

## CONSENSUS STATEMENT

# Updated consensus statement on biological agents, specifically tumour necrosis factor $\alpha$ (TNF $\alpha$ ) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases, 2005

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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 institutions had no part in the decisions about the specific programme or about the academic participants at this conference. Further, they did not participate in the preparation or writing of this document.

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

The 140 rheumatologists and bioscientists who attended the consensus conference were chosen from a worldwide group of physicians and other scientists from 19 countries. They had 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.

Additional information has come to light in the last year, both corroborating the major positive effect these drugs have had in rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and other rheumatic diseases, as well as further documenting adverse events. Therefore an update of the previous consensus statement is appropriate.<sup>1</sup> The consensus statement is annotated to document the credibility of the data supporting it as much as possible. This annotation is that of Shekelle *et al* and is described in appendix 3.<sup>2</sup> As the number of possible references has become so large, reviews were sometimes used and, if they contained A level references, are referred to as A level evidence. All participants reviewed relevant clinical published articles relating to tumour necrosis factor (TNF) and interleukin (IL)-1 blocking agents. 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 severity of their disease, their perception of its severity, the concomitant structural damage associated with the disease, 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 TNF $\alpha$  blocking agents, efficacy and clinical use for these diseases will be treated separately from RA. Adverse reactions, however, will remain combined for all indications until individual data for each indication are accumulated and sufficiently different to justify separate consideration. 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<sup>3</sup>). Validated quantitative measures such as Disease Activity Score (DAS), Simple Disease Activity Index (SDAI), 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<sup>3,4</sup>). The physician should evaluate the 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, radiographs for assessment of structural damage, as well as measures of skin response have been used and appear responsive (category A evidence<sup>3</sup>). They remain, however, to be fully validated in this disease. For AS, measures such as the ASsessment in Ankylosing Spondylitis (ASAS) Working Group Response Criteria, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) have been used in the clinical trial setting. Radiographs and magnetic resonance imaging (MRI) scans of the spine are validated and have also been used in clinical trials. Low disease activity state (termed "Partial Remission Criteria"), joint tenderness and swelling, spinal motion,

**Abbreviations:** aCL, anticardiolipin antibodies; ACR, American College of Rheumatology; ANA, antinuclear antibodies; AS, ankylosing spondylitis; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; DAS, Disease Activity Score; DMARD, disease modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire disability index; IL-1(ra), interleukin-1 (receptor antagonist); MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index; SF-36, Medical Outcome Survey Short Form 36; TNF, tumour necrosis factor; VAS, visual analogue scale

global and pain response measures, functional indices, and acute phase reactants have been used and also appear responsive in clinical trials (category A evidence<sup>6-10</sup>).

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. Because these agents are not free of toxicity, patients or their representatives should be provided with information about potential risks and benefits so that they may give informed consent for treatment.

**TNF BLOCKING AGENTS**

TNF blocking agents differ in composition, precise mechanisms of action, pharmacokinetics, biopharmaceutical properties, etc., 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**

The optimal approach to the treatment of active RA is thought to require early and intensive intervention with close monitoring of response to treatment (category A evidence<sup>11</sup>). If response is not optimal, switching of therapeutic strategies is recommended (category B evidence<sup>12-13</sup>).

TNF blockers are recommended for the treatment of active RA, generally after an adequate trial of another effective DMARD, of which methotrexate (MTX) is the most commonly used example. They have also been used successfully with other DMARDs, including sulfasalazine, leflunomide, etc. (category A evidence<sup>11-40</sup>). TNF blocking agents can be added to pre-existing therapy, or, when appropriate, may replace previous DMARDs (category A evidence<sup>11-39</sup>). There is evidence that TNF blockers are effective for the treatment of RA in MTX naive patients (category A evidence<sup>14-16-18-21-22-25-27-31-35-38-39</sup>; category D evidence<sup>23-29-30</sup>). The use of TNF blocking agents as the first DMARD for the treatment of RA (category A evidence<sup>11-12-14-16-18-21-22-25-31-35-38-39</sup>; category D evidence<sup>38</sup> (abstract<sup>39</sup>)) should, at present, be limited because one must consider emerging data on long term safety and effectiveness as well as their expense and one needs to include health economic considerations along with these other factors. However, as some patients had not yet received other DMARDs in trials of TNF blockers, TNF blocking agents may be considered as the initial DMARD in some patients (category A, D (abstract) evidence<sup>12-16-18-21-22-25-31-35-38-39</sup>).

Adalimumab and etanercept are both approved as monotherapy or in combination with other DMARDs for RA, while infliximab is approved for use with MTX in RA. However, the cumulative weight of the 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 (EULAR) remission) and radiological outcomes (category A evidence<sup>11-13-14-18-27-31-35-39-40-42</sup>). TNF $\alpha$  blocking agents have been used with combinations of background DMARDs (category B evidence<sup>24</sup>).

**Psoriatic arthritis**

Etanercept and infliximab have been approved in the USA and Europe for the treatment of PsA; adalimumab has been approved in Europe and is awaiting approval decision in the USA (category A, B, C evidence<sup>18-43-56</sup>). Controlled trial data to support conventional DMARDs as first line therapy for PsA are scant, showing modest effects of drugs such as MTX, sulfasalazine, leflunomide, and ciclosporin on joint and, in some cases, skin disease in PsA (category A evidence<sup>56-60</sup>).

Controlled trials with etanercept (category A evidence<sup>42-45-46</sup>) adalimumab (category A evidence<sup>51</sup>) and infliximab (category C evidence<sup>44-47</sup>) have demonstrated statistically significant improvement in a number of response measures. There are data supporting the inhibition of radiographic structural progression for adalimumab, etanercept, and infliximab (category A evidence<sup>46-49-51-54-55</sup>). These agents are of benefit both as monotherapy and as add-on therapy to other DMARDs such as MTX (category A evidence<sup>43-45-55</sup>). The skin lesions of psoriasis in patients with PsA have also improved (category A, D (abstract) evidence<sup>44-46-48-50-51-54-55-61-66</sup>). No dose ranging studies of TNF blocking agents have been published for PsA.

**Ankylosing spondylitis**

TNF blocking agents are recommended for the treatment of active AS after having failed treatment for the patient's predominant clinical manifestation (category A evidence<sup>6-10-67-73</sup>).

Etanercept has been approved for the treatment of severe, active AS in Europe and the USA and infliximab is approved for this indication in the USA (category A, C evidence<sup>6-10-67-73</sup>) (table 1). Adalimumab is being tested in this disease (unpublished data, Abbott Laboratories). In these clinical trials, TNF blocking agents were used as monotherapy and, in some trials, second line agents such as sulfasalazine or MTX were allowed as concomitant medications (category A, C evidence<sup>6-10-67-73</sup>). TNF $\alpha$  blocking agents maintain efficacy over two to four years in open studies.<sup>68-69-71-73-74</sup> The ASAS Working Group has published recommendations for the use of TNF blocking agents in AS (category A evidence<sup>67</sup>). The approved dose of infliximab in AS is 5 mg/kg every six to eight weeks after induction and the etanercept dose is the same as that used for RA (see the respective package insert for each drug). Adalimumab is being tested at the same dosing range as is approved for RA (unpublished data, Abbott Laboratories). No dose ranging studies have been done with these drugs in this indication.

Health economic data and long term safety data may change the circumstances when TNF blocking agents will be started in a practice setting. Cost efficacy data have been published in RA and are being explored in other indications. The varying results may in part be due to varying underlying assumptions and the varying sources of the analyses (category B evidence<sup>20-75-84</sup>).

**Other rheumatic diseases or those with prominent rheumatic manifestations**

- Trials that demonstrated a difference from placebo or positive control:
  - Etanercept has been approved for juvenile idiopathic arthritis of the polyarticular type (category A evidence<sup>19-34</sup>; FDA Summary Basis of Approval).
  - Infliximab has been approved to treat luminal and fistulising Crohn's disease, including those with

**Table 1** Permitted use of tumour necrosis factor (TNF) blocking agents in the European Union (EU) and the USA

	Rheumatoid arthritis		Psoriatic arthritis		Ankylosing spondylitis	
	EU	USA	EU	USA	EU	USA
Adalimumab	✓	✓	✓		✓	✓
Etanercept	✓	✓	✓	✓	✓	✓
Infliximab	✓	✓	✓	✓	✓	✓

articular manifestations (category A evidence<sup>85</sup>; FDA Summary Basis of Approval).

- Etanercept was effective for treating some of the mucocutaneous manifestations of Behçet's syndrome versus placebo over four weeks<sup>86</sup> (not true for iritis—see below for case reports and series)
- Trials that failed to demonstrate a difference from placebo:
  - Sjögren's syndrome (category A evidence<sup>87-89</sup>)
  - Wegener's granulomatosis (category A evidence<sup>90</sup>). Note: an open trial of infliximab was effective but associated with severe infections (category D (abstract evidence<sup>91</sup>)).
- Anecdotal series or studies with promising results:
  - see table 2.

