

CONSENSUS STATEMENT

Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases (May 2003)

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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 universities in the United States, 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 158 rheumatologists and bioscientists from 21 countries who attended the consensus conference were chosen from a worldwide group of doctors and other scientists interested in the use of biological agents for the treatment of immune mediated inflammatory diseases. The perspective of this consensus is from the treating doctor's point of view, rather than from the perspective of those paying for their use. The number of attendees and participants was limited so that not everyone who might have been appropriate could be invited.

Additional information has come to light in the past year, both corroborating the major positive effect these drugs have had in rheumatoid arthritis (RA) and other immune mediated inflammatory diseases, as well as documenting possible new and unexpected adverse events. Therefore an update of the previous consensus statement seems both appropriate and necessary (*Ann Rheum Dis* 2002;**61**(suppl II):ii2-7).

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 3.⁹⁹ All participants reviewed relevant clinical published articles relating to tumour necrosis factor (TNF) and interleukin 1 (IL1) 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. 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, when measuring response to treatment, the American College of Rheumatology (ACR) response criteria (as a combined index) should not be used in clinical practice to monitor individual response (category B evidence).¹⁰⁰ Validated quantitative measures such as the disease activity score (DAS), Health Assessment Questionnaire disease index

(HAQ-DI), visual analogue scales (VAS) or Likert scales of global response or pain by the patient or global response by the doctor, 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).¹⁰⁰ The doctor should evaluate the patient's response using the above measures to determine the patient's status and improvement.

The use of these drugs will require doctors experienced in the diagnosis, treatment, and assessment of RA and other rheumatic diseases. These doctors 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 which clearly have differentiated between compounds will be discussed if such areas can be identified.

Indications

TNF blockers are recommended generally for the treatment of active RA after an adequate trial of another effective DMARD, of which methotrexate (MTX) is a commonly used example (category A evidence¹⁻¹⁵; category D evidence (abstract)¹⁶⁻¹⁹). TNF blocking agents can be added to pre-existing treatment, or, when appropriate, may replace previous DMARDs (category A evidence^{2-4,9-11,13-15}; category D evidence (abstract)^{7,16,18,19}). There is evidence that TNF blockers are effective for the treatment of RA in MTX-naive patients (category A evidence^{2-5,12}; category D evidence (abstract)¹⁶). The use of TNF blocking agents as the first DMARD for the treatment of RA (category A evidence^{2-4,10,13}; category D evidence (abstract)¹⁶) should, at present, be limited because one must consider emerging data on long term safety and effectiveness as well as their expense and one also needs to include health

Abbreviations: aCL, anticardiolipin antibodies; ACR, American College of Rheumatology; ANA, antinuclear antibodies; CHF, congestive heart failure; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire disability index; IL, interleukin; IL1Ra, IL1 receptor antagonist; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor; VAS, visual analogue scale

economic considerations along with these other factors. However, patients in whom other DMARDs are relatively contraindicated may be considered for use of TNF blockers as the first DMARD (category D evidence (abstract)) and opinion^{1 9 16}).

Etanercept has been approved for juvenile idiopathic arthritis of the polyarticular type (category A evidence^{3 15 20}) and for psoriatic arthritis (category A evidence²¹). Infliximab is presently approved to treat ankylosing spondylitis in Europe (EMA, pending; category A evidence²²; category D evidence²⁵⁻²⁷) and etanercept has also been successfully used and is approved in this disease (category A evidence²³). A guidance document published by the ASessment in Ankylosing Spondylitis (ASAS) Group on the use of TNF blocking agents in ankylosing spondylitis has been published recently.¹⁰¹ Infliximab has been approved to treat luminal and fistulising Crohn's disease (category A evidence^{36 37}). TNF blocking agents have been shown to be efficacious in psoriasis (category B evidence²¹; category D evidence (abstract)⁴³). A trial of TNF blocker treatment for adult onset Still's disease has been published (category D evidence (abstract)²⁸⁻³⁰). Anecdotal data have been published about its use in the mucocutaneous lesions of Behçet's disease, Behçet's uveitis, and uveitis (category C and D evidence (abstract)³¹⁻³⁴). It has also been used in Wegener's granulomatosis,⁵³ Takayasu's arteritis, Sjögren's syndrome,³⁵ polymyositis,⁴² polycondritis⁴⁴, systemic sclerosis (category D evidence (abstract)⁴⁹), and giant cell arteritis,⁵⁰ nephrotic syndrome in inflammatory bowel disease (category A evidence^{36 37}), sarcoidosis,^{38 39} dermatomyositis,⁴⁰⁻⁴² secondary amyloidosis,^{45 46} Kawasaki's disease,^{47 48} and SAPHO syndrome.^{88 89} (All of the preceding uses, except as noted, were category D evidence (abstract).) These compounds may have potential in these and other conditions, although more work is needed in all cases.

Health economic data and long term safety data may change the circumstances when TNF blocking agents will be started.

