

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Mycobacterial Infections Associated with TNF- α Inhibitors

Sarah K. Brode and Theodore K. Marras
*University of Toronto
 Canada*

1. Introduction

Tumor necrosis factor (TNF) is a proinflammatory cytokine involved in the pathogenesis of rheumatoid arthritis and other chronic inflammatory diseases. TNF also plays a critical role in host responses to intracellular pathogens and in granuloma formation and maintenance. The TNF- α inhibitors are a class of highly effective, targeted anti-inflammatory medications in widespread use for the treatment of rheumatoid arthritis. However, evidence has accumulated since the introduction of the TNF-antagonists that they are also associated with an increased risk of granulomatous infections, including tuberculosis and non-tuberculous mycobacterial (NTM) infections.

This chapter will review the literature on the role of TNF in response to mycobacterial infection, the various TNF- α inhibitors and their biological differences, and the indications for TNF- α inhibitors in the treatment of rheumatoid arthritis. We will also review the literature to date on the risk of tuberculosis associated with rheumatoid arthritis and TNF-antagonist therapy. We will discuss the clinical evaluation and treatment of latent tuberculosis infection in the setting of proposed TNF-antagonist therapy, as well as the presentation and treatment of active tuberculosis. We will review the current literature on the risk of NTM disease associated with TNF- α inhibitor therapy, as well as the presentation, treatment, and prevention of NTM disease in this setting.

2. TNF and TNF- α inhibitors

2.1 TNF biology

TNF is produced primarily by activated monocytes/macrophages, T- and B-lymphocytes, and natural killer cells. It is made as a transmembrane protein (tmTNF), which is then cleaved to a soluble form (sTNF). Three monomers then associate to form trimeric TNF, which is biologically active. This trimeric TNF binds to cell-surface receptors TNFR1 and TNFR2. Both TNFR1 and TNFR2 can signal pro-inflammatory pathways and anti-apoptotic pathways. TNFR1 can also signal via death domain caspase-dependent pathways to induce apoptosis.

TNF plays a major role in the initial host response to infection. With respect to tuberculosis, TNF is involved in macrophage activation; it increases the phagocytic capacity of the macrophage and enhances its killing of intracellular bacteria, via the generation of reactive nitrogen and oxygen species (Bekker et al. 2001). TNF also stimulates macrophages and T-

lymphocytes to produce chemokines, and induces the expression of vascular adhesion molecules (Roach et al. 2002). These activities recruit immune cells and promote a focused accumulation of cells at the site of infection, which sequesters the mycobacteria and prevents their dissemination. This focused accumulation of cells is known as the granuloma, and TNF is involved in both the formation of the granuloma and the maintenance of its integrity. In TNF-deficient mice infected with *M. tuberculosis*, granuloma formation is delayed and malorganized. Treating chronically tuberculosis-infected mice (which are used as a model to simulate latent tuberculosis infection in humans) with a TNF-neutralizing antibody results in an increased bacillary load, compromised granuloma structure, and shortened survival (Mohan et al. 2001).

TNF therefore plays a critical role in the host response to mycobacterial infection, via its role in macrophage activation, cell recruitment, granuloma formation, and maintenance.

2.2 TNF- α inhibitors

There are currently four anti-TNF monoclonal antibodies in clinical use for the treatment of rheumatoid arthritis; infliximab, adalimumab, golimumab, and certolizumab pegol. Infliximab is a chimeric monoclonal antibody containing a human immunoglobulin (Ig)G1 constant region and a murine variable region. Adalimumab and golimumab both contain human IgG1 constant and variable regions. Certolizumab pegol is a pegylated, humanised monoclonal anti-TNF Fab' (fragment, antigen binding) fragment. Infliximab is administered by intravenous infusion. Adalimumab, certolizumab and golimumab are administered by subcutaneous injection, usually every other week.

Etanercept is a soluble TNF receptor; the only one of its kind in clinical use. It is comprised of two extracellular domains of human TNFR2 fused to the Fc (fragment, crystallizable) fragment of human IgG1. It binds trimeric TNF and lymphotoxin. It is administered by subcutaneous injection, usually once or twice per week.

All of the TNF-antagonists are approved for use in rheumatoid arthritis. They are also variably in use for the treatment of other chronic inflammatory conditions, including psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis.

There are several notable differences between the various TNF inhibitors. Firstly, peak blood levels of infliximab are several times greater than those of etanercept and adalimumab (Wallis 2008). The clinical implication of this difference is unclear, however, given that the infection risk with adalimumab seems similar to that of infliximab (see below). Also, the various TNF-antagonists may bind soluble TNF (sTNF) with different affinities, but results are conflicting; one study has shown that etanercept binds sTNF with less affinity than infliximab (Scallon et al. 2002), whereas another study has shown the opposite (Nesbitt et al. 2006 as cited in Wallis 2008). Additionally, the anti-TNF monoclonal antibodies inhibit T-cell activation and cytokine expression (other than TNF), whereas etanercept has little or no effect in these systems (Saliu et al. 2006).

