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, 2004

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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.

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

The 128 rheumatologists and bioscientists who attended the consensus conference were chosen from a worldwide group of physicians and other scientists from 20 countries with expertise in the use of biological agents for the treatment of rheumatic diseases. The number of attendees and participants were limited so that not everyone who might have been interested could be invited.

Additional information has come to light in the past year, corroborating the major positive effect these drugs have had in rheumatoid arthritis (RA) and other rheumatic diseases, as well as further documenting adverse events. Therefore an update of the previous consensus statement[1] is appropriate. 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*[2] and is described in appendix 3. As the number of possible references has become so large, sometimes reviews were used and, if they contained 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. 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 the patient, as must the toxicity of previous and/or alternative disease modifying antirheumatic drug (DMARD) use.

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 measures 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 psoriatic arthritis (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 ankylosing spondylitis (AS), measures such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and 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 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.

Abbreviations: aCL, anticardiolipin antibodies; ACR, American College of Rheumatology; ANA, antinuclear antibodies; AS, ankylosing spondylitis; CHF, congestive heart failure; DAS, Disease Activity Score; DMARD, disease modifying antirheumatic drug; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire disability index; IL-1ra, interleukin-1 receptor antagonist; MTX, methotrexate; NHL, Non-Hodgkin's lymphoma; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomised controlled trial; SDAI, Simple Disease Activity Index; TNF, tumour necrosis factor; VAS, visual analogue scale

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 which 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 a commonly used example. They have also been used successfully with other DMARDs (category A evidence[11–37]). TNF blocking agents can be added to pre-existing therapy, or, when appropriate, may replace previous DMARDs (category A evidence[11–37]). There is evidence that TNF blockers are effective for the treatment of RA in MTX naive patients (category A evidence[12 14 16 19 20 23–25 29 32 33 36 37]; category D evidence[21 27 28]). The use of TNF blocking agents as the first DMARD for the treatment of RA (category A evidence[11–14 16 19 20 23 25 29 33 36–38]; category D evidence[36 37]) 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 evidence[14 16 19 20 26 28 32 33 36 37]; category D evidence[21]).

Adalimumab and etanercept are both approved as monotherapy for RA, while infliximab is approved for use with MTX in RA. However, the cumulative weight of the evidence from several randomised controlled trials (RCTs) 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, EULAR remission) and radiological outcomes (category A evidence[16 25 29 33 37 39]). TNFα blocking agents have been used with combinations of background DMARDs (category B evidence[22]).

Psoriatic arthritis

Etanercept has been approved in the USA and Europe for the treatment of PsA while adalimumab and infliximab are being tested prior to submission for review (category A, B, C evidence[16 40–47]). 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 A on joint and skin disease in PsA (category A evidence[48–52]). Controlled trials with etanercept (category A evidence[43 44 53]) and infliximab[42 45] 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[40–47 53–55]). The skin lesions of psoriasis in patients with PsA have also improved (category A, D evidence[55–58]). No dose ranging studies of TNF blocking agents for PsA have been published.

Ankylosing spondylitis

Etanercept has been approved for the treatment of severe, active AS in Europe and the USA and infliximab is approved for this indication in Europe (category A, C evidence[6–10 59–63]). Adalimumab is being tested in this disease (unpublished). 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 59–63]). The Assessment in Ankylosing Spondylitis (ASAS) working group has published recommendations for the use of TNF blocking agents in AS (category A evidence[64]). 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 study has been done with either drug in this indication.

Health economic data and long term safety data may change the circumstances when TNF blocking agents will be started. The cost efficacy data to date are somewhat conflicting; this may in part be due to varying underlying assumptions and the varying sources of the analysis (category B evidence[17 65–67]).

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[16 31 68]; FDA Summary Basis of Approval)
  - Infliximab has been approved to treat luminal and fistulising Crohn's disease (category A evidence[69 70]; FDA Summary Basis of Approval)
- Trials that failed to demonstrate a difference from placebo:
  - Sjögren's syndrome (category B evidence[71–73])
  - Wegener's granulomatosis[74 75] (G Hoffman, unpublished data)
- Anecdotal series or studies with promising results:
  - See table 1

Clinical use

Efficacy

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 measures within 12 weeks[7 8 11–23 25–37 40–55 58 68 126] (category A, B, C, D (abstract) evidence[6 9 10 60–63 76–78 127]). 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 one TNF blocker is more effective than any other (see above) (category A, D evidence (abstract)[128–133]). Patients have been switched from one TNF blocking agent to another but no well controlled switch trials have been published (category B, D evidence (abstract)[128–133]). These studies suggest that failure to respond to one TNF blocking agent does not preclude response to another (category B, D evidence (abstract)[128–133]).