## Clinical use

### Efficacy

#### Rheumatoid arthritis

TNF blocking agents, when given using the maximum approved dosing regimens for RA, PsA, AS, and juvenile RA, should lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters within 12 weeks (category A, B, C, D (abstract) evidence<sup>6-55 68-75</sup>). There is no evidence that any one TNF blocking agent should be used before another one can be tried, just as there is no credible evidence that any TNF blocker is more effective than any other in RA (see above) (category A, D (abstract) evidence<sup>155-161</sup>). Patients have been switched from one TNF blocking agent to another but no well controlled switch trials have been published (category B, D (abstract) evidence<sup>155-161</sup>). These observational studies have shown that some patients who have not responded to one TNF blocking agent have a demonstrable improvement in disease activity when switched to another TNF blocking agent and they suggest that failure to respond to one TNF blocking agent does not preclude response to another (category B, D (abstract) evidence<sup>11-13 156-161</sup>).

Individually important validated responses including patient oriented measures (for example HAQ-DI, patients global VAS, Medical Outcome Survey Short Form 36 (SF-36)) or physical measures (for example joint tenderness or the DAS 28) should be demonstrated within 12 weeks for RA (category A evidence<sup>11-43 155-164</sup>), PsA (category A evidence<sup>19 44-55 61</sup>), AS (category A evidence<sup>6-10 68-75</sup>), and, probably, juvenile RA (category A evidence<sup>19 34 35</sup>). If such improvement occurs, treatment should be continued. If patients show no response to these agents, they should be stopped. Observations suggest that increasing the dose or reducing the dosing intervals or changing the TNF blocking agent may provide additional benefit in RA, as may the addition or substitution of other DMARDs (category A, D (abstract) evidence<sup>11 12 36 155-161</sup>). However, because regression to the mean may occur, caution is needed when interpreting apparent improvements following dose escalation in practice (category C evidence<sup>161</sup>).

There are data showing that TNF blocking agents slow radiographic progression in RA (category A evidence<sup>11 12 14 15 19 26-33 165-169</sup>), and in some individuals may inhibit it (category A, C evidence<sup>26 32 155</sup>). The clinical activity and radiographic progression are dissociated in some patients. Some RA patients treated with anti-TNF agents without reaching responder criteria have slowing of radiographic progress, although this may be a function of the response criteria being used (category A, C evidence<sup>162 167</sup>). The long term clinical implications of these changes are

**Table 2** Anecdotal studies

Disease	Author	Medication	No of patients
Adult Still's disease	Huffstutter and Sienknecht <sup>92</sup>	Infliximab	2
	Kraetsch <i>et al</i> <sup>93</sup>	Infliximab	6
	Weinblatt <i>et al</i> <sup>94</sup>	Etanercept	12
Amyloidosis	Elkayam <i>et al</i> <sup>95</sup>	Infliximab	1
	Gottenberg <i>et al</i> <sup>96</sup>	Etanercept/ infliximab	15
	Ortiz-Santamaria <i>et al</i> <sup>97</sup>	Infliximab	6
Behçet's disease	Tomero <i>et al</i> <sup>98</sup>	Infliximab	12
	Estrach <i>et al</i> <sup>99</sup>	Infliximab/ adalimumab	7
	Gulli <i>et al</i> <sup>100</sup>	Infliximab	1
Behçet's disease	Hassard <i>et al</i> <sup>101</sup>	Infliximab	1
	Licata <i>et al</i> <sup>102</sup>	Infliximab	1
	Melikoglu <i>et al</i> <sup>103</sup>	Etanercept	20
	Rozenbaum <i>et al</i> <sup>104</sup>	Anti-TNF $\alpha$	1
	Saulsbury and Mann <sup>105</sup>	Infliximab	1
	Sfikakis <i>et al</i> <sup>106</sup>	Infliximab	5
	Sfikakis <sup>107</sup>	Infliximab	11
	Shereen and Moore <sup>108</sup>	Infliximab	1
	Weiss <i>et al</i> <sup>109</sup>	infliximab	3
	Naveau <i>et al</i> <sup>110</sup>	Infliximab	36
Cirrhosis and alcoholic hepatitis	Wendling <i>et al</i> <sup>111</sup>	Infliximab	1
	Spahr <i>et al</i> <sup>112</sup>	Infliximab	20
Cutaneous T cell lymphoma	Tsimberidou <i>et al</i> <sup>113</sup>	Etanercept	13
Dermatomyositis	Hengstman <i>et al</i> <sup>114</sup>	Infliximab	2
	Miller <i>et al</i> <sup>115</sup>	Etanercept	10
	Saadeh <sup>116</sup>	Etanercept	1
Familial Mediterranean fever	Nzeusseu <i>et al</i> <sup>117</sup>	Infliximab	1
	Sprott <i>et al</i> <sup>118</sup>	Etanercept	1
	Hull <i>et al</i> <sup>119</sup>	TRAPS- etanercept	>50
Giant cell arteritis	Takada <i>et al</i> <sup>120</sup>	Etanercept	2
	Andonopoulos <i>et al</i> <sup>121</sup>	Infliximab	2
	Cantini <i>et al</i> <sup>122</sup>	Infliximab	4
Hepatitis C	Tan <i>et al</i> <sup>123</sup>	Etanercept	1
	Zein <i>et al</i> <sup>124</sup>	Infliximab/ etanercept	5
	Parke and Reveille <sup>124</sup>	Etanercept	3
Kawasaki's disease	Magliocco and Gotlieb <sup>125</sup>	Interferon alfa	27
	Cacoub <i>et al</i> <sup>126</sup>	Etanercept	10
	McMinn <i>et al</i> <sup>127</sup>	Etanercept	3
	Peterson <i>et al</i> <sup>128</sup>	Infliximab/ etanercept	24
	Pritchard <sup>129</sup>	Etanercept	1
Multicentric histiocytosis	Burns <i>et al</i> <sup>130</sup>	Infliximab	1
	Weiss <i>et al</i> <sup>131</sup>	Infliximab	1
	Calamia <i>et al</i> <sup>132</sup>	Etanercept	1
Myelodysplasia	Birnbaum and Gentile <sup>133</sup>	Etanercept	1
Periodic fever (children)	Athreya <i>et al</i> <sup>134</sup>	Etanercept	3
Pigmented villonodular synovitis	Kroot <i>et al</i> <sup>135</sup>	Anti-TNF $\alpha$	1
Polymyositis	Hengstman <i>et al</i> <sup>114</sup>	Infliximab	2
	Sprott <i>et al</i> <sup>118</sup>	Etanercept	1
Polychondritis	Ehresman <sup>136</sup>	Infliximab	1
	Furst <i>et al</i>	Etanercept	2
SAPHO syndrome	Wagner <i>et al</i> <sup>137</sup>	Anti-TNF $\alpha$	-
	Tutuncu <i>et al</i> <sup>138</sup>	Etanercept	1
Sarcoidosis	Khanna <i>et al</i> <sup>139</sup>	Etanercept	-
	Baughman and Iannuzzi <sup>140</sup>	Infliximab	3
	Weiss <i>et al</i> <sup>141</sup>	TNF inhibition	13
Sciatica	Utz <i>et al</i> <sup>142</sup>	Etanercept	17
	Korhonen <i>et al</i> <sup>144</sup>	Infliximab	12
	Acheson and Dymek <sup>145</sup>	Infliximab	1
Scleroderma	Genevay <i>et al</i> <sup>146</sup>	Etanercept	10
	Ellman <i>et al</i> <sup>147</sup>	Etanercept	8
Systemic lupus erythematosus	Aringer <i>et al</i> <sup>148</sup>	Infliximab	6
	Hernandez-Ibarra <i>et al</i> <sup>149</sup>	N/A	-
Takayasu's arteritis	Principi <i>et al</i> <sup>150</sup>	Infliximab	1
	Hoffman <i>et al</i> <sup>151</sup>	Anti-TNF $\alpha$	15
	Estrach <i>et al</i> <sup>99</sup>	Infliximab/ adalimumab	7
Uveitis	Joseph <i>et al</i> <sup>152</sup>	Infliximab	5
	Suhler <i>et al</i> <sup>153</sup>	Infliximab	13
	Booth <i>et al</i> <sup>154</sup>	Infliximab	32

N/A, not available; TRAPS, TNF receptor associated periodic syndrome.

unknown; therefore, both clinical and radiological effects should determine clinical decision making. MRI is beginning to be used to document response in RA although it is not yet a fully validated technique for this purpose (category A evidence<sup>167</sup>).

Direct, indirect, and economic costs of RA are substantial and have been generally under-appreciated. Evidence is appearing that all the TNF $\alpha$  blocking agents are cost effective when treating RA (category A, C<sup>76–82</sup>). In a comparison of etanercept and infliximab, both are cost effective. Cost utilities of both were equal (category C evidence<sup>20</sup>).

### Psoriatic arthritis

Individually important responses including patient oriented measures (for example HAQ-DI, patients global VAS, SF-36, BASDI, BASFI, Bath AS Metrology Index (BASMI)) or physical measures (for example, joint tenderness) should be demonstrated within 12 weeks for PsA (category A evidence<sup>43–56</sup>). Data show that adalimumab, etanercept, and infliximab slow radiographic damage in PsA (category A evidence<sup>49 51 54 55</sup>).

### Ankylosing spondylitis

Individually important responses including patient oriented measures (for example HAQ-DI, patients global VAS, SF-36) or physical measures (for example joint tenderness) should be demonstrated within 12 weeks for AS (category A evidence<sup>67–73</sup>). Specific recommendations for therapy have been published (category D evidence<sup>67</sup>).

