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**CONSENSUS STATEMENT**

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## Updated consensus statement on tumour necrosis factor blocking agents for the treatment of rheumatoid arthritis and other rheumatic diseases (April 2001)

As last year, the consensus group to consider the use of tumour necrosis factor (TNF) blocking agents was formed by an organising committee comprising rheumatologists from the universities of Erlangen, Leiden, and Vienna in Europe in cooperation with universities in the United States. Pharmaceutical support was obtained from a number of companies, but these institutions had no part in the decisions about the specific programme nor with regard to the participants or attendees at this conference.

The 148 rheumatologists and bioscientists from 21 countries who attended the consensus conference were chosen from a worldwide group of people felt to have experience or interest in the use of TNF blocking treatment for rheumatoid arthritis (RA) and other rheumatic diseases. Unfortunately, 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 RA and reporting possible new and unexpected adverse events. Therefore an update of the previous consensus statement seems both appropriate and necessary (Ann Rheum Dis 2000;59(suppl I):i1-2).

In this update the consensus statement is annotated to document the credibility of the data supporting it, as far as possible. This annotation is that of Shekelle *et al* and is described in appendix 1.<sup>1</sup> All participants reviewed relevant clinical published articles relating to the TNF blocking agents. They were given a draft consensus statement and were asked to revise the document; open discussion of the revisions led to a final document, representing this updated consensus statement.

TNF blocking agents differ in composition, precise mechanisms of action, pharmacokinetics, biopharmaceutical properties, etc, but this document emphasises areas of commonality. Data which clearly differentiate compounds will be discussed, if such areas exist.

### Indications

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 anti-TNF treatment for the patient, as must the toxicity of previous and/or alternative disease modifying antirheumatic drug (DMARD) use.

TNF blockers are recommended for the treatment of active RA after an adequate trial of another effective DMARD, of which methotrexate is a commonly used example<sup>2-16</sup> (category A evidence). TNF blocking agents can be added to pre-existing treatment, or, when appropriate, may replace previous DMARDs<sup>7-16</sup> (category A evidence). There is evidence that TNF blockers are effective for the treatment of RA in methotrexate naive patients<sup>2-9</sup> (category A evidence). The use of TNF blocking agents as the first DMARD for the treatment of RA<sup>2</sup>

(category A evidence) should, at present, be limited owing to considerations of long term safety and cost. However, patients in whom other DMARDs are relatively contra-indicated may be considered for treatment with TNF blockers as the first DMARD (category D evidence).

At least one TNF blocking agent has been approved for juvenile idiopathic arthritis of the polyarticular type<sup>17 18</sup> (category A evidence). TNF blocking agents have been shown to be efficacious in psoriatic arthritis and ankylosing spondylitis<sup>18-22</sup> (category A evidence). 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 one TNF blocker is more effective than another (category B evidence).

TNF blocking agents are being evaluated in Wegener's granulomatosis, adult onset Still's disease, polymyositis, and systemic sclerosis<sup>23-26</sup> (category C evidence). These compounds may have potential in these diseases and in other conditions, but more work is needed in all cases.

Pharmacoeconomic data and long term safety data may change the circumstances when TNF blocking agents will be started, added to, or replace other DMARDs.

### Clinical use

TNF blocking agents, when given in adequate doses and sufficiently frequent dosing regimens, should lead to significant, documentable improvement in symptoms, signs, and/or laboratory parameters within 8-12 weeks<sup>2-15</sup> (category A evidence). Neither the American College of Rheumatology (ACR) response criteria nor the disease activity score (DAS) should be used in clinical practice as the sole measure to monitor individual response (category B evidence). Estimations of individual response require a combination of clinical judgment and quantitative measures, including the above and other validated quantitative measures, such as 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. Any may be used and may be the most appropriate measures for individual patients (category B evidence). These measures of response should be followed and individually important responses should be seen within 8-12 weeks<sup>2-15</sup> (category A evidence). If such improvement occurs, treatment should be continued. If patients show no response to these agents, they should be stopped<sup>8 27 28</sup> (category B evidence). In patients with an incomplete response, observations suggest that an increased dose or reduced dosing intervals may provide additional benefit. However, further study of this issue is required<sup>8 27 28</sup> (category D evidence).

Data show that TNF blocking agents slow radiographic progression in RA<sup>11 28</sup> (category A evidence). Although radiographic progression slows down in some patients without a clinical response, the long term clinical implications of these changes are unknown. Until the long term implications of slowing radiological damage are clear,

radiological changes, alone, should not determine clinical decision-making.

Some patients have inadvertently become pregnant while being treated with TNF blocking agents and these pregnancies have resulted in the birth of normal infants (category D evidence). However, there are insufficient data to advise continuation of anti-TNF treatment if a patient becomes pregnant.

Rare cases of lupus-like disease have occurred in patients receiving TNF blocking agents, and treatment should be stopped if there is clinical evidence of a lupus-like syndrome<sup>9 12 29</sup> (category C evidence). There is no evidence that patients with RA who had, or develop, positive anti-nuclear antibodies (ANA), anticardiolipin antibodies (aCL), and/or dsDNA are at increased risk for the development of drug-induced lupus<sup>2-5 7-12 18 29</sup> (category C evidence).

### Warnings

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<sup>2-18</sup> (category B evidence). Previous tuberculosis may be reactivated in patients given TNF blockers; screening and prophylaxis according to local recommendations should be undertaken in patients with previous tuberculosis or patients at risk for developing tuberculosis<sup>30</sup> (category C evidence). Treatment with TNF blockers in such patients should only be resumed if the infections have been adequately treated (category D evidence).

