CONSENSUS STATEMENT

Updated consensus statement on biological agents, specifically tumour necrosis factor α (TNFα) 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.[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 3.[2] 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 TNFα 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[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 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[5]). 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[6–10]).

The use of biological agents will require physicians experienced in the diagnosis, treatment, and assessment of RA, PsA, AS, and other rheumatic diseases. These physicians will need to make long term observations for efficacy and toxicity. 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[11]). If response is not optimal, switching of therapeutic strategies is recommended (category B evidence[12 13]).

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[11–40]). TNF blocking agents can be added to pre-existing therapy, or, when appropriate, may replace previous DMARDs (category A evidence[11–39]). There is evidence that TNF blockers are effective for the treatment of RA in MTX naive patients (category A evidence[14 16 18 21 22 25–27 31 35 38 39]; category D evidence[23 29 30]). The use of TNF blocking agents as the first DMARD for the treatment of RA (category A evidence[11 12 14–16 18 21 22 25–31 35 38 39]; category D evidence[38] (abstract[39])) 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[12 16 18 21 22 25–31 35 38 39]).

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[11 13 14 18 27 31 35 39 40–42]). TNFα blocking agents have been used with combinations of background DMARDs (category B evidence[24]).

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[18 43–56]). 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[56–60]). Controlled trials with etanercept (category A evidence[42 45 46]) adalimumab (category A evidence[51]) and infliximab (category C evidence[44 47]) 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[46 49 51 54 55]). These agents are of benefit both as monotherapy and as add-on therapy to other DMARDs such as MTX (category A evidence[43 45–55]). The skin lesions of psoriasis in patients with PsA have also improved (category A, D (abstract) evidence[44–46 48 50 51 54 55 61–66]). 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[6–10 67–73]).

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[6–10 67–73]) (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[6–10 67–73]). TNFα blocking agents maintain efficacy over two to four years in open studies.[68 69 71 73 74] The ASAS Working Group has published recommendations for the use of TNF blocking agents in AS (category A evidence[67]). 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[20 75–84]).

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[19 34]; 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[85]; FDA Summary Basis of Approval).
- Etanercept was effective for treating some of the mucocutaneous manifestations of Behçet's syndrome versus placebo over four weeks[86] (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[87–89])
  - Wegener's granulomatosis (category A evidence[90]). Note: an open trial of infliximab was effective but associated with severe infections (category D (abstract) evidence[91]).

- 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[6–55 68–75]). 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[155–161]). 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[155–161]). 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[11–13 156–161]).

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[11–43 155–164]), PsA (category A evidence[19 44–55 61]), AS (category A evidence[6–10 68–73]), and, probably, juvenile RA (category A evidence[19 34 35]). 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[11 12 36 155–161]). However, because regression to the mean may occur, caution is needed when interpreting apparent improvements following dose escalation in practice (category C evidence[161]).