Clinical use

TNF blocking agents, when given using adequate dosing regimens, should lead to significant improvement in symptoms, signs, and/or laboratory parameters within 12 weeks (category A, B, C, and D evidence^{4-15 20-30 51}). 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 (see above) (category D evidence (abstract)⁵⁵⁻⁶⁰). Switching from one TNF blocker to another has been documented but well controlled trials to record the efficacy of such changes have not been fully published (category D evidence (abstract)⁵⁵⁻⁶⁰). Individually important responses, including patient oriented measures (for example, HAQ-DI, patients global VAS) or physical measures (for example, joint tenderness), should be demonstrated within 8 to 12 weeks for RA (category A evidence^{1 2 4-15 18 20-24 51}). If such improvement occurs, treatment should be continued. If patients show no response to these agents, they should be stopped. In patients with an incomplete response, observations suggest that increasing the dose or reducing the dosing intervals may provide additional benefit, as may the addition or substitution of other DMARDs (category B evidence^{1 2 14}).

Some data show that TNF blocking agents slow radiographic progression in RA (category A evidence^{4 7-9 15 19 54}), and in some people may halt it (category C and D evidence (abstract)^{54 61}). Although radiographic progression slows in some patients without ACR20 clinical response, 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.

Some patients have become pregnant while being treated with TNF blocking therapy. Pharmacovigilance data show that

the rate of normal live births, miscarriages, and therapeutic terminations are consistent with published rates for the normal population (category D evidence (abstract)⁶²). However there are insufficient data to advise continuation of anti-TNF therapy if a patient becomes pregnant.

Rare cases of lupus-like disease have occurred in dsDNA positive patients receiving TNF blocking agents, and treatment should be stopped if there is clinical evidence of a lupus-like syndrome (category C evidence; category D evidence (abstract)^{2 5 15 36 52 63-67}). There is no evidence that patients with RA who become positive for antinuclear antibodies (ANA), anticardiolipin antibodies (aCL), and/or dsDNA are at significantly increased risk for the development of drug induced lupus (category C evidence; category D evidence (abstract)^{2 5 15 36 52 63-67}).

A well controlled trial of the combination of IL1 receptor antagonist (IL1Ra) and etanercept demonstrated no increased efficacy from the combination at the usual doses and did show increased serious infections. Therefore the combination of TNF blocking agents and IL1Ra should not be used together (category D⁸⁵).

In clinical studies, injection site reactions are more common with TNF blocking agents which are given subcutaneously than with placebo. Infusion reactions for TNF blocking agents given intravenously may occasionally be serious and were more common in the treatment groups than the placebo groups (category A evidence^{3-9 12 14 15}; category B and C evidence^{16 19 36 67}; category D evidence (abstract)^{36 72}).

Warnings

Serious and opportunistic infections have been described in patients receiving TNF blocking agents, but it is not clear that their incidence is higher than in patients with RA using other forms of DMARD treatment and/or corticosteroids. TNF blocking agents should not be started or should be discontinued when serious infections occur, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections, *Listeria* etc (category C evidence), (FDA).^{15-19 67-71} Treatment with TNF blockers in such patients should only be resumed if the infections have been treated adequately (category D evidence (abstract)⁷⁴⁻⁷⁷; FDA).

Susceptibility to primary tuberculosis may be increased and previous tuberculosis may be reactivated in patients given TNF blockers. As the incidence of reactivation of latent tuberculosis by TNF blockers is highest in the first 12 months, particular vigilance should be exercised during that period (category B and D evidence (abstract)^{74 77 78}). Screening patients with tuberculosis seems to reduce the risk of activating tuberculosis (category D evidence (abstract)⁹⁴). Every patient should be evaluated for the possibility of latent tuberculosis—a history should be taken and a physical examination carried out, together with screening tests, such as skin tests and chest radiograph, according to local recommendations. The treatment for the possibility of latent tuberculosis should be started according to local recommendations (category D evidence^{73 86}; category C evidence⁷⁷). Based on HIV data, some authorities suggest that TNF blockers may be started as soon as the antituberculosis treatment is started, although this approach needs further investigation (FDA; category D evidence (abstract)^{73 78}).

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 differs from that of a comparable group of patients with RA who have not received TNF blocking agents (category C evidence^{2 15 17 67 72 79}). 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).

A few instances of pancytopenia and aplastic anaemia have been reported (category C evidence^{2 15 17 67}). Because the incidence of these adverse effects is not known and their relative incidence compared with that in the general population is also not known, specific recommendations about monitoring cannot be given at this time. If pancytopenia and/or aplastic anaemia occur, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease or other causative drug as well as the possible effect of the TNF blockade (category D evidence).

High dose infliximab (usually at doses such as 10 mg/kg) seems to be associated with an increased relative risk of worsening congestive heart failure and mortality (FDA; category D evidence (abstract)^{72 80}). Etanercept (25 mg three times weekly) may also adversely affect congestive heart failure (category B evidence⁸⁷). There is presently no evidence that infliximab, 5 mg/kg, or etanercept at 25 mg twice a week increases the incidence of congestive heart failure (CHF) or CHF related mortality in patients with functional class I CHF (FDA; category B and D evidence (abstract)^{72 80 87}). However, it should be noted that RA studies have excluded patients with complicating illnesses, including CHF. 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).