Instances of demyelinating-like disorders have been reported in patients receiving TNF blockers<sup>30 31</sup> (category C evidence). These agents should be stopped if a demyelinating-like disorder occurs. Patients with a history of definite demyelinating disease should not receive TNF blocking agents (category C evidence).

A very few instances of pancytopenia and aplastic anaemia have been reported<sup>30 31</sup> (category C evidence). Because the incidence of these adverse effects is not known, specific recommendations about monitoring cannot be given at this time. If pancytopenia or aplastic anaemia, or both, occur, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease and a potential relationship with the TNF blockade (category C evidence).

### Precautionary statements

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

- 1 Lymphoma, lymphoproliferative disease, and other malignancies
- 2 Chronic infections, including HIV, hepatitis B or C, etc
- 3 During pregnancy or lactation
- 4 When considering primary vaccinations or live attenuated vaccines.

Other areas in which knowledge is lacking are highlighted in the recommendations of the consensus group for areas most urgently requiring further research.

### Research

Among a number of potential areas requiring action or further research, or both, the consensus groups felt the following projects or directions were most important in each of three areas: registries, efficacy, and safety.

#### REGISTRY

- 1 Long term registries have been developed to monitor efficacy and toxicity of TNF blocking agents and should continue, with cooperative efforts between payers, government, industry, and rheumatologists.

- 2 Registries of pregnancy outcomes for patients receiving anti-TNF therapy (and after cessation of treatment) should be continued.
- 3 What standards are required for long term trials and observational studies of TNF blockers? What are the outcomes of such studies in control subjects not taking TNF blockers?

#### EFFICACY

- 1 Are there predictors of response and toxicity for TNF blocking agents?
- 2 What are the optimal dosing regimens when using TNF blocking agents?
- 3 Is there a correlation between radiological effect and long term effectiveness for TNF blocking agents?

#### SAFETY

- 1 Can patients with evidence of previously treated mycobacterial infection, or fungal infection, use TNF blocking agents with safety in comparison with patients without such a history?
- 2 Can TNF blocking agents be used safely in pregnant or lactating women?
- 3 Do TNF blocking agents affect the efficacy of primary vaccination or the safety of live attenuated vaccination?
- 4 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?

### Summary

TNF blocking agents have proved to be effective DMARDs and they have been a major advance in the treatment of RA.<sup>2-17</sup> Their use is expanding to other rheumatic diseases.<sup>18-26 32</sup> 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. 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 of efficacy and toxicity. Further considerations which must be made when using TNF blocking agents in this disease include the cost and a recognition 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 modified by expert opinion, will facilitate the optimal use of these agents for our patients with RA and other rheumatic diseases.

### Appendix 1

- 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 or on extrapolated recommendations 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 on extrapolated recommendations from randomised controlled trials, meta-analyses, non-randomised controlled trials, experimental studies, or non-experimental descriptive studies.

## Appendix 2: Summary of the “Updated consensus statement on TNF blocking agents for the treatment of RA and other rheumatic diseases”

### INDICATIONS

- Individual patients differ in many aspects of their disease so one must frequently individualise treatment.
- TNF blockers are recommended for the treatment of active RA after using another DMARD (methotrexate 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.
- TNF blockers are effective in methotrexate naive patients.
- At present, TNF blocking agents as the first DMARD for the treatment of RA should be limited owing to considerations of long term safety and cost.
- In patients where other DMARDs are relatively contraindicated, TNF blockers may be considered as the first DMARD.
- At least one TNF blocking agent has been approved for juvenile idiopathic arthritis of the polyarticular type.
- TNF blockers are efficacious in psoriatic arthritis and ankylosing spondylitis.
- 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, though individual differences may exist between patients.
- TNF blocking agents are being evaluated in Wegener’s granulomatosis, adult onset Still’s disease, polymyositis, systemic sclerosis, and other conditions, though more work is needed in all cases.
- Pharmacoeconomic data and long term safety may change all of the above statements.

### CLINICAL USE

- When used in adequate doses and sufficiently frequent dosing regimens, TNF blocking agents should lead to significant, documentable improvement within 8–12 weeks.
- The ACR response criteria or DAS should not be used alone to monitor individual response; other validated quantitative measures such as 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, these agents should be stopped.
- If an incomplete response occurs, increased doses or reduced dosing intervals may provide additional benefits, though further study of 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.
- Insufficient data are available about the use of anti-TNF therapy during pregnancy to allow advice in this circumstance.
- In the rare cases when lupus-like symptoms develop, TNF blocking agents should be stopped.
- The presence or development of a positive ANA, aCL, and/or dsDNA does not increase the risk of developing drug-induced lupus.

### WARNINGS

- 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; screening and prophylaxis according to local recommendations should be undertaken in patients with previous tuberculosis or patients at high risk for developing tuberculosis.
- Instances of demyelinating-like disorders have been reported in patients receiving TNF blockers. These agents should be stopped if a demyelinating-like disorder occurs.
- Patients with a history of definite demyelinating disease should not receive TNF blocking agents.
- A very few instances of pancytopenia and aplastic anaemia have been reported, though 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.

### PRECAUTIONARY STATEMENT

- The safety of TNF blockade is unknown in the following situations: lymphomas and similar illnesses; chronic infections, including HIV

and chronic hepatitis; during pregnancy or lactation; when considering primary vaccinations or live attenuated vaccines.

- Research: a large number of research questions still need to be answered, but the reader is referred to the full consensus document for those research questions.

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