The differential binding of the TNF antagonists for transmembrane TNF (tmTNF) may partially explain differences in clinical efficacy and possibly infection risk. Infliximab binds transmembrane TNF (tmTNF) with more affinity than etanercept, and inhibits tmTNF-mediated cellular activation more effectively (Scallon et al. 2002). Additionally, some studies have shown that the anti-TNF antibodies can cross-link tmTNF and thereby induce apoptosis in TNF-expressing T cells, whereas etanercept lacks this activity (Wallis 2008). This induction of apoptosis may play a role in their efficacy in Crohn's disease, where

defective apoptosis in gut lymphocytes is believed to be a major feature in the pathogenesis of the disease (Wallis 2008).

However, the clinical importance of tmTNF-mediated apoptosis is still a matter of debate, as highlighted by the activity of certolizumab pegol. Certolizumab cannot crosslink tmTNF nor participate in complement activation given its monovalent structure and lack of Fc. It therefore cannot induce apoptosis in TNF-expressing cells. However, it appears to be effective in the treatment of Crohn's disease (Sandborn et al. 2007), and does appear to increase the risk of tuberculosis (see below). This implies that the induction of cell death may be less important in the mechanism of action of these medications than other properties (Wallis 2008). Nonetheless, several animal experiments have shown that selective inhibition of sTNF (and not tmTNF) may be beneficial in reducing infection risks. For instance, one study showed that inhibition of both sTNF and tmTNF protected from clinical signs of inflammation in a murine model of rheumatoid arthritis, yet increased the risk of reactivation of latent tuberculosis, and increased susceptibility of infection to *Listeria monocytogenes* (Spohn et al. 2007). However, specific inhibition of sTNF, while sparing tmTNF was still effective in reducing inflammation, yet did not increase the risk of infection with these pathogens.

2.3 TNF- α inhibitor therapy in rheumatoid arthritis

The first randomized controlled clinical trial of a TNF antagonist was published in 1994; this study showed a significant improvement in signs and symptoms of rheumatoid arthritis compared with placebo (Elliott et al. 1994). There have since been numerous clinical trials demonstrating the efficacy of all five TNF antagonists in rheumatoid arthritis, in various endpoints including signs and symptoms, health-related quality of life, and delayed progression of joint damage (Saag et al. 2008). TNF-antagonists given alone are not significantly better than methotrexate in controlling rheumatoid arthritis signs and symptoms, but they do result in a significant improvement compared with traditional DMARDs when given *together* with methotrexate in patients who do not completely respond to DMARD therapy. Therefore, treatment with TNF- antagonists in combination with methotrexate or other DMARDs is recommended in most guidelines for rheumatoid arthritis patients who partially respond to at least one DMARD including methotrexate (Saag et al. 2008).

The American College of Rheumatology also recommends the use of TNF antagonists in combination with methotrexate in DMARD-naïve patients with early rheumatoid arthritis (disease duration of less than 3 months) who have high disease activity and markers of poor prognosis (Saag et al. 2008). However, the European League against Rheumatism recommends initial treatment with methotrexate alone in early rheumatoid arthritis because of a favourable benefit to risk ratio, given that better outcomes with early combination therapy are seen mainly in a subset of patients with severe disease (Combe et al. 2007).

To date, there have not been any randomized clinical trials comparing the efficacy of the different TNF- α inhibitors.

3. Tuberculosis in the setting of TNF- α inhibitors

3.1 The risk of tuberculosis associated with rheumatoid arthritis

Patients with autoimmune rheumatic diseases, including systemic lupus erythematosus and rheumatoid arthritis, are at higher risk of infections, including tuberculosis. This increased

risk is thought to be related to the immune disturbances caused by the disease itself, as well as to treatment with immunosuppressive drugs. Several studies have looked at the risk of tuberculosis associated with rheumatoid arthritis.

In Quebec, Canada, one retrospective cohort study of 24,282 patients with rheumatoid arthritis identified 50 cases of tuberculosis from 1992 to 2003 (Brassard et al. 2009). The standardized incidence rate was 45.8 cases per 100,000 person-years of follow-up. This rate is much higher than the incidence of tuberculosis in the general population of Quebec, of 4.2 cases per 100,000 person-years. This translates to a standardized incidence ratio of 10.9 (95% confidence interval [CI] 7.9–15.0). Using a nested-case control design, they found that some of the increased risk may be explained by the use of non-biologic DMARDs; the adjusted relative risk of tuberculosis was 2.4 (95%CI 1.1–5.4) with corticosteroid use and 3.0 (95%CI 1.6–5.8) with other nonbiologic DMARD use (including methotrexate, leflunamide, and others).

