CONSENSUS STATEMENT

Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2006

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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 United States, Canada, and Europe. Pharmaceutical industry support was obtained from a number of companies, but the institutions had no part in the decisions regarding the specific programme or about the academic participants at this conference. These sponsors participated in the initial small break-out groups with emphasis on supplying factual information. The companies, on the other hand, had no part in the larger, final consensus group or in the final consensus statement.

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

The 143 rheumatologists and bioscientists who attended the consensus conference were chosen from a worldwide group of physicians and other scientists from 21 countries, with expertise in the use of biological agents for the treatment of rheumatic diseases. The number of attendees and participants was limited so that not everyone who might have been interested could be invited.

Additional information has come to light in the past 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, and further documenting adverse events. Therefore an update of the previous consensus statement is appropriate.[1] The consensus statement is annotated to document the credibility of the data supporting it as much as possible. This annotation is that of Shekelle *et al* and is described in appendix.[2] As the number of possible references has become so large, reviews are sometimes used and, if they contain category A references, will be referred to as category A evidence. All participants reviewed relevant clinical published articles relating to tumour necrosis factor (TNF) and interleukin (IL)-1 blocking agents, and abatacept and rituximab. They were given a draft consensus statement and were asked to revise the document in small discussion groups; open discussion of the revisions led to a final document, representing this updated consensus statement.

GENERAL STATEMENTS

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

As increasing evidence has accumulated for treating PsA and AS with biological agents, efficacy and clinical use for these diseases will be treated separately from RA. Adverse reactions, however, will remain combined for all indications. In general, in RA, when measuring response to therapy or when following patients over time, the American College of Rheumatology (ACR) response criteria (as a combined index) should not be used in a clinical practice setting to monitor individual response, although some validated measure of response (such as those which follow) should be employed (category B evidence[3]). Validated quantitative measures such as Disease Activity Score (DAS), Simple Disease Activity Index (SDAI), Health Assessment Questionnaire disability index (HAQ-DI), visual analogue scales (VAS), or Likert scales of global response or pain by the patient or global response by the physician, other validated measures of pain for individual patient care, joint tenderness and/or swelling counts, and laboratory data all may be used and may be the most appropriate measures for individual patients (category B evidence[3 4]). The physician should evaluate a patient's response using the above measures to determine the patient's status and improvement.

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

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 mechanism of action, pharmacokinetics, biopharmaceutical properties, etc.,

Abbreviations: ACR, American College of Rheumatology; AS, ankylosing spondylitis; CHF, congestive heart failure; DAS, Disease Activity Score; DMARD, disease modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire disability index; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SF-36, Medical Outcome Survey Short Form 36; TNF, tumour necrosis factor; VAS, visual analogue scale

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

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[11–35]). TNF blocking agents can be added to pre-existing therapy, or, when appropriate, may replace previous DMARDs[11–38] (category A evidence). There is evidence that TNF blockers are effective for the treatment of RA in MTX-naive patients (category A evidence[11 13 15 18 19 22 26 30 33–35 37 39]; category D evidence[20 24 25]). TNF blocking agents can be used as the first DMARD in some patients (category A evidence[11–13 15 18 19 22–26 30 33–35 37–40]; category D evidence[20 33 38 39]). Adalimumab and etanercept are both approved as monotherapy for RA, whereas 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 remission) and radiological outcomes (category A evidence[11 15 22 26 30 33 35 36 39–41]). TNFα blocking agents have been used with combinations of background DMARDs (category B evidence[21]).

Psoriatic arthritis

Etanercept, adalimumab, and infliximab have been approved in the USA and Europe for the treatment of PsA(category A, B evidence[15 41–49]). Controlled trial data to support conventional DMARDs as first line therapy for PsA are scant, showing modest effects of drugs such as MTX, sulfasalazine, and ciclosporin on joint and skin disease in PsA (category A evidence[50–54]). Controlled trials with etanercept (category A evidence[43 46 47]) adalimumab,[55] and infliximab[45 48] have demonstrated statistically significant improvement in a number of response measures These agents are of benefit both as monotherapy and as add-on therapy to other DMARDs such as MTX(category A evidence[41–49 55–59]). The skin lesions of psoriasis in patients with PsA have also improved (category A, B evidence[56 57 60–64]). No dose ranging studies of TNF blocking agents have been published for PsA.

