D evidence[19 26 35 36]). Adalimumab and etanercept are both approved as monotherapy for RA. Infliximab is only approved for use with MTX in RA. However, observational data indicate that infliximab, too, is sometimes used as monotherapy (Category C evidence[11 23 37]). Evidence from several randomised controlled trials suggests that the combination of a TNF blocking agent and MTX yields superior results for RA when compared with monotherapy, particularly with respect to excellent clinical responses (ACR 70, European League Against Rheumatism remission) and radiological outcomes (Category A evidence).[11–16 18–20 22–35 37]

Evidence has become available which shows that TNF-blocking agents are cost-effective from a societal perspective (Category D evidence[38 39]).

Psoriatic arthritis

The three available anti-TNF medications, etanercept, infliximab and adalimumab, have been approved globally for the treatment of psoriatic arthritis (PsA) based on demonstration of control of signs and symptoms of joint and skin disease, improvement of function (HAQ), quality of life (SF-36), and inhibition of structural damage evidenced by *x* ray (Category A evidence[40–47]).

A comparator trial of methotrexate versus anti-TNF therapy showed that the latter yielded superior results in joint and skin signs and symptoms, function and quality of life (Category B evidence[47 48]).

Preliminary data suggest that anti-TNF therapy can benefit cardiovascular risk in PsA (Category A evidence[49]). Anti-TNF therapy has been demonstrated to reduce healthcare resource utilisation (Category B evidence[50]), and improve employment status, time lost from work and productivity (Category B evidence[44]).

Ankylosing spondylitis

Adalimumab, etanercept and infliximab have been approved for the treatment of severe, active AS in Europe and North America (Category A evidence,[6–10 51–56] Category D evidence[57]). In the clinical trials, efficacy of the TNF blocking agents was demonstrated as monotherapy as well as with concomitant second-line agents including sulfasalazine or MTX (Category A evidence[6–10 51–56]). TNFα blocking agents maintain efficacy over 1–5 years in open-label studies (Category B evidence[55 56 58]).

The approved doses of TNF blockers for treatment of AS are as follows: infliximab, 5 mg/kg intravenously every 6–8 weeks after induction; etanercept, subcutaneously 25 mg twice a week or 50 mg once a week; and adalimumab 40 mg subcutaneously every other week (Category A and B evidence[6–10 38 51–59]). No dose-ranging studies have been done with any of these drugs. There is no evidence that one TNF blocking agent is more effective than any other for the treatment of musculoskeletal manifestions of AS. TNF blocking agents used for AS may reduce economic resource utilisation (Category D evidence[38]).

Juvenile idiopathic arthritis of the polyarticular type

Adalimumab, etanercept and infliximab have been approved for juvenile idiopathic arthritis of the polyarticular type (Category A evidence;[60–62] Food and Drug Administration (FDA) Summary Basis of Approval).

Use in other rheumatic diseases or those with prominent rheumatic manifestations

Chronic inflammatory bowel disease

Infliximab has been approved to treat luminal and fistulising Crohn's disease and ulcerative colitis in the USA (Category A evidence;[63 64] FDA Summary Basis of Approval). Infliximab is approved for ulcerative colitis and Crohn's disease in Europe (Category A evidence;[65 66] European Medicines Agency Summary). Adalimumab is approved for Crohn's disease in the USA.

Controlled trials that demonstrated a difference from placebo or positive control

- Etanercept was effective for treating some of the mucocutaneous manifestations of Behçet's syndrome compared with placebo over 4 weeks (Category A evidence[67]).
- Etanercept improved hepatitis C viraemia but not symptoms, compared with placebo, when given on a background of interferon αand ribavirin (Category A evidence[68]).
- Infliximab improved the signs and symptoms of ulcerative colitis (abstracts from double blind trials (Category D evidence, n = 364 patients in each of two trials)[65 66]).
- Infliximab improved Pyoderma gangrenosum (abstract of a double blind trial (Category D evidence, n = 30[69])).
- Infliximab improved pulmonary sarcoidosis (Category A evidence, n = 86[70]).

Controlled trials that failed to demonstrate a difference from placebo

- Etanercept and infliximab in Sjögren's syndrome (Category A evidence[71–73]) (see also anecdotal data in table 1).
- Etanercept in Wegener's granulomatosis (Category A evidence[74]) (see also anecdotal data in table 1).
- Etanercept in autoimmune ear disease (Category A evidence,[75] very small (n = 21)).
- Infliximab in chronic obstructive pulmonary disease (Category A evidence,[76] very small (n = 30)).
- Infliximab for disc herniation (abstract of a double blind trial, Category D evidence,[77] very small (n = 40)).
- Infliximab in giant cell arteritis (GCA) (Category B evidence,[78] very small (n = 44)).
- Infliximab for polymyalgia rheumatica (PMR) (abstract of a double blind trial, Category B evidence,[79] very small (n = 51)).
- Anecdotal series or studies with promising results (see Appendix 1).

Clinical use

Rheumatoid arthritis and juvenile idiopathic arthritis

TNF blocking agents, when given up to the maximum approved dosing regimens for RA and juvenile idiopathic arthritis of the polyarthritic variety, are expected to lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters within 12 weeks (Category A and B evidence[6–10 12–20 22 24–29 31–37 56 80–93]). There is no evidence that any one TNF

blocking agent should be used before another one can be tried, just as there is no evidence that any TNF blocker is more effective than any other in RA (Category A and B evidence[12 15 24 85 88–90 94 95]). Patients have been switched from one TNF blocking agent to another, but no well-controlled switch trials have been published (Category B and D evidence[58 72 85 88–90 94 95 168–171]). There is evidence that loss of response to a TNF blocking agent can occur and studies suggest that failure to respond to one TNF blocking agent does not preclude response to another (Category B and D evidence[85 88–90 94 95]).

Initial observational data suggest the possibility that primary non-responding patients are less likely to respond to a second anti-TNF agent. Patients who have not tolerated one TNF blocker may respond to a second but are also less likely to tolerate a second TNF blocking agent (Category B and D evidence[85 90 94 95]). The optimal therapy of patients not responding to TNF blockers remains to be determined.

Individually important responses including patient-oriented measures (eg, HAQ-DI, patient's global VAS, Medical Outcome Survey Short Form 36 (SF-36)) or physical measures (for example, joint tenderness)) should be demonstrated within 12 weeks for RA (Category A evidence[6–10 12–20 25–29 31–37 56 80–84]). If such improvement occurs, treatment should be continued. If patients show no response to these agents, their continued use should be re-evaluated. Observations with infliximab suggest that increasing the dose or reducing the dosing intervals may provide additional benefit in RA, as may the addition or substitution of other DMARDs (Category A evidence[15 18 31 37]). Raising the dose of etanercept does not seem to have an added benefit at 12 or 24 weeks in RA (Category D evidence[89–91]). However, because regression to the mean may occur, caution is needed when interpreting apparent improvements following dose escalation in practice (Category C evidence[92]).

There are data showing that TNF blocking agents slow and/or inhibit radiographic progression in RA, even in some patients without a clinical response (Category A evidence[12 15 19 21 22 27 34 40 82 84 93 96]). Although some RA patients without measurable clinical response have slowing of radiographic progression (Category A evidence[34 93 97]), the long-term clinical implications of these changes still remain unknown.

Psoriatic arthritis

As noted above, the three available anti-TNF medications, etanercept, infliximab and adalimumab, have been approved globally for the treatment of psoriatic arthritis (PsA).[40–51 98–101] In addition, statistically significant improvement of enthesitis and dactylitis has been demonstrated with infliximab.[42 100 102 103] Also, improvement of fatigue has been noted with adalimumab.[40] Improvement of signs and symptoms, function and quality of life occurs within 12 weeks.[40–51] A systematic evidence-based review of the various domains of PsA (joints, enthesitis, spondyloarthropathy, skin) and efficacy of their treatment has recently been published.[99–101 103–108]

Durability of clinical and radiographic data at 2 years in PsA has been demonstrated with etanercept and adalimumab.[43 47] Similar durability at 1 year has been demonstrated with infliximab in PsA.[44 46]

Preliminary data suggest that one can achieve benefit for joint and skin signs and symptoms by switching to a different anti-TNF medication, even if efficacy from a previous anti-TNF agent was never achieved, was lost or if toxicity occurred.[48–50 109 110]

Anti-TNF therapy is superior to methotrexate for joint and skin signs and symptoms, function and quality of life.[48]

An exploratory trial with anakinra in PsA failed to demonstrate significant clinical or synovial improvement as determined histologically and by MRI.[111] An exploratory trial with efalizumab, approved for the treatment of psoriasis in the USA and Europe, failed to show statistically significant improvement in PsA.[112] An exploratory trial with alefacept, approved for treatment of psoriasis in the USA, did show statistically significant improvement in joint and skin signs and symptoms in PsA.[113]

Safety

Safety and tolerability of anti-TNF therapy in PsA is no different than an RA clinical trial. Psoriasis, particularly pustular psoriasis, can rarely occur when using anti-TNF therapy.[109]

Ankylosing spondylitis

Generally, a reduction in signs and symptoms, and improvement in quality of life will be observed by 12–16 weeks in response to treatment with a TNF blocking agent.[114] In clinical trials, improvement in signs and symptoms was assessed by patient-reported outcomes (BASDAI, BASFI, patient global VAS, SF-36), physical measures and laboratory parameters. The Assessment in Ankylosing Spondylitis working group has published recommendations for the use of TNF blocking agents in AS (Category A evidence[54 115]). If a 50% improvement or an absolute improvement of 2 points (on a 0–10 scale) of the BASDAI is not reached within 12 weeks, their continued use should be re-evaluated (Category A and B evidence[6 7 9 10 53 54 57 81 115]).

Several studies have demonstrated that active inflammation of the sacroiliac joints or spine, as shown by MRI, is significantly reduced by all three TNF blocking agents (Category C evidence).[41–43 57] Inhibition of radiographic progression, as measured by plain radiography, has not been evaluated in prospective randomised controlled trials in AS. In addition, changes in MRI findings have not yet been correlated with changes in plain radiographs in the spine or sacroiliac joints in patients with AS (Category C evidence).[57 116 117]

Other for the treatment of AS

Clinical trial data with conventional DMARDs are few but suggest efficacy of sulfasalazine for the peripheral, but not spinal, manifestations of AS.[54 115] In those who fail to respond to sulfasalazine, a TNF blocking agent should be considered next (Category D evidence[115]).

The IL-RA antagonist anakinra has been investigated in two open-label studies in AS with no clear efficacy (see section on IL1 receptor blockade). No data are available at the moment regarding efficacy of other biologicals such as rituximab or abatacept in AS.

Warnings/adverse events

General reviews of TNF blocking agent safety have been published.[20 51 58 95 118–120]

Infections

An increased susceptibility to tuberculosis (TB) or reactivation of latent TB should be considered a characteristic of TNF blocking agents. The risk of TB is increased by the use of DMARD per se and is increased further by TNF blocking agents.[121–123]

The clinical picture of active TB may be atypical in these patients (for example, miliary or extrapulmonary presentations) as has been seen with other immunocompromised patients (Category C evidence[118 119 123–126]). There have been more reported cases of TB as a proportion of the total number of individuals treated in patients using infliximab and adalimumab than using etanercept (Category C evidence[118 120 122–129]). This may be due in part to differences in mechanism of action,

biology or kinetics as compared to the soluble receptor (Category D evidence)[123 126 128] but may also be, in part, due to the fact that populations treated with the various TNF blocking agents differ and the data come from registries and voluntary reporting systems. No head-to-head comparisons among TNF blocking agents have been carried out and thus no definitive data on comparisons between these agents are available regarding the incidence of reactivation of latent TB.

Screening of patients about to start TNF blocking agents has reduced the risk of activating TB for patients treated with these agents (Category B evidence[118 119 123 129–131]). Every patient should be evaluated for the possibility of latent TB, including a history that includes evaluation for the risk of latent TB (Category B evidence[58 119 120 126 127 129 132]). This history should include seeking a history of prior exposure, prior drug addiction or active drug addiction, HIV infection, birth or extended living in a region of high TB prevalence and a history of working or living in TB high-risk settings such as jails, homeless shelters and drug rehabilitation centres (Category D evidence[132]). In addition, physical examination and screening tests such as skin tests and chest radiographs should be carried out before anti TNF-therapy is initiated, according to local recommendations (Category B, C and D evidence[118 119 122 123 129–131]). Continued vigilance is required to prevent activation of latent tuberculosis or acquisition of new cases. The role of repeated or serial tuberculin skin testing during anti-TNF therapy is unclear. In the USA, repeat or annual testing has not been recommended in this or other settings of immune suppression unless patients are at risk for ongoing TB exposure.[132]

In treating latent TB, the optimal timeframe between starting preventive therapy for latent TB infection and starting TNF blockade is unknown. Given the low numbers of bacilli present in latent TB infection, it is likely that waiting long time periods between initiating preventive TB therapy and TNF blockade are unnecessary. While there are no prospective trials assessing this question, observational data from Spain suggest that initiating isoniazid therapy 1 month prior to TNF blockade substantially decreases the risk of latent TB reactivation (Category C evidence[122 129–131]).

Treatment of TB in immunocompromised hosts is as effective as in non-immunocompromised patients, suggesting that long periods of preventive treatment prior to starting TNF blocking agents may not be as necessary as previously thought. Prior to initiating preventive anti-TB therapy in accordance with local guidelines, consulting with a TB expert should be considered.

Opportunistic infections have occurred in the setting of TNF blocking agent use (Category C evidence[12 13 15–17 19–22 24 25 64 84 118–120 132–141]). Particular vigilance is needed when considering those infections whose containment is macrophage/granuloma-dependent, such as listeriosis, coccidiomycosis or histoplasmosis, including reactivation of latent histoplasmosis, (Category C and D evidence[118–120 126 127 134 137 139–142]) but the incidence of opportunistic infections is extremely low (Category C and D evidence[126 127 129]).

Serious bacterial infections have been observed in patients receiving TNF blocking agents at rates between 0.07 and 0.09/patient year compared with 0.01–0.06/patient year in controls using other DMARDs but not TNF blocking agents (Category C evidence[118–120 143 144]). Risk ratios of 1 to up to 3 were documented (Category B evidence[144 145]). High doses of TNF blocking agents may further increase the risk of serious infections (Category B evidence[146]). Other studies indicate that serious infections in certain sites are more common when using TNF blocking agents, such as the skin, soft tissues and joints (Category B evidence[144 147]).The possible contribution of corticosteroids to increasing the risk of infection should always be considered (Category C evidence[148]). The incidence of other infections (not designated as serious) may be increased when using TNF blocking agents (relative risk (RR) 2.3–3.0, 95% confidence interval (CI) 1.4 to 5.1) (Category C evidence[143]). The incidence of serious infections is higher when IL1rα and etanercept or abatacept with any of several biologicals are used in combination (3.9% in combination vs 1.0–1.6% in controls) (Category A evidence[118–120 149 150]). Therefore, a combination of biologicals is not recommended. TNF blocking agents should not be started or their discontinuation should be considered when serious infections and/or opportunistic infections occur, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections and listeriosis (Category C evidence; FDA[12 13 15–17 19–22 24 25 33 64 84 119 120 126 134 135 137 139–142 145]). Treatment with TNF blockers in such patients may be resumed if the infections have been treated adequately (Category D evidence; FDA [120 123–126 134 137 139–142 145]).

TNF blocking agents do not significantly influence the development of protective antibodies after vaccination, although there is a small decrease in the prevalence of adequate protection and titre of response, especially in combination with methotrexate (Category B evidence[151 152]). Vaccination with live attenuated vaccines (eg, BCG, yellow fever) is not recommended (Category D evidence).

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 blocking agents than with placebo (Category B evidence[10 12–18 24 25 31–33 61 62 82 83 96 119]). One study indicates that human antichimeric antibodies (HACA) against infliximab was associated with decreased response and increased infusion reactions (Category C evidence[153]). Infusion reactions after infliximab and adalimumab are uncommon and are usually mild to moderate, but may, rarely, be serious (Category A evidence,[12 15 21 24 25 31 62 82 83 96 119] Category B and C evidence[18 22 63 84]).

Treatment limiting infusion reactions can be treated by the use of corticosteroids or antihistamines, or by slowing the infusion rate (Category C and B evidence [153 154]).

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[155 156]). The risk for lymphoma is increased two to fivefold in patients with RA as compared to the general population (especially non-Hodgkin's lymphoma). A similar risk is seen in RA patients who have received anti-TNF therapy (Category C evidence[120 155 157]). There are conflicting data about whether there is an increased risk for lymphoma and solid malignancies with anti-TNF therapies for RA. Several large observational databases and a case control study did not demonstrate an increased incidence of solid tumours in patients receiving TNF blocking agents compared with matched controls, while two meta-analyses of anti-TNF therapies (on infliximab and adalimumab) reported a higher rate of solid malignancies including skin cancers (Category A and C evidence[156–161]). One population-based study showed that the incidence of both melanoma and non-melanoma skin cancer were slightly increased when TNF blocking agents were used (RR: 1.4–2.0; Category C evidence[160]). In patients at risk for malignancies (for example, smokers) or in patients with chronic obstructive pulmonary disease (COPD), there may be an increased risk of lung cancers. In a trial of patients with COPD 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[162]). 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[163]). The concomitant use of azathioprine with infliximab in adolescents has been associated with the occurrence of rare hepatosplenic lymphomas (FDA). There is limited information about the risk of developing a future malignancy in patients receiving anti-TNF therapy who had a previous malignancy (Category D evidence[164]). Vigilance with respect to the occurrence of lymphomas and other malignancies, including recurrence of solid tumours, remains warranted in patients using these medications.

Haematological

Rare instances of pancytopaenia and aplastic anaemia have been reported (Category A and C evidence[18 31 33 82 119 165]). If haematological adverse events occur, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease or other causative medications (Category D evidence).

Cardiovascular

High-dose infliximab (10 mg/kg) appears to be associated with an increased relative risk of worsening congestive heart failure (CHF) and mortality, particularly in RA patients with New York Heart Association class III–IV CHF (Category B and D evidence[118 120 166 167]). There is presently no substantive evidence that infliximab 5 mg/kg, or etanercept at 25 mg twice a week increases the incidence of CHF or CHF-related mortality in patients with functional class I CHF (Category B and D evidence[118 166 167]). However, it should be noted that well-controlled RA studies have excluded patients with complicating illnesses, including CHF, and RA per se appears to be associated with increased atherosclerotic cardiovascular disease (ASCVD) and ASCVD-related mortality (Category C evidence[118]). One RA study using infliximab demonstrated an increase in total, HDL and LDL lipids (Category D evidence[168]). One cohort observational study in RA patients without overt CHF showed a possible decrease in myocardial infarction-related mortality when using TNF blocking agents (Category D evidence[3 169]). Each patient's risk versus benefit should be carefully considered before TNF blocking agents are begun or continued (Category D evidence; FDA).

Pulmonary

Rare instances of new onset interstitial lung disease have been documented in patients using infliximab both with and without baseline pulmonary findings (Category C[171] and D evidence[170 171]).

Hepatitis

The long-term safety of TNF blockers in patients with chronic viral hepatitis is not known. In Hepatitis C, observational studies and one controlled investigation revealed that etanercept did not have an effect on viral load and there was no increased incidence of adverse effects; in addition, there was evidence, in this study, that symptoms and liver function tests improved (Category C and D evidence[167 172–178]).

With respect to hepatitis B, patients treated with all three agents have experienced increased symptoms and worsening of viral load (Category C evidence,[173] Category D evidence.[177 179]). Elevations have been observed in liver function tests with therapeutic strategies employing the use of adalimumab, infliximab and etanercept with ALT-AST elevated in 3.5–4.9% and elevations of these liver enzymes >2X ULN in about 0.1–0.2%, although concomitant medications and other clinical circumstances confound the interpretation of this information (FDA; Category C evidence[18 173 175–177 180 181]). As a result, specific warnings regarding hepatitis B reactivation have been added to the US label by the FDA (FDA). Therefore TNF blockers should not be used in patients with known hepatitis B infection; in the event that hepatitis B infection is discovered during use of TNF blockers, prophylactic antiviral therapy can be employed (Category C evidence;[58 173 177 179 182] Canadian Regulatory Authorities).

The follow-up and monitoring for liver function test elevations should be governed by the patient's concomitant medications, conditions and patient-related risk factors.

