

# Consensus Statements on the Indications and Monitoring of Anti-tumor Necrosis Factor (TNF) Therapy for Rheumatic Diseases in Hong Kong

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**Abstract:** The development and use of the tumor necrosis factor (TNF) antagonists is a recent major breakthrough in the treatment of many rheumatic diseases. Although these novel agents are undoubtedly superior to conventional therapeutic modalities, their costs and potential adverse effects are of concern. The current consensus statements were developed in order to help practicing rheumatologists identify which adult patients may benefit from the anti-TNF therapies and highlight their potential toxicities. The Hong Kong Society of Rheumatology has developed a registry on the use of the biologics in our local patients with chronic rheumatic disorders. Because the indications and novel data regarding the TNF inhibitors are ever changing, this consensus will be updated regularly.

**Keywords:** Antagonist, biologics, guideline, local, novel therapeutics

## Introduction

In recent years, the emergence of the tumor necrosis factor (TNF) antagonists has represented one of the major therapeutic advances in the treatment of a variety of rheumatic diseases. Well designed randomized controlled trials have consistently shown that the TNF antagonists are very effective agents for the treatment of persistently active rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) despite the use of conventional disease modifying anti-rheumatic drugs (DMARDs).<sup>1-11</sup> While rheumatologists are elated with the efficacy of these agents, post-marketing surveillance has reported a number of untoward side effects. Of these, tuberculosis (TB) is one of the major concerns because this infection is endemic in our locality.<sup>12-14</sup> Moreover, the TNF blockers are very expensive items. Although it is unlikely that the public health care system is going to bear the costs of these novel agents, we feel that it is essential to set up a local consensus on the indications of these agents in patients with rheumatic diseases and the monitoring regimes for their side effects.

During the recent meetings of the Hong Kong Society of Rheumatology, we have decided to set up a working group comprising rheumatologists, chest physicians and other relevant specialists to establish a local consensus on the use of the TNF antagonists in patients with various rheumatic disorders.

## Indications of the TNF Blockers in Rheumatic Disorders

The TNF blockers have been shown to be effective in a great variety of rheumatic diseases. Because the indications are ever developing, we would like to focus on RA, AS and PsA in the present consensus statements.

### *Rheumatoid Arthritis (RA)*

There is convincing evidence that the TNF blockers are more effective than placebo in the treatment of active RA which is refractory to methotrexate (MTX).<sup>1,4</sup> A randomized controlled study demonstrated that etanercept monotherapy was more effective than MTX in the treatment of early RA.<sup>3</sup> Combination of etanercept or infliximab with MTX was also shown to be more effective than either agent alone in the treatment of early and established RA.<sup>2,5</sup> In addition, the TNF inhibitors are also options in patients with juvenile polyarticular RA.<sup>6</sup> In view of an increasing number of local

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RA patients who responded suboptimally to conventional combination DMARD therapies, we recommend that the TNF inhibitors can be considered if patients fulfill the following characteristics:

1. Fulfilling the 1987 American College of Rheumatology criteria for the classification of RA.
2. Active RA as evidenced by the following for at least 1 month:
  - (i)  $\geq 6$  swollen and tender joints.
  - (ii) Elevated ESR and CRP levels.
  - (iii) morning stiffness  $\geq 45$  minutes/day.
3. Failure to respond or tolerate adequate trials of  $\geq 2$  standard DMARDs (IM gold, sulphasalazine, hydroxychloroquine, azathioprine, methotrexate or leflunomide). One of the failed or not tolerated therapies must be methotrexate, unless the drug is contraindicated. The maximum tolerated dosage should have been tried for more than 3 months.

There are circumstances that certain DMARDs, especially methotrexate, are relatively contraindicated or not used so that the TNF inhibitors may be considered early in the course of RA. Indeed, as mentioned above, there is evidence to support this approach. However, before there is any policy regarding financial subsidy for patients to use the TNF inhibitors from the local public health sector, it is immature at this juncture to make any recommendations on this aspect.

### **Ankylosing Spondylitis (AS)**

The TNF blockers have also been proven useful in active ankylosing spondylitis by several randomized controlled trials.<sup>7-9</sup> The benefits of the TNF inhibitors on pain scores, mobility, function, quality of life, and inflammatory markers are evident in patients with both early and long-standing disease. Longer term data on the disease modifying effects of these agents are pending. The TNF agents can be considered in patients with ankylosing spondylitis if they fulfill the following characteristics:

1. Fulfilling the modified New York criteria for ankylosing spondylitis (Appendix 1).<sup>15</sup>
2. Active axial disease not responsive to at least two non-steroidal anti-inflammatory drugs (NSAIDs) with adequate dosage within a 3-month period.
3. Active peripheral joint disease that is refractory to an adequate trial of sulphasalazine for at least 3 months.