Ankylosing spondylitis

Etanercept, adalimumab, and infliximab have been approved for the treatment of severe, active AS in Europe and the USA. (category A evidence[6–10 65–70]; category D evidence[71] (abs)). In the 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 evidence [6–10 65–70]). TNFα blocking agents maintain efficacy over two to four years in open studies.[69 70 72] The ASsessment in Ankylosing Spondylitis (ASAS) working group has published recommendations for the use of TNF blocking agents in AS (category A evidence[65]). 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 respective package insert for each drug). No dose ranging studies have been done with either drug in this indication.

Etanercept has been approved for juvenile idiopathic arthritis of the polyarticular type (category A evidence[15 28]; Food and Drug Administration (FDA) Summary Basis of Approval). Infliximab has been approved to treat luminal and fistulising Crohn's disease in the USA (category A evidence[73–75]; FDA Summary Basis of Approval). Infliximab is approved for ulcerative colitis and Crohn's disease in Europe (category A evidence; European Medicines Agency (EMEA) Summary).

Use in other rheumatic diseases or those with prominent rheumatic manifestations

- Controlled trials that demonstrated a difference from placebo or positive control:
  - Etanercept was effective for treating some of the mucocutaneous manifestations of Behçet's syndrome compared with placebo over four weeks (category A evidence[76]).
  - Etanercept improved hepatitis C viraemia but not symptoms, compared with placebo, when given on a background of interferon alfa and ribavirin (category A evidence[75]).
- Controlled trials that failed to demonstrate a difference from placebo:
  - Sjögren's syndrome (category A evidence[77–79]).
  - Wegener's granulomatosis (category A evidence[80]).
  - See also anecdotal data in table 1.
  - Autoimmune ear disease (category A evidence[81]—very small (N = 21)).
- Anecdotal series or studies with promising results
  - See table 1.

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 evidence[6–36 38 40–54 56–58 65–68 166 167]). 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, B evidence[58 168–170]). Patients have been switched from one TNF blocking agent to another, but no well-controlled switch trials have been published (category B evidence[72 168–171]). These studies suggest that failure to respond to one TNF blocking agent does not preclude response to another (category B evidence[58 168 169 171]).

Individually important responses including patient oriented measures (e.g. HAQ-DI, patients global VAS, Medical Outcome Survey Short Form 36 (SF-36)) or physical measures (for example, joint tenderness) should be demonstrated within 12 weeks for RA (category A evidence[6–36 38 40–54 56 57 167 168]), PsA (category A evidence[15 42–48 50–53 55]), AS (category A evidence[7–10 15 50–54 66 67 172]) and, probably, JRA (category A evidence[28 29]). If such improvement occurs, treatment should be continued. If patients show no response to these agents, *their continued use should be re-evaluated*. Observations suggest that increasing the dose or reducing the dosing intervals may provide additional benefit in RA, as may the addition or substitution of other DMARDs (category A evidence[30 31 35 40]). However, because regression to the mean may occur, caution is needed when interpreting apparent improvements following dose escalation in practice (category C evidence[173]).