Conception and pregnancy

There is insufficient information at present to safely counsel the continuation of TNF blockers during pregnancy. Some women have become pregnant while being treated with TNF blocking therapy. A small pharmacovigilance study and a survey study comprising about 200 pregnancies in women being treated with TNF blockers[187] revealed that the rates of normal live births, miscarriages and therapeutic terminations in patients taking TNF blockers did not differ from published rates for the normal population (Category D evidence[183–186 188 189]). Pre-pregnancy planning is strongly recommended in patients who are either on TNF blockers or considering their use; the need for disease control with alternate methods should be the subject of these conversations. There are no data available on the subsequent safety of a pregnancy if the male partner is taking TNF blockers.

It is advised that women and physicians discuss the issue of TNF blocking therapy when pregnancy planning takes place or if pregnancy is discovered during ongoing TNF blocking therapy, and that this discussion is documented.

Using peak concentrations as a measure, only about 0.0001% of the peak plasma concentration of etanercept is found in the breast milk (Category D evidence[190]).

Autoimmune-like syndromes

Antiphospholipid syndrome, syndromes resembling drug-induced lupus and vasculitis have occurred in patients receiving TNF blocking agents, and treatment should be stopped if there is clinical evidence of a drug-induced lupus-like syndrome. These symptoms are highly likely to resolve on discontinuation of the TNF blocking agent (Category C and D evidence[31 33 63 82 118 120 191–199]). There is an increased incidence of several autoantibodies (for example, antinuclear antibody (ANA), anti-double-stranded DNA) after infliximab and it is probably not a class effect (category C evidence[191–195 198 199]). However, there is no evidence that patients with RA who had, or develop, a positive ANA, anticardiolipin antibodies and/or dsDNA are at significantly increased risk for the development of drug-induced lupus (FDA; Category C and D evidence[18 31 82 120 191 192 196–199]).

Neurological diseases

The incidence of demyelinating-like syndromes, optic neuritis, transverse myelitis, multiple sclerosis and Parkinson's disease is no greater than expected in the general population (Category C evidence[31 82 120 165 200–202]). However, rare cases of these syndromes have been reported, more often with etanercept than with infliximab, most but not all improving or remitting after the TNF blocker was withdrawn (Category C evidence[82 120 165 200–203]). There is insufficient evidence to suggest that TNFα blockers unmask latent disease, although this remains a possibility. These agents should be stopped if a demyelinating-like disorder or optic neuritis occurs. Patients with a history of definite demyelinating disease or optic neuritis should not receive TNF blocking agents (Category D evidence).

Psoriatic skin lesions
Some cases of new-onset psoriatic skin lesions or exacerbations of pre-existing psoriasis have been reported in patients with RA who used TNF blocking agents. (Category C evidence[109]).

Issues specific to PsA
Safety and tolerability data with anti-TNF medications in PsA have not demonstrated any adverse events that were significantly different from RA trials. However, because liver biopsy studies suggest that patients with psoriasis and PsA demonstrate a greater proclivity for hepatotoxicity with MTX therapy than RA patients (Category B evidence[204]), it is not known if the safety profile from RA trials is completely comparable with PsA.

Precautionary statements
The safety of TNF blockade is unknown or has not been established in the following situations:

- HIV, and so on
- during lactation.

Other areas where knowledge is lacking are highlighted in the consensus group's recommendations for areas most urgently requiring further research.

Research
Among a number of potential areas requiring action and/or further research, the consensus group felt the following projects or directions were most important in each of three areas: registries, efficacy and toxicity.

Registry
1. Long-term registries continue to be needed to monitor the toxicity of biologicals and are strongly recommended, requiring a cooperative effort between payers, government, industry and rheumatologists.
2. Registries of pregnancy outcomes under anti-TNF therapy (and after cessation of therapy) should be continued.

Efficacy
1. What are the optimal dosing regimens when using TNF blocking agents?
2. Are there predictors of toxicity for TNF blocking agents?
3. Is there a correlation between radiological effect and long-term effectiveness for TNF blocking agents?
4. What are the outcomes in patients treated with TNF blocking agents where disease activity persists without joint destruction and where joint destruction is observed with little disease activity?
5. Can biologicals be administered at lower than currently used doses and/or at dosing intervals longer than currently employed to slow or halt radiographic progression of RA in the absence of an ACR 20 response?
6. What is the effect of TNF blocking agents on growth in children with juvenile chronic arthritis?
7. What, if any, dose response exists for the use of TNF blocking agents in PsA and/or AS?
8. Do AS patients with advanced spinal fusion respond to TNF blocking agents?
9. Do TNF blocking agents decrease the incidence of cardiovascular events or cerebrovascular incidents?
10. What are the predictors of response to TNF blocking agents in early and advanced AS?
11. Can TNF blocking agents be discontinued after an initial response?

Safety
1. Can TNF blocking agents be used safely in pregnant women?
2. What is the safety profile of TNF blocking agents during surgery? How does it compare with the safety profile of patients undergoing surgery without concomitant TNF blocker use?
3. What duration of tuberculosis prophylaxis/treatment is necessary when patients are being treated with TNF blocking agents?
4. Can TNF blocking agents be used in patients with a history of lymphoma and non-Hodgkin lymphoma or solid tumours? What is the time interval needed before TNFα blockers can be used after patients with malignancies have reached a full remission?
5. What is the sensitivity and specificity of the quantiferon test compared with the purified protein derivative (PPD) in RA patients?

Summary
TNF blocking agents have proved to be effective DMARDs and are a major advance in the treatment of RA, PsA, AS and juvenile idiopathic arthritis. Their use is expanding to other rheumatic diseases. Studies in selected areas of efficacy, toxicity and general use of TNF blocking agents are needed to help further define the most appropriate use of these agents. Further considerations when using TNF blocking agents in these diseases should balance efficacy, toxicity and cost issues, and recognise that data in subpopulations are still being acquired. 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 RA.

IL1 BLOCKING AGENTS
Only one IL1 blocking agent (anakinra) has been approved and the discussion below refers to this agent.

Indications
Anakinra may be used for treatment of active RA, alone or with MTX, at a dose of 100 mg per day subcutaneously (Category A evidence[205–210]). In Europe, the anakinra label requires its use with methotrexate. Anakinra is recommended for the treatment of active RA after an adequate trial of another conventional DMARD, of which MTX is a common example (Category D evidence). The safety of anakinra has also been studied with other DMARDs (Category A evidence[207 208]).

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

Anakinra has been investigated in two open-label studies in AS with no clear efficacy (see section on IL1 receptor blockade).[211 212]

Anakinra has been studied for a variety of off-label indications (see Appendix 2). It appears to be highly active in the auto-inflammatory syndromes (also called ''periodic fever syndromes''), such as Muckle–Wells syndrome, neonatal-onset multisystem inflammatory disease (NOMID) and TNF receptor-associated periodic syndrome (TRAPS). It also appears to be active in systemic-onset juvenile arthritis and adult-onset Still's disease. It has been used to treat osteoarthritis (Category D evidence[213 214]) and SLE (Category D evidence[215 216]).

Clinical use
Anakinra can lead to significant improvement in symptoms, signs and/or laboratory parameters within 16 weeks, and can

slow the rate of radiographic progression (Category A evidence[205 206 209]). If improvement is not observed by 16 weeks, the continued use of anakinra should be re-evaluated.

Trials of patients failing TNF blocking agents demonstrate mixed responses (Category C evidence[210]). Anakinra did not inhibit anti-tetanus antibody response in a controlled trial (Category A evidence[217]). A dose-related incidence of injection site reactions, affecting up to 70% of patients, has occurred with the use of anakinra. These reactions often do not require treatment and seem to moderate with continued use in some patients (Category A evidence[205–207]). There are no data to advise either termination or continuation of anakinra if a woman becomes pregnant.

Warnings

Serious infections are increased in patients receiving anakinra, and its incidence is higher than in patients with RA using other DMARDs. This increased incidence was magnified by corticosteroid use (Category A evidence[208]). Anakinra should not be started or should be discontinued when serious infections occur (Category A evidence,[12 36 61 96] Category D evidence[34]). Treatment with anakinra in such patients should only be resumed if the infection(s) has been adequately treated (Category D evidence). To date, there is no indication that anakinra is associated with an increased incidence of TB (Category D evidence).

In combination with etanercept, there was an increased rate of serious infections compared to either monotherapy, and no increase in efficacy. Therefore, the combination should not be used (Category A evidence[150]).

Precautionary statements

The safety of anakinra is unknown or has not been established in the following situations:

- lymphoma, lymphoproliferative and other malignancies
- during pregnancy and/or lactation.

Other areas where knowledge is lacking are highlighted in the consensus group's recommendations for areas most urgently requiring further research.

Research

Among a number of potential areas requiring action and/or further research, the consensus group felt the following projects or directions were most important in each of three areas: registries, efficacy and toxicity.

Registry

1. Long-term registries to monitor the toxicity of biologicals are recommended, requiring a cooperative effort between payers, government, industry and rheumatologists.
2. Registries of pregnancy outcomes under anakinra blocking therapy (and after cessation of therapy) should be continued.

Efficacy

1. What is the efficacy of anakinra in polyarticular juvenile arthritis, systemic-onset juvenile and other rheumatic diseases including osteoarthritis?

Toxicity

1. Can anakinra be used in patients who cannot be treated with TNF blocking agents because they have a history of TB or latent TB and cannot tolerate appropriate therapy for the latter, for some reason?

Summary

Anakinra is effective for the treatment of rheumatoid arthritis but its specific place (for example, before or after TNF blocking agents) in the rheumatological armamentarium is not yet defined. Publication of studies in selected areas of efficacy, toxicity and general use of anakinra is needed to help further define the most appropriate use of these agents. Further considerations when using anakinra in this disease must include cost issues and the recognition that data in subpopulations are still being acquired. It is hoped that this statement, which is based on the best evidence available at the time of its creation and is modified by expert opinion, will facilitate the optimal use of anakinra for patients with RA.

ABATACEPT

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

Indications

Abatacept is approved in North America for use alone or with background DMARDs for treatment of active RA. It is administered as intravenous infusions of up to 10 mg/kg (500 mg for weights less than 60 kg; 750 mg for weights of 60–100 kg and 1000 mg for weights over 100 kg) at 0, 2, 4 weeks then monthly (FDA product label[218 219]). However, it is not recommended for use with other biologicals (although there are no data regarding the use of rituximab in combination with abatacept). Abatacept is recommended for treatment of active RA after an adequate trial of MTX, another effective DMARD or TNFα blocking agent (Category A evidence[218–222]).

Abatacept may be substituted directly for the next dose of a TNF blocking agent, when switching is undertaken (Category C evidence[223]). Abatacept has been used with MTX and other DMARDs (Category A evidence[149]). (Pharmacoeconomics studies are being carried out (Category D evidence).)

Clinical use

Abatacept is indicated to decrease signs and symptoms (including major clinical response), slow and/or inhibit progression of structural damage and improve physical function in adult patients with moderate to severely active RA who have had an inadequate response to one or more DMARDs such as MTX or TNF blocking agents (Category A evidence,[218 219 223] FDA label). Improvement occurs within 16 weeks, although additional improvement can occur for up to 2 years (Category D evidence).[224 225] If clinical improvement occurs, treatment should be continued (Category D evidence);where no meaningful improvement occurs within 12–16 weeks the continued use of abatacept should be re-evaluated.

Abatacept in combination with MTX inhibits ra**di**ographic progression in RA (category A evidence[149 219 224]). A study of abatacept for psoriasis vulgaris showed efficacy (Category C evidence[226]).

There is evidence for efficacy in juvenile idiopathic arthritis (Category C evidence[227]). Studies in early RA, undifferentiated arthritis and systemic lupus erythematosus are ongoing (Category D evidence).

Warnings

An increased incidence of serious infection has been observed when comparing abatacept to placebo (3.0% with abatacept vs 1.9% with placebo). In combination with other biological agents, the rate of serious infections is 4.4% (vs 1.5% in controls).[228] The use of abatacept with other biologicals is not

recommended (Category A evidence[221 228]). There are no data regarding the combination of abatacept and rituximab. Patients with COPD treated with abatacept had more adverse events than patients treated with placebo; therefore use in RA patients with COPD should be undertaken with caution (Category D evidence[149]).

Based on theoretical concerns, live vaccines should not be given with abatacept or within 3 months of using abatacept (Category D evidence).

A numerical imbalance was reported in the number of lung cancers observed in the placebo-controlled trials (4 abatacept, 0 controls). An additional nine cases were reported during open-label extension studies (cumulatively 13 cases/4134 patient years). The overall incidence of lung cancer in abatacept-treated patients during these studies was not higher than expected, based on large RA cohorts, although it was higher than in the general population.

There has been one case of lymphoma occurring in double-blind period with abatacept versus 0 in the placebo group and four additional cases in the open-label extension (cumulatively 5/4134 patient years) (Category B evidence[229]). While this number is consistent with that expected from large RA cohorts, ongoing surveillance is necessary.

All patients in abatacept phase 3 trials were screened for TB and excluded if the screen was positive. The risk for activation of latent TB or for developing new TB when using abatacept is unknown. Until the risk is known, it is prudent to screen patients considered for abatacept therapy for TB according to local practice (Category D evidence).

Precautionary statements

The safety of abatacept is unknown or has not been established in the following situations:

- viral infections, including HIV, hepatitis B and C
- during pregnancy and/or lactation.

Other areas where knowledge is lacking are highlighted in the consensus group's recommendations for areas most urgently requiring further research.

Research

Among a number of potential areas requiring action and/or further research, the following projects or directions are important in each of three areas: registries, efficacy and toxicity:

Registry

1. As per anti-TNF agents.

Efficacy

1. What is the efficacy of abatacept in polyarticular juvenile arthritis, early arthritis, systemic lupus undifferentiated early arthritis and other rheumatic diseases?
2. Rituximab versus abatacept in TNF failures.

Toxicity

1. Can abatacept be used in patients who cannot be treated with TNF blocking agents because of CHF, demyelinating diseases, serious infections or tuberculosis?

RITUXIMAB

Rituximab is a chimeric anti-CD20 monoclonal antibody, which was approved in 1997 for treatment of indolent CD20, B cell non-Hodgkin's lymphoma. More than 1 000 000 patient exposures (usually four infusions per patient) have been documented over 9 years in post-marketing surveillance of these non-rheumatic diseases. Recently, a consensus statement on the use of rituximab in patients with RA (Category D evidence[248]) has been published.

Indications

Rituximab has been approved by the FDA in the USA for the treatment of moderate-to-severe RA in patients who have had an inadequate response to TNF inhibitors (Category A and D evidence;[230–232] FDA and European Medicines Agency label; Category C and D evidence[233–239]). Patients should have at least moderate disease activity despite MTX therapy. Rituximab is administered intravenously as two 1 g rituximab infusions (given with 100 mg methylprednisolone or equivalent) separated by an interval of 2 weeks; two 500 mg doses can also be used with little decrease in efficacy (Category A evidence[233–240]). It may also be used when TNF inhibitors are not suitable (Category D evidence[232 241 242]). In RA, it may be used alone or in combination with MTX (Category A and D evidence[230–232 241–244]). Appropriate supportive equipment should be available when rituximab is used in case of rare anaphylactoid reactions.

Current evidence on the efficacy of rituximab relates to rheumatoid factor (RF) positive patients (Category D evidence[233 234]). Divergent ACR responses were seen with rituximab in RF-negative patients, in TNF non-responders and in DMARD non-responders (Category D evidence[233–235]). Patients who were both RF and anti-CCP negative had a reduced response in TNF non-responders (Category D evidence[242 244]). Since small numbers of RF-negative patients were evaluated, the role of RF and anti-CCP antibodies is not clear.

Clinical use

In clinical trials, rituximab results in significant improvement in signs and symptoms and/or laboratory measures by 8–16 weeks (Category D evidence[230–238 241–244]) in patients with an inadequate response to MTX who have failed conventional DMARDS or have one or more TNF inhibitors (Category A evidence[240 245]). Improvement has also been demonstrated in patient-related outcomes such as HAQ-DI, patient global VAS, fatigue, disability and quality of life. Evidence from randomised controlled trials show that the combination of rituximab with MTX yields superior clinical efficacy for RA when compared with monotherapy (Category A evidence[233–235 240 245]). The optimal treatment schedule is currently under investigation (Category D evidence[230 233–235 242 244]). Preliminary data have shown that repeat treatment courses are effective in previously responsive RA patients (Category D evidence;[236] FDA). Most of the patients who received subsequent courses did so after 24 weeks after the previous course and none received repeated courses earlier than 16 weeks from the previous course (Category D evidence;[236] FDA). No data are available on repeated treatment in patients who failed to respond to the initial course.

There are data indicating that rituximab can slow radiographic progression in patients who have had an inadequate response to one or more TNF inhibitors (Category D evidence[234]).

Rituximab has been used in primary Sjögren's syndrome, systemic lupus erythematosus, Wegener's granulomatosis, hepatitis C-associated cryoglobulinaemia, antineutrophilic cytoplasmic antibodies (ANCA), associated vasculitis disorders other than Wegener's such as polyarteritis nodosa, dermatomyositis/polymyositis (Category C evidence),

autoimmune haemolytic anaemia, idiopathic thrombocytopenia purpura, antiphospholipid syndrome and scleroderma (see Appendix 3).

Warnings

The most frequent adverse events are infusion reactions, which are most common with the first infusion of each course (approximately 35%) and are reduced with the second infusion (approximately 10%). Intravenous corticosteroids were shown to reduce the incidence and severity of infusion reactions by about 30% without changing efficacy (Category A, C and D evidence[230 231 233–235 240–242 244]).

Recently, two cases of progressive multifocal leukoencephalopathy (PML) have been communicated in cases of patients with severe SLE who had received an extensive additional immunosuppressive therapy. Twenty-three cases of PML in SLE cases not using rituximab have also been documented. Twenty-seven cases of PML are known in the NHL literature. It is unclear whether this incidence reflects the overall PML occurrence in these heavily immunocompromised individuals. As of today, no case of PML has been reported in RA (FDA reports).

Serious infections, including bacterial infections, have been observed in patients receiving rituximab. Similar to the anti-TNF agents and the other biologicals, a small increase in serious infections (not intracellular infections) in patients receiving rituximab 2×1000 mg compared to placebo has occurred: 4.7/100 versus 3.2/100 patient years in the DANCER study and 5.2/100 versus 3.7/100 patient years in the REFLEX trial (Category D evidence[230 233–235 239 241]).

Rituximab should not be given in the presence of serious or opportunistic infections (Category D evidence).

In general, patients who did not respond to TNF inhibitors will also have been pre-screened for the presence of active or latent TB. In the RA clinical trials of rituximab in TNF inhibitor non-responders, patients with active TB were excluded. Others were screened by chest *x* ray, but were not screened for latent TB by PPD testing. Moreover, there is no evidence of an increased frequency of TB in patients with lymphoma treated with rituximab (Category D evidence). Based on expert opinion, it is felt that at this time there is no evidence indicating the necessity to screen for TB prior to initiating rituximab in RA (Category D evidence).

Since decreased levels of immunoglobulin (Ig) M, A and G have been observed with rituximab, it may be useful to determine baseline Ig levels (Category D evidence,[231 237 241 244]). In clinical trials no increase in serious infections have been reported in the very few patients with reduced levels of IgM after rituximab therapy compared to their normal IgM levels previously (Category D evidence[237 244]). Further analyses are required to address this issue. B cell levels have been measured in clinical trials but their utilisation in routine practice has not been proven. Depletion of peripheral levels of the CD20+ B cell subpopulation was not found to be predictive of achieving or maintaining a clinical response in RA patients (Category D evidence[238]). This suggests that the timing of retreatment should be based on disease activity rather than repletion of peripheral B cell levels (Category D evidence).

The safety of TNF inhibitor use in patients (n = 78) who did not respond to rituximab and who had B cell levels below normal demonstrated a numerical increase in serious infections (Category D evidence[239]). Further data are needed to address this important issue.

Since rituximab causes B cell depletion, it is recommended that any vaccinations required by the patient, such as those to prevent pneumonia and influenza, should be given before commencing this agent. While on therapy, appropriate vaccination (such as against influenza) should be given when indicated, although the success may be suboptimal.

Until further data are available, the use of live attenuated vaccines should only be given prior to the use of rituximab (Category D evidence).

Patients should be screened for hepatitis B and C before starting rituximab as hepatitis B reactivation has been reported in oncological practice (Category D evidence[246]).