The long term safety or efficacy of TNF blockers in patients with hepatitis C is not known; controlled studies are awaited.⁸¹ A short, pilot study of TNF blockade in patients with hepatitis C showed no increased viral load over six months (category D evidence (abstract)⁸¹).

The incidence of lymphoma is increased in RA, particularly in patients with high disease activity. An increase is also seen in patients using TNF blocking agents. It is not clear whether the increased evidence of lymphoma in patients using TNF blocking agents exceeds that in patients with RA with equivalent disease severity and duration (FDA; category D evidence and abstract⁸²⁻⁸⁴). There is thus far no evidence that TNF blocking agents are associated with other malignancies. There are insufficient data available on the use of TNF blocking agents in patients who have had previous solid tumours to exclude their future use (category D evidence). Vigilance with respect to the occurrence of lymphomas and other malignancies including recurrence of solid tumours remains necessary in patients using these drugs.

Precautionary statements

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

- (1) Chronic infections, including HIV, hepatitis B, etc.
- (2) During lactation.
- (3) When IL1 blocking agents and TNF blocking agents are used together; infections are common and serious infections have occurred and this combination should be used with great caution until new data become available (category D evidence (abstract)⁴¹).
- (4) When using 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 biological agents are strongly recommended, requiring a cooperative effort among payers, government, industry, and rheumatologists.

- (2) Registries of pregnancy outcomes during anti-TNF therapy (and after treatment has stopped) 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 TNF blockers be used as induction therapies in conjunction with, and during continuation of, traditional DMARDs?
- (6) Can biological agents be given 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 ACR20 response?
- (7) Is there a role for pharmacoeconomic evaluations to help clinicians treat individual patients?
- (8) How long do clinical and radiological benefits last in patients who stop using TNF blocking agents?
- (9) Can the dose of TNF blocking agents be escalated if therapeutic effect is lost?

Safety

- (1) Can TNF blocking agents be used safely in pregnant or lactating women?
- (2) Do TNF blocking agents affect the efficacy of primary vaccination or the safety of live attenuated vaccination?
- (3) What is the safety profile of TNF blocking agents during close up surgery? How does it compare with the safety profile of patients undergoing surgery without concomitant TNF blocker use?
- (4) What duration of tuberculosis prophylaxis/treatment is necessary when patients are being treated with TNF blocking agents?
- (5) Can data from earlier studies be used to ascertain the incidence of CHF, myocardial infarction, arrhythmias, and/or angina in patients with histories of cardiovascular disease and who are being treated with TNF blocking agents?
- (6) Can TNF blocking agents be used in patients with a history of lymphoma and non-Hodgkin's lymphoma or solid tumours?
- (7) What is the time interval needed, before TNF α blockers can be used after patients with malignancies have reached a full remission?

Summary

TNF blocking agents have proved to be effective DMARDs and are a major advance in the treatment of RA. 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 subgroups 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.

IL1 BLOCKING AGENTS

To date only one IL1 blocking agent (anakinra) has reached the market and references are therefore to this product. As other agents of this class become available, 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

IL1 blocking agents may be used for treatment of active RA, alone or with MTX (category A evidence⁹⁰⁻⁹²). Despite this evidence, the anakinra label presently requires its use with MTX in Europe. IL1 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 (abstract)⁹⁷).

The use of IL1 blocking agents as the first DMARD for the treatment of RA should, at present, be limited because these compounds are expensive and one needs to include cost considerations along with those of efficacy, effectiveness, and long term safety (category D evidence).

Clinical use

IL1 blocking agents can lead to significant, documentable improvement in symptoms, signs, and/or laboratory measures within 2 to 16 weeks (category A evidence^{90-92,93}). Measures of patient related outcomes such as global patient VAS or HAQ may be more sensitive to the effects of one IL1 blocking agent (anakinra) than physical measures such as joint tenderness/swelling (category D evidence (abstract)⁹³). These measures of response should be followed and individually important responses should be demonstrated within 8–16 weeks (category A evidence⁹⁰⁻⁹²). If clinically important improvement occurs, treatment should be continued (category D evidence).

Data show that IL1 blocking agents, of which anakinra is the marketed prototypic compound, slows radiographic progression in RA (category A evidence⁹⁰⁻⁹¹).

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^{90-92,93}; category D evidence (abstract)⁹⁷).

There are no data to advise either termination or continuation of IL1 blocking agents if a patient becomes pregnant.

The efficacy and toxicity of IL1 blocking compounds in rheumatic diseases other than RA is unknown, although an open study in juvenile rheumatoid arthritis was encouraging (category D evidence (abstract)⁹⁸).

Warnings

Possibly, there is a small increased incidence of infections, including serious infections, when using IL1 blocking compounds. Therefore, these compounds should not be started or should be discontinued when serious infections occur^{90-92,93,96} (category A evidence⁹⁰⁻⁹³; category D evidence (abstract)⁹⁷). To date, there is no indication that IL1 blocking compounds are associated with an increased incidence of tuberculosis (category D evidence). Treatment with IL1 blocking therapy in such patients should only be resumed if the infections have been adequately treated (category D evidence).