Table 1 Anecdotal studies

Disease	Author(s)	Medication	No. of patients
Adult Still's disease	Huffstutter and Sienknechet[82]	Infliximab	2
	Kraetsch *et al*[83]	Infliximab	6
	Weinblatt *et al*[84]	Etanercept	12
Amyloidosis	Elkayam *et al*[85]	Infliximab	1
	Gottenberg *et al*[86]	Etanercept/ infliximab	15
	Ortiz-Santamaria *et al*[87]	Infliximab	6
	Tomero *et al*[88]	Infliximab	12
Aphthous stomatitis	Robinson and Guitart[89]	Etanercept	1
	Vujevich and Zirwas[90]	Adalimumab	1
Behçet's disease	Estrach *et al*[91]	Infliximab/ adalimumab	7
	Gulli *et al*[92]	Infliximab	1
	Hassard *et al*[93]	Infliximab	1
	Licata *et al*[94]	Infliximab	1
	Melikoghu *et al*[95]	Etanercept	20
	Rozenbaum *et al*[96]	TNFα	1
	Saulsbury and Mann[97]	Infliximab	1
	Sfikakis *et al*[98]	Infliximab	5
	Sfikakis[99]	Infliximab	11
	Ribi *et al*[100]	Infliximab	1
	Sweiss *et al*[101]	Infliximab	3
Bronchiolitis	Cortot *et al*[102]	Etanercept	1
Cirrhosis and alcoholic hepatitis	Naveau *et al*[103]	Infliximab	36
	Spahr *et al*[104]	Infliximab	20
	Wendling *et al*[105]	Infliximab	1
Cutaneous T cell lymphoma	Tsimberidou *et al*[106]	Etanercept	13
Dermatitis, hidradenitis, miscellaneous	Bongartz *et al*[107]	Infliximab	1
	Cortis *et al*[108]	Etanercept	1
	Cummins *et al*[109]	Etanercept	1
	Massarotti and Sobell[110]	Etanercept	1
	Zeichner *et al*[111]	Adalimumab	1
Dermatomyositis	Hengstman *et al*[112]	Infliximab	2
	Miller *et al*[113]	Etanercept	10
	Sprott *et al*[114]	Etanercept	1
	Nzeusseu *et al*[115]	Infliximab	1
	Saadeyh[116]	Etanercept	4
Familial Mediterranean fever	Takada *et al*[117]	Etanercept	2
	Ozgocmen *et al*[118]	Etanercept	1
Giant cell arteritis	Andonopoulos *et al*[119]	Infliximab	2
	Cantini *et al*[120]	Infliximab	4
	Tan *et al*[121]	Etanercept	1
Graft *v* host disease (acute)	Wolff *et al*[122]	Etanercept	21
Hepatitis C	Cacoub *et al*[123]	Interferon alfa	27
	McMinn *et al*[124]	Etanercept	3
	Peterson *et al*[125]	Infliximab/ etanercept	24
	Pritchard[126]	Etanercept	1
	Ince *et al*[127]	Etanercept	4
	Magliocco and Gottlieb[128]	Etanercept	3
Immunodeficiency (common variable)	Smith and Skelton[129]	Etanercept	1
Kawasaki's disease	Weiss *et al*[130]	Infliximab	1
	Burns *et al*[131]	Infliximab	16
Multicentric histiocytosis	Lovelace *et al*[132]	Etanercept	1
	Matejicka *et al*[133]	Etanercept	1
Myelodysplasia	Birnbaum and Gentile[134]	Etanercept	1
Periodic fever (children)	Athreya *et al*[135]	Etanercept	3
Pigmented villonodular synovitis	Kroot *et al*[136]	TNFα	1
Polymyositis	Hengstman *et al*[112]	Infliximab	2
	Sprott *et al*[114]	Etanercept	1
	Adams *et al*[137]	Adalimumab	2
Polychondritis	Carter (with literature review)[138]	Infliximab	1
	Ehresman[139]	Etanercept	5
SAPHO syndrome	Furst *et al*[1]	TNFα	–
	Anker and Coats[140]	Infliximab/ etanercept	150
	Sweiss *et al*[141]	Infliximab	3
	Callejas-Rubio *et al*[142]	Adalimumab	1
	Korhonen *et al*[143]	Infliximab	12
	Korhonen *et al*[144]	Infliximab	40
	Lam *et al*[145]	Infliximab	18
SAPHO syndrome	Pasternack *et al*[146]	Etanercept	4
	Tobinick and Davoodifar[147]	Etanercept	43
	Khanna *et al*[148]	Etanercept	1
	Utz *et al*[149]	Etanercept	17
	Wagner *et al*[150]	Etanercept	2
Sarcoidosis	Khanna *et al*[148]	Etanercept	1
	Utz *et al*[149]		
Scleroderma	Ellman *et al*[151]	Etanercept	8
	Bosello *et al*[152]	Etanercept	4
Silicone granulomas	Pasternack *et al*[146]	Etanercept	2
Sweet's syndrome	Gindi *et al*[153]	Etanercept	1
Systemic lupus erythematosus	Aringer *et al*[154]	Infliximab	6
	Hernandez-Ibarra *et al*[155]	N/A	–
	Principi *et al*[156]	Infliximab	1
Takayasu's arteritis	Hoffman *et al*[157]	Anti-TNFα	15
	Tato *et al*[158]	Adalimumab	1
TRAP	Hull *et al*[159]	Etanercept	>50
Uveitis	Estrach *et al*[91]	Infliximab/ adalimumab	7
	Joseph *et al*[160]	Infliximab	5
	Smith *et al*[161]	Etanercept	7
	Schmeling and Horneff (negative study)[162]	Etanercept	20
Vasculitis	Booth *et al*[163]	Infliximab	32
	Feinstein and Arroyo[164]	Etanercept	1
Wegener's granulomatosis	Gause *et al*[165]	Infliximab	10

contd.

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

There are data showing that TNF blocking agents slow radiographic progression in RA (category A evidence[11 15 20 22 23 26 27 34 37 55 167 174]) and in PsA (category A evidence[45 47 55]). In some individuals, TNF blocking agents may inhibit radiographic progression (category A evidence[26 37 174]). Although some RA patients without clinical response have slowing of radiographic progression, (category A evidence[27 34]) the long term clinical implications of these changes are unknown. Until the long term implications of slowing radiological damage are clear, radiological effects alone should not determine clinical decision making. Magnetic resonance imaging (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[175]).