## Warnings/adverse events

### Infections

An increased evidence of reactivation of latent tuberculosis and some increased susceptibility to new tuberculosis should be considered a class characteristic of TNF blocking agents. The clinical picture of tuberculosis is often atypical in these patients (for example miliary or extrapulmonary presentations) as has been seen in other immunocompromised patients (category C evidence<sup>168–182</sup>). There have been more reported cases of tuberculosis in patients using infliximab than in patients using the other presently marketed agents (category C evidence<sup>168 171–173</sup>). This may be due in part to the fact that populations treated with the various TNF blocking agents differ and the data come from registries and voluntary reporting systems, although the explanation for the observed differences is not yet clear.

Screening of patients about to start TNF blocking agents has reduced the risk of activating tuberculosis (category D evidence<sup>1 168–171 173 176</sup>). Every patient should be evaluated for the possibility of latent tuberculosis, including a history which includes evaluation for the risk of latent tuberculosis (category C evidence<sup>1 168–173</sup>). Patients should be asked questions about their place of birth, residence and past travel, history of prior tuberculosis exposure, bacille Calmette Guérin (BCG) inoculation or prior tuberculosis treatment, high risk behaviours, human immunodeficiency virus (HIV) infection or high degrees of exposure, and a history of working in a high risk tuberculosis setting such as jail, homeless shelter, drug rehabilitation centre, etc. (category D evidence). In addition, physical examination and such screening tests as skin tests and chest radiographs should be done and interpreted according to local recommendations (category C, D evidence<sup>1 168 179</sup>). Continued vigilance is required to prevent activation of latent tuberculosis or acquisition in new cases. The occurrence of opportunistic infections should also be sought.

In treating latent tuberculosis, the time frame after initiating tuberculosis therapy to starting the TNF blocking agent remains to be determined. Experts recommend starting

antitubercular therapy before beginning TNF blocking agents (category D evidence).

Opportunistic infections have occurred in the setting of TNF blocking agent use (category C evidence<sup>14 15 19 28–31 72 160 168–173 179 183</sup>). Particular vigilance is needed when considering those infections whose containment is macrophage/granuloma dependent such as listeriosis, coccidiomycosis, or histoplasmosis (category C, D evidence<sup>160 168 170 173 176–181</sup>) but the incidence of opportunistic infections is extremely low (category C, D evidence<sup>168 179 180</sup>). The incidence of such infections, perhaps due to their very low incidence, has not been shown to be higher than for other DMARDs or for corticosteroids.

Serious bacterial infections have been observed in patients receiving TNF blocking agents.<sup>184 185</sup> The incidence of serious bacterial infections is increased when using infliximab, although only when using 10 mg/kg. Except for this specific dose of this specific drug, it is not clear if the incidence of serious bacterial infections when using TNF blocking agents is higher than in patients with RA using other forms of DMARD therapy and/or corticosteroids (category D evidence). TNF blocking agents should not be started or should be discontinued when serious infections and/or opportunistic infections occur, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections, listeriosis, etc. (category C evidence<sup>14 15 29 31 168 179 183 186</sup>). Treatment with TNF blockers in such patients should only be resumed if the infections have been treated adequately (category D evidence<sup>1 168 179</sup> package insert). Patients should be instructed regarding the rudiments of differentiating simple viral illnesses and minor infections from those with the potential to cause serious harm and should be instructed to inform their prescriber when signs of the more serious infections occur.

Vaccinations against pneumonia and influenza may be slightly affected by the use of TNF blocking agents, these vaccinations should be given, if possible, before commencing the use of these agents (category A evidence<sup>187–189</sup>).

In placebo-controlled trials, injection site reactions, some of which resulted in drug discontinuation, were commoner with subcutaneously administered TNF blocking agents than with placebo. Infusion reactions for TNF blocking agents given intravenously (that is infliximab) are uncommon and are usually mild-moderate, but may, rarely, be serious (category A evidence<sup>13–15 29–31 36–38 170 179</sup>; category B, C evidence<sup>11 75 160 168 174 179</sup>).

### Malignancies

The incidence of lymphoma is increased in RA, particularly in RA with high disease activity (category B evidence<sup>190–193</sup>). In clinical trials of TNF blocking agents, there is a two to sixfold increase in lymphomas (especially non-Hodgkin's lymphomas) in RA and AS populations (category C evidence<sup>168 179 190–193</sup>). When compared with a matched RA population, the relative risks and incidence were equivalent between those using TNF blocking agents and those not using them. This may be due to the application of these agents in patients with more severe and longstanding disease who have higher risk of develop lymphomas (category C evidence<sup>190 193</sup>).

### Solid tumours

There is thus far no evidence that TNF blocking agents are associated with an increased incidence of solid tumours in RA patients with the exception of smoking related cancers of the lung (category B, C evidence<sup>179 191 192</sup>). There is no evidence that TNF blocking agents increase the solid tumour recurrence rate in RA patients who have had solid malignancies previously (category C evidence<sup>179 191 192</sup>), although patients with recent solid malignancies (<5 years ago) have

generally been excluded from clinical trials (category D evidence). In a study of Wegener's granulomatosis patients, etanercept (25 mg twice weekly) in combination with cyclophosphamide in the past or given concurrently resulted in an increase in common, solid, non-bladder cancers (category A evidence<sup>194</sup>).

Vigilance and studies regarding the occurrence of lymphomas and other malignancies (including recurrence of solid tumours) remains warranted in patients using these medications.

### Haematological

A few rare instances of pancytopenia and aplastic anaemia have been reported (category A, C evidence<sup>14 15 19 29 31 36 168 179</sup>). If haematological adverse events occur, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease or other causative medications before ascribing the event as potentially related to the TNF blockade (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 (NYHA) Class III–IV CHF (category B, D evidence<sup>139 168 179</sup>). 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, D evidence<sup>139 168 179 195</sup>).

It should be noted that well controlled RA studies have excluded patients with complicating illnesses, including CHF. Each patient's risk versus benefit should be considered before TNF blocking agents are begun or continued in patients with CHF (FDA, category D evidence). It has been shown that RA is associated with increased preclinical and clinical atherosclerotic cardiovascular disease (ASCVD) and ASCVD related mortality. ASCVD in RA can occur independent of conventional risk factors and may be related to the underlying inflammation of RA or the drugs used to treat RA (category C evidence<sup>168 179 196</sup>).

One observational cohort study in RA patients without overt CHF showed no increase in MI related mortality when using TNF-blocking agents.<sup>3</sup>

### Hepatitis

The long term safety or efficacy of TNF-blockers in chronic hepatitis B and C patients is not known. Two observational studies of small numbers of hepatitis C patients who used TNF blocking agents demonstrated no increase in viral load or adverse event (category C evidence<sup>128 197</sup>). One controlled study of hepatitis C patients given etanercept on a background of interferon alfa and ribavirin revealed no effect on viral load and no increased incidence of adverse events; further, symptoms and liver function tests may have improved (category A evidence<sup>85</sup>). TNF blockers should not be used in patients with hepatitis B infection, although anecdotal data indicate that reactivation of hepatitis B infection after TNF blocker withdrawal can be prevented by using prophylactic antiviral therapy (category C evidence<sup>198–200</sup>). Cases of hepatic failure, not preceded by liver function test abnormalities, have occurred after infliximab was used (Inflix package insert).

Elevations in liver function tests have been observed with infliximab, adalimumab, and etanercept, although confounding medications and circumstances make the meaning and aetiology of these elevations unclear (category C, D evidence<sup>14 168 179</sup>). Frequently the liver function test abnormalities return to normal despite continued use of the TNF

blocking agents (category D evidence). Follow-up and monitoring for liver function test elevations should be governed by the patient's concomitant medications, health status, and patient related risk factors.

### Pregnancy

Some patients have become pregnant while being treated with TNF blocking therapy. Small, pharmacovigilance studies have not shown that the rate of normal live births, miscarriages, and therapeutic terminations is different from published rates for the normal population (category C evidence<sup>201</sup>). In these patients TNF-blocking agents were generally stopped when pregnancy was discovered. In most cases, exposure to anti-TNF blocking agents was in the three months prior to or immediately surrounding the time of conception. It is not known if the anti-TNF exposure affected the outcome (category D evidence). It should be noted that infliximab does not cross the placenta during the first 10 weeks of pregnancy, at least in rodents. There are insufficient data to advise continuation or starting of anti-TNF therapy if a patient becomes pregnant. It is advised that patients and physicians discuss the issue of TNF blocking therapy when pregnancy is being planned or if pregnancy is discovered during ongoing TNF-blocking therapy and that this discussion is documented. In general, see the package insert.

### Autoimmune-like syndromes

Syndromes resembling drug induced lupus 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 upon discontinuation of the TNF blocking agent (category C, D (abstract) evidence<sup>28 75 168 179 202</sup>). Patients treated with TNF blocking agents may develop autoantibodies (for example antinuclear antibody (ANA), anti-ds-DNA, anticardiolipin antibodies (aCL)) (category C evidence). However, there is no evidence that patients with RA who had, or develop, positive ANA, aCL, and/or ds-DNA are at significantly increased risk for the development of drug induced lupus (FDA) (category C, D (abstract) evidence<sup>28 75 168 179 202–208</sup>).