These results are in stark contrast to an American study (Wolfe et al. 2004) which prospectively followed 10,782 patients with rheumatoid arthritis from 1998 to 1999 with surveys. They only identified one case of tuberculosis, translating to a rate of 6.2 cases per 100,000 patients. This rate is *not* increased compared with the rate in the general US population. However, this study may have underestimated the rate of tuberculosis in rheumatoid arthritis, owing to decreased study participation of foreign-born and minority populations.

In Asia, one prospective Japanese study identified 4 cases of tuberculosis in 5544 patients with rheumatoid arthritis followed for 1 year (Yamada et al. 2006). The age-adjusted incidence of tuberculosis was 42.4 per 100,000 patients, and the relative risk for tuberculosis was 3.21 (95%CI 1.21–8.55) compared with the general Japanese population. They also found a much higher risk of tuberculosis in men compared with women. One retrospective Korean study of 1285 rheumatoid arthritis patients found 9 cases of tuberculosis from 2001 to 2005, resulting in a rate of 257 per 100,000 person-years of follow-up (Seong et al. 2007). This rate was 8.9 times higher than the rate in the general Korean population (95%CI 4.6–17.2).

A report from Spain (Carmona et al. 2003) studied a cohort of 788 patients with rheumatoid arthritis over 10 years, and found 7 cases of tuberculosis, yielding a mean annual incidence (1990–2000) of 134 per 100,000 patients. The incidence risk ratio of pulmonary tuberculosis in patients with rheumatoid arthritis compared to the general Spanish population was 3.68 (95%CI 2.36–5.92). A Swedish study examined a cohort of rheumatoid arthritis patients from 1999 to 2001 and looked at the risk of hospitalization for tuberculosis (Askling et al. 2005). They found that rheumatoid arthritis patients were at a two-fold increased risk of being hospitalized for tuberculosis compared with the general population (relative risk 2.0, 95%CI 1.2–3.4).

In summary, several observational studies from different countries around the world have shown that patients with rheumatoid arthritis are at increased risk of tuberculosis. This increased risk is independent of TNF- α inhibitors, but may be due to other disease modifying drugs, and possibly to the disease itself. The magnitude of the relative risk ranges between 2 and 11. Only one study, which was from the United States, showed no increased risk of tuberculosis in rheumatoid arthritis patients compared with the general population.

3.2 The risk of tuberculosis associated with TNF- α inhibitors

Studies estimating the risk of tuberculosis associated with TNF- α inhibitors face many challenges. For one, tuberculosis rates are relatively low in North America and Europe, and they may vary significantly by country, ethnicity of the individual, and underlying medical condition. Also, patients with rheumatoid arthritis and other rheumatic diseases may be

treated with several different disease modifying medications, in addition to TNF-α inhibitors, which may also increase the risk of tuberculosis. Additionally, when studying the risk associated with a particular drug, it is unclear if the risk is increased only during active drug treatment, or if there is a carry-over effect when the patient is no longer taking the medication but is still at risk. Also, the rate of active tuberculosis is affected by the rate of screening and treatment for latent tuberculosis infection, which may vary based on local practice. Despite these challenges, a large number of observational studies from all over the world have been conducted examining this issue. The methods of data collection have varied from retrospective voluntary reporting to prospective national registries. The results are also variably reported; some report rates of tuberculosis per number of people treated with drug, while others report rates per number of people treated *per time*, and time may be time on drug or time at risk or follow-up time. The major studies examining the risk of tuberculosis associated with TNF-α inhibitors will be reviewed below, and are summarized in Table 1.

Study (first author, year)	Country	Type of study	TB incidence rate per 100,000 person-years			Rate ratio I:A:E	Rate ratio compared with RA
			Infliximab	Adalimumab	Etanercept		
FDA AERS (Wallis, 2004)	USA	Cases voluntarily reported	54*	--	28*	1.9:N/A:1	--
PharMetrics (Brassard, 2006)	USA	Search of pharmacy database	--	--	--	--	1.5
NDB (Wolfe, 2004)	USA	Data from registry	52.5	--	0	N/A	10 [∞]
RATIO (Tubach, 2009)	France	Data from registry	187.5	215.0	9.3	20.1:23.1:1	--
RABBIT (Listing, 2005)	Germany	Data from registry	310	--	0	N/A	--
GEARSPR (Fonseca, 2006)	Portugal	Data from registry	1754*	2339*	300*	5.8:7.8:1.0	--
BIOBADASER (Gomez-Reino 2007)	Spain	Data from registry	383	176	114	3.4:1.5:1	2.4
BIOBADASER (Gomez-Reino 2003)	Spain	Data from registry	1503	--	0	N/A	15.8
ARTIS (Askling, 2005)	Sweden	Data from registry	145	--	80	1.8:N/A:1	4.0
BSRBR (Dixon, 2010)	UK	Data from registry	123	217	53	2.2:4.2:1	--
Single centre cohort (Seong, 2007)	Korea	Retrospective chart review	2558	--	0	N/A	30.1