Psoriatic arthritis

Individually important responses including patient oriented measures (for example, patient global VAS, DAS 28, SF-36) laboratory or physical measures (for example, joint tenderness) should be demonstrated within 12 weeks for PsA (category A evidence[15 42–49 176]). Data show that at least adalimumab and etanercept may slow the appearance of new erosions in PsA (category A evidence[46 47]). Analyses also using other, as yet not validated radiographic measures, also

demonstrate inhibition of radiographic damage in PsA (category A evidence[46 47 176]).

Ankylosing spondylitis

Individually important responses including patient oriented measures (for example, BASDAI, BASFI, patient global VAS, SF-36) or physical measures should be demonstrated within 12 weeks for AS (category A, B evidence[6 7 9 10 14 65 67 172]).

Warnings/adverse events

General reviews of TNF blocking agent safety have been published.[177–180]

Infections

The appearance or incidence of infections in immunocompromised patients may be a surrogate for too much immunosuppression, although the drug mechanism(s) of action will help determine the specific infections that are seen.

An increased susceptibility to tuberculosis or reactivation of latent tuberculosis should be considered a class characteristic of TNF blocking agents. The clinical picture of latent tuberculosis may be atypical in these patients (for example, miliary or extrapulmonary presentations) as has been seen with other immunocompromised patients (category C evidence[177–179 181–183]). There have been more reported cases of tuberculosis as a proportion of the total number of individuals treated in patients using infliximab and adalimumab than etanercept (category C evidence[177–179 181 183 185]). 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. No head-to-head comparisons among TNF blocking agents have been done and thus no definitive data on comparisons between these agents are available regarding the incidence of reactivation of latent tuberculosis.

Screening of patients about to start TNF blocking agents has reduced the risk of activating tuberculosis (EULAR 2003; category D evidence[178 181 184]). Every patient should be evaluated for the possibility of latent tuberculosis, including a history that includes evaluation for the risk of latent tuberculosis (category C evidence[72 179 182 184 185]). This history should include seeking a history of prior exposure, prior drug addiction or active drug addiction, human immunodeficiency virus (HIV) infection, birth or extended living in a region of high tuberculosis prevalence and a history of working in a tuberculosis high risk setting such as jails, homeless shelters, drug rehabilitation centres, etc. (category D evidence). In addition, physical examination and screening tests such as skin tests and chest *x* rays should be done, according to local recommendations (category C, D evidence[178 181 184]). Continued vigilance is required to prevent activation of latent tuberculosis or acquisition of 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 have recommended anywhere from simultaneously starting both treatments to waiting until the completion of anti-tuberculous therapy before beginning anti-TNF agents (category D evidence).

Opportunistic infections have occurred in the setting of TNF blocking agent use (category C evidence[11–25 37 41 73 167 178–180 186–193]). Particular vigilance is needed when considering those infections whose containment is macrophage/granuloma dependent such as listeriosis, coccidiomycosis, or histoplasmosis (category C, D evidence[178 180 182 185 187–190 193 179]) but the incidence of opportunistic infections is extremely low (category C, D evidence[182 184 185]). 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 at rates between 0.05 and 0.06/patient year compared with 0.03–0.09/patient year in controls using other DMARDs but not TNF blocking agents The incidence of other infections (not designated as serious) may be slightly increased when using TNF blocking agents (relative risk (RR) 2.3–3.0, 95% confidence interval (CI) 1.4 to 5.1).[194] The incidence of serious infections is higher when some biologicals are used in combination (3.9% in combination *v* 1.0–1.6% in controls) (category A evidence[195]). When using combinations of biologicals full doses of each agent should not be used. 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[21–25 34 34 37 40 41 46 180 187–191 193 179]; FDA). Treatment with TNF blockers in such patients should only be resumed if the infections have been treated adequately (category D evidence[177 180 182–184 187–190]; FDA).

Injection site/infusion reactions

In placebo controlled trials, injection site reactions, some of which resulted in drug discontinuation, were more common 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[11 15 22–25 27 29–31 37 180]; category B, C evidence[21 40 74 167 169 192]).