4. Active spinal AS is defined as follows (lasting for at least 4 weeks):
  - (i) Bath ankylosing spondylitis disease activity index (BASDAI)  $\geq 4$ .<sup>16</sup>
  - (ii) Morning stiffness of the back ( $\geq 45$  minutes /day).
  - (iii) Inflammatory back pain ( $\geq 40$  mm on a 100 mm VAS scale).
  - (iv) Patients' global assessment ( $\geq 40$  mm on a 100 mm VAS scale, with 100 being more severe).

### **Psoriatic Arthritis (PsA)**

More recently, etanercept has been shown to be highly effective in the treatment of skin psoriasis and psoriatic arthropathy.<sup>10,11</sup> The differences between etanercept-treated and placebo-treated patients in terms of American College of Rheumatology (ACR) 20 response rate, Psoriasis Area and Severity Index (PASI) and erosion scores were highly significant. The use of TNF inhibitors in psoriatic arthritis may be considered if patients fulfill the following characteristics:

1. Belonging to one of the clinical subtypes of psoriatic arthropathy as described by Moll and Wright:<sup>17</sup> Distal interphalangeal joint involvement, polyarticular arthritis, asymmetric peripheral oligoarthritis, arthritis mutilans and ankylosing spondylitis-like arthritis.
2. Persistently active arthritis despite an adequate trial of methotrexate for at least 3 months and at the maximum tolerated dosage (unless intolerant to methotrexate).
3. Active arthritis is defined as:
  - (i)  $\geq 3$  swollen and tender joints.
  - (ii) Elevated ESR and CRP levels.
  - (iii) Morning stiffness  $\geq 45$  minutes/day.

### **Exclusion Criteria for the TNF Antagonists**

1. Pregnant or lactating women.
2. Active infections including TB.
3. New York Heart Association (NYHA) grade 3 or 4 congestive heart failure.
4. History of demyelinating disease.

### **Warning of Possible Toxicities**

#### **(I) Reactivation of Tuberculosis (TB)**

Post-marketing surveillance in western countries has shown

that the incidence of TB is markedly increased in users of the TNF blockers.<sup>12-14</sup> What is more alarming is that more than half of the cases of TB are extra-pulmonary or disseminated. Most patients with TB require invasive procedures for diagnosis and biopsies often fail to reveal the typical granulomas in infected tissues. Most cases of TB occur within the first year of the anti-TNF therapies. Particularly with infliximab infusion, most TB cases occur within the first 3 cycles of treatment.

As TB is not prevalent in the western world, the sudden dramatic increase in TB after the launch of the TNF blockers is of a major concern. TB is endemic in Hong Kong and it is expected that the problem of TB reactivation will be even greater. Thus, it is essential to have a local consensus for TB screening and monitoring during the administration of anti-TNF therapies.

#### *Pre-treatment Evaluation*

1. Detailed information with regard to the past history, extent and treatment of pulmonary and extra-pulmonary TB.
2. Symptoms of active TB infection.
3. Baseline CXR is mandatory.
4. Tuberculin skin / Mantoux test (2 units of purified protein derivative [PPD]-RT23, ie. MT2, should be done initially; if it is negative, the test may be repeated).
5. Active TB should be ruled out by appropriate microbiological, radiologic and pathologic studies, and adequately treated before the institution of the TNF blockers.
6. Latent TB infection is diagnosed when a tuberculin skin test yields a positive result of  $\geq 10$  mm induration.

Latent TB should be treated with isoniazid (5 mg/kg/day) for at least 9 months. If there are no urgent indications for anti-TNF treatment, it may be preferable to initiate isoniazid treatment for a minimum of one month for tolerability before concomitant administration of the TNF inhibitors.

Anti-TNF treatment should better be avoided in patients with history of extensive / life-threatening pulmonary or extra-pulmonary TB infection. If treatment is absolutely necessary, close collaboration with a TB specialist with regard to prophylaxis against reactivation of TB is recommended.

Patients with minor abnormalities of CXR such as small calcified foci and apical fibrosis are not candidates for isoniazid treatment if the tuberculin skin test is negative.