Until further data are available, rituximab should not be used during pregnancy.

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

Research

The consensus group felt the following projects or directions were most important in each of three areas: registry, efficacy and toxicity.

Registry

1. As per anti-TNF agents.

Efficacy

1. What is the minimal effective dose of rituximab?
2. What is the optimal strategy in using rituximab including timing, repeat dosing and combination with other drugs?
3. Are there predictors of treatment response?
4. What is the long-term efficacy of repeat dosing?
5. What are the cost-effectiveness and ethical issues when treating patients with rituximab?
6. What are the mechanisms underlying the efficacy of rituximab?
7. Is induction therapy with rituximab possible with subsequent withdrawal or dose reduction?
8. What is the role of rituximab in the treatment of other rheumatoid diseases (for example, systemic lupus erythematosus, scleroderma, myositis, Sjögren's syndrome, vasculitis, psoriatic arthritis and AS)?

Safety

1. What are the safety issues associated with long-term B cell depletion and lowered Ig levels?
2. What is the safety profile with respect to immunoglobulin reduction vis-a-vis infection and response to vaccination?
3. Does rituximab increase the frequency of TB and opportunistic infection?
4. Can TNF blocking agents and other immunomodulators be used safely in patients with B cell depletion who are unresponsive to rituximab?
5. What are the optimal strategies including vaccination to lower the risk of infection during treatment with rituximab?
6. Can rituximab be used safely in pregnant and lactating women?
7. Will long-term use of rituximab result in secondary loss of effect?
8. Will long-term use of rituximab substantially reduce the incidence of B cell lymphoproliferative disorders?
9. Can rituximab be used in patients with remote or current solid malignancies?
10. Can rituximab be used safely in hepatitis C?

Authors' affiliations

D E Furst, David Geffen School of Medicine, Los Angeles, California, USA
F C Breedveld, Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands
J R Kalden, Department of Internal Medicine III, Institut for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany
J S Smolen, Institute of Rheumatology, Clinic for Internal Medicine III, Vienna General Hospital, Vienna, Austria
G R Burmester, Department of Rheumatology, and Clinical Immunology, Charité Hospital, Berlin, Germany
J Sieper, University Clinic Benjamin Franklin, Germany
P Emery, Leeds University, Department of Rheumatology, Leeds General Infirmary, Leeds, UK
E C Keystone, Department of Rheumatology, Mount Sinai Hospitial, Toronto, Canada
M H Schiff, Denver Arthritis Clinic, Denver, Colorado, USA
P Mease, Seattle Rhumatology Associates, Seattle, Washington 98104, USA
P L C M van Riel, University Nijmegen Medical Centre, Nijmegen, The Netherlands
R Fleischmann, University of Texas Southwestern Medical Center, Dallas, Texas USA
M H Weisman, Cedar Sinai Hospital, Los Angeles, California, USA
M E Weinblatt, Brigham and Women's Hospital, Boston, Massachusetts, USA

Correspondence to: D E Furst, David Geffen School of Medicine, UCLA – RM 32-59, 1000 Veteran Avenue, Los Angeles, CA 90025, USA; defurst@mednet.ucla.edu

REFERENCES

1 **Furst DE**, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Bijlsma JW, *et al.* Updated consensus statement on biological agents for the treatment of rheumatic diseases. *Ann Rheum Dis* 2004;**65**(Suppl 2):ii2–15.
2 **Shekelle PG**, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999;**318**:593–6.
3 **Wolfe F**, Pincus T, O'Dell J. Evaluation and documentation of rheumatoid arthritis disease status in the clinic: which variables best predict change in therapy. *J Rheumatol* 2001;**28**:1712–7.
4 **Smolen JS**, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, *et al.* A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)* 2003;**42**:244–57.
5 **Gladman DD**, Helliwell P, Mease PJ, Nash P, Ritchlin C, Taylor W. Assessment of patients with psoriatic arthritis: a review of currently available measures. *Arthritis Rheum* 2004;**50**:24–35.
6 **Brandt J**, Khariouzov A, Listing J, Haibel H, Sorensen H, Grassnickel L, *et al.* Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003;**48**:1667–75.
7 **Braun J**, Brandt J, Listing J, Zink A, Alten R, Golder W, *et al.* Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002;**359**:1187–93.
8 **Davis Jr JC**, Van Der HD, Braun J, Dougados M, Cush J, Clegg DO, *et al.* Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;**48**:3230–6.
9 **Gorman JD**, Sack KE, Davis Jr JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002;**346**:1349–56.
10 **Van Den BF**, Kruithof E, Baeten D, Herssens A, de KF, Mielants H, *et al.* Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. *Arthritis Rheum* 2002;**46**:755–65.
11 **Agarwal SK**, Maier AL, Chibnik LB, Coblyn JS, Fossel A, Lee R, *et al.* Pattern of infliximab utilization in rheumatoid arthritis patients at an academic medical center. *Arthritis Rheum* 2005;**53**:872–8.
12 **Bang LM**, Keating GM. Adalimumab: a review of its use in rheumatoid arthritis. *BioDrugs* 2004;**18**:121–39.
13 **Breedveld FC**, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, *et al.* Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis* 2004;**63**:149–55.
14 **Breedveld FC**, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van VR, *et al.* The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;**54**:26–37.
15 **Culy CR**, Keating GM. Etanercept: an updated review of its use in rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis. *Drugs* 2002;**62**:2493–537.
16 **Elliott MJ**, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, *et al.* Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum* 1993;**36**:1681–90.
17 **Elliott MJ**, Maini RN, Feldmann M, Long-Fox A, Charles P, Bijl H, *et al.* Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. *Lancet* 1994;**344**:1125–7.
18 **Fleischmann RM**, Iqbal I, Stern RL. Considerations with the use of biological therapy in the treatment of rheumatoid arthritis. *Expert Opin Drug Saf* 2004;**3**:391–403.
19 **Furst DE**, Keystone E, Maini RN, Smolen JS. Recapitulation of the round-table discussion: assessing the role of anti-tumour necrosis factor therapy in the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 1999;**38**(Suppl 2):50–3.
20 **Furst DE**, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, *et al.* Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003;**30**:2563–71.
21 **Genovese MC**, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, *et al.* Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;**46**:1443–50.
22 **Harriman G**, Harper LK, Schaible TF. Summary of clinical trials in rheumatoid arthritis using infliximab, an anti-TNFalpha treatment. *Ann Rheum Dis* 1999;**58**(Suppl 1):I61–4.
23 **Hyrich KL**, Symmons DP, Watson KD, Silman AJ. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006;**54**:1786–94.
24 **Jones RE**, Moreland LW. Tumor necrosis factor inhibitors for rheumatoid arthritis. *Bull Rheum Dis* 1999;**48**:1–4.
25 **Kavanaugh AF**. Anti-tumor necrosis factor-alpha monoclonal antibody therapy for rheumatoid arthritis. *Rheum Dis Clin North Am* 1998;**24**:593–614.
26 **Keystone EC**, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, *et al.* Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;**50**:1400–11.
27 **Klareskog L**, Van Der HD, de Jager JP, Gough A, Kalden J, Malaise M, *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;**363**:675–81.
28 **Maini RN**, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;**41**:1552–63.
29 **Mariette X**, Malalse MG, Rainer F, *et al.* Adalimumab (Humira) is effective and safe with different traditional concomitant DMARDS in treating rheumatoid arthritis in real-life clinical practice: a full-set analysis of the REACT trial. *ARD* 2006;**65**(Suppl 11):FR10144.
30 **Mariette X**. ReAct Trial. *Ann Rheum Dis* 2007;**64**:1382.
31 **Markham A**, Lamb HM. Infliximab: a review of its use in the management of rheumatoid arthritis. *Drugs* 2000;**59**:1341–59.
32 **Pavelka K**. Adalimumab in the treatment of rheumatoid arthritis. *Aging Health* 2006;**2**:533–45.
33 **Scheinfeld N**. Adalimumab (HUMIRA): a review. *J Drugs Dermatol* 2003;**2**:375–7.
34 **Smolen JS**, Han C, Bala M, Maini RN, Kalden JR, Van Der HD, *et al.* Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005;**52**:1020–30.
35 **St Clair EW**, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, *et al.* Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;**50**:3432–43.
36 **van de Putte LB**, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, *et al.* Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004;**63**:508–16.
37 **Weaver AL**, Lautzenheiser RL, Schiff MH, Gibofsky A, Perruquet JL, Luetkemeyer J, *et al.* Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. *Curr Med Res Opin* 2006;**22**:185–98.
38 **van der Heijde D**, Kivitz A, Schiff MH, *et al.* Treatment with adalimumab reduces signs and symptoms and induces partial remission in patients with Ankylosing Spodylitis: 1 year results from ATLAS. *Arthritis & Rheumatism* 2006;**54**(Suppl):s792 (abs 2017).
39 **van Vollenhoven R**, Cullinane Carli C, Bratt J, *et al.* Patients treated with TNFA antagonists increase their participation in the work-force: potential for significant long-term indirect cost gains. EULAR SAT02200. 2006.
40 **Mease PJ**, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, *et al.* Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;**52**:3279–89.
41 **Mease PJ**, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, *et al.* Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;**50**:2264–72.
42 **Mease PJ**, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000;**356**:385–90.
43 **Mease PJ**, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, *et al.* Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006;**33**:712–21.
44 **Kavanaugh A**, Antoni C, Mease P, Gladman D, Yan S, Bala M, *et al.* Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis. *J Rheumatol* 2006;**33**:2254–9.

45 **Antoni C**, Krueger GG, de VK, Birbara C, Beutler A, Guzzo C, *et al.* Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005;**64**:1150–7.
46 **Kavanaugh A**, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, *et al.* Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Ann Rheum Dis* 2007;**66**:498–505.
47 **Gladman DD**, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, *et al.* Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum* 2007;**56**:476–88.
48 **Heiberg MS**, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinckel P, *et al.* The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6-month results from a longitudinal, observational, multicenter study. *Ann Rheum Dis* 2007;**66**:1038–42.
49 **Sattar N**, Crompton P, Cherry L, Kane D, Lowe G, McInnes IB. Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum* 2007;**56**:831–9.
50 **Kimball AB**, Jackson JM, Sobell JM, Boh EE, Grekin S, Pharmd EB, *et al.* Reductions in healthcare resource utilization in psoriatic arthritis patients receiving etanercept therapy: results from the educate trial. *J Drugs Dermatol* 2007;**6**:299–306.
51 **Baeten D**, Kruithof E, Van Den BF, Van den BN, Herssens A, Mielants H, *et al.* Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? *Ann Rheum Dis* 2003;**62**:829–34.
52 **Brandt J**, Haibel H, Reddig J, *et al.* Anti-TNF alpha treatment of patients with severe anklyosing spondylitis: a one year follow-up. *Arthritis Rheum* 2000;**44**(Suppl):S403.
53 **Brandt J**, Kavenaugh AF, Listing J, *et al.* Six months results of a German double-blind placebo controlled Phase III clinical trial in active ankylosing spondylitis. *Arthritis Rheum* 2004;**46**:S429.
54 **Braun J**, Pham T, Sieper J, Davis J, van der LS, Dougados M, Van Der HD. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003;**62**:817–24.
55 **Braun J**, Brandt J, Listing J, Zink A, Alten R, Burmester G, *et al.* Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. *Ann Rheum Dis* 2005;**64**:229–34.
56 **Schiff M**, Kavanaugh A, Weisman M, Segurado O. Safety and efficacy of more than 4 years of adalimumab therapy in rheumatoid arthritis. Annual Meeting of the American Academy of Dermatology, New Orleans. 18 February 2005.
57 **Haibel H**, Rudwaleit M, Brandt HC, Grozdanovic Z, Listing J, Kupper H, *et al.* Adalimumab reduces spinal symptoms in active ankylosing spondylitis: clinical and magnetic resonance imaging results of a fifty-two-week open-label trial. *Arthritis Rheum* 2006;**54**:678–81.
58 **Schiff MH**, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB, *et al.* Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;**65**:889–94.
59 **Bansback N**, Booner A, Marra C, *et al.* A review of economic evaluations in ankylosing spondylitis: considerations and proposal for an omeract reference case. *EULAR THU0528* 2006.
60 **Cummins C**, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. *Health Technol Assess* 2002:1–43.
61 **Lovell DJ**, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, *et al.* Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;**342**:763–9.
62 **Lovell DJ**, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, *et al.* Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 2003;**48**:218–26.
63 **Baert F**, Noman M, Vermeire S, Van AG, D' HG, Carbonez A, *et al.* Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;**348**:601–8.
64 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
65 **Sandborn W**, Rachmilewitz D, Hanauer S, *et al.* Infliximab induction and maintenance therapy for ulcerative colitis: the Act 2 Trial. *AGA Abstracts* 2007;**688**:A104.
66 **Rutgeerts P**, Feagan BG, Olsen A, *et al.* A randomized placebo-controlled trial of infliximab therapy for active ulcerative coiltis: Act 1 Trial. *AGA Abstracts* 2007;**689**:A105.
67 **Sfikakis PP**, Markomichelakis NN, Alpsoy E, Assaad-Khalil S, Bodaghi B, Gul A, *et al.* Anti-TNF therapy in the management of Behcet's disease: review and basis for recommendations. *Rheumatology (Oxford)* 2007;**46**:736–41.
68 **Zein NN**. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol* 2005;**42**:315–22.
69 **Brooklyn TN**, Dunnill MG, Shetty A, Bowden JJ, Williams JD, Griffiths CE, *et al.* Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut* 2006;**55**:505–9.
70 **Kavaru M**, duBois RM, Costabel U, *et al.* Chest x-ray assessment using a detailed scoring method in a randomized trail of infliximab in subjects with chronic pulmonary sarcoidosis. *Chest* 2007;**128(4)**:203s.
71 **Mariette X**, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, *et al.* Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). *Arthritis Rheum* 2004;**50**:1270–6.
72 **Sankar V**, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, *et al.* Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. *Arthritis Rheum* 2004;**50**:2240–5.
73 **Steinfeld SD**, Demols P, Salmon I, Kiss R, Appelboom T. Infliximab in patients with primary Sjogren's syndrome: a pilot study. *Arthritis Rheum* 2001;**44**:2371–5.
74 **Steinfeld SD**, Demols P, Salmon I, Kiss R, Appelboom T. Infliximab in patients with primary Sjogren's syndrome: a pilot study. *Arthritis Rheum* 2001;**44**:2371–5.
75 **Cohen S**, Shoup A, Weisman MH, Harris J. Etanercept treatment for autoimmune inner ear disease: results of a pilot placebo-controlled study. *Otol Neurotol* 2005;**26**:903–7.
76 **van der Vaart H**, Koeter GH, Postma DS, Kauffman HF, ten Hacken NH. First study of infliximab treatment in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;**172**:465–9.
77 **Karppien J**, Korhonen T, Paimela L, *et al.* The efficacy of infliximab for disc herniation-induced sciatica. A 1-year follow-up of first 2, a randomised controlled trial. *OASIS* 2007;**159**:1383.
78 **Hoffman GS**, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, *et al.* Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007;**146**:621–30.
79 **Salvarani C**, Macchioni P, Manzini C, Paolazzi G, Trotta A, Manganelli P, *et al.* Infliximab plus prednisone or placebo plusprednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. *Ann Intern Med* 2007;**146**:631–9.
80 **Bathon JM**, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, *et al.* A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;**343**:1586–93.
81 **Combe B**, C. C.F.U.e.a. Double-blind comparison of etanercept and sulphasalazine alone and combined in patients with active RA. *Arthritis Rheum* 2007;**46**(Suppl):S519.
82 **Jarvis B**, Faulds D. Etanercept: a review of its use in rheumatoid arthritis. *Drugs* 1999;**57**:945–66.
83 **Moreland LW**, Margolies G, Heck Jr LW, Saway A, Blosch C, Hanna R, *et al.* Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. *J Rheumatol* 1996;**23**:1849–55.
84 **Burmester GR**, van de Putte LB, Rau P, *et al.* Long term efficacy and safety of adalimumab monotherapy in patients with DMARD-refractory RA: results from a two year study. *Arthritis Rheum* 2002;**46**(Suppl):S537.
85 **Cohen G**, Courvoisier N, Cohen JD, Zaltni S, Sany J, Combe B. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005;**23**:795–800.
86 **Guis S**, Balfour I, Bowyer SL, *et al.* 308 A/G polymorphism in the tumor necrosis factor alpha gene influences outcome of etanercept treatment in rheumatoid arthritis (RA). *OASIS* 2007.
87 **Van der Laken CJ**, Vujevich J, de Jager JP, *et al.* Imaging and serum analysis of complex formation of radiolabeled infliximab and anti-infliximab in responders and non-responders to treatment of rheumatoid arthritis. *OASIS* 2007.
88 **Buch MH**, Seto Y, Bingham SJ, Bejarano V, Bryer D, White J, *et al.* C-reactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: defining subtypes of nonresponse and subsequent response to etanercept. *Arthritis Rheum* 2005;**52**:42–8.
89 **Furst DE**, *et al.* PULSE study. [accepted abstract] ACR/ARHP Annual Scientific Meeting, Boston MA. 2007.
90 **Furst DE**, *et al.* PULSE study. [accepted abstract] ACR/ARHP Annual Scientific Meeting, Boston MA. 2007.
91 **Johnson AK**, Schiff MH, Mease PJ, *et al.* Comparison of 2 Doses of Etanercept (50 vs 100 mg) in Active RA: A Randomized Double Blind Study. *J Rheumatol* 2006;**33**:659–64.
92 **van Vollenhoven RF**, Brannemark S, Klareskog L. Dose escalation of infliximab in clinical practice: improvements seen may be explained by a regression-like effect. *Ann Rheum Dis* 2004;**63**:426–30.
93 **Keystone E**, Kavanaugh AF, Sharp JT, *et al.* Adalimumab, a fully human anti-TNF-alpha monoclonal antibody, inhibits the progression of structural joint damage in patients with active RA despite concomitant methotrexate therapy. *Arthritis Rheum* 2002;**46**(Suppl):S205.
94 **Hochberg MC**, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2003;**62**(Suppl 2):ii13–6.
95 **Maksymowych WP**, Mallon C, Spady B, Peerani R. Alberta Capital Health region studies in rheumatoid arthritis prospective observational inception cohort: efficacy, adverse events and withdrawal. *Arthritis Rheum* 2001;**44**(Suppl):S82.
96 **Lipsky PE**, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;**343**:1594–602.
97 **Quinn MA**, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, *et al.* Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;**52**:27–35.
98 **Genovese MC**, Mease P, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, *et al.* Safety and efficacy of adalimumab in the treatment of patients with Psoriatic Arthritis who had failed disease-modifying antirheumatic drug therapy. *J Rheumatol* 2007;**34**:1040–50.
99 **Boehncke WH**, Prinz J, Gottlieb AB. Biologic therapies for psoriasis. A systematic review. *J Rheumatol* 2006;**33**:1447–51.