Malignancies

The incidence of lymphoma is increased in chronic inflammatory diseases such as in RA with high disease activity or AS (category D evidence[196 197](abs) (category B evidence; category D evidence). The possibility of an increased risk of malignancy in AS remains controversial (category D evidence). TNF blocking agents used in RA appear to be associated with between a twofold to fivefold increase in the risk for lymphomas (especially non-Hodgkin's lymphomas) relative to the risk in RA patients on other drugs (category C evidence[180 196 198]). This may be due to the application of these agents in patients with more severe and longstanding disease who are at a higher risk to develop lymphomas (category C evidence[196]). There is thus far no credible evidence that TNF blocking agents are associated with an increased incidence of other malignancies or recurrence in patients who have had solid malignancies previously (category C evidence[197]). Several large observational databases and a case–control study did not demonstrated an increased incidence of solid tumours after TNF blocking agents compared with matched RA controls, although one somewhat flawed meta-analysis of randomised controlled trials indicated that malignancies may be increased (category A, B evidence[199 197]). In patients at high risk for malignancies (for example, smokers) or in patients with chronic obstructive pulmonary disease (COPD), there may be an increased risk of lung cancers. In a trial of COPD patients, 9 apparently developed lung cancers during the trial and another 4 lung cancers were found during open label follow-up (data presented at the American Thoracic Society, 2005, unpublished). In a small study of Wegener's granulomatosis, the use of etanercept with cyclophosphamide was associated with six solid malignancies *v* none in the cyclophosphamide-placebo group (category A evidence[200]). An interaction of etanercept and cyclophosphamide in these patients cannot be excluded.[199] Vigilance with respect to the

occurrence of lymphomas and other malignancies including recurrence of solid tumours remains warranted in patients using these medications.

Haematological

Rare instances of pancytopenia and aplastic anaemia have been reported (category A, C evidence[23 30 40 41 180 201]). If haematological adverse events occur, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease or other causative medications (category D evidence).

Cardiovascular

High dose infliximab (10 mg/kg) appears to be associated with an increased relative risk of worsening congestive heart failure (CHF) and mortality, particularly in RA patients with New York Heart Association class III–IV CHF (category B, D evidence[140 178 180 202]). 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[140 178 202]). However, it should be noted that well controlled RA studies have excluded patients with complicating illnesses, including CHF, and RA per se appears to be associated with increased atherosclerotic cardiovascular disease (ASCVD) and ASCVD related mortality (category C evidence[178]). One cohort observational study in RA patients without overt CHF showed a possible decrease in myocardial infarction related mortality when using TNF blocking agents.[3] Each patient's risk versus benefit should be carefully considered before TNF blocking agents are begun or continued (FDA; category D evidence).

Hepatitis

The long term safety or efficacy of TNF blockers in patients with chronic hepatitis B and C is not known. Observational studies and one controlled study (the latter with interferon alfa and ribavirin background) revealed no effect on viral load and no increased incidence of adverse events; further, symptoms and liver function tests may have improved (category C, D evidence[103 123 202–205 127 129]).

In a few cases of patients treated with infliximab, hepatitis B symptoms and viraemia worsened (category C evidence[127 205]). TNF blockers should not be used in patients with hepatitis B infection, although data indicate that reactivation of hepatitis B infection during infliximab use or after TNF blocker withdrawal can be prevented by using prophylactic antiviral therapy (category C evidence[70 105 204 205]; Canadian Regulatory Authorities).

Elevations have been observed in liver function tests with infliximab and etanercept, although confounding medications and circumstances make the meaning and aetiology of these elevations unclear (FDA; category C evidence[40 103 203–206]). The follow up and monitoring for liver function test elevations should be governed by the patient's concomitant medications, conditions, and patient related risk factors.

Pregnancy

Some women have become pregnant while being treated with TNF blocking therapy and a small, pharmacovigilance study and a survey study comprising about 185 pregnancies has not shown that the rates of normal live births, miscarriages, and therapeutic terminations are different from published rates for the normal population (category C evidence (references 207–209 and Orozco C, *et al,* unpublished work)). In these women TNF blocking agents were generally stopped when pregnancy was discovered but it is not known if this affected the outcome (category D evidence). There are insufficient data to advise continuation or starting of anti-TNF therapy if a woman becomes pregnant. It is advised that women and physicians discuss the issue of TNF blocking therapy when pregnancy planning takes place or if pregnancy is discovered during ongoing TNF blocking therapy, and that this discussion is documented.

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 evidence[23 30 41 74 178 210–214]). There is an increased incidence of several autoantibodies (for example, antinuclear antibody (ANA), anti-double-stranded DNA) after infliximab and it is probably not a class effect (category C evidence[213–216]). However, there is no evidence that patients with RA who had, or develop, a positive ANA, anticardiolipin antibodies, and/or ds-DNA are at significantly increased risk for the development of drug induced lupus (FDA; category C, D evidence[23 30 40 180 210–215 217]).