TB: tuberculosis; I:A:E: infliximab:adalimumab: etanercept relative risk; RA:rheumatoid arthritis, *:cases per 100,000 treated persons; --: not reported; N/ A: not applicable; ∞: for infliximab only

Table 1. Major studies reporting tuberculosis risk in patients treated with TNF-α antagonists

Several studies have been published estimating the incidence of tuberculosis associated with TNF inhibitors in North America. In 2004, Wallis *et al.* reported rates of tuberculosis and other granulomatous infections associated with infliximab and etanercept (Wallis *et al.* 2004). The cases were voluntarily reported to the United States Food and Drug Administration (FDA) Adverse Events Reporting System (AERS) from January 1998 to September 2002. A correction was published soon after (Wallis *et al.* 2004), which removed erroneously included tuberculosis cases from Europe. This study published a tuberculosis rate of 54 per 100,000 treated persons associated with infliximab, and 28 per 100,000 persons treated with etanercept. Infliximab was therefore associated with a two-fold increased risk compared with etanercept. Their overall tuberculosis rate was 41 per 100,000 persons.

Wolfe *et al.* published a study in 2004 that looked at rates of tuberculosis in patients with rheumatoid arthritis registered in the National Data Bank (NDB) of Rheumatic Disease in the United States (Wolfe *et al.* 2004). They prospectively collected data on rheumatoid arthritis patients treated with infliximab and etanercept over a 30-month period, from January 2000 to June 2002. They identified 4 cases of tuberculosis, all in patients treated with infliximab; this translates to a rate of 62 per 100,000 infliximab-treated persons.

Brassard *et al.* published a study in 2006 that used medical and pharmaceutical claims data to determine rates of tuberculosis in American patients with rheumatoid arthritis (Brassard *et al.* 2006). A nested case-control design was used to estimate the risk of tuberculosis associated with disease modifying anti-rheumatic drugs (DMARDs), including infliximab and etanercept. They identified 357 cases of tuberculosis, 51 of which were associated with anti-TNF agents. This translates to a tuberculosis rate of 257 per 100,000 person-years of follow-up associated with anti-TNF agents. The tuberculosis risk was higher with infliximab than with etanercept (adjusted rate ratio 1.6 vs 1.2). However, cases of latent tuberculosis infection may have been misclassified as active disease (Mines & Novelli 2007). Indeed, the tuberculosis rate in the entire rheumatoid arthritis cohort was much higher than expected.

The incidence of tuberculosis in the United States in the general population in 1999 was 6.4 per 100,000 persons. The incidence in rheumatoid arthritis patients during the same year was 6.2 per 100,000 persons (Wolfe *et al.* 2004). The rates reported in these studies are therefore many times higher than these background rates (see Table 1).

National registries of biological agents have been established in many European countries to collect data on the long-term effects of these medications. Studies using these registries have consistently shown increased risks of tuberculosis associated with TNF- α inhibitors. The first was from the BIOBADASER (Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases) registry (Gomez-Reino *et al.* 2003). This study published mostly prospectively collected data on rates of tuberculosis in patients with rheumatic diseases being treated with infliximab or etanercept in Spain from 1999 to 2002. They reported 17 cases of tuberculosis in patients receiving infliximab, 15 of whom had rheumatoid arthritis. There were no cases of tuberculosis in patients treated with etanercept. The tuberculosis incidence in patients receiving infliximab was 1,893 per 100,000 patients in 2000 and 1,113 cases per 100,000 patients in 2001. The risk ratio of tuberculosis in patients treated with infliximab compared to the background rate in Spain was 90.1 (95%CI 58.8-146.0) in 2000 and 53.0 (95%CI 34.5-89.0) in 2001. The risk ratio of tuberculosis in infliximab-treated rheumatoid arthritis patients vs. rheumatoid arthritis patients not exposed to therapy was 19.9 (95%CI 16.2-24.8) in 2000 and 11.7 (95%CI 9.5-14.6) in 2001.

A follow-up study using the same registry was published in 2007 (Gomez-Reino *et al.* 2007). This study prospectively collected data on patients in Spain treated with infliximab,

etanercept, and adalimumab from March 2002 (after national guidelines on screening and treatment of latent tuberculosis infection were introduced) to January 2006. They had 15 cases of tuberculosis translating to an incidence of 172 per 100,000 patient-years. The risk ratio compared with the general population was 7 (95%CI 3-13), and the risk ratio compared to Spanish rheumatoid arthritis patients was 2.4, which was not statistically significantly increased. There appeared to be differential risks posed by the three TNF- α inhibitors, with the risk seemingly highest with infliximab, but the differences were not statistically significant.