### Neurological diseases

Cases of demyelinating-like syndromes, optic neuritis, transverse myelitis, multiple sclerosis, or Parkinson's disease have been reported, more often with etanercept than with infliximab, all improving or disappearing after the TNF blocker was withdrawn. It is unclear whether these syndromes occur more frequently than expected in the general population (category C, D evidence<sup>28 75 168 179 209</sup>). These agents should be stopped if a demyelinating-like disorder or optic neuritis occurs. In patients with a history of definite demyelinating disease or optic neuritis, the benefits and risks of a TNF blocking agent should be carefully considered (category D evidence).

### Research questions

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

### Registry

- (1) Long term registries continue to be needed to monitor the toxicity of biologicals and are strongly recommended, requiring a cooperative effort among 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 is the optimal strategy in using TNF blocking agents in RA, AS, PsA, juvenile idiopathic arthritis, including timing, dosing, and combination with other drugs?
- (2) Are there predictors of treatment response (for example genetic profiling, MRI)?
- (3) Is there a correlation between the effects of TNF blocking agents on radiological progression and long term function?
- (4) What are the mechanisms underlying the loss of response to treatment with TNF blocking agents?
- (5) What are the cost/effect and ethical issues in treating patients with TNF blockers?
- (6) What are the radiological and clinically valid measures of response in PsA?
- (7) Is the MRI a valid measure of response in RA?
- (8) Is induction therapy with TNF inhibitors possible (with subsequent withdrawal on RA, PsA, or AS)?
- (9) In controlled trials, are there differences in response and/or toxicity when patients switch from one TNF blocking agent to another?
- (10) If the MRI proves to be a valid measure of response in RA, PsA, or AS, can they be valid surrogates of long term outcome in these diseases?

### Safety

- (1) Can TNF blocking agents be used safely in pregnant and lactating women?
- (2) What is the safety profile of TNF blocking agents during surgery?
- (3) What is the optimal timing and regimen of tuberculosis prophylaxis and treatment in patients receiving TNF blockers?
- (4) Can TNF blocking agents be used in patients with a history of lymphoma or solid tumours?
- (5) What are the optimal strategies, including vaccination, to lower the risk of infections during treatment with TNF blocking agents?

### Summary

TNF blocking agents have proved to be effective DMARDs and are a major advance in the treatment of RA, PsA, AS, and juvenile chronic arthritis. Their use is expanding to other rheumatic diseases. However, rare to uncommon and unexpected toxicities have been found and others may yet be found during their use. 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 this disease should balance efficacy, toxicity, and cost issues and then recognise that data in subpopulations are still being acquired. It is hoped that this statement, which is based upon the best evidence available at the time of its creation and is modified by expert opinion, will facilitate the optimal use of these agents for our patients with RA, PsA, and AS.

### IL-1 BLOCKING AGENTS

To date only one IL-1 blocking agent (anakinra) has been approved and references are therefore to this product. As

other agents of this class are approved this will be changed. With the advent of clinical and radiographic data from TNF blocking agents, in comparison with data regarding anakinra, some experts recommend that anakinra should be considered as a DMARD which should be initiated in patients who have had an inadequate response to TNF blocking agent failures, following cessation of those drugs (category D evidence).

### Indications

Anakinra may be used for treatment of active RA, alone or with MTX (category A evidence<sup>210–213</sup>). Despite this evidence, the anakinra label presently requires its use with MTX in Europe. IL-1 blocking agents are recommended for the treatment of active RA after an adequate trial of another effective DMARD, of which MTX is a common example (category D evidence).

Anakinra has been used in juvenile RA, adult onset Still's disease, neonatal multi-inflammatory disease (NOMID), Muckle–Wells syndrome, and systemic lupus erythematosus (category C, D evidence<sup>214–219</sup>). Evidence regarding the use of anakinra in AS is conflicting.<sup>220 221</sup>

### Clinical use

In clinical trials, anakinra can lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters in 2–16 weeks (category A evidence<sup>210–213</sup>). Measures of patient related outcomes such as global patient VAS or HAQ may be more sensitive to the effects of anakinra than physical measures such as joint tenderness/swelling (category D evidence<sup>210–213</sup>). If clinically important improvement occurs based on standard outcome assessment, treatment can be continued (category D evidence). There are data showing that IL-1 blocking agents, of which anakinra is the approved prototypic compound, slows radiographic progression in RA (category A evidence<sup>222–224</sup>).

Recent data indicate that anakinra may be useful in reducing signs and symptoms in systemic juvenile RA, adult onset Still's disease, systemic lupus erythematosus and other periodic febrile anti-inflammatory syndromes (for example Muckle–Wells syndrome).

### Warnings

A numerical increase of serious infections in patients receiving anakinra has been seen relative to other DMARD treatments. These compounds should not be started or should be discontinued when serious infections occur (category A, D evidence<sup>210–213 225</sup>). Treatment with IL-1 blocking therapy in such patients should only be resumed if the infections have been adequately treated (category D evidence). To date, there is no indication that IL-1 blocking compounds are associated with an increased incidence of tuberculosis (category D evidence).

Common and serious infections have occurred when using anakinra and TNF blocking agents together. Anakinra in combination with other biologicals should be used with caution until additional data become available (category D evidence<sup>226</sup>). 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<sup>210–213</sup>). Preliminary data suggest that vaccination with diphtheria and tetanus toxoid are unaffected by anakinra. There are no data to advise discontinuation of anakinra if a patient becomes pregnant.

### Precautionary statements

The safety of IL-1 blocking agents is unknown or has not been established in the following situations:

- (1) lymphoma, lymphoproliferative and other malignancies
- (2) during pregnancy and/or lactation
- (3) other areas where knowledge is lacking are highlighted in the consensus group's recommendations for areas most urgently requiring further research.

### Research questions

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

### Registry

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

### Efficacy

- (1) What is the efficacy of IL-1 blocking agents in polyarticular systemic rheumatic diseases?
- (2) What is the efficacy of IL-1 blocking agent in osteoarthritis?

### Toxicity

- (1) Do IL-1 blocking agents increase susceptibility to tuberculosis or other opportunistic infections?
- (2) Do IL-1 blocking agents increase the susceptibility to serious bacterial infections?

### Summary

IL-1 blocking agents, of which anakinra is the prototypic and sole example, are effective for the treatment of RA but they appear less effective, clinically, than TNF blocking agents. Anakinra appears to be effective in some periodic fever syndromes, such as Muckle–Wells syndrome, and may be effective in systemic juvenile RA and adult onset Still's disease.

Publication of studies in selected areas of efficacy, toxicity, and general use of IL-1 blocking agents are needed to help further define the most appropriate use of these agents. Further considerations when using IL-1 ra 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 upon the best evidence available at this time of its creation and modified by expert opinion, will facilitate the optimal use of IL-1ra for our patients with RA.

## APPENDIX 1: ABBREVIATED SUMMARY OF THE "UPDATED CONSENSUS STATEMENT ON BIOLOGICAL AGENTS FOR THE TREATMENT OF RHEUMATIC DISEASES, 2005"

- Early, intensive therapy of RA with intensive monitoring of response is recommended.
- Rheumatologists and bioscientists from many countries met to develop the consensus statement.
- The process included a review of relevant clinical published articles and, through an iterative process, the reaching of consensus.

- Individual patients differ in many aspects of their disease and may respond differently to various TNF blocking agents, so one must individualise therapy.

### Indications

- TNF blockers are recommended for the treatment of active RA, PsA, AS, and juvenile chronic arthritis after using another DMARD (MTX is the most common of several DMARDs frequently used).
- TNF blocking agents can be added to pre-existing therapy or, when appropriate, may replace previous DMARD or other biologicals.
- TNF blockers are effective in MTX naive patients.
- At present, TNF blocking agents as the first DMARD for the treatment of RA should be limited due to considerations of long term safety and cost considerations, although individual patient needs should be considered.
- When other DMARDs are contraindicated, TNF blockers may be considered as the first DMARD.
- Etanercept has been approved for juvenile idiopathic arthritis of the polyarticular type as well as PsA and AS.
- Infliximab is approved in Europe for AS.
- Infliximab is approved for Crohn's disease.
- Adalimumab and infliximab are being tested in PsA.
- There is no evidence that any one TNF blocking agent should be used before another or that any TNF blocker is more effective than another, although individual differences may exist between patients.
- TNF blocking agents are being evaluated in Wegener's granulomatosis, giant cell arteritis, Takayasu's arteritis, adult onset Still's disease, Sjögren's syndrome, hepatitis C, Behçet's disease, uveitis, polymyositis, dermatomyositis, systemic lupus erythematosus, systemic sclerosis, and other conditions, although more work is needed in all cases.
- Evidence is appearing that adalimumab, etanercept, and infliximab are cost effective in RA.

### Clinical use

- When used in adequate doses and sufficiently frequent dosing regimens, TNF blocking agents should lead to significant, documented improvement within 12 weeks for RA, AS, PsA, and juvenile RA.
- The ACR response criteria (as a combined index) should not be used to monitor individual response, whereas other validated quantitative measures such as the DAS, HAQ-DI, SDAI, VAS, Likert scales, joint tenderness and/or swelling, and laboratory data may be more appropriate measures for individual patients.
- If documentable significant improvement occurs, treatment should be continued.
- If an incomplete response occurs, increase in dose or reduction in dosing intervals may provide additional benefits, as may other DMARDs or other biologicals, although further study regarding this issue is required.
- TNF blocking agents slow radiographic progression in RA and may do so in PsA. Until the long term implications of this slowing are clear, radiological changes alone should not determine clinical decision making.