Table 1 Anecdotal studies

Adult Still's disease[76–78]	Periodic fever (children)[112]
Amyloidosis[79–82]	Polymyositis[96 98]
Behçet's disease[83–92]	Polychondritis[113]
Cirrhosis and hepatitis[93–95]	SAPHO syndrome[1 114]
Dermatomyositis[96–99]	Sarcoidosis[115–119]
Familial Mediterranean fever[100 101]	Sciatica[115 117–119]
Giant cell arteritis[102–104]	Scleroderma[120]
Hepatitis C[105–108]	Systemic lupus erythematosus[121]
Kawasaki's disease[109]	Takayasu's arteritis[122]
Multicentric histiocytosis[110]	Uveitis[83 123 124]
Myelodysplasia[111]	Vasculitis[125]

Individually important responses including patient oriented measures (for example HAQ-DI, patient's global VAS, Short Form (SF)-36) or physical measures (for example joint tenderness) should be demonstrated within 12 weeks for RA, PsA, AS and, probably, juvenile RA (category A evidence[6–17 19–21 23 25–31 33–37 40–55 58 63 68 126 127]). 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 may provide additional benefit in RA, as may the addition or substitution of other DMARDs (category B evidence[11 33 34 37]). However, because regression to the mean may occur, caution is needed when interpreting apparent improvements following dose escalation in practice (category C evidence[133]).

There are data showing that TNF blocking agents slow radiographic progression in RA (category A evidence[12 16 21 23–26 30 126]), and in some individuals may inhibit it (category C, D evidence[24 29 134]). Although some patients with RA without clinical response have slowing of radiographic progression,[30 135] 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.

Data show that at least one TNF blocking agent may slow the appearance of new erosions in PsA (category A evidence[43 44]). Analyses using other as yet unvalidated radiographic measures as well, also demonstrate inhibition of radiographic damage in PsA (category A evidence[43 44]).

Warnings/adverse events

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 tuberculosis may be atypical in these patients (for example miliary or extrapulmonary presentations) as has been seen in other immunocompromised patients (category C evidence[136]). 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[136 137]). 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 of TNF blocking agents have been done and thus no definitive comparative data of these agents are available about 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 (abstract)[138]). All patients should be evaluated for the possibility of latent tuberculosis, including a history which includes evaluation for the risk of latent tuberculosis (category C evidence[136 137]). This should include seeking a history of prior exposure, prior or active drug addiction, human immunodeficiency virus (HIV) infection, birth or extended living in a region of high prevalence of tuberculosis, 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 screening tests such as skin tests and chest *x* rays should be done according to local recommendations (category C, D (abstract) evidence[1 139 140]). 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 timeframe from after initiating antituberculous 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 antituberculous 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 15 18 22 26 36 69 126 141–144]). Particular vigilance is needed when considering those infections whose containment is macrophage/granuloma dependent such as listeriosis, coccidiomycosis, or histoplasmosis (category C, D evidence[136 137]) but the incidence of opportunistic infections is extremely low (category D evidence[136]). 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, but it is not clear for the most part that their incidence is higher than in patients with RA using other forms of DMARD therapy and/or corticosteroids. 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 (FDA; category C evidence[11 15 18 22 26 36 43 141–145]). Treatment with TNF blockers in such patients should only be resumed if the infections have been treated adequately (FDA; category D evidence[137–140 147–151 (abstract)146]).

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[12 13 16 21 23 25–28 30 32 34 148]); (category B, C evidence[11 22 70 126 145]); (category D evidence (abstract) [131 143]).

Malignancies

The incidence of lymphoma is increased in RA, particularly in RA with high disease activity (category B evidence[152]). It may also be increased in patients with AS (category D evidence). TNF blocking agents used in RA appear to be associated with an approximate doubling of the risk for non-Hodgkin's lymphomas (NHLs) relative to the risk in patients with RA (category C evidence[148 152 153]). This may be due to the application of these agents in patients with more severe and longstanding disease who have higher risk to develop lymphomas. There is thus far no 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 D evidence). Vigilance with respect to 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[26 33 145 148 154] (category A, C evidence). 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 and mortality, particularly in RA patients with New York Heart Association (NYHA) class III–IV congestive heart failure (CHF) (category B, D evidence[148 155]). 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[114 148 155]). However, it should be noted that well controlled RA studies have excluded patients with complicating illnesses, including CHF. One cohort observational study in patients with RA without overt CHF showed no increase 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 in those circumstances (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. One observational 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 evidence[93 95 105 107 148 156]). TNF blockers should not be used in patients with hepatitis B infection (category C evidence[148]).