There are data showing that TNF blocking agents slow radiographic progression in RA (category A evidence[11 12 14 15 19 26–33 165–169]), and in some individuals may inhibit it (category A, C evidence[26 32 155]). 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[162 167]). 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 Sienknechet[92]	Infliximab	2
	Kraetsch *et al*[93]	Infliximab	6
	Weinblatt *et al*[94]	Etanercept	12
Amyloidosis	Elkayam *et al*[95]	Infliximab	1
	Gottenberg *et al*[96]	Etanercept/ infliximab	15
	Ortiz-Santamaria *et al*[97]	Infliximab	6
	Tomero *et al*[98]	Infliximab	12
Behçet's disease	Estrach *et al*[99]	Infliximab/ adalimumab	7
	Gulli *et al*[100]	Infliximab	1
	Hassard *et al*[101]	Infliximab	1
	Licata *et al*[102]	Infliximab	1
	Melikoglu *et al*[103]	Etanercept	20
	Rozenbaum *et al*[104]	Anti-TNFα	1
	Saulsbury and Mann[105]	Infliximab	1
	Sfikakis *et al*[106]	Infliximab	5
	Sfikakis[107]	Infliximab	11
	Shereen and Moore[108]	Infliximab	1
	Sweiss *et al*[109]	infliximab	3
Cirrhosis and alcoholic hepatitis	Naveau *et al*[110]	Infliximab	36
	Wendling *et al.*[111]	Infliximab	1
	Spahr *et al*[112]	Infliximab	20
Cutaneous T cell lymphoma	Tsimberidou *et al*[113]	Etanercept	13
Dermatomyositis	Hengstman *et al*[114]	Infliximab	2
	Miller *et al*[115]	Etanercept	10
	Saadeh[116]	Etanercept	1
	Nzeusseu *et al*[117]	Infliximab	1
	Sprott *et al*[118]	Etanercept	1
Familial Mediterranean fever	Hull *et al*[119]	TRAPS-etanercept	>50
	Takada *et al*[120]	Etanercept	2
Giant cell arteritis	Andonopoulos *et al*[121]	Infliximab	2
	Cantini *et al*[122]	Infliximab	4
	Tan *et al*[123]	Etanercept	1
Hepatitis C	Zein *et al*[85]	Infliximab/ etanercept	5
	Parke and Reveille[124]	Etanercept	3
	Magliocco and Gotlieb[125]	Interferon alfa	27
	Cacoub *et al*[126]	Etanercept	10
	McMinn *et al*[127]	Etanercept	3
	Peterson *et al*[128]	Infliximab/ etanercept	24
	Pritchard[129]	Etanercept	1
Kawasaki's disease	Burns *et al*[130]	Infliximab	1
	Weiss *et al*[131]		
Multicentric histiocytosis	Calamia *et al*[132]	Etanercept	1
Myelodysplasia	Birnbaum and Gentile[133]	Etanercept	1
Periodic fever (children)	Athreya *et al*[134]	Etanercept	3
Pigmented villonodular synovitis	Kroot *et al*[135]	Anti-TNFα	1
Polymyositis	Hengstman *et al*[114]	Infliximab	2
	Sprott *et al*[118]	Etanercept	1
Polychondritis	Ehresman[136]	Infliximab	1
SAPHO syndrome	Furst *et al*[]	Etanercept	2
	Wagner *et al*[137]	Anti-TNFα	–
Sarcoidosis	Tutuncu *et al*[138]	Etanercept	1
	Khanna *et al*[139]	Etanercept	–
	Baughman and Iannuzzi[140]		
	Sweiss *et al*[141]	Infliximab	3
	Sweiss *et al*[142]	TNF inhibition	13
	Utz *et al*[143]	Etanercept	17
Sciatica	Korhonen *et al*[144]	Infliximab	12
	Atcheson and Dymeck[145]	Infliximab	1
	Genevay *et al*[146]	Etanercept	10
Scleroderma	Ellman *et al*[147]	Etanercept	8
Systemic lupus erythematosus	Aringer *et al*[148]	Infliximab	6
	Hernandez-Ibarra *et al*[149]	N/A	–
	Principi *et al*[150]	Infliximab	1
Takayasu's arteritis	Hoffman *et al*[151]	Anti-TNFα	15
Uveitis	Estrach *et al*[99]	Infliximab/ adalimumab	7
	Joseph *et al*[152]	Infliximab	5
	Suhler *et al*[153]	Infliximab	13
Vasculitis	Booth *et al*[154]	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[167]).

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

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[43–56]). Data show that adalimumab, etanercept, and infliximab slow radiographic damage in PsA (category A evidence[49 51 54 55]).

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[67–73]) Specific recommendations for therapy have been published (category D evidence[67]).

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[168–182]). There have been more reported cases of tuberculosis in patients using infliximab than in patients using the other presently marketed agents (category C evidence[168 171–173]). 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[1 168–171 173 176]). 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[1 168–173]). 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[168 179]). 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[14 15 19 28–31 72 160 168–173 179 183]). Particular vigilance is needed when considering those infections whose containment is macrophage/granuloma dependent such as listeriosis, coccidiomycosis, or histoplasmosis (category C, D evidence[160 168 170 173 176–181]) but the incidence of opportunistic infections is extremely low (category C, D evidence[168 179 180]). 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.[184 185] 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[14 15 29 31 168 179 183 186]). Treatment with TNF blockers in such patients should only be resumed if the infections have been treated adequately (category D evidence[1 168 179] package insert). Patients should be instructed regarding the rudiments of differentiating simple viral illneses 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[187–189]).

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[13–15 29–31 36–38 170 179]; category B, C evidence[11 75 160 168 174 179]).

Malignancies

The incidence of lymphoma is increased in RA, particularly in RA with high disease activity (category B evidence[190–193]). 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[168 179 190–193]). 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[190 193]).

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[179 191 192]). 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[179 191 192]), 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[194]).

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[14 15 19 29 31 36 168 179]). 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[139 168 179]). 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[139 168 179 195]).

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[168 179 196]).

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

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[128 197]). 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[85]). 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[198–200]). 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[14 168 179]). 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[201]). 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[28 75 168 179 202]). 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[28 75 168 179 202–208]).

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[28 75 168 179 209]). 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, ore 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[210–213]). 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[214–219]). Evidence regarding the use of anakinra in AS is conflicting.[220 221]

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[210–213]). 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[210–213]). 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[222–224]).

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[210–213 225]) 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[226]). 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[210–213]). 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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