### Warnings

- Tuberculosis may be reactivated in patients given any TNF blocker; numerically more reactivation of tuberculosis

- occur with infliximab than with the other two agents, although analyses and circumstances do not permit differentiation among these drugs with respect to reactivation of latent tuberculosis.
- Screening for latent tuberculosis is necessary, especially in countries with a high prevalence of latent tuberculosis infection.
  - Individual evaluations, including history, physical examinations, chest x ray and/or purified protein derivative test, should be done and therapy for latent tuberculosis considered according to local recommendations.
  - Serious bacterial infections have been observed in patients receiving TNF blocking agents. It is not clear, however, if the incidence of these infections is higher than in well matched RA populations using other DMARDs.
  - TNF blocking agents should not be started or should be discontinued when serious infections occur.
  - TNF blocking agents affect pneumococcal and viral vaccinations although the effect is not large. These vaccinations should, if possible, be given before the TNF blocking agents are started. Live attenuated vaccines should be avoided if possible.
  - Opportunistic infections have occurred in the setting of TNF blocking agent use. The incidence, however, is low.
  - Injection site reactions (etanercept, adalimumab) and infusion reactions (infliximab) occur more commonly in patients receiving these agents than in controls. They are usually mild-moderate.
  - Lymphomas, particularly non-Hodgkin's lymphomas, have occurred in patients using TNF blocking agents and the incidence is approximately two to five times that in patients given other DMARDs, although it is not clear if the incidence of these tumours is increased relative to an appropriate disease control group.
  - There is thus far no evidence that TNF blocking agents are associated with an increased incidence of solid tumours in RA patients with the exception of smoking related cancers of the lung.
  - It is possible that patients with Wegener's granulomatosis may develop common solid cancers if they are given etanercept on a background of cyclophosphamide.
  - A few instances of pancytopenia and aplastic anaemia have been reported although the relation and frequency of this adverse event is not sufficiently understood to make specific recommendations regarding monitoring at this time.
  - If pancytopenia or aplastic anaemia occurs, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease.
  - Severe CHF (Class III–IV by NYHA criteria) represents a situation where TNF blockade needs to be used with great caution, particularly in high doses. There are no credible data in patients without CHF or with class I disease preventing the use of TNF blockers, and it appears that RA per se, with its associated inflammation, is associated with increased ASCVD related mortality.
  - The safety of TNF blocking agents in the treatment of chronic hepatitis C is unknown, although some data indicate that viral load is not increased, that the incidence of adverse events is not increased and that liver function may normalise. Caution in the use of these agents in hepatitis C patients is, nevertheless, recommended.
  - The use of TNF blocking agents in patients with hepatitis B is not recommended, although they have used successfully when antiviral prophylaxis was also used.
  - Rare cases of hepatic failure, not preceded by liver function abnormalities on routine testing, have occurred in patients using infliximab.
  - Insufficient data are available with regard to the use of anti-TNF therapy prior to or during pregnancy to allow advice in this circumstance. Although pharmacovigilance data have shown the same rate of normal births, miscarriages, and therapeutic terminations as in the general population, patients and physicians should discuss this issue if pregnancy occurs or is planned, and this discussion should be documented.
  - In the rare cases when a syndrome resembling drug induced lupus develop, TNF blocking agents should be stopped.
  - Presence or development of a positive ANA, aCL and/or ds-DNA does not significantly increase the risk of developing drug induced lupus.
  - Cases of demyelinating-like syndromes, optic neuritis, transverse myelitis, and multiple sclerosis have been reported, more often with etanercept than with infliximab, all improving or disappearing after the TNF blocker was withdrawn. It is unclear whether these syndromes occur more frequently than expected in the general population.
  - These agents should be stopped if a demyelinating-like disorder or optic neuritis occurs.
  - In patients with a history of definite demyelinating syndrome, the benefits and risks of a TNF blocking agent should be carefully considered.

## APPENDIX 2: ABBREVIATED SUMMARY OF THE "UPDATED CONSENSUS STATEMENT FOR THE USE OF BIOLOGICAL AGENTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS AND OTHER RHEUMATIC DISEASES – IL-1 BLOCKING AGENTS – ANAKINRA – SUBSECTION"

- Rheumatologists and bioscientists from numerous countries met to develop the consensus statement.
- The process included a review of relevant clinical published articles and, through an iterative process, the reaching of consensus.

### Indications

- Some experts recommend that in RA anakinra should be considered in patients in whom TNF blocking agents have failed. Anakinra may be used for the treatment of active RA, alone or with MTX. In Europe, anakinra should presently be used in conjunction with MTX.
- Anakinra will probably be effective when used with other effective DMARDs.

### Clinical use

- Anakinra can lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters of RA within 2–16 weeks.
- Response measures should be followed and individually important responses should be demonstrated within 8–16 weeks.
- If a clinically important response to anakinra occurs, the agent(s) should be continued.
- Anakinra slows radiographic progression in RA.
- Injection site reactions occur in up to 70% of patients in a dose–response manner. These injection site reactions often do not require treatment and may diminish with continued use.



- There are no data to advise continuation or termination of anakinra if the patient becomes pregnant.
- Anakinra has been used successfully in juvenile idiopathic arthritis, Adult onset Still's disease and Muckle–Wells syndrome and NOMID.
- Preliminary evidence suggests that vaccination with diphtheria and tetanus toxoid is unaffected by anakinra.

### Warnings

- It is possible that there is an increased incidence of infections, including serious infections, when using IL-1 blocking agents.
- IL-1 blocking agents should not be started or should be discontinued when serious infections occur.
- Treatment with IL-1 blocking agents should be resumed only if the infections have been adequately treated.

### Precautionary statement

- The safety of IL-1 blocking agents is unknown or has not been established in the following situations: lymphoma, lymphoproliferative disease or other malignancies; pregnancy and/or lactation; in combination with other biologicals, including TNF blocking agents (where great caution ought to be used if these drugs are used together); when using primary vaccinations or live attenuated vaccines.

### APPENDIX 3: CATEGORIES OF EVIDENCE

- *Category A evidence*: based on evidence from at least one randomised controlled trial or on the 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 is published, or may not be published as full papers at all. Evidence from abstracts alone, therefore, is considered as category D evidence and noted as “(abstract)” until that data are published as a complete, peer reviewed paper.

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### REFERENCES

- 1 **Furst DE**, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Bijlsma JW, *et al*. Updated consensus statement on biological agents, specifically tumour necrosis factor alpha (TNFalpha) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases, 2004. *Ann Rheum Dis*, 2004;**63** Suppl 2, ii2–ii12.
- 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**:1712–17.
- 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 JC Jr**, 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 JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002;**346**:1349–56.
- 10 **Van Den BF**, Kruijthof E, Baeten D, Herrensens A, De Keyser F, 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 **Goekoop-Ruiterman YPM**, de Vries-Bouwstra JK, van Zeben D, Kerstens PJSM, Hazes JMW, Zwinderman AE, *et al*. Clinical and radiological efficacy of different treatment strategies: 2 year follow-up of the Best study [abstract]. *Ann Rheum Dis* 2005;**64**(suppl III):58.
- 12 **Burmester GR**, Monteagudo Saez I, Malaise MG, Canas da Silva J, Webber DG, Kupper H. Adalimumab (Humira) is effective in patients who have previously been treated with TNF-antagonists (Etanercept and/or Infliximab) in widespread clinical practice: 12-week outcomes in the REACT trial [abstract]. *Ann Rheum Dis* 2005;**64**(suppl III):423.
- 13 **Kafka SP**, Hinkle K, Reed G, Kremer JM. Discontinuing or switching TNF antagonists in patients with rheumatoid arthritis: data collected from the CORRONA database [abstract]. *Ann Rheum Dis* 2005;**64**(suppl III):467.
- 14 **US Food and Drug Administration**. Adalimumab: summary basis of approval. Available at [www.fda.gov/cder/biologics/review/adalabb123102r1.htm](http://www.fda.gov/cder/biologics/review/adalabb123102r1.htm).
- 15 **Bang LM**, Keating GM. Adalimumab: a review of its use in rheumatoid arthritis. *BioDrugs* 2004;**18**:121–39.
- 16 **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.
- 17 **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.
- 18 **Combe B**, Condreanu C, Frosco U, *et al*. Double-blind comparison of etanercept and sulphasalazine alone and combined in patients with active RA [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S519.
- 19 **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.