Precautionary statements

The safety of anakinra 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 biological agents/targeted therapy, such as TNF blocking agents, infections are common and serious infections have occurred when using IL1 blocking agents and TNF blocking agents together; this combination should be used with great caution until new data become available (category D evidence (abstract)⁹⁶).

(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

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

Registry

(1) Long term registries to monitor the toxicity of biological agents are strongly recommended, requiring a cooperative effort among payers, government, industry, and rheumatologists.

(2) Registries of pregnancy outcomes under IL1 blocking therapy (and after treatment has stopped) should be continued.

Efficacy

(1) What is the efficacy of IL1 blocking agents in patients who have used TNF blockers but have not responded or have not responded sufficiently?

(2) What is the efficacy of IL1 blocking agents in polyarticular juvenile arthritis and other rheumatic diseases, including osteoarthritis?

(3) Do IL1 blocking agents have an effect on pain?

Toxicity

(1) Can IL1 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 treatment for the latter, for some reason?

Summary

IL1 blocking agents, of which anakinra is the prototype and sole example, are effective for the treatment of RA but their specific place (for example, before, after or with TNF blocking agents) in the rheumatological armamentarium has not yet been defined. Publication of studies in selected areas of efficacy, toxicity, and general use of IL1 blocking agents are needed to help define further the most appropriate use of these agents. Further considerations when using IL1Ra in this disease must include cost issues and the recognition that data in subgroups of patients 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 modified by expert opinion, will facilitate the optimal use of IL1Ra for our patients with RA.

APPENDIX 1: Abbreviated summary of the "Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases—TNF blocking agents subsection

- Rheumatologists and bioscientists from countries met to develop the consensus statement.
- A new consensus statement was required because additional information has corroborated the major positive

effect of these drugs, and possible new and unexpected adverse events have occurred.

- The process included a review of all relevant clinical published articles and, through an iterative process, the reaching of consensus.
- Individual patients differ in many aspects of their disease so one must frequently individualise treatment.
- TNF blocking agents differ in many ways but this document emphasises areas of commonality, until clear differences can be shown among TNF blockers.

Indications

- TNF blockers are recommended for the treatment of active RA after using another DMARD (MTX is the most common of several DMARDs frequently used).
- TNF blocking agents can be added to pre-existing treatment or, when appropriate, may replace a previous DMARD or other biological agent.
- 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 because of considerations of long term safety. Cost considerations should be included when considering the use of TNF blocking agents.
- When other DMARDs are relatively 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 psoriatic arthritis.
- TNF blockers are efficacious in ankylosing spondylitis, and infliximab is approved in Europe for this indication. Infliximab is approved for Crohn's disease.
- There is no evidence that any one TNF blocking agents 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, 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.

Clinical use

- When used in adequate doses and sufficiently frequent dosing regimens, TNF blocking agents should lead to significant, documental improvement within 12 weeks for 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, RA disease activity index (RADAI), 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 they should be stopped.
- If an incomplete response occurs, increased doses or reduced dosing intervals may provide additional benefits, as may other DMARDs or other biological agents, although further study on this issue is required.
- TNF blocking agents slow radiographic progression in RA. Until the long term implications of this slowing are clear, radiological changes alone should not determine clinical decision making.

Warnings

- Insufficient data are available about the use of anti-TNF therapy 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.
- In the rare cases when lupus-like symptoms develop, TNF blocking agents should be stopped.
- The presence or development of positive ANA, aCL, and/or dsDNA does not significantly increase the risk of developing drug-induced lupus.
- TNF blocking agents should not be started or should be discontinued when serious infections occur.
- Previous tuberculosis may be reactivated in patients given TNF blockers; individual evaluations, including history, physical examination, chest x ray examination, and/or purified protein derivative test, should be done and treatment for latent tuberculosis considered according to local recommendations
- Severe CHF represents a situation where TNF blockade needs to be used with great caution.
- 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.
- 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 in patients evaluated for evidence of other underlying disease.
- Lymphomas have occurred in patients using TNF blocking agents, although it is not clear if the incidence of these tumours is increased relative to an appropriate disease control group.

Precautionary statements

- The safety of TNF blockade is unknown in the following situations: chronic infections including HIV and chronic hepatitis, during pregnancy or lactation, and when considering primary vaccinations or live attenuated vaccines.

APPENDIX 2: Abbreviated summary of the "Updated consensus statement for the use of biological agents in the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases—IL1 blocking agents subsection"

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

Indications

- IL1 blocking agents may be used for the treatment of active RA, alone or with MTX. In Europe, IL1 blocking agents (anakinra) should presently be used in conjunction with MTX.
- IL1 blocking agents will probably be effective when used with other effective DMARDs

Clinical use

- IL1 blocking agents (anakinra) can lead to significant documentable improvement in symptoms, signs, and/or laboratory parameters within 2 to 16 weeks.
- Response measures should be followed and individually important responses should be demonstrated within 8 to 16 weeks.
- If a clinically important response to anakinra occurs, the agent should be continued.
- IL1 blocking agents (anakinra) slow 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 the effect may diminish with continued use.
- There are no data to advise continuation or termination of IL1 blocking therapy if the patient becomes pregnant.
- The efficacy and toxicity of IL1 blocking agents in rheumatic diseases other than RA are unknown.