Neurological diseases

The incidence of demyelinating-like syndromes, optic neuritis, transverse myelitis, multiple sclerosis, and Parkinson's disease is no greater than expected in the general population.[23 30 180 201 218] However, rare cases of these syndromes have been reported, more often with etanercept than with infliximab, all improving or disappearing after the TNF blocker was withdrawn. (category C evidence[23 180 201 218]) There is insufficient evidence to suggest that it remains possible that TNFα blockers may unmask latent disease. These agents should be stopped if a demyelinating-like disorder or optic neuritis occurs. Patients with a history of definite demyelinating disease or optic neuritis should not receive TNF blocking agents (category D evidence).

Psoriatic skin lesions

Some cases of new onset psoriatic skin lesions or exacerbations of pre-existing psoriasis have been reported in patients with RA who used TNF blocking agents, irrespective of the TNF blocker used (Karg *et al*, unpublished data (category D evidence)).

Issues specific to PsA

Safety and tolerability data with anti-TNF medications in PsA have not demonstrated any adverse events that were significantly different from RA trials. However, because liver biopsy studies suggest that patients with psoriasis and PsA demonstrate a greater proclivity for hepatotoxicity with MTX therapy than RA patients (category B evidence[219]), it is not known if the safety profile from RA trials is completely comparable with PsA.

Precautionary statements

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

- chronic infections, including HIV, etc.
- during lactation.

Other areas where knowledge is lacking are highlighted in the consensus groups' 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 continue to be needed to monitor the toxicity of biologicals and are strongly recommended, requiring a cooperative effort between payers, government, industry, and rheumatologists.
(2) Registries of pregnancy outcomes under anti-TNF therapy (and after cessation of therapy) should be continued.

Efficacy

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

Safety

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

Summary

TNF blocking agents have proved to be effective DMARDs and are a major advance in the treatment of RA, PsA, AS, and juvenile 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 these diseases should balance efficacy, toxicity, and cost issues, and recognise that data in subpopulations are still being acquired. It is hoped that this statement, which is based on the best evidence available at this time and is modified by expert opinion, will facilitate the optimal use of these agents for our patients with RA.

IL-1 BLOCKING AGENTS

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

Indications

Anakinra may be used for treatment of active RA, alone or with MTX (category A evidence[220–225]). Despite this evidence, the anakinra label presently requires its use with MTX in Europe. Anakinra 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 with other effective DMARDs (category D evidence[34]).

The use of anakinra blocking agents as the first DMARD for the treatment of RA should, at present, be limited because: no trials in early RA have been performed; these compounds are expensive; and one needs to include cost considerations along with those of efficacy, effectiveness, and long term safety (category D evidence). Anakinra may be the treatment of choice for: adult onset Still's disease (category C evidence[226–228]); neonatal onset multisystem inflammatory disease (NOMID) (category C evidence[229]); Muckle–Wells syndrome (category C evidence[230 231]; and TNFα associated periodic syndrome (TRAPS) (category C evidence[226 227 229 231 232]).

Anakinra has been used in AS[233 234]; osteoarthritis (category C evidence[236 237]) (given intra-articularly); juvenile idiopathic arthritis[228]; PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) (category C evidence[236]); Schnitzler's syndrome (urticaria, fever, arthritis, and monoclonal gammopathy); and systemic lupus erythematosus (category A, D evidence[220–224 226–238]).

Clinical use

Anakinra can lead to significant, documentable improvement in symptoms, signs, and/or laboratory parameters within 2–16 weeks (category A evidence[220 222]). 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[24]). These measures of response should be followed and individually important responses should be demonstrated within 8–16 weeks (category A evidence[220–224]). If clinically important improvement occurs, treatment should be continued. (category D evidence).

There are data showing that anakinra slows radiographic progression in rheumatoid arthritis (category A evidence[220 222 223]).

Trials of patients failing TNF blocking agents demonstrate mixed responses (category C evidence[225]). Anakinra did not inhibit anti-tetanus antibody response in a controlled trial (category A evidence[239]). It did not improve mortality in a phase 3 study of sepsis and did not prevent acute graft versus host response in patients undergoing allogeneic bone marrow transplantation (category A evidence[240 241]).

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[220–222]).

There are no data to advise either termination or continuation of IL-1blocking agents if a woman becomes pregnant.