- 20 **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.
- 21 **Curran SA**, FitzGerald OM, Costello PJ, Selby JM, Kane DJ, Bresnihan B, et al. Nucleotide sequencing of psoriatic arthritis tissue before and during methotrexate administration reveals a complex inflammatory T cell infiltrate with very few clones exhibiting features that suggest they drive the inflammatory process by recognizing autoantigens. *J Immunol* 2004;**172**:1935–44.
- 22 **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.
- 23 **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.
- 24 **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.
- 25 **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.
- 26 **Garrison L**, McDonnell ND. Etanercept: therapeutic use in patients with rheumatoid arthritis. *Ann Rheum Dis* 1999;**58**(suppl 1):165–9.
- 27 **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.
- 28 **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):161–4.
- 29 **Jarvis B**, Faulds D. Etanercept: a review of its use in rheumatoid arthritis. *Drugs* 1999;**57**:945–66.
- 30 **Jones RE**, Moreland LW. Tumor necrosis factor inhibitors for rheumatoid arthritis. *Bull Rheum Dis* 1999;**48**:1–4.
- 31 **Kavanaugh AF**. Anti-tumor necrosis factor-alpha monoclonal antibody therapy for rheumatoid arthritis. *Rheum Dis Clin North Am* 1998;**24**:593–614.
- 32 **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.
- 33 **Lipsky PE**, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Infliximab and methotrexate in the treatment of rheumatoid arthritis, et al. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;**343**:1594–602.
- 34 **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.
- 35 **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.
- 36 **Markham A**, Lamb HM. Infliximab: a review of its use in the management of rheumatoid arthritis. *Drugs* 2000;**59**:1341–59.
- 37 **Moreland LW**, Margolies G, Heck LW Jr, 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.
- 38 **Moreland LW**, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;**130**:478–86.
- 39 **Smolen J**, Maini R, Keystone E, Bathon JM, Emery P, Kalden J, et al. Treatment of early rheumatoid arthritis with infliximab plus methotrexate or methotrexate alone: preliminary results of the ASPIRE trial. EULAR, 18–21 June, 2003, Lisbon, Portugal, 2003 (abstract).
- 40 **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 for whom previous DMARD treatment has failed. *Ann Rheum Dis* 2004;**63**:508–16.
- 41 **St Clair EW**, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Active-controlled study of patients receiving infliximab for the treatment of rheumatoid arthritis of early onset study group. combination of infliximab and methotrexate therapy for early rheumatoid arthritis. *Arthritis Rheum* (in press).
- 42 **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.
- 43 **Scheinfeld N**. Adalimumab (HUMIRA): a review. *J Drugs Dermatol* 2003;**2**:375–7.
- 44 **Antoni C**, Dechant C, Hanns-Martin Lorenz PD, Wendler J, Ogilvie A, Luefl M, et al. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. *Arthritis Rheum* 2002;**47**:506–12.
- 45 **Mease PJ**. Etanercept, a TNF antagonist for treatment for psoriatic arthritis and psoriasis. *Skin Therapy Lett* 2003;**8**:1–4.
- 46 **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.
- 47 **Feletar M**, Brockbank JE, Schentag CT, Lapp V, Gladman DD. Treatment of refractory psoriatic arthritis with infliximab: a 12 month observational study of 16 patients. *Ann Rheum Dis* 2004;**63**:156–61.
- 48 **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.
- 49 **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.
- 50 **Ogilvie AL**, Antoni C, Dechant C, Manger B, Kalden JR, Schuler G, et al. Treatment of psoriatic arthritis with antitumor necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate. *Br J Dermatol* 2001;**144**:587–9.
- 51 **Mease PJ**, Gladman DD, Ritchlin CT, et al. Adalimumab therapy in patients with psoriatic arthritis: 24 week results of a phase III study [abstract]. *Arthritis Rheum* 2004;**50**:4097.
- 52 **Salvarani C**, Cantini F, Olivieri I, Macchioni P, Padula A, Niccoli L, et al. Efficacy of infliximab in resistant psoriatic arthritis. *Arthritis Rheum* 2003;**49**:541–5.
- 53 **Antoni C**, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of PsA: results of IMPACT 2 Trial. *Ann Rheum Dis* 2005;**64**:1150–7.
- 54 **Antoni C**, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2005;**52**:1227–36.
- 55 **Mease PJ**, Gladman DD, Ritchlin C, Ruderman EM, Steinfeld S, Choy E, et al. Adalimumab in Psoriatic Arthritis: 24-week Results of a Phase II Study ADEPT—Adalimumab Effectiveness in Psoriatic Arthritis Trial. American Academy of Dermatology Annual Meeting, 2005. (abstract).
- 56 **Clegg DO**, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996;**39**:2013–20.
- 57 **Dougados M**, van der LS, Leirisalo-Repo M, Huitfeldt B, Juhlin R, Veys E, et al. Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum* 1995;**38**:618–27.
- 58 **Goupille P**, Valat JP. Sulfasalazine: a definitively efficient treatment for psoriatic arthritis. *J Rheumatol* 1996;**23**:791–2.
- 59 **Spadaro A**, Riccieri V, Sili-Scavalli A, Sensi F, Taccari E, Zoppini A. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. *Clin Exp Rheumatol* 1995;**13**:589–93.
- 60 **Willkens RF**, Williams HJ, Ward JR, Egger MJ, Reading JC, Clements PJ, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 1984;**27**:376–81.
- 61 **Mentor A**, Evans R, Dooley L, et al. Infliximab improves signs of plaque psoriasis in patients with psoriatic arthritis. Annual Scientific Meeting, American College of Rheumatology, 25–27 October 2003, Orlando, USA, (abstract).
- 62 **Tutrone WD**, Saini R, Weinberg JM. Biological therapy for psoriasis: an overview of infliximab, etanercept, efalizumab and alefacept. *IDrugs* 2004;**7**:45–9.
- 63 **Chaudhari U**, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 2001;**357**:1842–7.
- 64 **Scheinfeld N**. Adalimumab (Humira): a brief review for dermatologists. *J Dermatolog Treat* 2004;**15**:348–52.
- 65 **Gottlieb AB**, Chaudhari U, Mulcahy LD, Li S, Dooley LT, Baker DG. Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis. *J Am Acad Dermatol* 2003;**48**:829–35.
- 66 **Leonardi CL**, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003;**349**:2014–22.
- 67 **Braun J**, Pham T, Sieper J, Davis J, van der LS, Dougados M, et al. 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.
- 68 **Davis J**, Van Der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann Rheum Dis* 2005 (in press).
- 69 **Braun J**, Baraliakos X, Brandt J, Listing J, Zink A, Alten R, et al. Persistent clinical response to the anti-TNF antibody infliximab in patients with ankylosing spondylitis over 3 years. *Rheumatology* 2005 [Epub ahead of print 9 March 2005].
- 70 **Van Der Heijde D**, Dijkmans B, Geusens P, Sieper J, Dewoody K, et al. Group ATAS. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo controlled trial (ASSERT). *Arthritis Rheum* 2005;**52**:582–91.
- 71 **Baraliakos X**, Listing J, Brandt J, Zink A, Alten R, Burmester G, et al. Clinical response to withdrawal of anti-TNF therapy in patients with ankylosing spondylitis (AS) after 3 years of continuous treatment with Infliximab. *Arthritis Res Ther* 2005;**7**:R439–R444.
- 72 **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 spondyloarthritis 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.
- 73 **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.
- 74 **Scheinfeld N**. Adalimumab: a review of side effects. *Expert Opin Drug Saf* 2005;**4**:637–41.
- 75 **Emery P**. Review of health economics modelling in rheumatoid arthritis. *Pharmacoeconomics* 2004;**22**(2 suppl):55–69.
- 76 **Kavanaugh A**, Han C, Bala M. Functional status and radiographic joint damage are associated with health economic outcomes in patients with rheumatoid arthritis. *J Rheumatol* 2004;**31**:849–55.
- 77 **Yelin EH**, Tripin LS, Katz PP. Import of managed care on the use of agents for RA. *Arthritis Rheum* 2005;**53**:423–30.
- 78 **Chiou C**, Wanke L, Yu E, et al. A cost-effectiveness analysis of biological treatments for rheumatoid arthritis [abstract]. *ISPOR* 2004;**7**:631-AR2.
- 79 **Wong JB**. Cost effectiveness of anti-tumour necrosis factor agents. *Clin Exp Rheumatol* 2004;**22**(suppl 35):s65–70.
- 80 **Merkedal S**, Ruof J, Mittendorf T, Zeidler H. Cost-effectiveness of TNF-alpha-blocking agents in the treatment of rheumatoid arthritis. *Expert Opin Pharmacother* 2004;**5**:1881–6.
- 81 **Bansback NJ**, Regier DA, Ara R, Brennan A, Shojania K, Esdaile JM, et al. An overview of economic evaluations for drugs used in RA: focus on TNFa antagonists. *Drugs* 2005;**65**:473–96.
- 82 **Bansback NJ**, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe RA in Sweden. *Arthritis Rheum Dis* 2005;**64**:995–1002.
- 83 **Kaplan RM**, Groessl EJ, Sengupta N, Sieber WJ, Ganiats TG. Comparison of measured utility scores and imputed scores from the SF36 in patients with rheumatoid arthritis. *Med Care* 2005;**43**:74–87.
- 84 **Lyseng-Williamson KA**, Plosker GL. Etanercept: a pharmacoeconomic review of its use in rheumatoid arthritis. *Pharmacoeconomics* 2005;**22**:71–95.
- 85 **Zein NN**. Etanercept as an adjuvant to interferon and ribavirin in treatment-naïve patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol* 2005;**42**:315–22.
- 86 **Melikoglu M**, Fresko I, Mat C, Ozyazgan Y, Gogus F, Yurdakul S, et al. Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. *J Rheumatol* 2005;**32**:98–105.
- 87 **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.
- 88 **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.
- 89 **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.
- 90 **Wegener's Granulomatosis Etanercept Trial (WG-E-T) Research Group**. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005;**352**:351–61.
- 91 **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, 25–27 October 2003, Orlando, USA, [abstract no 450].
- 92 **Huffstuter J**, Sienknechet C. Resistant adult Still's disease treated with infliximab—a report of two cases [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S326.
- 93 **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, iii55–iii57.
- 94 **Weinblatt ME**, Maier AL, Mease PJ, Overman SS, Fraser P, Gravallese EM. Etanercept in the treatment of adult patients with Still's disease. *Arthritis Rheum* 2002;**46**:1171–6.
- 95 **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**:2571–3.
- 96 **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.
- 97 **Ortiz-Santamaria V**, Vals-Roc M, Sanmarti M, et al. Treatment of secondary amyloidosis with infliximab [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S71.
- 98 **Tomero E**, Carmona L, Gonzalez I, et al. Infliximab in secondary amyloidosis complicating inflammatory arthropathies [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S70.
- 99 **Estrach C**, Mpofu S, Moots RJ. Efficacy and safety of infliximab and adalimumab in Behçet's syndrome. Annual Scientific Meeting, American College of Rheumatology, 25–27 October 2003, Orlando, USA, [abstract no 1125].
- 100 **Gulli S**, Arrigo C, Bocchino L, Morgante L, Sangari D, Castagna I, et al. Remission of Behçet's disease with anti-tumor necrosis factor monoclonal antibody therapy: a case report. *BMC Musculoskelet Disord* 2003;**4**:19.
- 101 **Hassard PV**, Binder SW, Nelson V, Vasiliauskas EA. Anti-tumor necrosis factor monoclonal antibody therapy for gastrointestinal Behçet's disease: a case report. *Gastroenterology* 2001;**120**:995–9.
- 102 **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 Behçet's syndrome. *Ann Rheum Dis* 2003;**62**:280–1.
- 103 **Melikoglu M**, Fresko I, Mat C, et al. Etanercept is beneficial in controlling the mucocutaneous lesions of Behçet's syndrome [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S206.
- 104 **Rozenbaum M**, Rosner I, Portnoy E. Remission of Behçet's syndrome with TNFalpha blocking treatment. *Ann Rheum Dis* 2002;**61**:283–4.
- 105 **Saulsbury FT**, Mann JA. Treatment with infliximab for a child with Behçet's disease. *Arthritis Rheum* 2003;**49**:599–600.
- 106 **Sfikakis PP**, Theodossiadi PG, Katsiari CG, Kaklamanis P, Markomichelaklis NN. Effect of infliximab on sight-threatening panuveitis in Behçet's disease. *Lancet* 2001;**358**:295–6.
- 107 **Sfikakis PP**. Behçet's disease: a new target for anti-tumour necrosis factor treatment. *Ann Rheum Dis* 2002;**61**(suppl 2):ii51–ii53.
- 108 **Shereen F**, Moore TL. Successful resolution of mucocutaneous ulcers in Behçet's disease with use of infliximab—a case series. Annual Scientific Meeting, American College of Rheumatology, 25–27 October 2003, Orlando, USA, [abstract no 1619].
- 109 **Swiss NJ**, Uiset TO, Curran J, Ellman M. TNF-inhibition as novel therapy for refractory uveitis in behçet's syndrome and sarcoidosis [abstract]. *Arthritis Rheum* 2003;**48**(suppl):s618.
- 110 **Naveau S**, Challet-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.
- 111 **Wendling D**, Auge B, Bettinger B, Lohse A, Le Huede G, 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.
- 112 **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**:448–455.
- 113 **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.
- 114 **Hengstman G**, van den Hoogen F, van Engelen B, et al. Anti-TNF blockade with infliximab (Remicade) in polymyositis and dermatomyositis [abstract]. *Arthritis Rheum* 2000;**43**(suppl):S193.
- 115 **Miller M**, Mendez E, Klein-Gitelman M, Pachman L. Use of etanercept in juvenile dermatomyositis [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S306.
- 116 **Saadeh C**. Etanercept is effective in the treatment of polymyositis/dermatomyositis which is refractory to conventional therapy [abstract]. *Arthritis Rheum* 2000;**43**(suppl):S193.
- 117 **Nzeusseu A**, Durez P, Houssiau F. Successful use of infliximab in a case of refractory juvenile dermatomyositis. *Arthritis Rheum* 2001;**44**(suppl):S90.
- 118 **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.
- 119 **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.
- 120 **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.
- 121 **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.
- 122 **Canfani 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.
- 123 **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.
- 124 **Parke FA**, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. *Arthritis Rheum* 2004;**51**:800–4.
- 125 **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.
- 126 **Cacoub P**, Lidove O, Maissonobe 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.
- 127 **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.
- 128 **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.
- 129 **Pritchard C**. Etanercept and hepatitis C. *J Clin Rheum* 1999;**5**:179.
- 130 **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.
- 131 **Weiss JE**, Eberhard BA, Chowdhury D, Gottlieb BS. Infliximab as a novel therapy for refractory Kawasaki disease. *J Rheumatol* 2004;**31**:808–10.
- 132 **Calamia K**, Walsh JS, Kovach B, Ginsburg WW. Treatment of multicentric reticulohistiocytosis with etanercept: a case report. Annual Scientific Meeting, American College of Rheumatology, 25–27 October 2003, Orlando, USA, [abstract no 16808].
- 133 **Birbaum AJ**, Gentile P. Treatment of myelodysplasia in a patient with active rheumatoid arthritis. *Ann Intern Med* 2000;**133**:753–4.