Warnings

- Possibly, there is a small increased incidence of infections, including serious infections, when using IL1 blocking agents.
- IL1 blocking agents should not be started or should be discontinued when serious infections occur.
- Treatment with IL1 blocking agents should only be resumed if infections have been adequately treated.

Precautionary statements

- The safety of IL1 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 biological agents, 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: Evidence scheme

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 are 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 those data are published as a complete, peer reviewed paper.

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Differences in the management of shoulder pain between primary and secondary care in Europe: time for a consensus

We read with great interest the articles of Van der Windt and Bouter¹ and Hay *et al.*² There is no doubt that the study of Hay *et al.* is well designed and has practical implications. They showed that physiotherapy or subacromial joint injection are equally effective for shoulder pain. This is new evidence as, so far, there has been little evidence to support the effectiveness of any common intervention for shoulder pain.³ However, the definition of "shoulder pain" illustrates the practical problem in diagnosis that general practitioners and hospital specialists face in routine clinical practice. We agree that the positive outcome for physiotherapy may reflect the increased contact time between physiotherapist and patient or the better understanding of the anatomical problem by the physiotherapist. The differences in management and in the effectiveness of physiotherapy by the British compared with the Dutch may also represent a cultural difference between the expectations and beliefs of patients in the two countries. It is likely that physiotherapy departments could be overloaded with referrals from primary care doctors if they are always the first next step in the pathway of managing shoulder problems. Hay *et al.* did not carry out a cost-benefit analysis of the different treatments for shoulder pain (that is, injection *v* physiotherapy). A course of physiotherapy would cost around £200–320 (€284–454), whereas an injection would cost around £60 (€85).

There is a lack of consensus in the UK about the exact role of the general practitioner in the treatment of shoulder disease.⁴ A survey among rheumatologists and physiotherapists practising in the Southeast Thames Region of London (47 rheumatologists and 9 physiotherapists) showed that the management of adhesive capsulitis in secondary care varied widely. Nearly all the rheumatologists

(98%) used intra-articular steroid injection, but the time, site, and frequency of injections were variable, with 72% believing that early injections are a priority. One of five rheumatologists (22%) believed that physiotherapy and mobilisation offered no benefit. Only a small number of rheumatologists (14%) believed physiotherapy to be the only means of treatment.⁵ Interestingly, 90% of physiotherapists working in secondary care wanted to see patients with a frozen shoulder as early as possible before or immediately after steroid injections. However their waiting time varied considerably (range of 3 days–3 months).

Similarly, across Europe treatment of shoulder pain varies considerably between primary and secondary care.^{6,7} Therefore we propose that European consensus guidelines on the management of the painful shoulder should be developed.^{8,9} This consensus may be weakened by the lack of an adequate evidence base. In addition, we would suggest a third and fourth arm to future studies—steroid injection with physiotherapy and a no intervention control group.

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Author's reply

Kassimos and Panayi deal with several important issues about the management of shoulder pain in their comments on the article by Hay *et al.*¹ and our leader.² We agree that differences in the effect of treatment between the Netherlands and England may, at least partly, reflect differences in the organisation of care, as well as differences in expectations and beliefs between the two countries. We are also aware of the lack of consensus among general practitioners, physiotherapists, and rheumatologists about the management of shoulder pain. Between primary and secondary care, especially, the differences are large. This can partly be explained by the fact that the primary care doctor is confronted with an entirely different spectrum of disease than the specialist.³ Many patients in primary care present with signs and symptoms that are troublesome and cause worry, but are relatively benign and have a favourable prognosis. Patients referred to secondary care have been pre-selected by the nature and severity of symptoms, and have another prognosis, resulting in different treatment requirements.

The lack of consensus among health professionals, indeed, emphasises the need for multidisciplinary guidelines for the management of shoulder pain. Regardless of the quality of the evidence base, multidisciplinary guidelines will facilitate communication among health professionals and may optimise diagnosis and treatment of patients with shoulder pain. We suggest that the AGREE Instrument (Appraisal of Guidelines for Research and Evaluation)⁴ is used in the development of any guideline for shoulder pain. This instrument includes recommendations for the description of the scope and purpose of a guideline, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence.

The development of a European guideline for shoulder pain will be quite an undertaking. The authors of the EULAR guideline for the management of knee osteoarthritis indicated that there was often discordance between research evidence and the opinion of experts.⁵ In this international guideline, variation across countries in healthcare delivery systems, access to health professionals, ways of funding, and attitudes towards the disease, all contributed to this discordance. The use of a Delphi system permitted consensus agreement on difficult issues, but still the applicability in individual countries may be limited. In the case of shoulder pain, it may be wise to start out with the development of national (multidisciplinary) guidelines. As yet, only a few European countries or professional organisations have developed such guidelines.