A prospective French study using the RATIO (French Research Axed on Tolerance of Biotherapies) registry identified 69 cases of tuberculosis from 2004 to 2006 in patients treated with infliximab, etanercept, or adalimumab (Tubach et al. 2009). The tuberculosis incidence rate was 117 per 100,000 person-years (adjusted for sex and age), which is 12.2 times greater than the incidence of tuberculosis in the general French population. Most of this risk seemed to be caused by infliximab (standardized incidence ratio (SIR) = 18.6, 95%CI 13.4-25.8) and adalimumab (SIR = 29.3, 95%CI 20.3-42.4), rather than etanercept (SIR=1.8, 95%CI 0.7-4.3). A Portuguese registry, GEARS PR (Grupo de Estudos de Artrite Reumatoide da Sociedade Portuguesa de Reumatologia), also found that the risk of tuberculosis posed by infliximab and adalimumab was much higher than that posed by etanercept (Fonseca et al. 2006). They reported 13 cases of tuberculosis between 1999 to 2005 in patients exposed to anti-TNF therapy. The risk of tuberculosis with adalimumab and infliximab was 8-fold and 6-fold higher, respectively, than that with etanercept.

Recently, a prospective observational study from the United Kingdom using the BSRBR registry (The British Society for Rheumatology Biologics Register) identified 40 cases of tuberculosis in patients on TNF- α inhibitors from 2001 to 2008 (Dixon et al. 2010). This resulted in a tuberculosis rate of 118 per 100,000 person-years at risk, which is 8 times higher than the general UK population. Again, the risk of tuberculosis was greater with the monoclonal antibodies than the soluble TNF receptor. Specifically, the rate of tuberculosis associated with adalimumab was 144 per 100,000 person-years on therapy, that with infliximab was 136 per 100,000 person-years, and the rate with etanercept was 39 per 100,000 person-years. The adjusted incidence rate ratio compared with etanercept was 3.1 for infliximab and 4.2 for adalimumab.

Smaller registries from Sweden and Germany have also reported an increased risk of tuberculosis in association with TNF- α inhibitors. The Swedish registry ARTIS (Anti-Rheumatic Treatment in Sweden) identified 15 cases of tuberculosis, with an incidence of 118 per 100,000 person-years treated (Askling et al. 2005). Rheumatoid arthritis patients treated with TNF antagonists had a 4-fold increased risk of tuberculosis compared with rheumatoid arthritis patients not treated with TNF antagonists. The risk was 2-fold higher with infliximab versus etanercept. The German registry RABBIT (Rheumatoid Arthritis-Observation of Biologic Therapy) identified 1 case of tuberculosis in a patient on infliximab; there were no cases in patients on etanercept (Listing et al. 2005).

An important Asian study describing rates of tuberculosis amongst patients on TNF- α inhibitors comes from Korea (Seong et al. 2007). This publication reports retrospective data collected at one medical centre in Seoul between 2001 and 2005. They reviewed the records of 90 patients treated with infliximab and 103 patients treated with etanercept; they identified 2 cases of tuberculosis amongst infliximab-treated patients, and none with etanercept. The rate of tuberculosis with infliximab was 2558 per 100,000 person-years of follow-up, this was 30.1-fold higher than the risk of tuberculosis in the general Korean population, and was also higher than the risk of tuberculosis in Korean patients with rheumatoid arthritis.

In summary, this large body of epidemiological evidence confirms an increased risk of tuberculosis associated with TNF- α inhibitors, above national background rates and above rates in patients with rheumatoid arthritis. The risk of tuberculosis associated with TNF-inhibitors appears to be between 1.5 and 30 times greater than the risk associated with rheumatoid arthritis alone. Unfortunately, limitations of the available data make more precise estimates of risk impossible.

The risk of tuberculosis differs amongst the various TNF- α inhibitors. The monoclonal antibodies infliximab and adalimumab portend more risk than the soluble TNF receptor etanercept (see Table 1 for relative risk estimates). Additionally, the time from initiation of treatment to onset of tuberculosis seems to be shorter with infliximab than etanercept. The FDA AERS study showed that median time from initiation of TNF-antagonist therapy to presentation of tuberculosis was 17 weeks for infliximab versus 48 weeks for etanercept (Wallis et al. 2004); the Pharmetics study reported 17 weeks for infliximab and 79 weeks for etanercept (Brassard et al. 2006). The BSRBR reported a median time to tuberculosis diagnosis from the start of anti-TNF therapy of 13.4 months for etanercept, 5.5 months for infliximab, and 18.5 months for adalimumab (Dixon et al. 2010). Their results are somewhat surprising given the longer median onset time with adalimumab, which would be expected to behave similarly to infliximab. However, the RATIO study showed similar tuberculosis onset times for infliximab and adalimumab, with the onset time being longer with etanercept (Tubach et al. 2009). The reason for the difference in risk and time to development of tuberculosis amongst the drugs of this class is not known, but may be related to different pharmacokinetic properties of the drugs, differential binding of soluble and transmembrane receptors, and differential effects on immune cell function and death, as described in section 2.2.