100 **Cassell S**, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. *J Rheumatol* 2006;**33**:1452–6.
101 **Gladman DD**, Mease PJ. Towards international guidelines for the management of psoriatic arthritis. *J Rheumatol* 2006;**33**:1228–30.
102 **Cauza E**, Spak M, Cauza K, Hanusch-Enserer U, Dunky A, Wagner E. Treatment of psoriatic arthritis and psoriasis vulgaris with the tumor necrosis factor inhibitor infliximab. *Rheumatol Int* 2002;**22**:227–32.
103 **Helliwell PS**. Therapies for dactylitis in psoriatic arthritis. A systematic review. *J Rheumatol* 2006;**33**:1439–41.
104 **Kavanaugh AF**, Ritchlin CT. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. *J Rheumatol* 2006;**33**:1417–21.
105 **Nash P**. Therapies for axial disease in psoriatic arthritis. A systematic review. *J Rheumatol* 2006;**33**:1431–4.
106 **Ritchlin CT**. Therapies for psoriatic enthesopathy. A systematic review. *J Rheumatol* 2006;**33**:1435–8.
107 **Soriano ER**, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. *J Rheumatol* 2006;**33**:1422–30.
108 **Strober BE**, Siu K, Menon K. Conventional systemic agents for psoriasis. A systematic review. *J Rheumatol* 2006;**33**:1442–6.
109 **de Gannes GC**, Ghoreishi M, Pope J, Russell A, Bell D, Adams S, *et al*. Psoriasis and pustular dermatitis triggered by TNF-{alpha} inhibitors in patients with rheumatologic conditions. *Arch Dermatol* 2007;**143**:223–31.
110 **Delaunay C**, Farrenq V, Marini-Portugal A, Cohen JD, Chevalier X, Claudepierre P. Infliximab to etanercept switch in patients with spondyloarthropathies and psoriatic arthritis: preliminary data. *J Rheumatol* 2005;**32**:2183–5.
111 **Gibbs A**, Gogarty M, Veale D, *et al*. Efficacy of anakinard (Kineret) in psoriatic arthritis, a clinical and immunohistological study. *Ann Rheum Dis* 2006;**65**(Suppl II):ii65–216.
112 **Papp K**, Mease P, Garovoy M, *et al*. Efalizumab in patients with psoriatic arthritis: results of a phase II randomized double-blind placebo controlled study. *J Cutan Med Surg* 2006;**11**:57–66.
113 **Mease PJ**, Gladman DD, Keystone EC. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2006;**54**:1638–45.
114 **Davis JC**, Van Der HD, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. *Arthritis Rheum* 2005;**53**:494–501.
115 **Braun J**, Davis J, Dougados M, *et al*. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006;**65**:316–20.
116 **Braun J**, Landewe R, Hermann KG, Han J, Yan S, Williamson P, *et al*. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. *Arthritis Rheum* 2006;**54**:1646–52.
117 **Rudwaleit M**, Baraliakos X, Listing J, Brandt J, Sieper J, Braun J. Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. *Ann Rheum Dis* 2005;**64**:1305–10.
118 **Hyrich KL**, Silman AJ, Watson KD, Symmons DP. Anti-tumour necrosis factor alpha therapy in rheumatoid arthritis: an update on safety. *Ann Rheum Dis* 2004;**63**:1538–43.
119 **Keystone EC**. Safety of biologic therapies: an update. *J Rheumatol* 2005;**74**(Suppl):8–12.
120 **Khanna D**, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. *Drug Saf* 2004;**27**:307–24.
121 **Bassard P**, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. *Clinical Infectious Diseases* 2006;**43**:717–22.
122 **Ruderman EM**, Markenson JA. Granulomatous infections and tumor necrosis factor antagonist therapies: update through June 2002. *Arthritis Rheum* 2003;**48**(Suppl 9).
123 **Furst DE**, Wallis R, Broder M, Beenhouwer DO. Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. *Semin Arthritis Rheum* 2006;**36**:159–67.
124 **Mohan AK**, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis* 2004;**39**:295–9.
125 **Wallis RS**, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis* 2004;**39**:1254–5.
126 **Wallis RS**, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004;**38**:1261–5.
127 **Keane J**, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, *et al*. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;**345**:1098–104.
128 **Saliu OY**, Sofer C, Stein DS, Schwander SK, Wallis RS. Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. *J Infect Dis* 2006;**194**:486–92.
129 **Centers for Disease Control and Prevention**. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha: California, 2002-2003. *MMWR Morb Mortal Wkly Rep* 2004;**53**:683–6.
130 **Carmona L**, Gomez-Reino JJ, Rodriguez-Valverde V, Montero D, Pascual-Gomez E, Mola EM, *et al*. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005;**52**:1766–72.
131 **Perez JL**, Kupper H, Spencer-Green G. Impact of screening for latent TB prior to initiating ANTI-TNF therapy in North America and Europe. [abstract] *EULAR Ann Rheum Dis* 2005. Fri OPOCB.
132 **Winthrop KL**, Siegel JN, Jereb J, Taylor Z, Iademarco MF. Tuberculosis associated with therapy against tumor necrosis factor alpha. *Arthritis Rheum* 2005;**52**:2968–74.
133 **Cummins C**, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. *Health Technol Assess* 2002;**6**:1–43.
134 **Bargstrom L**, Yocum D, Tesser J, *et al*. Coccidiomycosis (Valley Fever) occurring during infliximab therapy. *Arthritis Rheum* 2004;**46**:s169.
135 **Doran MF**, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002;**46**:2287–93.
136 **Elkayam O**, Caspi D, Reitblatt T, Charboneau D, Rubins JB. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. *Semin Arthritis Rheum* 2004;**33**:283–8.
137 **Filler SG**, Yeaman MR, Sheppard DC. Tumor necrosis factor inhibition and invasive fungal infections. *Clin Infect Dis* 2005;**41**(Suppl 3):S208–12.
138 **Garrison L**, McDonnell ND. Etanercept: therapeutic use in patients with rheumatoid arthritis. *Ann Rheum Dis* 1999;**58**(Suppl 1):I65–9.
139 **Lee JH**, Slifman NR, Gershon SK, Edwards ET, Schwieterman WD, Siegel JN, *et al*. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. *Arthritis Rheum* 2002;**46**:2565–70.
140 **Manadan AM**, Block JA, Sequeira W. Mycobacteria tuberculosis peritonitis associated with etanercept therapy. *Clin Exp Rheumatol* 2003;**21**:526.
141 **Slifman NR**, Gershon SK, Lee JH, Edwards ET, Braun MM. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. *Arthritis Rheum* 2003;**48**:319–24.
142 **Jain VV**, Evans T, Peterson MW. Reactivation histoplasmosis after treatment with anti-tumor necrosis factor alpha in a patient from a nonendemic area. *Respir Med* 2006;**100**:1291–3.
143 **Listing J**, Strangefeld A, Rau R, *et al*. Infections in RA patients treated with infliximab or etanercept. *Ann Rheum Dis* 2005;**54**:433.
144 **Salliot C**, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, *et al*. Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. *Rheumatology (Oxford)* 2007;**46**:327–34.
145 **Jacobsson LT**, Turesson C, Gulfe A, *et al*. No increase of severe infections in RA patients treated with TNF-blockers. *OASIS* 2007.
146 **Westhovens R**, Yocum D, Han J, Berman A, Strusberg I, Geusens P, Rahman MU. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum* 2006;**54**:1075–86.
147 **Dixon WG**, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006;**54**:2368–76.
148 **Wolfe F**, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006;**54**:628–34.
149 **Weinblatt M**, Combe B, White A, *et al*. Safety of abatacept in patients with active rheumatoid arthritis receiving background non-biologic DMARDs: 1 year results of the ASSURE Trial. *Ann Rheum Dis* 2005;**64**:60.
150 **Genovese MC**, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, *et al*. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004;**50**:1412–9.
151 **Kapetanovic MC**, Saxne T, Nilsson JA, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. *Rheumatology (Oxford)* 2007;**46**:608–11.
152 **Fomin I**, Caspi D, Levy V, Varsano N, Shalev Y, Paran D, *et al*. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. *Ann Rheum Dis* 2006;**65**:191–4.
153 **Lequerre T**, Vittecoq O, Klemmer N, Goeb V, Pouplin S, Menard JF, *et al*. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. *J Rheumatol* 2006;**33**:1307–14.
154 **Augustsson J**, Eksborg S, Ernestam S, Gullstrom E, van Vollenhoven RF. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis (RA). *Ann Rheum Dis*. Published Online First: 16 August 2007. doi: 10.1136/ard.2007. 070771.
155 **Baecklund E**, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* 1998;**317**:180–1.
156 **Geborek P**, Bladstrom A, Turesson C, Gulfe A, Petersson IF, Saxne T, *et al*. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis* 2005;**64**:699–703.
157 **Prior P**, Symmons DP, Hawkins CF, Scott DL, Brown R. Cancer morbidity in rheumatoid arthritis. *Ann Rheum Dis* 1984;**43**:128–31.
158 **Bongartz T**, Harle P, Friedrich S, Karrer S, Vogt T, Seitz A, *et al*. Successful treatment of psoriatic onycho-pachydermo periostitis (POPP) with adalimumab. *Arthritis Rheum* 2005;**52**:280–2.

159 **Okada SK**, Siegal JN. Anti-TNF antibody therapy in RA and risk of serious infections and malignancies. *JAMA* 2006;**296**:2201–2.
160 **Askling J**, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, *et al*. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. *Ann Rheum Dis* 2005;**64**:1421–6.
161 **Setoguchi S**, Solomon DH, Avorn J, Katz J, Weinblatt M, Glynn R, *et al*. Use of anti-TNF alpha drugs and incidence of hematologic and solid cancers in patients with rheumatoid arthritis. *Arthritis Rheum* 2005;**52**(Suppl).
162 **Rennard SI**, Fogarty C, Kelson SI, *et al*. The safety and efficancy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;**175**:926–34.
163 **Stone JH**, Holbrook JT, Marriott MA, Tibbs AK, Sejismundo LP, Min YI, *et al*. Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. *Arthritis Rheum* 2006;**54**:1608–18.
164 **Watson KD**, Dixon WG, Hyrich KL, *et al*. Influences of Anti-TNF therapy and previous malignancy on cancer incidence in patients with rheumatoid arthritis (RA): Result from the BSR biologics register. EULAR 2006 June:21–24, Amsterdam.
165 **Cush J**, Spiera R. Etanercept update on ''dear doctor'' safety letter. *Amer College of Rheum. Hotline*. Nov 2002.
166 **Anker SD**, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *Int J Cardiol* 2002;**86**:123–30.
167 **Khanna D**, McMahon M, Furst DE. Anti-tumor necrosis factor alpha therapy and heart failure: what have we learned and where do we go from here? *Arthritis Rheum* 2004;**50**:1040–50.
168 **Tam L**, Li E, Tomlinson B. Effects of infliximab treatment on insulin sensitivity and lipid profile in patients with active rheumatoid arthritis (RA). *OASIS* 2007;**879**:181.
169 **Jacobsson LT**, Turesson C, Nilsson J, *et al*. Treatment with TNF-blockers is associated with reduced premature mortality in patients with rheumatoid arthritis. EULAR 21–24 June 2006, Amsterdam 2006.
170 **Martin L**, Barr S, Green F, Fritzler M. Severe fatal complications associated with infliximab therapy in rheumatoid arthritis. *J Rheumatol* 2006;**33**:2.
171 **Ostor AJ**, Chilvers ER, Somerville MF, Lim AY, Lane SE, Crisp AJ, *et al*. Pulmonary complications of infliximab therapy in patients with rheumatoid arthritis. *J Rheumatol* 2006;**33**:622–8.
172 **Cacoub P**, Lidove O, Maisonobe T, Duhaut P, Thibault V, Ghillani P, *et al*. Interferon-alpha and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum* 2002;**46**:3317–26.
173 **Esteve M**, Saro C, Gonzalez-Huix F, Suarez F, Forne M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004;**53**:1363–5.
174 **Ince A**, Rusche W, Daud U, Ross SC, Weiss TD, Moore TL, *et al*. Etanercept in the treatment of rheumatoid arthritis patients with chronic hepatitis C infection. *Ann Rheum Dis* 2002;**61**(Supp 1):191.
175 **Khanna M**, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. *J Dermatolog Treat* 2003;**14**:229–32.
176 **Naveau S**, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, *et al*. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004;**39**:1390–7.
177 **Oniankitan O**, Duvoux C, Challine D, Mallat A, Chevalier X, Pawlotsky JM, *et al*. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol* 2004;**31**:7–109.
178 **Smith KJ**, Skelton H. Common variable immunodeficiency treated with a recombinant human IgG, tumour necrosis factor-alpha receptor fusion protein. *Br J Dermatol* 2001;**144**:597–600.
179 **Millonig G**, Kern M, Ludwiczek O, Nachbaur K, Vogel W. Subfulminant hepatitis B after infliximab in Crohn's disease: need for HBV-screening? *World J Gastroenterol* 2006;**12**:974–6.
180 **Blum E**, Katz J. Infliximab therapy and LFT abnormalities in patients with Crohn's disease. *AGA Abstracts* 2007:A659–660.
181 **Schiemann U**, Kellner H. [Gastrointestinal side effects in the therapy of rheumatologic diseases]. *Z Gastroenterol* 2002;**40**:937–43.
182 **Wendling D**, Auge B, Bettinger D, Lohse A, Le HG, Bresson-Hadni S, *et al*. Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthropathy. *Ann Rheum Dis* 2005;**64**:788–9.
183 **Roux' CH**, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. *Rheumatology (Oxford)* 2007;**46**:695–8.
184 **Vesga L**, Terdiman JP, Mahadevan U. Adalimumab use in pregnancy. *Gut* 2005;**54**:890.
185 **Katz JA**, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am J Gastroenterol* 2004;**99**:2385–92.
186 **Antoni CE**, Furst DE, Manger B, *et al*. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease or rheumatoid arthritis. *Arthritis Rheum* 2001;**44**(Suppl):S152.
187 **Chambers CD**, Johnson DL, Jones KL. Pregnancy outcome in women exposed to anti-TNF-alpha medications: The OTIS Rheumatoid Arthritis in Pregnancy Study. [abstract] ARD EULAR 2007;**66**(sup II):THUR0162.
188 **Chambers CD**, Johnson DL, Jones KL. Adalimumab and pregnancy outcome: The OTIS Autoimmune Diseases in Pregnancy Project. The OTIS Collaborative Research Group University of San Diego. *Amer Acad Derm* 2007;**56**(2):AB10.
189 **Joven BE**, Garcia-Gonzalez AJ, Ruiz T, *et al*. Pregnancy in women receiving anti-TNF-alpha therapy. Experience in Spain. *OASIS*, 2007 Pres;**884**:Poster 186.
190 **Ostensen M**. Etanercept in breast milk. Letter to the Editor. *J Rheumatol* 2004;**31**:1017–18.
191 **Allanore Y**, Sellam J, Batteux F, Job DC, Weill B, Kahan A. Induction of autoantibodies in refractory rheumatoid arthritis treated by infliximab. *Clin Exp Rheumatol* 2004;**22**:756–8.
192 **Hanauer SB**, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, *et al*. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004;**2**:542–53.
193 **Chadha T**, Hernandez JE. Infliximab-related lupus and associated valvulitis: a case report and review of the literature. *Arthritis Rheum* 2006;**55**:163–6.
194 **Pallotta P**, Cianchini G, Ruffelli M, Puddu P. Infliximab-induced lupus-like reaction in a patient with psoriatic arthritis. *Rheumatology (Oxford)* 2006;**45**:116–7.
195 **Perez-Garcia C**, Maymo J, Lisbona Perez MP, Almirall BM, Carbonell AJ. Drug-induced systemic lupus erythematosus in ankylosing spondylitis associated with infliximab. *Rheumatology (Oxford)* 2006;**45**:114–6.
196 **Bingham SJ**, Barcelos A, Buch M, *et al*. Induction of serological lupus in patients on leflunomide and infliximab. *Arthritis Rheum* 2002;**46**(Suppl):S168.
197 **Christopher L**, Wigley F. TNF-alpha antagonists induce lupus-like syndrome in patients with scleroderma and polyarthritis. *Arthritis Rheum* 2002;**46**(Suppl):S358.
198 **De RL**, Kruithof E, Van DN, Hoffman IE, Van den BN, Van Den BF, *et al*. Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. *Arthritis Rheum* 2003;**48**:1015–23.
199 **Eriksson C**, Engstrand S, Sundqvist KG, Rantapaa-Dahlqvist S. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. *Ann Rheum Dis* 2005;**64**:403–7.
200 **Mohan N**, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, *et al*. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* 2001;**44**:2862–9.
201 **Jarand J**, Zochodne DW, Martin LO, Voll C. Neurological complications of infliximab. *J Rheumatol* 2006;**33**:1018–20.
202 **Shin IS**, Baer AN, Kwon HJ, Papadopoulos EJ, Siegel JN. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. *Arthritis Rheum* **54**:1429–34.
203 **Ruppert M**, De CL, van OJ, Hubens G, Balliu L, Vaneerdeweg W. Intestinal necrosis in a patient with rheumatoid arthritis receiving anti-TNF treatment. *Acta Chir Belg* 2006;**106**:225–7.
204 **Whiting-O'Keefe QE**, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. *Am J Med* 1991;**90**:711–6.
205 **Bresnihan B**. The safety and efficacy of interleukin-1 receptor antagonist in the treatment of rheumatoid arthritis. *Semin Arthritis Rheum* 2001;**30**:17–20.
206 **Bresnihan B**, Newmark R, Robbins S, Genant HK. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. *J Rheumatol* 2004;**31**:1103–11.
207 **Fleischmann RM**, Schechtman J, Bennett R, Handel ML, Burmester GR, Tesser J, *et al*. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003;**48**:927–34.
208 **Fleischmann RM**, Tesser J, Schiff MH, Schechtman J, Burmester GR, Bennett R, *et al*. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;**65**:1006–12.
209 **Fleischmann R**, Stern R, Iqbal I. Anakinra: an inhibitor of IL-1 for the treatment of rheumatoid arthritis. *Expert Opin Biol Ther* 2004;**4**:1333–44.
210 **Schiff MH**. Lack of response to anakinra in rheumatoid arthritis following failure of tumor necrosis factor alpha blockade: comment on the article by Buch *et al*. *Arthritis Rheum* 2005;**52**:364–5.
211 **Haibel H**, Rudwaleit M, Listing J, Sieper J. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. *Ann Rheum Dis* 2005;**64**:296–8.
212 **Tan AL**, Marzo-Ortega H, O'Connor P, Fraser A, Emery P, McGonagle D. Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. *Ann Rheum Dis* 2004;**63**:1041–5.
213 **Chevalier X**, Mugnier B, Bouvenot G. [Targeted anti-cytokine therapies for osteoarthritis]. *Bull Acad Natl Med* 2006;**190**:1411–20.
214 **Chevalier X**, Giraudeau B, Conrozier T, Marliere J, Kiefer P, Goupille P. Safety study of intraarticular injection of interleukin 1 receptor antagonist in patients with painful knee osteoarthritis: a multicenter study. *J Rheumatol* 2005;**32**:1317–23.
215 **Moosig F**, Zeuner R, Renk C, Schroder J. IL-1RA in refractory systemic lupus erythematosus. *Lupus* 2004;**13**:605.
216 **Ostendorf B**, Iking-Konert C, Kurz K, Jung G, Sander O, Schneider M. Preliminary results of safety and efficacy of the interleukin 1 receptor antagonist anakinra in patients with severe lupus arthritis. *Ann Rheum Dis* 2005;**64**:630–3.
217 **Handwerger B**, Kafka S, Dhillon G, Thomson G, Dunn M, Ferbas J, *et al*. Effects of Anakinra (KINERET) on vaccine response in patients with rheumatoid arthritis. Annual Meeting of the American College of Rheumatology, San Antonio, Texas, USA, No. 1477, 16 October 2004.
218 **Genovese MC**, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, *et al*. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005;**353**:1114–23.
219 **Kremer JM**, Genant HK, Moreland LW, Russell AS, Emery P, Bud-Mendoza C, *et al*. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006;**144**:865–76.
220 **Kremer JM**, Westhovens R, Leon M, Di GE, Alten R, Steinfeld S, *et al*. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;**349**:1907–15.
221 **Kremer JM**, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, *et al*. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;**52**:2263–71.
222 **Moreland LW**, Alten R, Van Den BF, Appelboom T, Leon M, Emery P, *et al*. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding,