Finally, regarding the closing point by Kassimos and Panayi, we agree that there is a need for additional research comparing physiotherapy or corticosteroid injections with a no treatment control. It might be difficult or undesirable to carry out such a

trial in patients with severe pain and limitations in daily activities, but controlled trials will certainly be needed to demonstrate the effectiveness and cost effectiveness of physiotherapy and injections in patients with mild to moderate shoulder pain. Future trials may also evaluate the effectiveness of combined treatment (injections plus physiotherapy).

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Exercise in juvenile idiopathic arthritis: promise or passé

We were interested in the recently published article in the *Annals* by Takken *et al.*¹ Notwithstanding their substantial work, we have a few comments pertaining to the exercise regimens in children with juvenile idiopathic arthritis (JIA).

Firstly, we did not see any information about whether the patients had ever been following an exercise protocol before they were included in the study and also whether they were prescribed a protocol afterwards. Information about these two points is important for an interpretation of the patients' results and for providing evidence about the practical implications of the study.

Secondly, when mentioning the diminished loadbearing capacity of these subjects owing to their inflammatory disease and the immune suppressive drugs, they drew attention to a study in which weightbearing exercises were shown to improve the aerobic endurance of such patients.² At this point, it is noteworthy to add that the myopathic effects of corticosteroids should also be remembered when exercise is prescribed. It is known that eccentric muscle contractions in normal subjects are responsible for a much greater efflux of muscle enzymes into the circulation than is caused by concentric contractions, and are associated with ultrastructural indications of damage to the muscle.^{3,4} Thus in patients with JIA—where steroid use is prevalent—concentric types of exercise should preferably be prescribed. These may include simply walking, cycling, or running. However, the list of sports which can be played is endless and there is an excess of activities these—otherwise sedentary—children can be encouraged to take part in to obtain exercise.⁵ In this way not only will there be an increase in their aerobic

capacities but also they will encounter fewer disabilities related to muscle anaerobiosis—much more energy than adults during daily activities.

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Authors' reply

We would sincerely like to thank Özçakar and Özçakar for their response.

Firstly, the patients studied did not actively participate in endurance sports activities at the time of measurement. However, some of the patients had taken part in some sports activities in the period before the disease onset, but not in the six months before our study was performed. It is known from the literature that there is a rapid diminution in fitness once training stops.¹

We did not prescribe exercises based on the current findings. The Caltrac is a portable electronic activity monitor that measures movements in the vertical plane. It sums and integrates the absolute value of the acceleration versus time curve and derives a numerical count that is displayed on the monitor. There are no normal values for this instrument. The described data were baseline data from a randomised controlled trial for the effectiveness of aquatic exercise therapy.² Secondly, we did not discuss the effects of corticosteroid treatment on aerobic fitness, because only a small minority of our patients (four) had systemic juvenile idiopathic arthritis (JIA), in which steroids are the preferred treatment. In other JIA subgroups, non-steroidal anti-inflammatory drugs and methotrexate are the common treatment in our country nowadays. A discussion on the effects of drugs and inflammation on exercise capacity can be found elsewhere.^{3,4}

We could not comment on the paper cited by the authors because it had not yet been published when we wrote this letter. Furthermore, we would like to add that JIA and juvenile dermatomyositis (JDM) are distinct diseases and that the exercise capacities of these patients do differ significantly, with patients with JDM being more affected than patients with JIA.⁵ Therefore, the exercise prescription for patients with JIA and JDM

should be different, and adapted to the individual patients needs and capacity.

Moreover, we are not aware of studies showing an anaerobiosis in muscles of patients with JIA during activities of daily living.

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Progressive multifocal leucoencephalopathy and immunosuppression

We report an immunocompromised patient with progressive multifocal leucoencephalopathy (PML), who demonstrates the usefulness and limitation of the algorithm of Warnatz *et al.*¹ for investigation of patients with pre-existing autoimmune diseases and new onset neuropsychiatric abnormalities. A prerequisite for the use of this algorithm requires a high degree of awareness for infection to prevent misclassification of the underlying problem.

This 61 year old white woman had had dermatomyositis since 1996 as manifest by Gottron's papules, heliotrope rash, proximal muscle weakness, and antinuclear antibody (ANA) titre 1/1280 speckled pattern. Previous management included azathioprine, methotrexate, hydroxychloroquine, and intravenous immunoglobulin; the disease was controlled for the previous 20 months while receiving cyclophosphamide 100 mg and prednisone 5 mg daily.