There has been little published to date on the risk of tuberculosis associated with the newer drugs certolizumab pegol and golimumab. However, two phase III placebo-controlled trials of certolizumab in patients with rheumatoid arthritis (RAPID 1 and 2) each reported 5 cases of active tuberculosis in the certolizumab arms, and none in the placebo arms (Keystone et al. 2008; Smolen et al. 2009), suggesting an increased risk.

3.3 Diagnostic testing for latent tuberculosis infection

In areas of low tuberculosis prevalence and transmission, most active tuberculosis cases associated with TNF-antagonists are thought to be related to progression of latent infection acquired in higher prevalence regions or time periods. It is therefore felt that the most effective way of preventing active tuberculosis is to identify and treat latent tuberculosis infections before the initiation of anti-TNF- α therapy. National guidelines or statements have been published by several countries providing recommendations in this regard; the major English language guidelines are summarized in Table 2. These statements provide significantly different recommendations in a number of areas. Recently, a European consensus statement has been published by the TBNET group on this matter, which provides its own recommendations (Solovic et al. 2010).

The traditional method used to identify latent tuberculosis infection is the tuberculin skin test. This test elicits a cell-mediated, delayed hypersensitivity reaction after the volar aspect of the forearm is intradermally injected with purified protein derivative (PPD), a sterile extract derived from *M. tuberculosis*. The site of injection is observed within 48 to 72 hours; the largest diameter of the induration transverse to the long axis of the arm is recorded in millimetres. The test is positive if the induration is above a pre-specified size; the size cutoff for positivity varies depending upon the positive predictive value of the test.

Country (reference)	TST	TST: One or two step	Positive TST	IGRA	Criteria for LTBI treatment	LTBI treatment*
USA (Centers for Disease et al. 2004)	All	One	5 mm if IS, 10 mm if increased risk, 15 mm if low risk	No	TST+, TST- if clinical or epidemiological risks	9H
France (Salmon et al. 2002)	All	One	10 mm	No	TST+, previous TB inadequately treated, CXR lesions >1 cm ³ not treated	2RZ or 3RH or 9H
Germany (Diel et al. 2009)†	Only in certain circumstances¶	One	5 mm	Yes	IGRA+, abnormal CXR consistent with TB inadequately treated, history of exposure not treated	9H or 4R
Ireland (Kavanagh et al. 2008)	All	One	5 mm if IS, others 10 mm	No	TST+	9H or 4R or 4RH
Portugal (Fonseca et al. 2006)†	All	Two	5 mm	No	TST+, consider in TST-	9H
Spain (Carmona et al. 2005)	All	Two	5 mm	No	TST+, previous TB inadequately treated, abnormal CXR consistent with TB inadequately treated	9H
Switzerland (Beglinger et al. 2007)	No	N/A	N/A	Yes	IGRA+, abnormal CXR consistent with past TB inadequately treated, history of exposure not treated	9H or 4R
UK (British Thoracic Society Standards of Care 2005)	All	One	5 mm if no BCG, 15 mm if BCG	No	TST+, previous TB or abnormal CXR inadequately treated, IS patients with epidemiologic risk	6H or 3RH
TBNET (Solovic et al. 2010)	Only if no history of BCG	One	10 mm	Yes	TST+ or IGRA+	9-12H or 3RH

TST: tuberculin skin test; IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; IS: immunosuppressed; mm: millimetres; BCG: Bacille Calmette-Guérin vaccination; H: isoniazid; R: rifampin; Z: pyrazinamide; ¶: TST should be given only if a discrepancy exists between strong epidemiological evidence of prior TB exposure and negative IGRA; *: the number is the number of months of latent TB treatment; †: English abstract only.

The LTBI treatment regimen of rifampin and pyrazinamide for 2 months, presented in the French recommendations of 2002, is generally not a recommended regimen because of high rates of severe hepatotoxicity (Centers for Disease et al. 2001).