- 134 **Athreya B**, Doughty R, Kastner D, *et al*. Periodic fever syndrome in children [abstract]. *Arthritis Rheum* 2000;**43**(suppl):S117.
- 135 **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.
- 136 **Ehresman G**. Infliximab in the treatment of polyarthritides [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S170.
- 137 **Wagner AD**, Andreson J, Jendro MC, Hulseman JL, Zeidler H. Sustained response to tumor necrosis factor alpha-blocking agents in two patients with SAPHO syndrome. *Arthritis Rheum* 2002;**46**:1965–8.
- 138 **Tutuncu Z**, Morgan GJ, Kavanaugh A. Anti-TNF Therapy for other inflammatory conditions. *Clin Exp Rheumatol* 2002;**20**(6 Suppl 28):S146–S151.
- 139 **Khanna D**, Liebling MR, Louie JS. Etanercept ameliorates sarcoidosis arthritis and skin disease. *J Rheumatol* 2003;**30**:1864–7.
- 140 **Baughman RP**, Iannuzzi M. TNF in sarcoidosis and its potential for targeted therapy. *BioDrugs* 2003;**17**:425–31.
- 141 **Swiss N**, Ellman N, Curran J, Utset T, *et al*. TNF-inhibitor as novel treatment for refractory sarcoidosis [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S324.
- 142 **Swiss N**, Curran J, Ellman N. TNF-inhibition as a novel treatment for refractory sarcoidosis. Annual Scientific Meeting, American College of Rheumatology, 25–27 October 2003, Orlando, USA, (abstract no 1605).
- 143 **Utz JP**, Limper AH, Kalra S, Specks U, Scott JP, Vuk-Pavlovic Z, Schroeder DR. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. *Chest* 2003;**124**:177–85.
- 144 **Korhonen T**, Karpainen J, Malmivaara A, Autio R, Niinimäki J, Paimela L, *et al*. Efficacy of infliximab for disc herniation-induced sciatica: one year follow-up. *Spine* 2004;**29**:2115–19.
- 145 **Atcheson SG**, Dymek T. Rapid resolution of chronic sciatica with intravenous infliximab after failed epidural steroid injections. *Spine* 2004;**29**:E248–E250.
- 146 **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.
- 147 **Ellman MH**, MacDonald PA, Hayes FA. Etanercept treatment for diffuse scleroderma: a pilot study [abstract]. *Arthritis Rheum* 2000;**43**(suppl):S392.
- 148 **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.
- 149 **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 erythematosus. Annual Scientific Meeting, American College of Rheumatology, 25–27 October 2003, Orlando, USA, (abstract no 378).
- 150 **Principi M**, Di Leo A, 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.
- 151 **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.
- 152 **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.
- 153 **Suhler E**, Smith J, Kurz D, *et al*. A prospective trial of infliximab therapy for patients with refractory uveitis: preliminary results. Annual Scientific Meeting, American College of Rheumatology, 25–27 October 2003, Orlando, USA, (abstract no 1102).
- 154 **Booth A**, Harper L, Hamm 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.
- 155 **Burmester GR**, van de Putte LBRau 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**:s537.
- 156 **Brocq O**, Plubel Y, Breuil V, Grisot C, Flory P, Mousnier A, *et al*. Etanercept–infliximab switch in rheumatoid arthritis 14 out of 131 patients treated with anti TNF $\alpha$ . *Presse Med* 2002;**31**:1836–9.
- 157 **Buch MH**, Bingham SJ, Rees-Evans B, *et al*. Do patients with rheumatoid arthritis with high disease activity on infliximab demonstrate improvement on etanercept? BSR Annual Meeting [abstract]. *Rheumatology* 2003;**42**.
- 158 **Nikas SN**, Voulgari PV, Papadopoulos CG, Venetsanopoulou A, Georgiadis AN, Drosos AA. The efficacy and safety of switching from infliximab to adalimumab. A prospective controlled study [abstract]. *Ann Rheum Dis* 2005;**64**(suppl III):422.
- 159 **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–ii16.
- 160 **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 [abstract]. *Arthritis Rheum* 2001;**44**(suppl):S82.
- 161 **Shergy WJ**, Phillips RM Jr, Hunt RE, Hernandez J. Safety and efficacy of infliximab therapy after etanercept failure: a case series [abstract]. *Arthritis Rheum* 2001;**44**(suppl):S81.
- 162 **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.
- 163 **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.
- 164 **Heiberg MS**, Nordvag BY, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, *et al*. The comparative effectiveness of TNF-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. *Arthritis Rheum* 2005;**52**:2506–12.
- 165 **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 [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S205.
- 166 **Smolen JS**, Han C, Bala M, Maini R, Kalden J, van der Heijde DM, *et al*. ATTRACT study group. Evidence of radiographic benefit of 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.
- 167 **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.
- 168 **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.
- 169 **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.
- 170 **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.
- 171 **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.
- 172 **Baeten D**, De Keyser F, Kruihof E, *et al*. Systematic review of the serious and atypical infections in spondyloarthropathy patients treated with anti-TNF $\alpha$  [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S432.
- 173 **Furst DE**, Wallis R, Beenhouwer D, *et al*. Tumor necrosis factor antagonists and granulomatous infections: mechanisms of action. *Semin Arthritis Rheum* 2005 (in press).
- 174 **Hanauer SB**. Review article: safety of infliximab in clinical trials. *Aliment Pharmacol Ther* 1999;**13**(suppl 4):16–22.
- 175 **Schiff M**, van der Putter LB, Breedveld FC, Kupper H, Fischkoff S, *et al*. Rates of infection in adalimumab rheumatoid arthritis clinical trials [abstract]. *Ann Rheum Dis* 2003;**62**:abstract no 184.
- 176 **Wallis RS**, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis* 2004;**39**:1254–5.
- 177 **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.
- 178 **Bargstrom L**, Yocum D, Tesser J, *et al*. Coccidiomycosis (Valley Fever) occurring during infliximab therapy [abstract]. *Arthritis Rheum* 2004;**46**:abstract no 5169.
- 179 **Khanna D**, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. *Drug Saf* 2004;**27**:307–24.
- 180 **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.
- 181 **Manadan AM**, Block JA, Sequeira W. Mycobacteria tuberculosis peritonitis associated with etanercept therapy. *Clin Exp Rheumatol* 2003;**21**:526.
- 182 **Zhao S**, Makuch RW, Wentworth C, *et al*. Incidence rates of tuberculosis in patients with rheumatoid arthritis or ankylosing spondylitis in comparison with the general population. *J Rheumatol* 2005 (in press).
- 183 **Jacobsson LTH**, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, *et al*. No increase of severe infections in RA patients treated with TNF-blockers [abstract]. *Ann Rheum Dis* 2005;**64**(suppl III):461.
- 184 **Doran MF**, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:2294–300.
- 185 **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.
- 186 **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.
- 187 **Elkayam O**, Caspi D, Reiblat 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.
- 188 **Mease PJ**, Ritchlin CT, Martin RW, Gottlieb AB, Baumgartner SW, Burge DJ, *et al*. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. *J Rheumatol* 2004;**31**:1356–61.
- 189 **Van der Bijl AE**, Gelincik LB, Breedveld FC, Van Hozegand RA, Rimmelzwaan GF, Visser LG, *et al*. Anti-TNF-Alpha inhibits the antibody response to influenza vaccination [abstract]. *Ann Rheum Dis* 2005;**64**(suppl III):181.