Elevations of liver function test have been observed with infliximab and etanercept, although confounding medications and circumstances make the meaning and aetiology of these elevations unclear (FDA; category C, D evidence[11 94 157]). 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 patients have become pregnant while being treated with TNF blocking therapy and small, pharmacovigilance studies have not shown that rates of normal live births, miscarriages, and therapeutic terminations are different from published rates for the normal population (category D evidence (abstract)[158]). In these patients 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 patient becomes pregnant. It is advised that patients and physicians discuss the issue of TNF blocking therapy when pregnancy planning takes place or if pregnancy occurs 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 (abstract) evidence[26 28 33 70 141 142 145 159–162]). There is no evidence that patients with RA who had, or develop, positive antinuclear antibodies (ANA), anticardiolipin antibodies (aCL), and/or ds-DNA are at significantly increased risk for the development of drug induced lupus (FDA; category C, D (abstract) evidence[11 26 28 33 141–145 148 159–163]).

Instances of demyelinating-like disorders and optic neuritis have been reported in patients receiving TNF blockers, although it is not known currently if the incidence in patients receiving TNF blockers is different from a comparable group of patients with RA who have not received TNF blocking agents (category C evidence; category D evidence[26 33 145 148 154 164]). 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).

Issues specific to PsA

Safety and tolerability data of anti-TNF medications in PsA did not demonstrate 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 patients with RA (category B evidence[165]), 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:

(1) Chronic infections, including HIV, etc.
(2) During lactation.
(3) When IL-1 blocking agents and TNF blocking agents are used together—infections are common and serious infections have occurred. This combination should be used with great caution until new data become available (category D evidence[144]).

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 group 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 are the optimal dosing regimens when using TNF blocking agents?
(2) Are there predictors of response and 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 of 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 role of pharmacoeconomic evaluations to help clinicians treat individual patients?

(7) How long do clinical and radiological benefits last in patients who stop using TNF blocking agents?
(8) Can the dose of TNF blocking agents be escalated in the event of therapeutic loss of effect?
(9) What is the effect of TNF blocking agents on growth in children with juvenile chronic arthritis?
(10) Are ACR 20/50/70, DAS, Rheumatoid Arthritis Disease Activity Index (RADAI), SDAI, the Psoriatic Arthritis Response Criteria (PsARC), and HAQ valid measures of response in PsA?
(11) What, if any, dose response exists for the use of TNF blocking agents in PsA and/or AS?
(12) Are TNF blocking agents superior to other DMARDs such as sulfasalazine or leflunomide for treating PsA and/or AS?
(13) Do TNF blocking agents modify structural damage in AS?
(14) Do patients with AS and advanced spinal fusion respond to TNF blocking agents?
(15) What are the predictors of response to TNF blocking agents in early and advanced AS and/or PsA?

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 NHL 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 among TNF blocking agents as regards the incidence or prevalence of opportunistic infections or other infections?

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.

IL-1 BLOCKING AGENTS

To date only one IL-1 blocking agent (anakinra) has reached the market and references are therefore to this product. As other agents of this class reach the market, the document below will be changed appropriately, but it may appear somewhat inconsistent at present as an attempt is made to separate presumed class characteristics from data relating to this prototypic compound.

Indications

IL-1 blocking agents may be used for treatment of active RA, alone or with MTX (category A evidence[32 37]). 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 with other effective DMARDs (category D evidence[23]).

The use of IL-1 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).

IL-1 receptor antagonist (IL-1ra) has been used in juvenile RA, adult onset Still's disease, neonatal onset multisystem inflammatory disease, Muckle–Wells syndrome, and systemic lupus erythematosus (category C, D evidence).

Clinical use

IL-1 blocking agents can lead to significant, documentable improvement in symptoms, signs, and/or laboratory measures within 2–16 weeks (category A evidence[30 32 37]). Measures of patient related outcomes such as global patient VAS or HAQ may be more sensitive to the effects of one IL-1 blocking agent (anakinra) than physical measures such as joint tenderness/swelling (category D evidence[27]). These measures of response should be followed and individually important responses should be demonstrated within 8–16 weeks (category A evidence[32 33 37]). If clinically important improvement occurs, treatment should be continued (category D evidence).

Data show that IL-1 blocking agents, of which anakinra is the marketed prototypic compound, slows radiographic progression in RA (category A evidence[33 37]). Data are conflicting about the usefulness of IL-1ra after patients have failed TNF blocking agents. One open trial showed no response while some observational data were more favourable (category D evidence). Recent data indicate that IL-1ra may be effective in treating adult onset Still's disease (category D evidence (abstract)[166]).

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[30 32 37]; category D evidence[23]).

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

Warnings

Severe infections have been described in patients receiving IL-1ra, but it is not clear that their incidence is higher than in patients with RA using other DMARD treatments with or without corticosteroids. These compounds should not be started or should be discontinued when serious infections occur (category A evidence[12 30 32 37]) (category D evidence[23]). 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).

Precautionary statements

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

(1) Lymphoma, lymphoproliferative and other malignancies.
(2) During pregnancy and/or lactation.