Table 2. Published recommendations on identification and treatment of latent tuberculosis infection in the setting of TNF-α inhibitor therapy (Modified from Solovic et al. 2010)

Tuberculin skin testing does not distinguish between persistent *M. tuberculosis* infection and immunological memory of a previous infection that has been eradicated. Additionally, tuberculin skin test responses may be falsely positive in individuals who have been previously vaccinated with Bacille Calmette-Guerin (BCG) or who have nontuberculous mycobacterial infections, as the PPD contains antigens that are shared amongst many mycobacterial species. However, the BCG vaccine is less likely to be the cause of a positive test in adulthood if it is administered before 1 year of age (Menzies & Vissandjee 1992).

Tuberculin skin test responses are decreased in rheumatoid arthritis (Ponce de Leon et al. 2005), likely due to the use of immunosuppressive medications, but also possibly secondary to the disease itself. For this reason, some experts recommend reducing the size threshold for positivity in these patients (for example, to 5 mm) and/or repeated testing (boosting) 7-10 days after a negative test (the two step skin test). These strategies may increase the sensitivity of the test, but reduce the specificity.

More recently, tests that measure the cell-mediated reaction to *M. tuberculosis* antigens *in vitro* have been developed and implemented in clinical practice. With these tests, peripheral blood cells are stimulated with specific *M. tuberculosis* antigens; T-cells previously sensitized to *M. tuberculosis* antigens then recognize them upon re-exposure and secrete a variety of cytokines, including interferon gamma. The tests measure release of interferon gamma, and are therefore termed interferon gamma release assays (IGRAs). One type of IGRA incubates peripheral blood mononuclear cells with *M. tuberculosis* antigens and measures the percentage of T-cells releasing interferon gamma via an enzyme-linked immunospot (ELISPOT) assay; this is commercially available as the T-SPOT.TB (Oxford Immunotec). In the other available test, whole blood is incubated with *M. tuberculosis* antigens and the amount of interferon gamma released into the supernatant is measured using an enzyme-linked immunosorbent assay (ELISA); this is the QuantiFERON-TB Gold In-Tube (Cellestis). The major advantage of IGRAs over tuberculin skin tests is an increased specificity. This feature is derived from the fact that the stimulating antigens used in IGRAs are not found in Bacille Calmette-Guérin (BCG) vaccine nor in most non-tuberculous mycobacterial species. Therefore, IGRAs are less likely to produce a false-positive test in individuals with previous BCG vaccination or NTM infection (Pai et al. 2008).

A question of particular relevance in the population of patients with rheumatic diseases is whether interferon gamma release assays have increased sensitivity compared with the tuberculin skin test, as patients with rheumatic diseases are known to have a reduced response to the tuberculin skin test. Calculating the sensitivity (and specificity) of IGRAs is challenging, because of the lack of a 'gold standard' for the diagnosis of latent tuberculosis infection. Nonetheless, a number of such studies have been performed, as has a meta-analysis (Pai et al. 2008). The results are inconsistent. The sensitivity seems to depend on the individual's level of immunosuppression and the IGRA test used, as the ELISPOT-based assay has been shown to be more sensitive in immunocompromised patients than the ELISA-based test (Pai et al. 2008; Solovic et al. 2010).

A number of observational studies have been conducted to evaluate the clinical use of IGRAs as an alternative to the tuberculin skin test in identifying latent tuberculosis infection in patients with chronic inflammatory conditions. These studies have been compiled and reviewed by the TBNET group (Solovic et al. 2010). To summarize, they found that the results of IGRAs and tuberculin skin tests correlate poorly. However, correlation is best in areas with low tuberculosis prevalence and low rates of individuals with previous BCG

vaccination. IGRAs are more frequently positive than tuberculin skin tests in unvaccinated populations, suggesting that IGRAs are more sensitive than tuberculin skin tests in patients with chronic inflammatory conditions. Additionally, positive IGRAs seem to be more closely associated with risk factors for latent tuberculosis infection, implying that they are more specific than the tuberculin skin test in this setting (Solovic et al. 2010).

Despite this emerging evidence supporting the clinical utility of IGRAs, to date no studies have been conducted examining the positive predictive value of IGRA responses for the development of tuberculosis in patients treated with TNF- α inhibitors. Additionally, some studies have shown discordant results between tuberculin skin tests and IGRAs, which are as yet unexplained. Concern regarding the increased cost of IGRAs above that of the tuberculin skin test has also hindered their universal acceptance.

Most national guidelines, other than those from Germany and Switzerland, currently recommend the tuberculin skin test as the diagnostic tool of choice for latent tuberculosis infection prior to TNF- α inhibitor therapy. The European TBNET consensus guidelines endorse the IGRA, but suggest the tuberculin skin test as an alternative in patients not previously BCG-vaccinated. Guidelines also vary in how the tuberculin skin test should be administered; some suggest a one-step skin test while others suggest boosting. The TBNET consensus guidelines do not recommend the two-step approach, because of limited evidence of increased sensitivity but considerable evidence of reduced specificity. Controversy also exists in the interpretation of the tuberculin skin test in this setting. Some guidelines suggest a reduced cut-off of 5 mm in order to increase sensitivity, while others suggest 10 or 15 mm.