- 190 **Baecklund E**, Ekblom 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.
- 191 **Geborek P**, Bladstrom A, Turesson C, Gulfe A, Petersson I, Saxne T, et al. TNF blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with increased risk of lymphomas. *Ann Rheum Dis* 2005;**64**:699-703 [Epub 4 February 2005].
- 192 **Prior P**, Symmons DP, Hawkins CF, Scott DL, Brown R. Cancer morbidity in rheumatoid arthritis. *Ann Rheum Dis* 1984;**43**:128-31.
- 193 **Asklin J**, Fored CM, Brandt L, Baecklund E, Bertilsson L, Coster L, et al. Characteristics of malignant lymphomas following TNF-blockade. Preliminary results of an ongoing Swedish monitoring-programme of biologics in RA [abstract]. *Ann Rheum Dis* 2005;**64**(suppl III):449.
- 194 **Stone JH**, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. *Arthritis Rheum* 2001;**44**:1149-54.
- 195 **Cush J**, Spiera R. Etanercept update on "dear doctor" safety letter. *ACR Hotline* 12 May 2002; www.rheumatology.org
- 196 **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.
- 197 **Khanna M**, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. *J Dermatolog Treat* 2003;**14**:229-32.
- 198 **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**:107-9.
- 199 **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.
- 200 **Schiemann U**, Kellner H. [Gastrointestinal side effects in the therapy of rheumatologic diseases]. *Z Gastroenterol* 2002;**40**:937-43.
- 201 **Antoni CE**, Furst DE, Manger B, Lichtenstein GR, et al. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease or rheumatoid arthritis [abstract]. *Arthritis Rheum* 2001;**44**(suppl):S152.
- 202 **Bingham SJ**, Barcelos A, Buch M, et al. Induction of serological lupus in patients on leflunomide and infliximab [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S168.
- 203 **Christopher L**, Wigley F. TNF-alpha antagonists induce lupus-like syndrome in patients scleroderma and polyarthritis [abstract]. *Arthritis Rheum* 2002;**46**(suppl):S358.
- 204 **De Rycke L**, Kruihof E, Van Damme N, 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.
- 205 **Wagner C**, St Clair EW, Han C, et al. Effects of antibodies to infliximab on ACR response in patients with RA in the ATTRACT Study [abstract]. *Arthritis Rheum* 2002;**46**:S132.
- 206 **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.
- 207 **Allanore Y**, Sellam J, Bateux F, Job DC, Weill B, Kahan A. Induction of autoantibodies in refractory rheumatoid arthritis treated by infliximab. *Clin Exp Rheumatol* 2004;**22**:756-8.
- 208 **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.
- 209 **The Lenercept multiple sclerosis study group and the University of British Columbia MS/MRI analysis group**. TNF neutralization in MS: results of a randomized placebo controlled, multicenter study. *Lancet* 1999;**53**:457.
- 210 **Campion GV**, Lebsack ME, Lookabaugh J, Gordon G, Catalano M. Dose-range and dose frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. *Arthritis Rheum* 1996;**39**:1092-101.
- 211 **Cohen SB**, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, et al. 990145 Study Group. A multicentre, double-blind randomised, placebo controlled of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist in patients with rheumatoid arthritis treated with background methotrexate. *Ann Rheum Dis* 2004;**63**:1062-8.
- 212 **Cohen S**, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;**46**:614-24.
- 213 **Fleischmann RM**, Schechtman J, Bennett R, Handel ML, Burmester GR, Tesser J, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-methHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003;**48**:927-34.
- 214 **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.
- 215 **Muller K**, Zak M, Nielson S, Pederson FK, de Nully P, Bendtzen K. Interleukin-1 receptor antagonist in neonates, children and adults, and in patients with pauci- and polyarticular onset juvenile chronic arthritis. *Clin Exp Rheumatol* 1997;**15**:439-44.
- 216 **Vasques Godinho FM**, Parreira Santos MJ, Canas da Silva J. Refractory adult onset Still's disease successfully treated with anakinra. *Ann Rheum Dis* 2005;**64**:647-8.
- 217 **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.
- 218 **Hawkins PN**, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004;**50**:607-12.
- 219 **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* 2004;**64**:630-3 [Epub 2 September 2004].
- 220 **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 [Epub 5 April 2004].
- 221 **Haibal 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 [Epub 18 June 2004].
- 222 **Genant HK**. Interleukin-1 receptor antagonist treatment of rheumatoid arthritis patients: radiologic progression and correlation of Genant/Sharp and Larsen scoring methods. *Semin Arthritis Rheum* 2001;**30**(5 suppl 2):26-32.
- 223 **Jiang Y**, Genant HK, Watt I, Cobby M, Bresnihan B, Aitchison R, McCabe D. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. *Arthritis Rheum* 2000;**43**:1001-9.
- 224 **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.
- 225 **Tesser J**, Fleischmann R, Dore R, Bennett R, Solinger A, Joh T, et al. 990757 Study Group. Concomitant medication use in a large, international, multicenter, placebo-controlled trial of anakinra, a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis. *J Rheumatol* 2004;**31**:649-54.
- 226 **Genovese MC**, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al. 20000223 Study Group. 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**:1412-19.

# PostScript

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- Methodological requirements for surrogate end points in rheumatology trials
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## CORRECTION

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**Updated consensus statement on biological agents, specifically tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases, 2005** (Furst D E, Breedveld F C, J R Kalden, Smolen J S, Burmester G R, Bijlsma J W J, Dougados M, Emery P, Keystone E C, Klareskog L, Mease P J. *Ann Rheum Dis* 2005;64(suppl 4):iv2–14.)

An author has been omitted from the author list of this article. Arthur Kavanaugh, of University of California, San Diego, USA, should appear second from the end in the author list.

Corrections printed in the journal also appear on the *Annals* website [www.annrheumdis.com](http://www.annrheumdis.com) and are linked to the original publication