#### *Monitoring*

1. Symptoms of TB such as cough, hemoptysis, pleuritic chest pain, weight loss, fever, night sweats and systemic upset should be enquired on each follow-up visit.
2. Physical examination each visit for fever, lymphadenopathy, organomegaly and chest abnormalities. Note changes in body weight.
3. Regular surveillance CXR (at least 2-monthly in the first 6 months and then every 3 months). Surveillance should be continued for 6 months after discontinuation of infliximab because of the prolonged elimination of this agent.
4. Further imaging studies and investigations should be undertaken for patients with symptoms suggestive of TB.
5. Anti-TNF therapies should be withheld when patients develop microbiological or histological evidence of TB. Resumption of anti-TNF therapies during or after treatment of TB infection should only be considered after agreement in collaboration with a TB specialist.
6. Patients in close contact with individuals who are confirmed to have TB infection should be re-evaluated for the possibility of acquiring the infection, preferably in close collaboration with the chest physicians.

#### *(2) Opportunistic Infections*

Almost any kind of opportunistic infection has been reported with the use of the TNF antagonists. The best approach in the prevention of this is to minimize the use of corticosteroids and other immunosuppressive agents in combination with the TNF inhibitors. Anti-TNF therapies should not be initiated in the presence of serious infections and should be discontinued when intercurrent severe infections develop. Resumption of the anti-TNF therapies can be considered after complete resolution of the infections.

#### *(3) Induction of Lupus-like Disease*

Induction of the anti-dsDNA antibodies has been well reported with the use of the TNF antagonists but most of these antibodies are of low avidity or the IgM type. The occurrence of clinical systemic lupus erythematosus is rare. Patients should have a regular surveillance of lupus-like symptoms and anti-dsDNA should be checked when new symptoms such as skin rash, fever or serositis develop. Anti-TNF therapies should be withheld in such circumstances.

#### *(4) Malignancies*

Post-marketing survey has reported that the standardized incidence ratio (SIR) of lymphoma is increased in TNF users.

However, interpretation is confounded by the presence of disease activity and concomitant use of other DMARDs like methotrexate.<sup>12,13</sup> Patients with long standing rheumatoid arthritis and chronic exposure to immunosuppressive treatment are more prone to develop lymphomas. While the impact of the anti-TNF therapists on the incidence of malignant disorders has to be clarified, patients should be alerted of such a potential complication of the TNF antagonists.

Patients with a past history of malignant disorders are not absolutely contraindicated for the TNF antagonists. However, the potential risk of recurrence of the specific malignancy has to be considered and the risk-to-benefit ratio has to be carefully evaluated in individual patients. If patients have been free of any recurrence of their malignancies for 10 years or more, there is no solid evidence for a contraindication to anti-TNF therapy. Extra caution and monitoring has to be exercised when the TNF therapies are being used in patients with pre-malignant conditions such as cervical dysplasia, colonic polyps and Barrett's esophagus.

#### ***(5) Congestive Heart Failure and Demyelinating Disorders***

The TNF blockers may precipitate or exacerbate heart failure.<sup>12,13</sup> Patients with moderate to severe heart failure (NYHA grade 3 and 4) should not be started on these agents. Patients with mild heart failure should be closely monitored for symptomatic deterioration. Anti-TNF therapy should be discontinued when heart failure develops or increases during the course of treatment. Demyelinating disorders have also been reported with the use of the TNF antagonists. Patients with pre-existing demyelinating diseases such as multiple sclerosis are contraindicated for the TNF inhibitors.

#### ***(6) Hematological Complications***

There have been a few case reports of severe hematological complications with the use of all the three available anti-TNF agents. Pancytopenia can be fatal. Regular monitoring of the complete blood count is mandatory and the TNF inhibitors should be discontinued immediately when hematological complications are suspected.

#### ***(7) Reactivation of Chronic Hepatitis***

Two patients who developed severe reactivation of chronic hepatitis B after the use of infliximab were recently reported.<sup>18,19</sup> However, another report on 2 patients with chronic hepatitis B or C infection receiving infliximab

therapy for 12 months did not reveal any worsening of liver function or virological status.<sup>20</sup> In fact, an observational study of 24 patients with chronic hepatitis C did not report significant changes in serum hepatitis C RNA levels and liver transaminases during the administration of the TNF antagonists.<sup>21</sup> As hepatitis B is prevalent in our locality, the possibility of having a life-threatening reactivation of hepatitis B should be borne in mind. Although currently there is no definite evidence of a deleterious effect of the TNF inhibitors on the progression of chronic hepatitis infection, we suggest close monitoring for liver function and virological status in hepatitis B or C carriers who are candidates for anti-TNF therapies:

#### ***Pre-treatment Evaluation***

1. Routine screening of HBsAg and anti-HCV.
2. Liver function test.
3. For hepatitis B carriers, HBeAg, anti-HBe and serum HBV DNA level.
4. For hepatitis C carriers, serum HCV RNA level.