double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum* 2002;**46**:1470–9.
223 **Schiff M**, Pritchard C, Teng J, *et al*. The safety of Abatacept in patients with active RA and inadequate response to anti-TNF therapy: results from the ARRIVE trial. [abstract] ARD EULAR 2007:OP0212.
224 **Genovese MC**, Schiff M, Luggen M, *et al*. Sustained efficacy and safety through two years in patients with RA in the long term extension of the ATTAIN trial. *Arthritis & Rheum* 2006;**54**:s244:498.
225 **Kremer J**, Westhovens R, Russell A, *et al*. Long-term efficacy of abatecept through 2 years of treatment in rheumatoid arthritis patients in the AIM Trial. *Arthritis Rheum* 2006;**54**(Suppl 9):s247.
226 **Abrams JR**, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, *et al*. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. *J Clin Invest* 1999;**103**:1243–52.
227 **Lovell D**, Ruperto N, Prieur A, *et al*. Assessment of open label co-stimulation blockade with abatacept in children and adolescents with active juvenile idiopathic arthritis (JIA). *Arthritis Rheum* 2006;**54**(Suppl 9):s326.
228 **Moreland LW**, Combe B, Steinfeld S, *et al*. An integrated safety analysis of abatacept in the treatment of rheumatoid arthritis (RA) across patient types and background therapies. *Ann Rheum Dis Eular*, 2006;**65**(Supp 11), 110.
229 **Simon T**, Smitten A, Franklin J, *et al*. Malignancies in RA abatacept clinical development program and updated epidemiological assessment. ARD EULAR 2007 66;sup II; Fri OP0124.
230 **Emery P**, Fleischman RM, Filipowicz-Sosnowska A, *et al*. Rituximab in rheumatoid arthritis: a double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2005;**52**:1917.
231 **Emery P**, Sheeran T, Lehane PB, Saiedabadi N, Shaw TM. Efficacy and safety of rituximab at 2 years following a single treatment in patients with active rheumatoid arthritis. *Arthritis Rheum* 2004;**50**(Suppl 9):S659.
232 **Keystone EC**, Burmester GR, Furie R, Loveless JE, Emery P, Cravets MW, *et al*. Improved quality of life with rituximab plus methotrexate in patients with active rheumatoid arthritis who experienced inadequate response to one or more anti-TNF-alpha therapies. *Arthritis Rheum* 2005;**52**:287.
233 **Fleischmann R**, Racewicz A, Schechtman J, *et al*. Rituximab efficacy in rheumatoid arthritis is independent of coadministration of glucocorticoids: Results from the Dose-ranging Assessment iNternational Clinical Evaluation of Rituximab in rheumatoid arthritis (DANCER) Study. *Arthritis Rheum* 2005;**52**:263.
234 **van Vollenhoven R**, Schechtman J, Szczepanski L, Fleischmann R, Hazleman BL, Nash P, *et al*. Safety and tolerability of rituximab in patients with moderate to severe rheumatoid arthritis (RA): results from the Dose-ranging Assessment international Clinical Evaluation of Rituximab in RA (DANCER) study. *Arthritis Rheum* 2005;**52**:263.
235 **van Vollenhoven R**, Emery P, Fleischmann RM, Filipowicz-Sosnowska A, Szczepanski L, Racewicz A, *et al*. Safety and tolerability of rituximab in patients with moderate to severe rheumatoid arthritis (RA): results from the Dose-ranging Assessment iNternational Clinical Evaluation of Rituximab in RA (DANCER) study. *Ann Rheum Dis* 2005;**64**(Suppl 3):432.
236 **Edwards JC**, Cambridge G. Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. *Rheumatology (Oxford)* 2001;**40**:205–11.
237 **Emery P**, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Edwards JC, Magrini F, *et al*. Sustained efficacy at 48 weeks after single treatment course of rituximab in patients with rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:S439.
238 **Breedveld FC**, Agarwal SK, Yin M, Ng C, *et al*. Relationship between clinical response rituximab pharmacokinetics and peripheral B cell levels in Rheumatoid Arthritis. *EULAR* 2006 THU 0207.
239 **Breedveld FC**, Genovese MC, Emery P, *et al*. Safety of TNF inhibitors in rheumatoid arthritis patients previously treated with rituximab. *EULAR* 2006 THU 0206.
240 **Emery P**, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, *et al*. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIb double-blind, placebocontrolled, dose-ranging trial. (DANCER). *Arthritis Rheum* 2006;**54**:1390–00.
241 **Cohen SB**, Greenwald M, Dougados MR, Emery P, Furie R, Shaw TM, *et al*. Efficacy and safety of rituximab in active RA patients who experienced an inadequate response to one or more anti-TNF-alpha therapies. *Arthritis Rheum* 2005;**52**:1830.
242 **Looney RJ**. B cells as a therapeutic target in autoimmune diseases other than rheumatoid arthritis. *Rheumatology (Oxford)* 2005;**44**(Suppl 2):ii13–7.
243 **Edwards JC**, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, *et al*. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;**350**:2572–81.
244 **Shaw T**, Quan J, Totoritis MC. B cell therapy for rheumatoid arthritis: the rituximab (anti-CD20) experience. *Ann Rheum Dis* 2003;**62**(Suppl 2):ii*55*–9.
245 **Cohen SB**, Emery P, Greenwald MW, Dougados M, Furie R, Genovese M, *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006;**54**:2793–806.
246 **Tsutsumi Y**, Kanamori H, Mori A, Tanaka J, Asaka M, Imamura M, *et al*. Reactivation of hepatitis B virus with rituximab. *Expert Opin Drug Saf* 2005;**4**:599–608.
247 **Huffstutter J**, Sienknechet C. Resistant adult still's disease treated with infliximab: a report of two cases. *Arthritis Rheum* 2002;**46**(Suppl):S326.
248 **Kraetsch HG**, Antoni C, Kalden JR, Manger B. Successful treatment of a small cohort of patients with adult onset of Still's disease with infliximab: first experiences. *Ann Rheum Dis* 2001;**60**(Suppl 3):iii*55*–7.
249 **Fernandez-Nebro A**, Tomero E, Ortiz-Santamaria V, Castro MC, Olive A, de HM, *et al*. Treatment of rheumatic inflammatory disease in 25 patients with secondary amyloidosis using tumor necrosis factor alpha antagonists. *Am J Med* 2005;**118**:552–6.
250 **Elkayam O**, Hawkins PN, Lachmann H, Yaron M, Caspi D. Rapid and complete resolution of proteinuria due to renal amyloidosis in a patient with rheumatoid arthritis treated with infliximab. *Arthritis Rheum* 2002;**46**:571–2573.
251 **Gottenberg JE**, Merle-Vincent F, Bentaberry F, Allanore Y, Berenbaum F, Fautrel B, *et al*. Anti-tumor necrosis factor alpha therapy in fifteen patients with AA amyloidosis secondary to inflammatory arthritides: a followup report of tolerability and efficacy. *Arthritis Rheum* 2003;**48**:2019–24.
252 **Ortiz-Santamaria V**, Vals-Roc M, Sanmarti M, *et al*. Treatment of secondary amyloidosis with infliximab. *Arthritis Rheum* 2002;**46**(Suppl):S71.
253 **Tomero E**, Carmona L, Gonzalez I, *et al*. Infliximab in secondary amyloidosis complicating inflammatory arthropathies. *Arthritis Rheum* 2002;**46**:S70.
254 **Smith GR**, Tymms KE, Falk M. Etanercept treatment of renal amyloidosis complicating rheumatoid arthritis. *Intern Med J* 2004;**34**:570–2.
255 **Robinson ND**, Guitart J. Recalcitrant, recurrent aphthous stomatitis treated with etanercept. *Arch Dermatol* 2003;**139**:1259–62.
256 **Vujevich J**, Zirwas M. Treatment of severe, recalcitrant, major aphthous stomatitis with adalimumab. *Cutis* 2005;**76**:129–32.
257 **Atzeni F**, Sarzi-Puttini P, Capsoni F, Mecchia M, Marrazza MG, Carrabba M. Successful treatment of resistant Behcet's disease with etanercept. *Clin Exp Rheumatol* 2005;**23**:729.
258 **Sakellariou GT**, Chatzigiannis I, Tstouridis I. Infliximab infusions for presistent back pain in two patients with Schmorl's nodes. *Rheumatology* 2005;**44**:1588–90.
259 **Genevay S**, Stingelin S, Gabay C. Efficacy of etanercept in the treatment of acute, severe sciatica: a pilot study. *Ann Rheum Dis* 2004;**63**:1120–3.
260 **Estrach C**, Mpofu S, Moots RJ. Efficacy and safety of infliximab and adalimumab in Behçet's syndrome. Annual Scientific Meeting, American College of Rheumatology, Orlando, USA. 25 October 2003.
261 **Gulli S**, Arrigo C, Bocchino L, Morgante L, Sangari D, Castagna I, *et al*. Remission of Behcet's disease with anti-tumor necrosis factor monoclonal antibody therapy: a case report. *BMC Musculoskelet Disord* 2003;**4**:19.
262 **Hassard PV**, Binder SW, Nelson V, Vasiliauskas EA. Anti-tumor necrosis factor monoclonal antibody therapy for gastrointestinal Behcet's disease: a case report. *Gastroenterology* 2001;**120**:995–9.
263 **Licata G**, Pinto A, Tuttolomondo A, Banco A, Ciccia F, Ferrante A, *et al*. Anti-tumour necrosis factor alpha monoclonal antibody therapy for recalcitrant cerebral vasculitis in a patient with Behcet's syndrome. *Ann Rheum Dis* 2003;**62**:280–1.
264 **Magliocco MA**, Gottlieb AB. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. *J Am Acad Dermatol* 2004;**51**:580–4.
265 **Morrillas-Arques P**, Callejas J, Iglesias-Jimenez E, *et al*. Etanercept/adalimumab in the treatment of Behcet's syndrome. *Ann Rheum Dis* 2006;**65**(Suppl II):374.
266 **Rozenbaum M**, Rosner I, Portnoy E. Remission of Behcet's syndrome with TNFalpha blocking treatment. *Ann Rheum Dis* 2002;**61**:283–4.
267 **Saulsbury FT**, Mann JA. Treatment with infliximab for a child with Behcet's disease. *Arthritis Rheum* 2003;**49**:599–600.
268 **Sangle S**, Hughes G, D'Cruz D. Infliximab in the management of resistant systemic vasculitus: poor response and significant adverse effects. *OASIS* 2007.
269 **Sfikakis PP**, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behcet's disease. *Lancet* 2001;**358**:295–6.
270 **Sfikakis PP**. Behcet's disease: a new target for anti-tumour necrosis factor treatment. *Ann Rheum Dis* 2002;**61**(Suppl 2):ii51–3.
271 **Ribi C**, Sztajzel R, Delavelle J, Chizzolini C. Efficacy of TNF {alpha} blockade in cyclophosphamide resistant neuro-Behcet disease. *J Neurol Neurosurg Psychiatry* 2005;**76**:1733–5.
272 **Sweiss NJ**, Welsch MJ, Curran JJ, Ellman MH. Tumor necrosis factor inhibition as a novel treatment for refractory sarcoidosis. *Arthritis Rheum* 2005;**53**:788–91.
273 **van Laar JA**, Missotten T, van Daele PL, Jamnitski A, Baarsma GS, van Hagen PM. Adalimumab: a new modality for Behcet's disease? *Ann Rheum Dis* 2007;**66**:565–6.
274 **Cortot AB**, Cottin V, Miossec P, Fauchon E, Thivolet-Bejui F, Cordier JF. Improvement of refractory rheumatoid arthritis-associated constrictive bronchiolitis with etanercept. *Respir Med* 2005;**99**:511–4.
275 **Spahr L**, Rubbia-Brandt L, Frossard JL, Giostra E, Rougemont AL, Pugin J, *et al*. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. *J Hepatol* 2002;**37**:448–55.
276 **Menon KV**, Stadheim L, Kamath PS, Wiesner RH, Gores GJ, Peine CJ, *et al*. A pilot study of the safety and tolerability of etanercept in patients with alcoholic hepatitis. *Am J Gastroenterol* 2004;**99**:255–60.
277 **Tsimberidou AM**, Giles FJ, Duvic M, Kurzrock R. Pilot study of etanercept in patients with relapsed cutaneous T-cell lymphomas. *J Am Acad Dermatol* 2004;**51**:200–4.
278 **Cortis E**, De BF, Insalaco A, Cioschi S, Muratori F, D'Urbano LE, *et al*. Abnormal production of tumor necrosis factor (TNF): alpha and clinical efficacy of the TNF inhibitor etanercept in a patient with PAPA syndrome [corrected]. *J Pediatr* 2004;**145**:851–5.
279 **Cummins DL**, Hiatt KM, Mimouni D, Vander Kolk CA, Cohen BA, Nousari CH. Generalized necrobiosis lipoidica treated with a combination of split-thickness autografting and immunomodulatory therapy. *Int J Dermatol* 2004;**43**:852–4.
280 **Cusack C**, Buckley C. Etanercept: effective in the management of hidradenitis suppurativa. *Br J Dermatol* 2006;**154**:726–9.
281 **Zeichner JA**, Stern DWK, Lebwohl M. Intralesional etanercept for the treatment of necrobiosis lipoidica. Washington DC: Annual Meeting of the American Academy of Dermatology, 6 February, 2004.
282 **Hengstman G**, van den Hoogen F, ven Engelen B, *et al*. Anti-TNF blockade with infliximab (Remicade) in polymyositis and dermatomyositis. *Arthritis Rheum* 2000;**43**(Suppl):S193.
283 **Miller M**, Mendez E, Klein-Gitelman M, Pachman L. Use of etanercept in juvenile dermatomyositis. *Arthritis Rheum* 2002;**46**(Suppl):S306.

284 **Sprott H**, Glatzel M, Michel BA. Treatment of myositis with etanercept (Enbrel), a recombinant human soluble fusion protein of TNF-alpha type II receptor and IgG1. *Rheumatology (Oxford)* 2004;**43**:524–6.
285 **Nzeusseu A**, Durez P, Houssiau F. Successful use of infliximab in a case of refractory juvenile dermatomyositis. *Arthritis Rheum* 2001;**44**(Suppl):S90.
286 **Saadeyh C**. Etanercept is effective in the treatment of polymyositis/dermatomyositis which is refractory to conventional therapy. *Arthritis Rheum* 2000;**43**(Suppl):S193.
287 **Norman R**, Greenberg RG, Jackson JM. Case reports of etanercept in inflammatory dermatoses. *J Am Acad Dermatol* 2006;**54**:S139–42.
288 **Ortego-Centeno N**, Callejas-Rubio JL, Sanchez-Cano D, Caballero-Morales T. Refractory chronic erythema nodosum successfully treated with adalimumab. *J Eur Acad Dermatol Venereol* 2007;**21**:408–10.
289 **Takada K**, Aksentijevich I, Mahadevan V, Dean JA, Kelley RI, Kastner DL. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome. *Arthritis Rheum* 2003;**48**:2645–51.
290 **Ozgocmen S**, Ozcakar L, Ardicoglu O, Kocakoc E, Kaya A, Kiris A. Familial Mediterranean fever responds well to infliximab: single case experience. *Clin Rheumatol* 2006;**25**:83–7.
291 **Ghavami A**, Genevay S, Fulpius T, Gabay C. Etanercept in treatment of Felty's syndrome. *Ann Rheum Dis* **64**:1090–1.
292 **Andonopoulos AP**, Meimaris N, Daoussis D, Bounas A, Giannopoulos G. Experience with infliximab (anti-TNF alpha monoclonal antibody) as monotherapy for giant cell arteritis. *Ann Rheum Dis* 2003;**62**:1116.
293 **Cantini F**, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum* 2001;**44**:2933–5.
294 **Tan AL**, Holdsworth J, Pease C, Emery P, McGonagle D. Successful treatment of resistant giant cell arteritis with etanercept. *Ann Rheum Dis* 2003;**62**:373–4.
295 **Ahmed MM**, Mubashir E, Hayat S, Fowler M, Berney SM. Treatment of refractory temporal arteritis with adalimumab. *Clin Rheumatol* 2007;**26**:1353–5.
296 **Wolff D**, Roessler V, Steiner B, Wilhelm S, Weirich V, Brenmoehl J, *et al.* Treatment of steroid-resistant acute graft-versus-host disease with daclizumab and etanercept. *Bone Marrow Transplant* 2005;**35**:1003–10.
297 **Uberti JP**, Ayash L, Ratanatharathorn V, Silver S, Reynolds C, Becker M, *et al.* Pilot trial on the use of etanercept and methylprednisolone as primary treatment for acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2005;**11**:680–7.
298 **Kennedy GA**, Butler J, Western R, Morton J, Durrant S, Hill GR. Combination antithymocyte globulin and soluble TNFalpha inhibitor (etanercept) +/- mycophenolate mofetil for treatment of steroid refractory acute graft-versus-host disease. *Bone Marrow Transplant* 2006;**37**:1143–7.
299 **Chiang KY**, Abhyankar S, Bridges K, Godder K, Henslee-Downey JP. Recombinant human tumor necrosis factor receptor fusion protein as complementary treatment for chronic graft-versus-host disease. *Transplantation* 2002;**73**:665–7.
300 **Pavletic SZ**, Klassen LW, Pope R, O'Dell JR, Traynor AE, Haire CE, *et al.* Treatment of relapse after autologous blood stem cell transplantation for severe rheumatoid arthritis. *J Rheumatol* 2001;**64**(Suppl):28–31.
301 **Andolina M**, Rabusin M, Maximova N, Di LG. Etanercept in graft-versus-host disease. *Bone Marrow Transplant* 2000;**26**:929.
302 **Paridaens D**, van de Bosch F, van der Loos TL, Krenning EP, van Hagen PM. The effect of etanercept on Graves ophthalmopathy: a pilot study. *Eye* 2005;**19**:1286–9.
303 **McMinn Jr JR**, Cohen S, Moore J, Lilly S, Parkhurst J, Tarantino MD, *et al.* Complete recovery from refractory immune thrombocytopenic purpura in three patients treated with etanercept. *Am J Hematol* 2003;**73**:135–40.
304 **Peterson JR**, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. *Ann Rheum Dis* 2003;**62**:1078–82.
305 **Pritchard C**. Etanercept and hepatitis C. *J Clin Rheumtol* 1999;**5**:179.
306 **Moreno E**, Erra A, Leon Y, *et al.* Safety of etanercept treatment in patients with hepatitis B or C virus, and rheumatoid arthritis or ankylosing spondylitis. *Ann Rheum Dis* Eular 2004, FRI0106. [abstract].
307 **Parke Fa**, Reveville JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infections. *Arthritis & Rheum* 2004;**51**:800–4.
308 **Marotte H**, Fontanges E. Etanercept treatment for three months is safe in patients with rheumatological manifestations associated with hepatitis C virus. *Rheumatology (Oxford)* 2007;**46**:97–9.
309 **Rokhsar C**, Rabhan N, Cohen SR. Etanercept monotherapy for a patient with psoriasis, psoriatic arthritis, and concomitant hepatitis C infection. *J Am Acad Dermatol* 2006;**54**:361–2.
310 **Wallis RS**, Kyambadde P, Johnson JL, Horter L, Kittle R, Pohle M, *et al.* A study of the safety, immunology, virology, and microbiology of adjunctive etanercept in HIV-1-associated tuberculosis. *AIDS* 2004;**18**:257–64.
311 **Lin JH**, Liebhaber M, Roberts RL, Dyer Z, Stiehm ER. Etanercept treatment of cutaneous granulomas in common variable immunodeficiency. *J Allergy Clin Immunol* 2006;**117**:878–82.
312 **Cepeda E**, Williams F, Ishimori M, Weisman M. The use of anti-tumor necrosis factor therapy in HIV positive individuals with rheumatic disease. *Arthritis Rheum* 2007;**66**(Suppl 1):S123–4.
313 **Barohn RJ**, Herbelin L, Kissel JT, King W, McVey AL, Saperstein DS, *et al.* Pilot trial of etanercept in the treatment of inclusion-body myositis. *Neurology* 2006;**66**:S123–4.
314 **Singh R**, Cuchacovich R, Huang W, Espinoza LR. Inclusion body myositis unresponsive to etanercept. *J Clin Rheumatol* 2001;**7**:279–80.
315 **Olivieri I**, Scarano E, Gigliotti P, Giasi V, Padula A. Successful treatment of juvenile-onset HLA-B27-associated severe and refractory heel thesitis with adalimumab documented by magnetic reasonance imaging. *Rheumatology (Oxford)* 2006;**45**:1315–7.
316 **Weiss JE**, Eberhard BA, Chowdhury D, Gottlieb BS. Infliximab as a novel therapy for refractory Kawasaki disease. *J Rheumatol* 2004;**31**:808–10.
317 **Burns JC**, Mason WH, Hauger SB, Janai H, Bastian JF, Wohrley JD, *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005;**146**:662–7.
318 **Lovelace K**, Loyd A, Adelson D, Crowson N, Taylor JR, Cornelison R. Etanercept and the treatment of multicentric reticulohistiocytosis. *Arch Dermatol* 2005;**141**:1167–8.
319 **Matejicka C**, Morgan GJ, Schlegelmilch JG. Multicentric reticulohistiocytosis treated successfully with an anti-tumor necrosis factor agent: comment on the article by Gorman *et al. Arthritis Rheum* 2003;**48**:864–6.
320 **Kovach BT**, Calamia KT, Walsh JS, Ginsburg WW. Treatment of multicentric reticulohistiocytosis with etanercept. *Arch Dermatol* 2004;**140**:919–21.
321 **Birnbaum AJ**, Gentile P. Treatment of myelodysplasia in a patient with active rheumatoid arthritis. *Ann Intern Med* 2000;**133**:753–4.
322 **Deeg HJ**, Gotlib J, Beckham C, Dugan K, Holmberg L, Schubert M, *et al.* Soluble TNF receptor fusion protein (etanercept) for the treatment of myelodysplastic syndrome: a pilot study. *Leukemia* 2002;**16**:162–4.
323 **Rosenfeld C**, Bedell C. Pilot study of recombinant human soluble tumor necrosis factor receptor (TNFR:Fc) in patients with low risk myelodysplastic syndrome. *Leuk Res* 2002;**26**:721–4.
324 **Raza A**, Dutt D, Dean L, *et al.* Combination of thalidomide and embrel for the treatment of patients with myelodysplastic syndromes (MDS). *Blood* 2001;**98**:273b.
325 **Maciejewski JP**, Risitano AM, Sloand EM, Wisch L, Geller N, Barrett JA, *et al.* A pilot study of the recombinant soluble human tumour necrosis factor receptor (p75)-Fc fusion protein in patients with myelodysplastic syndrome. *Br J Haematol* 2002;**117**:119–26.
326 **Athreya B**, Doughty R, Kastner D, *et al.* Periodic fever syndrome in children. *Arthritis Rheum* 2000;**43**(Suppl):S117.
327 **Kroot EJ**, Kraan MC, Smeets TJ, Maas M, Tak PP, Wouters JM. Tumour necrosis factor alpha blockade in treatment resistant pigmented villonodular synovitis. *Ann Rheum Dis* 2005;**64**:497–9.
328 **Adams AB**, Kazim M, Lehman TJ. Treatment of orbital myositis with adalimumab (Humira). *J Rheumatol* 2005;**32**:1374–5.
329 **Carter JD**. Treatment of relapsing polychondritis with a TNF antagonist. *J Rheumatol* 2005;**32**:1413.
330 **Ehresman G**. Infliximab in the treatment of polychondritis. *Arthritis Rheum* 2002;**46**(Suppl):S170.
331 **Fonder MA**, Cummins DL, Ehst BD, Anhalt JH. Adalimumab therapy for recalcitrant pyoderma gangrenosum. *J Burns Wounds* 2006;**5**:e8.
332 **Heffernan MP**, Anadkat MJ, Smith DI. Adalimumab treatment for pyoderma gangrenosum. *Arch Dermatol* 2007;**143**:306–8.
333 **Magnano MD**, Chakravarty EF, Broudy C, Chung L, Kelman A, Hillygus J, *et al.* A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. *J Rheumatol* 2007;**34**:1323–7.
334 **Sweiss N**, Curran J, Ellman N. TNF-inhibition as a novel treatment for refractory sarcoidosis. Annual Scientific Meeting, American College of Rheumatology, Orlando, USA. 25 October 2003.
335 **Callejas-Rubio JL**, Ortego-Centeno N, Lopez-Perez L, Benticuaga MN. Treatment of therapy-resistant sarcoidosis with adalimumab. *Clin Rheumatol* 2006;**25**:596–7.
336 **Korhonen T**, Karppinen J, Malmivaara A, Autio R, Niinimaki J, Paimela L, *et al.* Efficacy of infliximab for disc herniation-induced sciatica: one-year follow-up. *Spine* 2004;**29**:2115–9.
337 **Korhonen T**, Karppinen J, Paimela L, Malmivaara A, Lindgren KA, Jarvinen S, *et al.* The treatment of disc herniation-induced sciatica with infliximab: results of a randomized, controlled, 3-month follow-up study. *Spine* 2005;**30**:2724–8.
338 **Lam K**, Woods A, Hummers K, Wigley F. Efficacy and safety of etanercept in scleroderma joint disease. *Arthritis Rheum* 2005;**52**:S588.
339 **Pasternack FR**, Fox LP, Engler DE. Silicone granulomas treated with etanercept. *Arch Dermatol* 2005;**141**:13–5.
340 **Tobinick E**, Davoodifar S. Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: a study of clinical observations in 143 patients. *Curr Med Res Opin* 2004;**20**:1075–85.
341 **Khanna D**, Liebling MR, Louie JS. Etanercept ameliorates sarcoidosis arthritis and skin disease. *J Rheumatol* 2003;**30**:1864–7.
342 **Utz JP**, Limper AH, Kalra S, Specks U, Scott JP, Vuk-Pavlovic Z, *et al.* Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. *Chest* 2003;**124**:177–85.
343 **Wagner AD**, Andresen J, Jendro MC, Hulsemann JL, Zeidler H. Sustained response to tumor necrosis factor alpha-blocking agents in two patients with SAPHO syndrome. *Arthritis Rheum* 2002;**46**:1965–8.
344 **Moul DK**, Korman NJ. Severe hidradenitis suppurativa treated with adalimumab. *Arch Dermatol* **142**:1110–2.
345 **Heffernan MP**, Smith DI. Adalimumab for treatment of cutaneous sarcoidosis. *Arch Dermatol* 2006;**142**:17–9.
346 **Querfeld C**, Bachmann P, Guitart J. The effectiveness of etanercept in treating cutaneous sarcoidosis. A case report. *Amer Acad Derm* 2007;**50**(suppl 1):P55.
347 **Hobbs K**. Chronic sarcoid arthritis treated with intraarticular etanercept. *Arthritis Rheum* 2005;**52**:987–8.
348 **Ellman MH**, MacDonald PA, Hayes FA. Etanercept treatment for diffuse scleroderma: a pilot study. *Arthritis Rheum* 2000;**43**(Suppl):S392.
349 **Bosello S**, De SM, Tolusso B, Zoli A, Ferraccioli G. Tumor necrosis factor-alpha inhibitor therapy in erosive polyarthritis secondary to systemic sclerosis. *Ann Intern Med* 2005;**143**:918–20.
350 **Zandbelt MM**, de WP, van DP, Hoyng CB, van de PL, van den HF. Etanercept in the treatment of patients with primary Sjogren's syndrome: a pilot study. *J Rheumatol* 2004;**31**:96–101.