One week before admission the patient developed dizziness, weakness, and left sided hearing loss. Meclizine was prescribed for possible Ménière's disease. Facial weakness and dysarthria developed. A physical examination showed left sided hearing loss, left facial droop, left hemiparesis with concomitant graphaesthesia, and impaired stereognosis; left patella hyperreflexia was also present. Magnetic resonance imaging (MRI) of the brain was performed at an outlying facility and was felt to demonstrate a subacute infarct. There was increased signal intensity in the right posterior temporal lobe measuring 4 cm in diameter without mass effect or haemorrhage, and an additional temporo-parietal lesion. Punctate areas of increased signal were seen in the mid-portion of the pons (fig 1A). She was admitted for further evaluation of stroke. Laboratory data included normal complete blood counts,

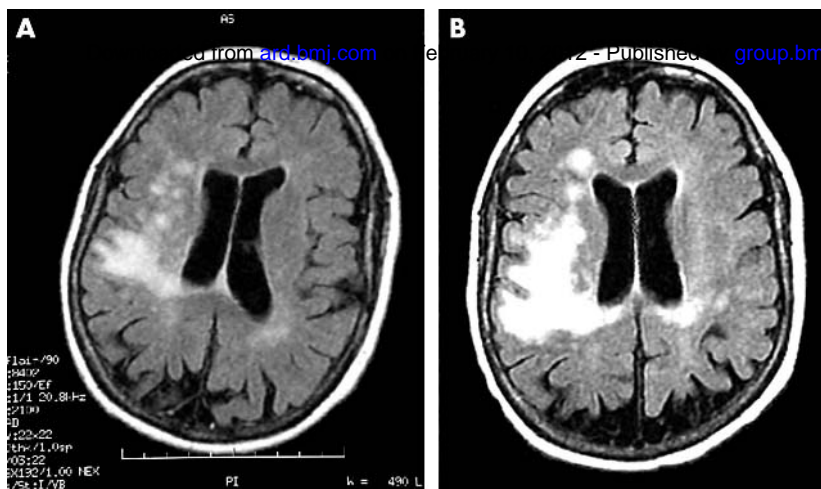


Figure 1 Magnetic resonance imaging of the brain. (A) 7 days and (B) 19 days after the initial symptoms in an immunocompromised patient with dermatomyositis and progressive multifocal leucoencephalopathy.

metabolic profile, and coagulation assays, including anticardiolipin antibodies and lupus anticoagulant. An echocardiogram and carotid Doppler ultrasound were normal.

Intensive physical and occupational therapy were prescribed. Over the next 12 days, the left sided weakness progressed. The patient also developed decreased sensation, hyperreflexia, and extensor plantar response on the left. Further evaluation was started. Cerebrospinal fluid showed 1 white blood cell/high powered field (hpf), 0 red blood cells/hpf, protein 0.43 g/l, glucose 2.9 mmol/l. A repeat MRI of the brain showed progressive changes of white matter affecting the right cerebral hemisphere, again with sparing of the cortex. Extensive involvement of the pons was present as well as minimal involvement of the right middle cerebellar peduncle. Additional cerebrospinal fluid studies included negative viral and bacterial cultures, negative paraneoplastic autoantibodies, and negative cytology. Polymerase chain reaction for JC virus was positive.

Several features of our patient's presentation are rare in PML and caused early diagnostic confusion with delay in the diagnosis. These included the acute nature of the neurological event as well as cranial nerve involvement. Ménière's disease was initially suspected owing to the sudden onset of dizziness and left sided hearing loss, and probably reflects CN VIII involvement, as MRI did not have findings to suggest a central lesion at the cerebellopontine angle. Stroke, being considerably more common than PML in immunocompromised patients, was a further consideration in this patient owing to the acute onset of symptoms and was suggested on the initial request for imaging studies. This influenced the interpretation of the MRI changes towards infarction despite predominance of white matter involvement. The more ominous diagnosis of PML was suspected after neurological symptoms worsened (12 days after hospital presentation and 19 days after the initial event).

Interpretation of the second MRI was that stroke was unlikely owing to the rapid progression, distribution, and cortical sparing, and PML was likely in this immunocompromised patient (fig 1B).

PML is well reported in HIV/AIDS publications, but there are fewer than 30 cases described in rheumatology patients, resulting in a low degree of awareness. This case emphasises the importance of informing radiologists about the immune status of patients being studied so that appropriate consideration for infection may be entertained. Otherwise, this algorithm may not be used, resulting in missed or delayed diagnosis.

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Authors' reply

Dr Cuevas and colleagues express the concern that a high degree of awareness for infection is needed to prevent misclassification of early progressive multifocal leucoencephalopathy (PML). As we point out in our article, the sole risk factor for cerebral opportunistic infections is immunosuppression. The clinical

distinction between PML and central nervous system involvement of systemic rheumatic diseases is always vague. Thus, in all immunosuppressed patients with a new onset or change of cerebral symptoms a careful diagnostic approach is recommended.

There is general agreement that close communication between rheumatologists and radiologists clearly helps to interpret brain images correctly.

We agree that subacute cerebrovascular disease may also be a differential diagnosis in early PML as may other diseases such as ADEM, multiple sclerosis, sarcoidosis, or multifocal glioma. The topographic pattern in PML (sparing of cortex) largely excludes large-vessel stroke, but it may be confused with subacute lacunar infarcts. Further, the neurological deficits, including cranial nerve involvement together with middle sized lesions at three typical locations, do not support the assumption of stroke. Acute onset of symptoms may occur in PML.¹ The early PML lesions are typically asymmetric and multifocally distributed in the white matter. On the other hand, acute and subacute ischaemic lesions can easily be differentiated from PML and similar lesions by diffusion weighted sequences. In later stages PML lesions are confluent and expand concentrically, strongly suggesting the diagnosis.