Warnings

Severe infections have been described in patients receiving an IL-1 receptor antagonist (IL-1ra), but it is not clear if their incidence is higher than in patients with RA using other DMARDs with or without corticosteroids. These compounds should not be started or should be discontinued when serious infections occur (category A evidence[11 27 29 33]) (category D evidence[34]). 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 on increased incidence of tuberculosis (category D evidence).

In combination with other biologicals/targeted therapies, such as TNF blocking agents, infections are common and serious infections are likely more common (see warning under TNF blocking agents consensus statement). The full dose of the drugs should not be given when using both drugs together (category A evidence).

Precautionary statements

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

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

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

Research

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 the toxicity of biologicals are recommended, requiring a cooperative effort between payers, government, industry, and rheumatologists.

(2) Registries of pregnancy outcomes under anakinra blocking therapy (and after cessation of therapy) should be continued.

Efficacy

(1) What is the efficacy of anakinra in polyarticular juvenile arthritis and other rheumatic diseases including osteoarthritis?

(2) Do anakinra blocking agents have an effect on pain?

Toxicity

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

Summary

Anakinra is effective for the treatment of rheumatoid arthritis but its specific place (for example, before or after TNF blocking agents) in the rheumatological armamentarium is not yet defined. Publication of studies in selected areas of efficacy, toxicity, and general use of anakinra is needed to help further define the most appropriate use of these agents. Further considerations when using anakinra in this disease must include cost issues and the recognition that data in subpopulations are still being acquired. It is hoped that this statement, which is based upon the best evidence available at the time of its creation and is modified by expert opinion, will facilitate the optimal use of anakinra for our patients with RA. Anakinra appears to be highly active in some periodic fever syndromes, such as Muckle–Wells syndrome, NOMID, and TRAPS, and may be active in adult onset Still's disease.

ABATACEPT

Only one costimulatory blocking agent (abatacept) has been approved in the USA, and references are therefore to this product.

Indications

Abatacept is approved by the FDA in the USA for use alone or with background DMARDs for treatment of active RA. It is administered as weekly intravenous infusions of up to 10 mg/kg (see package insert). However it is not recommended for use with etanercept, infliximab, adalimumab, or IL-1ra (category A evidence; FDA package insert). Abatacept is recommended for treatment of active RA after an adequate trial of another effective DMARD and for use in patients in whom TNFα blocking agent have failed (category A evidence[242–246]). Abatacept has been used with other effective DMARDs (category A evidence). Patients with early RA and early undifferentiated arthritis are presently being studied (category D evidence).

Pharmacoeconomics studies are being done (category D evidence).

Clinical use

Abatacept can lead to meaningful, documentable improvement in signs, symptoms and/or laboratory parameters within 16 weeks, although additional improvement can occur for up to one year. Measures of patient related outcomes such as global patient VAS, pain scores, HAQ-DI, DAS 28, and SF-36 usually show significant improvements in a similar time frame (category A evidence[195 242–246]). If clinical improvement occurs, treatment should be continued (category D evidence).

Abatacept slows radiographic progression in RA (category A evidence[195 246]).

Abatacept has been used in psoriasis (category C evidence[247]). There are ongoing studies in juvenile idiopathic arthritis and systemic lupus erythematosus (category D evidence).

Warnings

A small increased incidence of infection has been observed, including serious infections (3.0% with abatacept *v* 1.9% with placebo, p = not significant). In combination with other biological agents, the risk of serious infections is 4.5% (*v* 1.5% in controls) and the use of abatacept with other biologicals is not recommended (category A evidence[244 247]). This compound should not be started or should be temporarily discontinued when serious infections occur (category D evidence). Treatment with abatacept in such patients should only be resumed if the infections have been adequately treated (category D evidence). Patients with COPD treated with abatacept had more adverse events than patients treated with placebo; therefore use in RA patients with COPD should be undertaken with caution and should be monitored for worsening of respiratory status (category D evidence).

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

Data from a dataset of about 3000 patients including placebo controlled and open label experience indicates that there is a possibility that the risk of lung cancer is increased during controlled trials; 4 lung cancers were found among abatacept treated patients versus none in the control group; 4 more lung cancers were found during the open-label extension. As this may be higher than in the general population, further surveillance is needed (category D evidence).

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

Precautionary statements

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

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

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

Research

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

Registry

(1) As per anti-TNF agents.

Efficacy

(1) What is the efficacy of abatacept in polyarticular juvenile arthritis, early arthritis, systemic lupus undifferentiated early arthritis, and other rheumatic diseases?
(2) How/when does one start abatacept after rituximab is stopped?
(3) Is there a change in response to vaccines when using abatacept?