351 **Pessler F**, Monash B, Rettig P, Forbes B, Kreiger PA, Cron RQ. Sjogren syndrome in a child: favorable response of the arthritis to TNFalpha blockade. *Clin Rheumatol* 2006;**25**:746–8.
352 **Fautrel B**, Sibilia J, Mariette X, Combe B. Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: an observational study of 20 cases. *Ann Rheum Dis* 2005;**64**:262–6.
353 **Stern A**, Riley R, Buckley L. Worsening of macrophage activation syndrome in a patient with adult onset Still's disease after initiation of etanercept therapy. *J Clin Rheumatol* 2001;**7**:252–6.
354 **Asherson RA**, Pascoe L. Adult onset Still's disease: response to Enbrel. *Ann Rheum Dis* 2002;**61**:859–60.
355 **Kumari R**, Uppal SS. Prolonged remission in adult-onset Still's disease with etanercept. *Clin Rheumatol* 2006;**25**:106–8.
356 **Gindi V**, Lowe NJ, Koo S, Yamauchi PA. Treatment of Sweet's syndrome with the tumor necrosis factor antagonist etanercept in a patient with coexisting rheumatoid arthritis. Annual Meeting of the American Academy of Dermatology, New Orleans, USA. 18 February 2005.
357 **Yamauchi PS**, Turner L, Lowe NJ, Gindi V, Jackson JM. Treatment of recurrent Sweet's syndrome with coexisting rheumatoid arthritis with the tumor necrosis factor antagonist etanercept. *J Am Acad Dermatol* 2006;**54**:S122–6.
358 **Aringer M**, Graninger WB, Steiner G, Smolen JS. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus: an open-label study. *Arthritis Rheum* 2004;**50**:3161–9.
359 **Lurati A**, Teruzzi B, Salmaso A, *et al.* Macrophage activation syndrome (MAS) during anti-IL-1 receptor therapy (anakinra) in a patient affected by systemic onset idiopathic juvenile arthritis (soJIA): a report and review of the literature. *Pediatr Rheumatol Online J* 2007;**3(2)**:79–85.
360 **Lurati A**, Teruzzi B, Salmaso A, *et al.* Macrophage activation syndrome (MAS) during anti-IL-1 receptor therapy (anakinra) in a patient affected by systemic onset idiopathic juvenile arthritis (soJIA): a report and review of the literature. *Pediatr Rheumatol Online J* 2007;**3(2)**:79–85.
361 **Hernandez-Ibarra H**, Gutierrez L, Juarez S, *et al.* Prevalence, burden of illness and factors associated with neurocognitive dysfunction in Mexican patients with systemic lupus erythematous. Annual Scientific Meeting, American College of Rheumatology, Orlando, USA, No 378. 25 October 2003.
362 **Principi M**, Di LA, Ingrosso M, Pisani A, Marangi S, Amoruso A, *et al.* Lupus nephritis improvement after anti-tumor necrosis factor alpha monoclonal antibody (infliximab) treatment for Crohn's disease: a case report. *Immunopharmacol Immunotoxicol* 2004;**26**:243–8.
363 **Hoffman GS**, Merkel PA, Brasington RD, Lenschow DJ, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004;**50**:2296–304.
364 **Della RA**, Tavoni A, Merlini G, Baldini C, Sebastiani M, Lombardi M, *et al.* Two Takayasu arteritis patients successfully treated with infliximab: a potential disease-modifying agent? *Rheumatology (Oxford)* 2005;**44**:1074–5.
365 **Tato F**, Rieger J, Hoffmann U. Refractory Takayasu's arteritis successfully treated with the human, monoclonal anti-tumor necrosis factor antibody adalimumab. *Int Angiol* 2005;**24**:304–7.
366 **Hull KM**, Drewe E, Aksentijevich I, Singh HK, Wong K, McDermott EM, *et al.* The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. *Medicine (Baltimore)* 2002;**81**:349–68.
367 **Lamprecht P**, Moosig F, dam-Klages S, Mrowietz U, Csernok E, Kirrstetter M, *et al.* Small vessel vasculitis and relapsing panniculitis in tumour necrosis factor receptor associated periodic syndrome (TRAPS). *Ann Rheum Dis* 2004;**63**:1518–20.
368 **Drewe E**, McDermott EM, Powell RJ. Treatment of the nephrotic syndrome with etanercept in patients with the tumor necrosis factor receptor-associated periodic syndrome. *N Engl J Med* 2000;**343**:1044–5.
369 **Joseph A**, Raj D, Dua HS, Powell PT, Lanyon PC, Powell RJ. Infliximab in the treatment of refractory posterior uveitis. *Ophthalmology* 2003;**110**:1449–53.
370 **Smith JA**, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S, *et al.* A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005;**53**:18–23.
371 **Braun J**, Baraliakos X, Listing J, Sieper J. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etercept. *Arthritis Rheum* 2005;**52**:2447–51.
372 **Foster CS**, Tufail F, Waheed N, *et al.* Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. *Arch Ophthalmol* 2003;**121**:437–40.
373 **Biester S**, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, *et al.* Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007;**91**:319–24.
374 **Foeldvari I**, Nielsen S, Kummerle-Deschner J, Espada G, Horneff G, Bica B, *et al.* Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. *J Rheumatol* 2007;**34**:1146–50.
375 **Vazquez-Cobian LB**, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. *J Pediatr* 2006;**149**:572–5.
376 **Reiff A**, Takei S, Sadeghi S, *et al.* Etanercept therapy in children with treatment-resistant uveitis. *Arthritis Rheum* 2007;**44**:1411–5.
377 **Schmeling H**, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2005;**44**:1008–11.
378 **Guignard S**, Gossec L, Salliot C Ruy, Ruyssen-Witrand A, Luc M, Duclos M, et al. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. *Ann Rheum Dis* 2006;**65**:1631–4.
379 **Booth A**, Harper L, Hammad T, Bacon P, Griffith M, Levy J, *et al.* Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol* 2004;**15**:717–21.
380 **Feinstein J**, Arroyo R. Successful treatment of childhood onset refractory polyarteritis nodosa with tumor necrosis factor alpha blockade. *J Clin Rheumatol* 2005;**11**:219–22.
381 **van der Bijl AE**, Allaart CF, Van VJ, Van DS, Breedveld FC. Rheumatoid vasculitis treated with infliximab. *J Rheumatol* 2005;**32**:1607–9.
382 **Saji T**, Kemmotsu Y. Infliximab for Kawasaki syndrome. *J Pediatr* 2006;**149**:426.
383 **Arbach O**, Gross WL, Gause A. Treatment of refractory Churg-Strauss-syndrome (CSS) by TNF-a blockade. *Immunobiology* 2002;**206**:495–501.
384 **Gause AM**, Arbach O, Reinhold-Keller E, *et al.* Induction of remission with infliximab in active generalized Wegener's granulomatosis is effective but complicated by severe infections. Annual Scientific Meeting, American College of Rheumatology, Orlando, USA No.450. 25 October 2003.
385 **Emsley HC**, Smith CJ, Georgiou RF, Vail A, Hopkins SJ, Rothwell NJ, *et al.* A randomised phase II study of interleukin-1 receptor antagonist in acute stroke patients. *J Neurol Neurosurg Psychiatry* 2005;**76**:1366–72.
386 **Leslie KS**, Lachmann HJ, Bruning E, McGrath JA, Bybee A, Gallimore JR, *et al.* Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. *Arch Dermatol* 2006;**142**:1591–7.
387 **Rudinskaya A**, Trock D. Successful treatment of a patient with refractory adult-onset Still disease with anakinra. *J Clin Rheumatol* 2003;**9**:330–2.
388 **Quartier P**, Lequerre T, Rosellini D, *et al.* Anakinra in systemic-onset juvenile idiopathic arthritis and adult onset Still's disease. *EULAR OP0174* 2007.
389 **Aelion JA**, Odhav SK. Prompt responses to treatment with anakinra in adult onset Stills disease. *EULAR FRI0109* 2004.
390 **Haraoui B**, Bourrelle D, Kaminska E. Anakinra in the treatment of adult-onset Still's disease. *EULAR FRI0148* 2007.
391 **Kalliolias GD**, Georgiou PE, Antonopolus IA. Anakinra (AKR) Anakinra treatment in patients with adult-onset Still's disease is fast, effective, safe and steroid sparing:experience from and uncontrolled trial. *Ann Rheum Dis* 2007;**66**:842–3.
392 **Nordstrom D**, Aarnio M, Helve T, *et al.* Favorable response to anakinra in refractory adult-onset Still's disease. A clinical study is needed. *ACR* 2006;**1623**:294.
393 **Kalliolias G**, Antonopoulos L, Andonopoulos A, Liossis S. Beneficial effects of anakinra in patients with steriod-resistant adult onset Still's disease. *ACR* 2006;**1624**:295.
394 **Fitzgerald AA**, Leclercq SA, Yan A, Homik JE, Dinarello CA. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. *Arthritis Rheum* 2005;**52**:1794–803.
395 **Vasques Godinho FM**, Parreira Santos MJ, Canas da SJ. Refractory adult onset Still's disease successfully treated with anakinra. *Ann Rheum Dis* 2005;**64**:647–8.
396 **Antin JH**, Weisdorf D, Neuberg D, Nicklow R, Clouthier S, Lee SJ, *et al.* Interleukin-1 blockade does not prevent acute graft-versus-host disease: results of a randomized, double-blind, placebo-controlled trial of interleukin-1 receptor antagonist in allogeneic bone marrow transplantation. *Blood* 2002;**100**:3479–82.
397 **Birmingham J**, Kraus V, Toth A. Clinical benefits of intra-articular anakinra (kineret) of knee signs and symptoms of injury, arthritis and arthrofibrosis. *ACR* 2006;**F142(662)**.
398 **Behrens EM**, Kreiger PA, Cherian S, Cron RQ. Interleukin 1 receptor antagonist to treat cytophagic histiocytic panniculitis with secondary hemophagocytic lymphohistiocytosis. *J Rheumatol* 2006;**33**:2081–4.
399 **Metyas S**, Hoffman H. Anakinra prevents symptons of familial cold auto-inflammatory syndrome and Raynaud's disease. *J Rheumatol* 2006;**33(10)**:1–3.
400 **Bodar EJ**, van der Hilst JC, Drenth JP, van der Meer JW, Simon A. Effect of etanercept and anakinra on inflammatory attacks in the hyper-IgD syndrome: introducing a vaccination provocation model. *Neth J Med* 2005;**63**:260–4.
401 **Rigante D**, Ansuini V, Bertoni B, *et al.* Treatment with anakinra in the hyperimmunoglobulinemia D/periodic fever syndrome. *Rheumatol Int* 2006;**27**:97–100.
402 **Verbsky JW**, White AJ. Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. *J Rheumatol* 2004;**31**:2071–5.
403 **Ilowite NT**, Porras O, Reiff A, *et al.* A twelve-week open label safety and efficacy study of anakinra (KINERET) in juvenile rheumatoid arthritis. *EULAR* OP0071, 2003.
404 **Ilowite NT**, Reiff A, Rudge SR, Punaro MG, Martin J, *et al.* A randomized, multi-center, blinded, placebo-controlled study with an open-label run-in period to evaluate anakinra in polyarticular-course juvenile rheumatoid arthritis. [abstract] *Arthritis & Rheum* 2007;**54**:s327;723.
405 **Hawkins P**, Larchmann H. Interleukin-1-receptor antagonist in the Muckle Wells syndrome. *N Engl J Med* 2003;**348**:2583–4.
406 **Saha M**, Rustin M, Swale V, Hawkins P. Muckle-Wells syndrome successfully treated with an interleukin-1 receptor antagonist. *Br J Dermatol* 2004;**151**(Suppl 68):21–62.
407 **Ramos E**, Arostegui JI, Campuzano S, *et al.* Positive clinical and biochemical responses to anakinra in a 3-year-old patient with cryopyrin-associated periodic cyndrome (CAPS). *Rheumatology* 2005;**44**:1072–3.
408 **Rynne M**, Maclean C, Bybee A, McDermott MF, Emery P. Hearing improvement in a patient with variant Muckle-Wells syndrome in response to interleukin 1 receptor antagonism. *Ann Rheum Dis* 2006;**65**:533–4.
409 **Mirault T**, Launay D, Cuisset L, *et al.* Recovery form deafness in patients with muckle-wells syndrome treated with anakinra. *Arthritis Rheum* 2007;**54**:1697–700.
410 **Goldbach-Mansky R**, Daily N, Canna S, *et al.* Neonatal-onset multisystem inflammatory disease responsive to interleukin-1B inhabition. *N Engl J Med* 2007;**355**:581–92.