#### ***Recommendations***

1. If baseline liver function is abnormal, further investigations into the causes should be performed. Patients with chronic active hepatitis B or C infection should be referred to the hepatologists for proper evaluation before the commencement of the TNF antagonists.
2. If baseline liver function is normal and serum HBV DNA or HCV RNA level is not elevated, then close monitoring of the liver function should be performed during the use of TNF blockers. Like corticosteroids, extra caution should be given when the TNF inhibitors are being withdrawn.
3. If baseline liver function is normal but serum HBV DNA or HCV RNA level is elevated, referral to the hepatologists for opinion with regard to treatment is necessary before the TNF inhibitors are commenced.

#### ***(8) Surgical Procedures, Vaccination, Pregnancy and Lactation***

The anti-TNF agents should be withheld for 2 to 4 weeks prior to major surgical procedures. They can be resumed post-operatively if there is no evidence of infection and wound healing is satisfactory.

The effect of anti-TNF therapies on vaccination is unknown. Live attenuated vaccines are not recommended during anti-TNF therapy and within the first few months after discontinuation of the anti-TNF agents (at least 1 month for etanercept and 6 months for infliximab).

There are no data regarding the safety of the anti-TNF agents during pregnancy and lactation. The TNF inhibitors should be discontinued during pregnancy. Breast-feeding is contraindicated if anti-TNF treatment is resumed after delivery. Conception can be advised after discontinuation of the anti-TNF agents (at least 6 months for infliximab and 3 months for the other two TNF blockers).

### Criteria for Discontinuation of the TNF Blockers

1. Lack of response by objective criteria (e.g. failure to achieve ACR20, failure of the DAS28 score to improve by  $>1.2$ , or to reduce to a score of  $\leq 3.2$ ) after adequate use for 12 weeks.
2. Occurrence of adverse events such as active TB, severe infections and the development of lupus-like symptoms, heart failure, malignancies or demyelinating diseases.
3. Pregnancy (temporary withdrawal).

### Choice of TNF Inhibitors

There are still no head-to-head comparative studies of the efficacy of the anti-TNF agents. Selection of a TNF inhibitor is usually based on the preference of patients and the practical issues relating to drug administration, convenience, cost and insurance coverage. Etanercept and adalimumab do not require co-administration of MTX for reducing the incidence of the development of neutralizing antibodies, so that they are options for those who are intolerant to MTX. However, it should be borne in mind that there is recent evidence that addition of MTX to either etanercept or adalimumab is more efficacious than the individual agents used alone.<sup>2,22</sup>

There is limited evidence that patients who have no, or only a partial, response to an anti-TNF agent may benefit from shifting to an alternative anti-TNF agent.<sup>23,24</sup> For instance, infliximab can be useful when etanercept has failed, and vice versa.

Some patients who have responded well to anti-TNF therapy may be able to remain in remission with a reduced dose or frequency of treatment. On the other hand, patients who respond partially to infliximab may benefit from an increase in dose or frequency of treatment. While deviation from the routine dosage regimens is not generally recommended, tailoring of treatment regimes for individual patients may be required.

### Registry for the Use of Biologics in the Treatment of Various Rheumatic Diseases in Hong Kong

In order to have a surveillance of the indications and adverse events related to the ever-increasing use of the TNF antagonists in Hong Kong, a local registry is needed. This facilitates data collection and monitoring for complications such as TB, as well as future clinical trials. The Hong Kong Society of Rheumatology has launched a registry for the use of TNF inhibitors in various rheumatic diseases by doctors working in the public and private sectors. All practitioners are encouraged and will be reminded to supply basic information of their rheumatic patients who are receiving the TNF inhibitors.

### Conclusions

Although the anti-TNF agents have added to our armamentarium in the treatment of chronic rheumatic disorders, their costs and potential adverse effects are of major concern. A substantial proportion of patients may still be unresponsive to these agents. Of particular relevance in our local setting, reactivation of TB and chronic hepatitis B infection deserves extra caution during the use of anti-TNF therapies. With the establishment of a local registry on the use of the TNF antagonists, data on the incidence and trend of various adverse events can be prompted analyzed and disseminated to the practicing rheumatologists.

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## Appendix 1

Modified New York criteria for the diagnosis of ankylosing spondylitis

Radiological criterion

1. Sacroiliitis  $\geq$  grade 2 bilaterally OR
2. Sacroiliitis grade 3 or 4 unilaterally

Clinical criteria

1. Inflammatory back pain and stiffness for more than 3 months (improves with exercise but is not relieved with rest).
2. Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
3. Limitation of chest expansion relative to normal values correlated for age and sex.

*A definite diagnosis of ankylosing spondylitis requires the radiological criterion and at least one clinical criterion.*

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