Toxicity

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

RITUXIMAB

Rituximab is a chimeric anti-CD20 monoclonal antibody, which was approved in 1997 for treatment of indolent CD20, B cell non-Hodgkin's lymphoma. More than 730 000 patient exposures have been documented over seven years in post-marketing surveillance of these non-rheumatic diseases.

Indications

Rituximab has been approved by the FDA in the USA for the treatment of patients with RA who have had an inadequate response to TNF inhibitors. Rituximab is administered intravenously as two infusions (given with 100 mg of methylprednisolone (Solu-Medrol) or equivalent) each of 1 g rituximab separated by an interval of two weeks. It may be also used when TNF inhibitors are not suitable. In RA, it may be used alone or in combination with MTX (category A evidence[248–254]). Appropriate supportive equipment should be available when rituximab is used.

Clinical use

In clinical trials, rituximab results in significant improvement in signs and symptoms and/or laboratory measures by 8–16 weeks (category A evidence[248–258]; abs) in patients with an inadequate response to MTX. Improvement has also been demonstrated in patient related outcomes such as HAQ-DI, patient global VAS, fatigue, disability, and quality of life. Evidence from randomised controlled trials suggests that the combination of rituximab with MTX yields superior clinical efficacy for RA when compared with monotherapy (category A evidence[256–258]). The optimal treatment schedule is currently under investigation (category A evidence[250 253 254 256–258]). Preliminary data have shown that repeat treatment courses are effective in previously responsive RA patients (category A evidence; FDA package insert). Most of the patients who received subsequent courses did so 24 weeks after the previous course and none received repeated courses earlier than 16 weeks from the previous course (category A evidence; FDA package insert).

There are data indicating that rituximab can slow radiographic progression in patients who have had an inadequate response to one or more TNF inhibitors (category A evidence[257–259]).

Rituximab has been used in primary Sjögren's syndrome, systemic lupus erythematosus, Wegener's granulomatosis, hepatitis C associated cryoglobulinaemia, antineutrophilic cytoplasmic antibodies (ANCA) associated vasculitis disorders other than Wegener's such as polyarteritis nodosa, dermatomyositis/polymyositis (category C evidence), autoimmune haemolytic anaemia, idiopathic thrombocytopenia purpura, antiphospholipid syndrome, and scleroderma (category C evidence[253]).

Warnings

The most frequent adverse events are infusion reactions which are most common with the first infusion (approximately 35%) and reduce with the second infusion (approximately 10%). Intravenous corticosteroids were shown to reduce the incidence and severity of infusion reactions by about 30% without changing efficacy (category D (abs) evidence[257–259]).

Serious infections, including bacterial infections, have been observed in patients receiving rituximab. The incidence in clinical trials is slightly higher than placebo treated patients (2.1% *vs* 0.9% p = not significant) (category A, D (abs) evidence [250–254 256–259]). Rituximab should not be given in the presence of serious or opportunistic infections. The risk for activation of latent tuberculosis or for developing new tuberculosis when using rituximab is unknown as patients were screened for infectious disease during phase 3 clinical trials by means of a chest *x* ray and were excluded if deemed at risk. Until the risk is known, it is prudent to screen patients about to start rituximab for tuberculosis according to local practice (category D evidence).

Since rituximab appears to be effective by means of selective B cell depletion both locally and systemically, it is recommended that any vaccinations required by the patient, such as those to prevent pneumonia and influenza, should be given before commencing this agent. Until further data are available live attenuated vaccines should be given only prior to the use of rituximab (category D evidence).

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

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

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

Research questions

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

Registry

(1) As per anti-TNF agents.

Efficacy

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

Safety

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

APPENDIX 1: CATEGORIES OF EVIDENCE

- *Category A evidence*: based on evidence from at least one randomised controlled trial or meta-analyses of randomised controlled trials.
- *Category B evidence*: based on evidence from at least one controlled trial without randomisation or at least one other type of experimental study, or on extrapolated recommendations from randomised controlled trials or meta-analyses.
- *Category C evidence*: based on non-experimental descriptive studies such as comparative studies, correlational studies and case–control studies which are extrapolated from randomised controlled trials, non-randomised controlled studies or other experimental studies.
- *Category D evidence*: based on expert committee reports or opinions or clinical experience of respected authorities or both, or extrapolated recommendations from randomised controlled trials, meta-analyses, non-randomised controlled trials, experimental studies or non-experimental descriptive studies.

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

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