411 **Frenkel J**, Wulffraat N, Kuis W. Anakinra in mutation-negative NOMID/CINCA syndrome: comment on the articles by Hawkins *et al* and Hoffman and Patel. To the Editor. *Arthtitis & Rheum* 2007;**50**:3738–9.
412 **Rigante D**, Ansuini V, Calderelli M, *et al*. Hydrocephalus in CINCA syndrome treated with anakinra. *Childs Nerv Syst* 2006;**22**:334–7.
413 **Seitz M**, Kamgang RK, Simon HU, Villiger PM. Therapeutic interleukin (IL) 1 blockade normalises increased IL1 beta and decreased tumour necrosis factor alpha and IL10 production in blood mononuclear cells of a patient with CINCA syndrome. *Ann Rheum Dis* 2005;**64**:1802–3.
414 **Granel B**, Serratrice J, Disdier P, Weiller PJ. Dramatic improvement with anakinra in a case of chronic infantile neurological cutaneous and articular (CINCA) syndrome. *Rheumatology* 2005;**44**:689–90.
415 **Namde M**, Hill S, Duryea J, Plass N, Snyder C, *et al*. Arthropathy in patients with neonatal onset multisystem inflammatory disease (NOMID). *Arthritis & Rheum* 2006;**54**:s803;2046.
416 **Namde M**, Hildebrand P, Jain M, *et al*. Functional outcomes in neonatal onset multisystem inflammatory disease (NOMID) after 12 months of treatment with the recombinant IL-1 receptor antagonist anakinra. *Ann Rheum Dis* 2006;**65**(Suppl II):100.
417 **Namde M**, Canna S, Plass N, Rubin A, Kim J, Snyder B, *et al*. Twelve months after treating children with neonatal onset multisystem inflammatory disease (NOMID/CINCA) with the IL-1 receptor antagonist anakinra. *Ann Rheum Dis* 2006;**65**(Suppl II):448.
418 **Gattorno M**, Ferlito F, Pelagatti MA, *et al*. Clinical and biological effects of treatment with anakinra in CINCA syndrome and in systemic onset JIA. *Ann Rheum Dis* 2006;**65**(Suppl II):252.
419 **Caroli F**, Pontillo A, D'Osualdo A, Travan L, Ceccherini I, Crovella S, *et al*. Clinical and genetic characterization of Italian patients affected by CINCA syndrome. *Rheumatology (Oxford)* 2007;**46**:473–8.
420 **Lovell DJ**, Bowyer SL, Solinger AM. Interleukin-1 blockade by anakinra improves clinical symptoms in patients with neonatal-onset multisystem inflammatory disease. *Arthritis Rheum* 2005;**52**:1283–6.
421 **Dierselhuis MP**, Frenkel J, Wulffraat NM, Boelens JJ. Anakinra for flares of pyogenic arthritis in PAPA syndrome. *Rheumatology (Oxford)* 2005;**44**:406–8.
422 **Jung N**, Hoheisel R, Haase I, *et al*. Anakinra (IL1-RA) in the treatment of patients with active psoriatic arthritis refractory to or intolerant of methotrexate (MTX). *Ann Rheum Dis* 2005;**64**(Suppl 3):1092.
423 **Gibbs A**, Gogarty M, Bresnihan B, *et al*. Moderate clinical response and absence of MRI or immunohistological change suggest that anakinra is ineffective in psoriatic arthritis. *ACR* 2006;**1809**:481.
424 **Vounotrypidis P**, Sakellariou GT, Zisopoulos D, Berberidis C. Refractory relapsing polychondritis:rapid and sustained response in the treatment with an IL-1 receptor antagonist (anakinra). *Rheumatology* 2006;**45**:491–2.
425 **Martinez-Toboada V**, Fontalba A, Blanco R, Fernandez-Luna J. Successful treatment of refractory Schnitzler Syndrome with anakinra: comment on the article by Hawkins et al. *Arthritis Rheum* 2005;**52**:2226–8.
426 **Pascual V**, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005;**201**:1479–86.
427 **Henrickson M**. Sustained efficacy of anakinra in refractory systemic arthritis failing etanercept. *Arthritis & Rheum* 2005;**52**:s83;131.
428 **Reiff A**. The use of anakinra in juvenile arthritis. *Curr Rheumatol Rep* 2005;**7**:434–40.
429 **Mirkinson L**, Nagle D, Jones O, Kadom N. Anakinra therapy in a child with systemic-onset juvenile rheumatoid arthritis after human herpesvirus 6 encephalitis. *J Clin Rheumatol* 2006;**12**:83–6.
430 **Weiss J**, Henrickson M, Walco G, Feinstein A, Kimura Y, Sanzari J, *et al*. Combination therapy with anakinra and anti-TNF agents in refractory systemic JIA (SJIA). *Pediatric Rheumatology, Pres* 2007;**134**.
431 **Punaro L**, Allantaz F, Stichweh D, Pascual V. Clinical and microarray follow-up of systemic onset juvenile idiopathic arthritis patients threated with anakinra. *OASIS* 2007;**616**.
432 **Zeft A**, Schlesinger M, Bohnsack J. Anakinra in systemic juvenile idiopathic arthritis: The Intermountain West Experience. *ACR* 2006;**1704**:375.
433 **Gattorno M**, Ferlito F, Pelagatti MA, *et al*. Patterns of IL-1 B secretion and response to anti-IL-1 treatment in Cias-1 mutated patients and systemic onset JIA (soJIA). *ACR* 2006;**2115**.
434 **Strand V**, Balbir GA, Pavelka K, *et al*. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. *Rheumatology (Oxford)* 2006:1–9.
435 **Edwards JC**, Szczepanski L, Szechinski J, *et al*. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;**350**:2572–81.
436 **Popa C**, Leandro MJ, Cambridge G, *et al*. Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 years. *Rheumatology (Oxford)* 2007:1–5.
437 **Higashida J**, Wun T, Schmidt S. Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor treatment. *J Rheumatol* 2005;**32**:2109–15.
438 **Moore J**, Ma D, Will R, *et al*. A phase II study of rituximab in rheumatoid arthritis patients with recurrent disease following haematopoietic stem cell transplantation *Bone Marrow Transplant* 2004;**34**:241–7.
439 **Kneitz C**, Wilhelm M, Tony HP. Improvement of refractory rheumatoid arthritis after depletion of B cells. *Scand J Rheumatol* 2007;**33**:82–6.
440 **Leandro MJ**, Edwards JC, Cambridge G. Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. *Ann Rheum Dis* 2002;**61**:883–8.
441 **De Vita S**, Zaja F, Sacco S, *et al*. Efficacy of selective B cell blockage in the treatment of rheumatoid arthritis: evidence for a pathogenetic role of B cells. *Arthritis Rheum* 2007;**46**:2029–33.
442 **Scheinberg M**, Hamerschlak N, Kutner JM, *et al*. Rituximab in refractory autoimmune diseases: Brazilian experience with 29 patients (2002–2004). *Clin Exp Rheumatol* 2002;**24**:65–9.
443 **Maher L**, Wilson JG. Successful treatment of rheumatoid vasculitis-associated foot drop with rituximab. *Rheumatology (Oxford)* 2006;**45**:1450–1.
444 **Cambridge G**, Stohl W, Leandro MJ. Circulating levels of B lymphocyte simulator in patients with rheumatiod arthritis following rituximab treatment. *Arthritis Rheum* 2006;**54**:723–32.
445 **Leandro MJ**, Cambridge G, Ehrensten M, *et al*. Reconstitution of peripheral blook B cells after depletion with rituximab in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;**54**:613–20.
446 **Roll P**, Palanichamy A, Kneitz C, *et al*. Regeneration of B cell subsets after transient B cell depletion unsing anti-CD20 antibodies in rheumatoid arthritis. *Arthritis Rheum* 2007;**54**:2377–86.
447 **Stasi R**, Stipa E, Del Poeta G, *et al*. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. *Rheumatology (Oxford)* 2006;**45**:1432–6.
448 **Ericksson P**. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitus successfully treated with rituximab. *J Intern Med* 2005;**257**:540–8.
449 **Smith KGC**, Jones RB, Burns SM, *et al*. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitus. *Arthritis Rheum* 2006;**54**:2970–82.
450 **Aries PM**, Hellmich B, Voswinkel J, *et al*. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory grandulomatous manifestations. *Ann Rheum Dis* 2006;**65**:853–8.
451 **Keogh KA**, Ytterberg SR, Fervenza FC, *et al*. Rituximab for refractory Wegener's granulomatosis: report of a prospective, one-label pilot trial. *Am J Respir Crit Care Med* 2007;**173**:180–7.
452 **Sanchez-Cano D**, Callejas-Rubio JL, Rios-Fernandez R, *et al*. Use of rituximab in Wegener's granulomatosis: comment on the article by Wong. *Nephrol Dial Transplant* 2007;**22**:958–9.
453 **Tektonidou MG**, Skopouli FN. Sustained 3-year remission aftr rituximab treatment in a patient with refractory Wegener's granulomatosis. *Clin Exp Rheumatol* 2006;**24**:S103.
454 **Bachmeyer C**. Rituximab is an alternative in a case of contra-indication of cyclophosphamide with Wegener's granulomatosis. *Nephrol Dial Transplant* 2005;**20**:1274.
455 **Ferraro AJ**, Day CJ, Drayson MT, *et al*. Effective thearpeutic use of Rituximab in refractory Wegener's granulomatosis. *Nephrol Dial Transplant* 2005;**20**:622–5.
456 **Kallenbach M**, Duan H, Ring T. Rituximab induced remission in a patient with Wegener's granulomatosis. *Nephron Clin Pract* 2005;**99**:c92–6.
457 **Memet B**, Rudinskaya A, Kerbs T, *et al*. Wegener's granulomatosis with massive intracerebral hemorrhage. *J Clin Rheumatol* 2005;**11**:318.
458 **Specks U**, Fervensa, McDonald TJ, *et al*. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. *Arthritis Rheum* 2007;**44**:2840.
459 **Clatworthy MR**, Jayne DRW. Acquired hemophilia in association with ANCA-associated vasculitis: response to rituximab. *Am J Kidney Dis* 2006;**47**:680–2.
460 **Koukoulaki M**, Smith KGC, Jayne DRW. Rituximab in Churg-Strauss syndrome. *Ann Rheum Dis* 2006;**65**:557–9.
461 **Kaushik V**, Reddy HV, Bucknall RC. Successful use of rituximab in a patient with recalcitrant Churg-Strauss symdrome. *Ann Rheum Dis* 2006;**65**:1116–7.
462 **Sansonno D**, De Re V, Lauletta G. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. *Blood* 2003;**101**:3818–26.
463 **Quartuccio L**, Soardo G, Romano G, *et al*. Rituximab treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia: efficacy and safety in the absence of steroids. *Rheumatology (Oxford)* 2007;**45**:824–46.
464 **Bassee G**, Ribes D, Kamar N, *et al*. Rituximab therapy for mixed cryoglobulinemia in seven renal transplant patients. *Transplant Proc* 2007;**38**:2308–10.
465 **Cai FZJ**, Ahern M, Smith M. Treatment of cryoglobluinemia associated peripheral neuropathy with rituximab. *J Rheumatol* 2006;**33**:1197–8.
466 **Pekow J**, Chung RT. Treatment of type II cryoglobulinemia associated with hepatitis C with rituximab. *J Clin Gastroenterol* 2006;**40**:450.
467 **Telander DG**, Hollander G, Wax MB, *et al*. Rubeosis and anterior segment ischemia associated with systemic cryoglobulinemia. *Am J Ophthalmol* 2006;**142**:689.
468 **Bryce AH**, Kyle RA, Dispenzieri A, *et al*. Response to rituximab in patients with type II cryoglobulinemia. *Clin Lymphoma Myeloma* 2007;**7**:140–4.
469 **Zaja F**, De Vita S, Massaro C, *et al*. Efficacy and safety of fituximab in type II mixed cryoglobulinemia. *Blood* 2003;**101**:3827–34.
470 **Arzoo K**, Sadeghi S, Liebman HA. Treatment of refractory antibody mediated autoimmune disorders with an anti-CD20 monoclonal antibody (rituximab). *Ann Rheum Dis* 2002;**61**:922–4.
471 **Basse G**, Ribes D, Kamar N, *et al*. Rituximab therapy for de novo mixed cryoglobulinemia in renal transplant patients. *Transportation* 2005;**82**:1560–4.
472 **Ghijsels E**, Lerut E, Vanrenterghem Y, *et al*. Anti-CD20 monoclonal antibody (rituximab) treatment for hepatitis C-negative therapy-resistant essential mixed cryoglobulinemia with renal and cardiac failure. *Am J Kidney Dis* 2004;**43**:e34–8.
473 **Lamprecht P**, Lerin-Lozano C, Merz H, *et al*. Rituximab induces remission in refractory HCV associated cryoglobulinaemic vasculitis. *Ann Rheum Dis* 2003;**62**:1230–3.
474 **Bryce AH**, Kyle RA, Dispenzieri A, *et al*. Natural history and therapy of 66 patients with mixed cryoglobulinemia. *Am J Hematol* 2007;**81**:511–8.

475 **Nehme SH**, Korganow AS, Pasquail JL, *et al*. Rituximab inefficiency during type I cryoglobulinaemin. *Rheumatology (Oxford)* 2005;**44**:410–1.
476 **Ring T**, Kallenbach M, Praetorius J, *et al*. Successful treatment of a patient with primary Sjogren's syndrome with rituximab. *Clin Rheumatol* 2006;**25**:891–4.
477 **Touma Z**, Sayad J, Arayssi T. Successful treatment of Sjogren's syndrome with rituximab. *Scand J Rheumatol* 2006;**35**:323–5.
478 **Pijpe J**, Van-Imhoff GW, Spijkervet FKL, *et al*. Rituximab treatment in patients with primary Sjogren's syndrome. *Arthritis Rheum* 2005;**52**:2740–50.
479 **Pijpe J**, Van-Imhoff GW, Vissink A, *et al*. Changes in salivary gland immunohistology and function after rutiximab monotherapy in a patient with Sjogren's syndrome and associated MALT lymphoma. *Ann Rheum Dis* 2005;**65**:958–60.
480 **Voulgarelis M**, Giannouli S, Tzioufas AG, Moutsopoulos HM. Long term remission of Sjogren's syndrome associated aggressive B cell non-Hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). *Ann Rheum Dis* 2006;**65**:1033–7.
481 **Voulgarelis M**, Giannouli S, Anagnostou D, *et al*. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. *Rheumatology (Oxford)* 2004;**43**:1050–3.
482 **Gottenberg JE**, Guillevin L, Lambotte O, *et al*. Tolerance and short-term efficacy of rituximab in 43 patients with systemic autoimmune diseases. *Ann Rheum Dis* 2005;**64**:913–20.
483 **Ahmadi-Simab K**, Lamprecht P, Nolle B, *et al*. Successful treatment of refractory anterior scleritis in primary sjogren's syndrome with rituximab. *Ann Rheum Dis* 2005;**64**:1087–8.
484 **Harner KC**, Jackson LW, Drabick JJ. Normalization of anticardiolipin antibodies following rituximab therapy for marginal zone lymphoma in a patient with Sjogren's syndrome. *Rheumatology (Oxford)* 2004;**43**:1309–10.
485 **Somer GB**, Tsai DE, Downs L, *et al*. Improvement in Sjogren's syndrome following therapy with rituximab for marginal zone lymphoma. *Arthritis Rheum* 2003;**49**:394–8.
486 **Shih WJ**, Ghesani N, Hongming Z, *et al*. F-18 FDG positron emission tomography demonstrates resolution of non-Hodgkin's lymphoma of the parotid gland in a patient with Sjogren's syndrome: before and after anti-CD20 antibody rituximab therapy. *Clin Nucl Med* 2002;**27**:142–3.
487 **Ramos-Casals M**, Lopex-Guillermo A, Brito-Zeron P, *et al*. SS-HCV Study Group. Treatment of B-cell lymphoma with rituximab in two patients with Sjogren's syndrome associated with hepatitis C virus infection. *Lupus* 2004;**13**:969–71.
488 **Kuek A**, Hazleman BL, Gaston JH, *et al*. Successful treatment of refractory polyarticular juvenile idiopathic arthritis with rituximab. *Rheumatology (Oxford)* 2006;**45**:1448–9.
489 **Kelaidi C**, Tulliez M, Lecoq-Lafon C, *et al*. Long-term remission of an EBV-positive B cell lymphoproliferative disorder associated with rheumatoid arthritis under methotrexate with anti-CD20 monoclonal antibody (rituximab) monotherapy. *Leukemia* 2002;**16**:2173–4.
490 **Armstrong DJ**, McCarron MT, Wright GD. SLE-associated transverse myelitis successfully treated with Rituximab (anti-CD20 monoclonal antibody). *Rheumatol Int* 2006;**26**:772.
491 **Gomard-Mennesson E**, Ruivard M, Koenig M, *et al*. Treatment of isolated severe immune hemolytic anaemia associated with systemic lupus erythematosus: 26 cases. *Lupus* 2006;**15**:223–31.
492 **Haddad E**, Willems M, Niaudet P, *et al*. Rituximab therapy for childhood-onset systemic lupus erythematosus. *J Rheumatol* 2006;**33**:390.
493 **Jansson AF**, Wintergerst U, Renner ED, *et al*. Rituximab-induced long-term remission in two children with SLE. *Eur J Pediatr* 2007;**166**:177–81.
494 **Kotani T**, Takeuchi T, Kawasaki Y, *et al*. Successful treatment of cold agglutinin disease with anti-CD20 antibody (rituximab) in a patient with systemic lupus erythematosus. *Lupus* 2006;**15**:683–5.
495 **MacDermott EJ**, Lehman TJA. Prospective, open-label trial of rituximab in childhood systemic lupus erythematosus. *Curr Rheumatol Rep* 2006;**8**:439–11.
496 **Marks SD**, Tullus K. Successful outcomes with rituximab therapy for refractory childhood systemic lupus erythematosus. *Pediatr Nephrol* 2006;**21**:598–9.
497 **Ng KP**, Leandro MJ, Edwards JC, *et al*. Repeated B cell depletion in treatment of refractory systemic lupus erythematosus. *Ann Rheum Dis* 2007;**65**:942–5.
498 **Rech J**, Hueber AJ, Kallert S, *et al*. Immunoadsorption and CD20 antibody treatment in a patient with treatment resistant systemic lupus erythematosus and preterminal renal insufficiency. *Ann Rheum Dis* 2006;**65**:552–3.
499 **Risselada AP**, Kallenberg CGM. Therapy-resistent lupus skin disease successfully treated with rituximab. *Rheumatology (Oxford)* 2006;**45**:915–6.
500 **Tokunaga M**, Saito K, Kawabata D, *et al*. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. *Ann Rheum Dis* 2007;**66**:470–5.
501 **Leandro MJ**, Cambridge G, Edwards JC. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. *Rheumatology (Oxford)* 2005;**44**:1542–5.
502 **Leandro MJ**, Edwards JC, Cambridge G, *et al*. An open study of B lymphocyte depletion in systemic lupus erythematosus. *Arthritis Rheum* 2002;**46**:2677.
503 **Anolik JH**, Barnard J, Cappione A, *et al*. Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematosus. *Arthritis Rheum* 2004;**50**:3580–90.
504 **Looney RJ**, Anolik JH, Campbell D, *et al*. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. *Arthritis Rheum* 2004;**50**:2580–9.
505 **Anolik JH**, Campbell D, Felgar RE, *et al*. The relationship of FcãRIIIa genotype to degree of B cell depletion by rituximab in the treatment of systemic lupus erythematosus. *Arthritis Rheum* 2003;**48**:455–9.
506 **Tokunaga M**, Fujii K, Saito K, *et al*. Down-regulation of CD40 and CD80 on B cells in patients with life- threatening systemic lupus erythematosus after successful treatment with rituximab. *Rheumatology (Oxford)* 2005;**44**:176–82.
507 **Edelbauer M**, Jungraithmayr T, Zimmerhackl LB. Rituximab in childhood systemic lupus erythematosus refractory to conventional immunosuppression. *Pediatr Nephrol* 2005;**20**:811–3.
508 **Carroll RP**, Brown F, Kerr PG. Anti CD20 antibody treatment in refractory class IV lupus nephritis. *Nephrol Dial Transplant* 2007;**22**:291–3.
509 **Jacobson SH**, van VR, Gunnarsson I, *et al*. Rituximab-induced long-term remission of membranous lupus nephritis. *Nephrol Dial Transplant* 2006;**21**:1742–3.
510 **Vigna PM**, Hernandez CB, Paredes SO, *et al*. Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. *Arthritis Res Ther* 2006;**8**:1–9.
511 **Ahn ER**, Lander G, Bidot CJ, *et al*. Long-term remission from life-threatening hypercoagulable state associated with lupus anticoagulant (LA) following rituximab therapy. *Am J Hematol* 2005;**78**:127–9.
512 **Ames PRJ**, Tommasino C, Fossati G. Limited effect of rituximab on thrombocytopenia and anticardiolipin antibodies in a patient with primary antiphospholipid syndrome. *Ann Hematol* 2007;**86**:227–8.
513 **Trappe R**, Lowe A, Thuss PP, *et al*. Successful treatment of thrombocytopenia in primary antiphospholipid antibody syndrome with the anti-CD20 antibody rituximab-monitoring of antiphospholipid and anti-GP antibodies: a case report. *Ann Hematol* 2006;**85**:134–5.
514 **Veneri D**, Ambrosetti A, Franchini M, *et al*. Remission of severe antiphospholipid syndrome associated with non-Hodgkin's B-cell lymphoma after combined treatment with rituximab and chemotherapy. *Haematologica* 2005;**90**:15–6.
515 **Rubenstein J**, Arkfeld DG, Metyas S, *et al*. Rituximab treatment for resistant antiphospholipid syndrome. *J Rheumatol* 2006;**33**:355–7.
516 **Arlet JB**, Dimitri D, Pagnoux C, *et al*. Marked efficacy of a therapeutic strategy associating prednisone and plasma exchange followed by rituximab in two patients with refractory myopathy associated with antibodies to the signal recognition particle (SRP). *Neuromuscul Discord* 2006;**16**:334–6.
517 **Brulhart L**, Waldburger JM, Gabay C. Rituximab in the treatment of antisynthetase syndrome. *Ann Rheum Dis* 2006;**65**:974–5.
518 **Dinh HV**, McCormic C, Hall S, Prince HM. Rituximab for the treatment of the skin manifestations of dermatomyositis: a report of 3 cases. *J Am Acad Dermatol* 2007;**56**:148–53.
519 **Lambotte O**, Kotb R, Maigne G, *et al*. Efficacy of rituximab in refractory polymyositis. *J Rheumatol* 2005;**32**:1369–70.
520 **Chung L**, Genovese MC, Fiorentino D. Rituximab in the treatment of patients with dermatomyositis: 12 week interim analysis of a pilot trial. *Arthritis Rheum* 2005;**52**:4088.
521 **Levine TD**. Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum* 2005;**52**:601–7.
522 **Noss EH**, Hausner-Sypek DL, Weinblatt ME. Rituximab for refractory polymyositis and dermatomyositis. *J Rheumatol* 2007;**33**:1021–6.
523 **Ahnadi SK**, Lamprecht P, Jankowiak C. Successful treatment of refractory adult onset Still's disease with rituximab. *Ann Rheum Dis* 2006;**65**:1117–8.