(3) In combination with other biologicals/targeted therapy, such as TNF blocking agents. Infections are common and serious infections have occurred when using IL-1 blocking agents and TNF blocking agents together; this combination should be used with great caution until new data become available (category D evidence[25]).
(4) When considering primary vaccinations or live attenuated vaccines.

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 group 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 among payers, government, industry, and rheumatologists.
(2) Registries of pregnancy outcomes under 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 juvenile arthritis and other rheumatic diseases, including osteoarthritis?
(2) Do IL-1 blocking agents have an effect on pain?

Toxicity

(1) Can IL-1 blocking agents 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

IL-1 blocking agents, of which anakinra is the prototypic and sole example, are effective for the treatment of RA but their 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 IL-1 blocking agents is needed to help further define the most appropriate use of these agents. Further considerations when using IL-1ra 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. IL-1 blockers appear to be highly active in some periodic fever syndromes, such as Muckle–Wells syndrome, and may be active in adult onset Still's disease.

Appendix 1: Abbreviated summary of the ''Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2004''

- 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 DMARDs 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. Cost considerations should be included when considering the use of TNF blocking agents.
- 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.
- Pharmacoeconomic and long term safety data may modify all of the above statements but only conflicting data have been published to date.

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, while 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 patients show no response to these agents at their maximum approved dose they should be stopped in 12 weeks.
- If an incomplete response occurs, increased doses or reduced dosing intervals may provide additional benefits, as may other DMARDs or other biologicals, although further study on 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 blockers; numerically more reactivation of tuberculosis occurs with infliximab than etanercept, although analyses and circumstances do not permit differentiation among these drugs with respect to reactivation of latent tuberculosis. An early adalimumab study also showed more frequent tuberculosis reactivation after very high adalimumab dosing (no longer seen in later studies where tuberculosis screening was done).
- Screening for latent tuberculosis is necessary, specially in countries with high prevalence of tuberculosis.
- Individual evaluations, including history, physical examination, chest *x* ray examination, and/or purified protein derivative test, should be done and therapy for latent tuberculosis considered according to local recommendations.
- TNF blocking agents should not be started or should be discontinued when serious infections occur.
- Opportunistic infections have occurred in the setting of TNF blocking agent use. The incidence, however, is low.
- Injection site reaction (etanercept, adalimumab) and infusion reaction (infliximab) occur more commonly in patients receiving these agents than in controls. They are usually mild-moderate.
- NHLs have occurred in patients using TNF blocking agents, and the incidence may be approximately twice that of patients given other DMARDs although it is not clear if the incidence of these tumours is increased relative to an appropriate disease control group.
- No evidence to date links TNF blocking agents with solid tumours such as breast or gastrointestinal cancers.
- A few instances of pancytopenia and aplastic anaemia have been reported although the relationship and frequency of this adverse event is not sufficiently understood to make specific recommendations about 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.
- The safety of TNF blocking agents to treat 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 tests 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.
- Insufficient data are available about the use of anti-TNF therapy prior to or during pregnancy to allow advice in this circumstance. Although pharmacovigilance data have shown the same rates 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 develops, TNF blocking agents should be stopped.
- The presence or development of positive ANA, aCL, and/or ds-DNA does not significantly increase the risk of developing drug induced lupus.
- Instances of demyelinating-like disorders and optic neuritis have been reported in patients receiving TNF blockers. These agents should be stopped if a demyelinating-like disorder occurs.
- Patients with a history of a definite demyelinating disease should not receive TNF blocking agents.

Precautionary statements

- The safety of TNF blockade is unknown in the following situations: chronic infections including HIV, during pregnancy, or lactation.
- When considering primary vaccinations or live attenuated vaccines caution should be exercised, although some preliminary data show no differences in response to pneumococcal vaccine relative to normal controls.

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 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

- IL-1 blocking agents may be used for the treatment of active RA, alone or with MTX. In Europe, IL-1 blocking agents (anakinra) should presently be used in conjunction with MTX.
- IL-1 blocking agents will probably be effective when used with other effective DMARDs.

Clinical use

- IL-1 blocking agents (anakinra) can lead to significant documentable improvement in symptoms, signs, and/or laboratory measures 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 an IL-1 blocking agent occurs, the agent(s) should be continued.
- IL-1 blocking agents (anakinra) slow radiographic progression in RA.
- There are observational data that IL-1ra is effective in patients failing TNF blocking therapy.
- 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 IL-1 blocking therapy if the patient becomes pregnant.
- The efficacy and toxicity of IL-1 blocking agents in rheumatic diseases other than RA are unknown although they have been used in juvenile chronic arthritis, adult onset Still's disease, Muckle–Wells syndrome and NOMID (neonatal multi-inflammatory disease).

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 only be resumed if 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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