Cerebral vasculitis, which has been seen rarely in patients with dermatomyositis,^{2,3} could be differentiated from PML by the enhancement of the lesions after administration of gadolinium, and may be excluded by the lack of disease activity.

The differential diagnosis in immunosuppressed patients with systemic rheumatic diseases and cerebral symptoms is wide. The diagnosis may be time consuming and costly. Algorithms may be helpful in this setting.

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BOOK REVIEW

The antiphospholipid syndrome II

Eds R A Asherson, R Cervera, J C Piette, Y Shoenfeld (Pp 480, \$149.) Amsterdam: Elsevier, 2002. ISBN 0-4445-09879.

The Antiphospholipid Syndrome II, subtitled *Autoimmune Thrombosis*, aims to give an overview, in four parts, of this intriguing syndrome. First is a brief overview of the history and epidemiology, a second part deals with immunology and pathophysiology, a third deals with clinical features, and, finally, several chapters discuss management and prognosis of the syndrome. Each part consists of a series of topics written by authorities in the field. The separate chapters can be considered as in-depth reviews of the item discussed.

As suggested by the title, all aspects of the syndrome are highlighted. Most chapters have a structured format, are illustrated, and well referenced. References are updated to 2001. The subject index is useful and directs the reader adequately to the items searched for. The book is especially suited for such an approach because the introduction to each chapter supplies the reader with similar, general information about the APS. Moreover, various chapters overlap. The reason probably is that the chapters are somewhat heterogeneous in selecting studies and topics to be discussed, and are not always restricted to didactic overviews. For use in clinical practice the book would have gained by including diagnostic flow diagrams and discussion on differential diagnostic dilemmas. The ultimate answers of how to deal with certain clinical situations are lacking, simply because these answers are not available yet. APS is studied extensively and further insights are developing continuously, making parts of a book like this quickly outdated.

Nevertheless, *The Antiphospholipid Syndrome II* is a very valuable source for those who want to have an overview of the great progress which has been made in fundamental research, the increasing pathophysiological insights and the current treatment modalities in APS. It is particularly useful for researchers and of value for clinicians dealing with patients with APS and the various disease manifestations these patients can develop.

M Bijl, C G M Kallenberg

CORRECTION

Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases (May 2003) (Furst D E, *et al.* Ann Rheum Dis 2003;62(suppl II):ii2-9.)

One of the authors names was incorrectly spelt. It should have been **Kavanaugh A F**.

Corrections printed in the journal also appear on the Annals website www.annrheumdis.com and are linked to the original publication.

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Twelfth Intensive Applied Epidemiology Course for Rheumatologists

9-13 February 2004; Manchester, UK

No previous experience in epidemiology is required. Residential course limited to 20 places

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Tel: +44 (0) 161 275 5993
Fax: +44 (0) 161 275 5043
Email: Lisa.mcclair@man.ac.uk

International Congress on SLE and Related Conditions

9-13 May 2004; New York, New York, USA

Contact: The Oakley Group, 2014 Broadway, Suite 250, Nashville, Tennessee 37203, USA
Tel: +1 615 322 2785
Fax: +1 615 322 2784
Email: Lupus2004@theoakleygroup.com
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Contact: Congress Secretariat at info@osteofound.org
Website: www.osteofound.org

International Society for the Study of the Lumbar Spine

31 May-5 June 2004; Porto, Portugal

Contact: International Society for the Study of the Lumbar Spine, 2075 Bayview Avenue, Room MG 323, Toronto, Ontario, Canada M4N 3M5

Tel: 00 1 416 480 4833
Fax: 00 1 416 480 6055
Email: shirley.fitzgerald@sw.ca

XIth International Conference on Behçet's Disease

27-31 October 2004; Antalya, Turkey

Contact: Congress Secretariat, Figur Congress and Organization Services Ltd. STI, Ayazmaderesi Cad. Karadut Sok. No: 7 80888 Dikilitas, Istanbul, Turkey
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Email: autoim04@kenes.com
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Vth European Lupus Meeting

3-5 March 2005; Royal College of Physicians, London, UK

Contact: Julia Kermode, Conference organiser of the British Society of Rheumatology
Email: Julia@Rheumatology.org.uk

Future EULAR congresses

9-12 June 2004; EULAR 2004; Berlin, Germany
8-11 June 2005; EULAR 2005; Vienna, Austria
21-24 June 2006; EULAR 2006; Amsterdam, The Netherlands

Future ACR meeting

16-21 October 2004; 68th Annual Scientific Meeting; San Antonio, Texas



Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases (May 2003)

D E Furst, F C Breedveld, J R Kalden, et al.

Ann Rheum Dis 2003 62: ii2-ii9
doi: 10.1136/ard.62.suppl_2.ii2

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