APPENDICES: CATEGORIES OF EVIDENCE

- *Category A evidence*: based on evidence from at least one randomised controlled trial or meta-analyses of randomised controlled trials.
- *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.

Note: abstracts have not been considered in the above evidence scheme, as they are not complete and may change by the time the data are published, or they may not be published as full papers at all. Evidence from abstracts alone, therefore, is considered as Category D evidence and noted as ''abs'' until those data are published as a complete, peer-reviewed paper.

APPENDIX 1: ANECDOTAL STUDIES OF ANTI-TNF AGENTS

Anecdotal studies of anti-TNF agents

Disease	Author(s)	Medication	No. of patients
Adult Still's disease	Huffstutter and Sienknechet[247]	Infliximab	2
	Kraetsch *et al*[248]	Infliximab	6
	Weinblatt *et al*[149]	Etanercept	12
	Fernandez-Nibro[249]	Etanercept	3
Amyloidosis	Elkayam *et al*[250]	Infliximab	1
	Gottenberg *et al*[251]	Etanercept/infliximab	15
	Ortiz-Santamaria *et al*[252]	Infliximab	6
	Tomero *et al*[253]	Infliximab	12
	Kallinick *et al*[525]	Etanercept	1
	Ravindran *et al*[526]	Etanercept	1
	Smith *et al*[254]	Etanercept	1
Aphthous stomatitis	Robinson and Guitart[255]	Etanercept	1
	Vujevich and Zirwas[256]	Adalimumab	1
	Atzini *et al*[257]	Etanercept	1
Back pain (incl sciatica)	Sakellariou *et al*[258]	Infliximab	1
	Genevay *et al*[259]	Etanercept	10
Behçet's disease	Estrach *et al*[260]	Infliximab/ adalimumab	7
	Gulli *et al*[261]	Infliximab	1
	Hassard *et al*[262]	Infliximab	1
	Licata *et al*[263]	Infliximab	1
	Melikoghu *et al*[264]	Etanercept	20
	Morillas *et al*[265]	Adalimumab/ etanercept	
	Rosenbaum *et al*[266]	Anti-TNF	1
	Saulsbury and Mann[267]	Infliximab	1
	Sangle *et al*[268]	Infliximab	1
	Sfikakis *et al*[269]	Infliximab	5
	Sfikakis[270]	Infliximab	11
	Ribi *et al*[271]	Infliximab	1
	Sweiss *et al*[272]	Infliximab	3
	Van Laar et at[273]	Adalimumab	6
Bronchiolitis	Cortot *et al*[274]	Etanercept	1
Cirrhosis and alcoholic hepatitis	Naveau *et al*[176]	Infliximab	36
	Spahr *et al*[275]	Infliximab	20
	Wendling *et al*[182]	Infliximab	1
	Menon *et al*[276]	Etanercept	13
Cutaneous T cell lymphoma	Tsimberidou *et al*[277]	Etanercept	13
Dermatitis, hidradenitis, miscellaneous	Bongartz *et al*[158]	Infliximab	1
	Cortis *et al*[278]	Etanercept	1
	Cummins *et al*[279]	Etanercept	1
	Massarotti and Sobell[280]	Etanercept	[1]
	Zeichner *et al*[281]	Adalimumab	1
	Csusak *et al*[280]	Etanercept	6
	Jurgens-Meyer *et al*	Etanercept	1
Dermatomyositis	Hengstman *et al*[282]	Infliximab	2
	Miller *et al*[283]	Etanercept	10
	Sprott *et al*[284]	Etanercept	1
	Nzeusseu *et al*[285]	Infliximab	1
	Saadeyh[286]	Etanercept	4
	Norman *et al*[287]	Etanercept	2
Erythema nodosum refractory chronic	Ortego-Centeno *et al*[288]	Adalimumab	1
Familial Mediterranean fever	Takada *et al*[289]	Etanercept	2
	Ozgocmen *et al*[290]	Etanercept	1
Felty's syndrome	Ghavami *et al*[291]	Etanercept	1
Giant cell arteritis	Andonopoulos *et al*[292]	Infliximab	2
	Cantini *et al*[293]	Infliximab	4
	Tan *et al*[294]	Etanercept	1
	Ahmed *et al*[295]		1
Graft vs host disease (acute)	Wolff *et al*[296]	Etanercept	21
	Uberti *et al*[297]	Etanercept	20
	Kennedy *et al*[298]	Etanercept	20
	Chiang *et al*[299]	Etanercept	8
	Pavletic *et al*[300]	Etanercept	4
	Andolina[301]	Etanercept	1
Graves ophthalmopathy	Paridiena *et al*[302]	Etanercept	10
Hepatitis C	Cacoub *et al*[172]	Interferon alfa	27
	McMinn *et al*[303]	Etanercept	3
	Peterson *et al*[304]	Infliximab/etanercept	24
	Pritchard [305]	Etanercept	1
	Ince *et al*[127, FF 29 174]	Etanercept	12
	Moreno *et al*[306]	Etanercept	5
	Allen *et al*[307]	Etanercept	2
	Marotte *et al*[308]	Etanercept	9
	Rokhsar[309]	Etanercept	1
	Magliocco and Gottlieb[264]	Etanercept	3
HIV	Wallis *et al*[310]	Etanercept	16
Immunodeficiency (common variable)	Smith and Skelton[178]	Etanercept	1
	Lin *et al*[311]	Etanercept	1
	Capeda *et al*[312]	Etanercept	7
Inclusion body myositis	Barohn *et al*[313]	Etanercept	9 (ineffective)
	Singh *et al*[314]	Etanercept	1
Juvenile-onset HLA-B27-associated severe and refractory heal enthesitis	Olivieri *et al*[315]	Adalimumab	1
Kawasaki's disease	Weiss *et al*[316]	Infliximab	1
	Burns *et al*[317]	Infliximab	16
Multicentric histiocytosis	Lovelace *et al*[318]	Etanercept	1
	Matejicka *et al*[319]	Etanercept	1
	Kovach *et al*[320]	Etanercept	1
Myelodysplasia	Birnbaum and Gentile[321]	Etanercept	1
	Deeg *et al*[322]	Etanercept	14
	Rosenfeld *et al*[323]	Etanercept	19 (ineffective)
	Raza[324]	Etanercept	26
	Maciejewski[325]	Etanercept	16
Periodic fever (children)	Athreya *et al*[326]	Etanercept	3
Pigmented villonodular synovitis	Kroot *et al*[327]	TNF	1
Polymyositis	Hengstman *et al*[282]	Infliximab	2
	Sprott *et al*[284]	Etanercept	1
	Adams *et al*[328]	Adalimumab	2
Polychondritis	Carter (with literature review)[329]	Infliximab	1
	Ehresman[330]	Etanercept	5
Pyoderma gangrenosum	Fonder *et al*[331]	Adalimumab	1
	Heffernan *et al*[332]	Adalimumab	1
Osteoarthritis (erosive)	Magnano *et al*[333]	Adalimumab	12
SAPHO syndrome	Furst *et al*[1]	TNF	–
	Anker and Coats[166]	Infliximab/etanercept	150
	Sweiss *et al*[334]	Infliximab	3
	Callejas-Rubio *et al*[335]	Adalimumab	1
	Korhonen *et al*[336]	Infliximab	12
	Korhonen *et al*[337]	Infliximab	40
	Lam *et al*[338]	Infliximab	18
	Pasternack *et al*[339]	Etanercept	4
	Tobinick and Davoodifar[340]	Etanercept	43
	Khanna *et al*[341]	Etanercept	1
	Utz *et al*[342]	Etanercept	17
	Wagner *et al*[343]	Etanercept	2
	Moul *et al*[344]	Adalimumab	1

Continued

Disease	Author(s)	Medication	No. of patients
Sarcoidosis	Khanna *et al*[343]	Etanercept	1
	Utz *et al*[342]	Etanercept	1
	Hefferman *et al*[345]	Adalimumab	1
	Callejas-Rubio[335]	Adalimumab	1
	Querfeld *et al*[346]	Etanercept	1
	Sweiss *et al*[272]	Etanercept	1
	Hobbs *et al*[347]	Etanercept	1
Scleroderma	Ellman *et al*[348]	Etanercept	8
	Bosello *et al*[349]	Etanercept	4
Silicone granulomas	Pasternack *et al*[339]	Etanercept	2
Sjogren's syndrome	Zandfelt *et al*[350]	Etanercept	15 (ineffective)
	Sankar *et al*[72]	Etanercept	14 (ineffective)
	Pessler *et al*[351]	Etanercept	1
Still's disease (include Adult onset)	Fautrel *et al*[352]	Etanercept	20 (ineffective)
	Stern *et al*[353]	Etanercept	1 (worsening)
	Asherson *et al*[354]	Etanercept	1
	Kumari *et al*[355]	Etanercept	1
Sweet's syndrome	Gindi *et al*[356]	Etanercept	1
	Yamanuchi *et al*[357]	Etanercept	24
Systemic lupus erythematosus	Aringer *et al*[358]	Infliximab	6
	Fantrel *et al*[352]	Etanercept	1(SCLE)
	Lurati *et al*[359]	Etanercept	1
	Jackson *et al*[360]	Etanercept	1(SCLE)
	Norman *et al*[287]	Etanercept	1(SCLE)
	Hernandez-Ibarra *et al*[361]	N/A	–
	Principi *et al*[362]	Infliximab	1
Takayasu's arteritis	Hoffman *et al*[363]	Anti-TNF	15
	Della Rossa *et al*[364]	Infliximab	2
	Tato *et al*[365]	Adalimumab	1
TRAP	Hull *et al*[366]	Etanercept	>50
	Lamprecht *et al*[367]	Etanercept	2
	Drewe *et al*[368]	Etanercept	1
Uveitis	Estrach *et al*[260]	Infliximab/ adalimumab	7
	Joseph *et al*[369]	Infliximab	5
	Smith *et al*[370]	Etanercept	7
	Braun *et al*[371]	Etanercept/Infliximab	717 (uveitis in AS)
	Foster *et al*[372]	Etanercept	20 (ineffective)
	Biester *et al*[373]	Adalimumab	18
	Foeldvari *et al*[374]	Anti-TNF	47
	Vazquez-Cobain *et al*[375]	Adalimumab	14
	Reiff *et al*[376]	Etanercept	10
	Schmeling and Horneff[377]	Etanercept	20 (ineffective)
	Guignard *et al*[378]	Adalimumab	8
Vasculitis (see also Behcet's, GCA, Takayasu's, Wegener's)	Booth *et al*[379]	Infliximab	32
	Feinstein and Arroyo[380]	Etanercept	1
	Van dan Bijl[381]	Infliximab	11
	Saji *et al*[382]	Infliximab	1 (Kawasaki's)
	Sangle *et al*[268]	Infliximab	1 (Churg-Syrauss)
	Arbach *et al*[383]	Etanercept/infliximab	3
Wegener's granulomatosis	Gause *et al*[384]	Infliximab	10
	Sangle *et al*[268]	Infliximab	3

N/A, not available; TNF, tumour necrosis factor; TRAPS, TNF receptor-associated periodic syndrome.

APPENDIX 2: ANECDOTAL STUDIES OF IL1RA (ANAKINRA)

Anecdotal studies of IL1ra (anakinra)

Disease	Author(s)	No. of patients
Acute stroke	Emsley *et al*[385]	34
Additional data in hereditary autoinflammatory disorders	Leslie *et al*[386]	22
Adult-onset Still's disease	Rudinskaya *et al*[387]	1
	Quartier P *et al*[388]	15
	Aelion *et al*[389]	2
	Haraoui B *et al*[390]	3
	Kalliolias *et al*[391]	2
	Nordstrom *et al*[392]	3
	Kalliolias *et al*[393]	3
	Fitzgerald *et al*[394]	4
	Vasques Godinho *et al*[395]	1
	Haibel *et al*	1
	Tan *et al*[212]	1
Bone marrow transplant	Antin *et al*[396]	186
Consider intra-articular use of anakinra	Birmingham *et al*[397]	7
Cytophagic histiocytic panniculitis	Behrens *et al*[398]	1
FCAS	Hoffman *et al*[78]	2
	Metyas *et al*[399]	1
Diabetes mellitus	Larsen *et al* CM 2007;356:1517	?
GVD	Anton *et al*[396]	8
Hyper-IgD and periodic fever syndrome	Bodar *et al*[400]	3
	Rigante *et al*[401]	1
Juvenile idiopathic arthritis	Verbsky *et al*[402]	2
Juvenile polyarticular arthritis	Ilowite *et al*[403]	79
	Ilowite *et al*[404]	86
Muckle–Wells syndrome	Hawkins *et al*[405]	2
	Saha *et al*[406]	1
	Ramos *et al*[407]	1
	Rynne *et al*[408]	1
	Mirault *et al*[409]	1
	Simon *et al*[229]	1
NOMID/CINCA	Goldbach-Mansky *et al*[410]	18 NOMID
	Frenkel *et al*[411]	3
	Rigante *et al*[412]	1 CINCA
	Hawkins *et al*[405]	1
	Seitz *et al*[413]	1
	Granel *et al*[414]	1
	Boschan *et al*	1
	Callejas *et al*[335]	1
	Namde *et al*[415]	20
	Namde *et al*[416]	18
	Namde *et al*[417]	18
	Gattorno *et al*[418]	6 NOMID
	Caroli *et al*[419]	12
	Lovell *et al*[420]	2
Osteoarthritis	Chevallier *et al*[213]	?
Osteoarthritis (intra articular)	Chevalier *et al*[214]	14
PAPA	Dierselhuis *et al*[421]	1
Psoriatic arthritis	Jung *et al*[422]	20
	Gibbs *et al*[423]	12
Relapsing polychondritis	Vounotrypidis *et al*[424]	1
Schnitzler's syndrome	Martinez-Tabouda *et al*[425]	1
Systemic lupus erythematosus	Moosiq *et al*[215]	3
	Ostendorf *et al*[216]	4
Systemic-onset juvenile idiopathic arthritis	Pascual *et al*[426]	9
	Henrickson *et al*[427]	4
	Reiff[428]	1
	Lurati *et al*[359]	1
	Mirkinson *et al*[429]	6
	Verbsky *et al*[402]	2
	Weiss *et al*[430]	–
	Punaro *et al*[431]	13
	Zeft *et al*[432]	12
	Gattorno *et al*[418]	–
	Gattorno *et al*[433]	15
	Quartier *et al*[388]	23
	Simon *et al*[229]	1

APPENDIX 3: ABSTRACTS OR ANECDOTAL STUDIES OF RITUXIMAB

Abstracts or anecdotal studies of rituximab

Disease	Author(s)	No. of patients
Rheumatoid arthritis	Cohen *et al.*[245]	520
	Emery *et al.*[240]	465
	Strand *et al.*[434]	161
	Edwards *et al*[435]	161
	Popa *et al.*[436]	37
	Higashida *et al.*[437]	17
	Moore *et al.*[438]	10
	Kneitz *et al.*[439]	5
	Leandro *et al.*[440]	22
	De Vita *et al.*[441]	5
	Scheinberg *et al.*[442]	10
	Maher *et al.*[443]	1
	Cambridge *et al.*[444]	15
	Leandro *et al.*[445]	24
	Roll *et al.*[446]	17
Microscopic polyangiitis,	Stasi *et al.*[447]	10
	Eriksson *et al.*[448]	9
Microscopic polyangiitis, Churg-Strauss syndrome	Smith *et al.*[449]	11
Wegener's granulomatosis	Aries *et al.*[450]	8
	Keogh *et al.*[451]	10
	Sanchez-Cano *et al.*[452]	1
	Tektonidou *et al.*[453]	1
	Bachmeyer *et al.*[454]	1
	Ferraro *et al.*[455]	1
	Kallenbach *et al.*[456]	1
	Memet *et al.*[457]	1
	Specks *et al.*[458]	1
ANCA vasculitis	Clatworthy *et al.*[459]	1
Churg-Strauss syndrome	Koukoulaki *et al.*[460]	2
	Kaushik *et al.*[461]	1
Cryoglobulinaemia Type II and III	Sansonno *et al.*[462]	20
CryoglobulinaemiaType II.	Quartuccio *et al.*[463]	5
Cryoglobulinaemia Type III	Basse *et al.*[464]	7
Cryoglobulinaemia hepatitis C virus	Cai *et al.*[465]	1
Cryoglobulinaemia Type II hepatitis C virus	Pekow *et al.*[466]	3
Cryoglobulinemia Type I non-Hodgkin's lymphoma	Telander *et al.*[467]	1
Cryoglobulinaemia Type II	Bryce *et al.*[468]	8
	Zaja *et al.*[469]	15
	Arzoo *et al.*[470]	1
	Basse *et al.*[471]	3
	Ghijsels *et al.*[472]	1
	Koukoulaki *et al.*[460]	1
	Lamprecht *et al.*[473]	1
	Zaja *et al.*[469]	15
	Bryce *et al.*[474]	11
Cryoglobulinaemia Type I	Nehme *et al.*[475]	2
Sjögren's syndrome	Ring *et al.*[476]	1
	Touma *et al.*[477]	1
	Pijpe *et al.*[478]	15
	Pijpe *et al.*[479]	1
	Voulgarelis *et al.*[480]	6
	Voulgarelis *et al.*[481]	4
	Gottenberg *et al.*[482]	6
	Ahmadi-Simab *et al.*[483]	1
	Harner *et al.*[484]	1
	Somer *et al.*[485]	1
	Shih *et al.*[486]	1
	Ramos-Casals *et al.*[487]	2
Juvenile idiopathic arthritis polyarticular	Kuek *et al.*[488]	1
Juvenile idiopathic arthritis with EBV-associated lymphoproliferative disorder (LPD)	Kelaidi *et al.*[489]	1

Continued

Disease	Author(s)	No. of patients
Systemic lupus erythematosus	Armstrong *et al.*[490]	1
	Gormond-Mennesson *et al.*[491]	26
	Haddad *et al.*[492]	11
	Jansson *et al.*[493]	2
	Kotani *et al.*[494]	1
	MacDermott *et al.*[495]	7
	Marks, Tullus *et al.*[496]	7
	Ng *et al.*[497]	7
	Rech *et al.*[498]	1
	Risselada *et al.*[499]	2
	Smith *et al.*[449]	11
	Tokunaga *et al.*[500]	10
	Leandro *et al.*[501 502]	24
	Anolik *et al.*, Looney *et al.*[503–505]	17
	Tokunga *et al.*[506]	5
	Ng *et al.*[497]	24
	Elderbauer *et al.*[507]	1
SLE	Carroll *et al.*[508]	4
	Jacobson *et al.*[509]	1
	Vigna *et al*[510]	22
Antiphospholipid syndrome	Ahn *et al.*[511]	1
	Ames *et al.*[512]	1
	Trappe *et al.*[513]	1
	Veneri *et al.*[514]	1
Antiphospholipid syndrome and catastrophic antiphospholipd antibody syndrome	Rubenstein *et al.*[515]	3
Myopathy	Arlet *et al.*[516]	2
Antisynthetase syndrome	Brulhart *et al.*[517]	1
Dermatomyositis	Dinh *et al.*[518]	3
	Lambotte *et al.*[519]	1
	Chung *et al.*[520]	8
	Levine *et al.*[521]	7
Dermatomyositis and polymyositis	Noss *et al.*[522]	3
	Chiappetta *et al.*	1
Still's disease	Ahnadi *et al.*[523]	2