3.4 Clinical evaluation and treatment of latent tuberculosis infection

Given the strong epidemiological evidence confirming an increased risk of reactivation of tuberculosis in patients receiving TNF- α inhibitors, all patients should be screened for latent tuberculosis infection prior to the initiation of TNF-antagonists; active tuberculosis infection should also be ruled out. The clinical evaluation should include the following: a history to assess for previous active tuberculosis, previous tuberculosis therapy, known exposure to active tuberculosis, a history of residing in a high prevalence area, and symptoms of active tuberculosis; a chest radiograph, to assess for features of previous or current active tuberculosis; and either a tuberculin skin test or IGRA. Any patient suspected of having active tuberculosis based on symptoms and/or chest radiographic abnormalities such as infiltrates, cavities, pleural effusion, or mediastinal lymphadenopathy should be thoroughly investigated to rule out active disease prior to initiation of anti-TNF- α therapy. This work-up should include sputum microscopy for acid-fast bacilli and culture and/or aspiration or biopsy of extrapulmonary sites. Patients with confirmed active tuberculosis should be promptly treated based upon local guidelines and the patient's *M. tuberculosis* drug susceptibility results. Initiation of TNF- α inhibitor therapy should be delayed; most would recommend initiation of TNF-antagonist therapy only after a full course of treatment has been completed.

If there is no suspicion of active tuberculosis infection, the clinician must decide if the patient has a latent tuberculosis infection and requires prophylactic chemotherapy. The decision to treat a patient for latent tuberculosis infection should be based upon the entire clinical evaluation; local guidelines should be used to assist in defining those patients who require preventive chemotherapy (table 2) prior to the initiation of TNF- α inhibitor therapy. Although etanercept has been shown to carry a much lower risk of causing progression of

latent tuberculosis infection to active disease than the monoclonal antibodies, current guidelines universally recommend tuberculosis prophylaxis prior to *all* TNF- α inhibitors.

There has only been one study conducted which examined the effectiveness of preventive chemotherapy for latent tuberculosis infection prior to the initiation of TNF-antagonists (Carmona et al. 2005). This observational study came from Spain, where national recommendations were released in early 2002 that suggested patients be screened for latent tuberculosis infection with a chest x-ray and two-step tuberculin skin test using a 5 mm threshold, before the initiation of TNF-antagonist therapy. Patients diagnosed with latent tuberculosis infection were to receive 9 months of isoniazid therapy, and at least 1 month was to have been completed before starting a TNF- α inhibitor (infliximab, etanercept, or adalimumab). Tuberculosis rates in their biologics registry prior to the release of the recommendations were compared with those afterwards. They found a 78% reduction (incidence risk ratio 0.22, 95%CI 0.03-0.88) in rates of active tuberculosis after implementation of the recommendations. Additionally, there were no cases of serious liver toxicity amongst the 324 patients on isoniazid therapy for latent tuberculosis infection.

Based on this study and several large studies published decades ago (Comstock et al. 1979; Anonymous 1982), many national guidelines recommend isoniazid therapy for a duration of 9 months for the treatment of latent tuberculosis infection, both in general and prior to TNF-antagonist therapy. However, some national guidelines recommend other validated but less effective regimens, including 6 months of isoniazid, 3-4 months of rifampicin plus isoniazid, and 4 months of rifampicin. The French guidelines are unique in recommending 4 months of rifampicin plus pyrazinamide as a potential regimen; this combination has been avoided by others because of a risk of severe hepatotoxicity (Centers for Disease et al. 2001).

The duration of therapy required before starting anti-TNF- α therapy is also not well established, and national guidelines also vary in this regard. Most guidelines suggest a 1 month delay, but some suggest that no delay is necessary, while others suggest completion of prophylaxis before starting TNF-antagonists.

3.5 The presentation and treatment of active tuberculosis

In areas of low tuberculosis prevalence, active tuberculosis most commonly develops due to reactivation of latent infection. However, there may also be an increased risk of primary progression to active disease of newly acquired tuberculosis in patients on TNF- α inhibitors who have high-risk exposures. Several cases of this have been described (Arend et al. 2007; Wallis et al. 2009).

The presentation of active tuberculosis in patients on TNF- α inhibitors appears to differ from classically described tuberculosis. When associated with TNF- α inhibitors, tuberculosis is more likely to be extra-pulmonary and more likely to be disseminated at presentation. One report looked at the patterns of disease in 70 cases of infliximab-associated tuberculosis. They found that 56% had extrapulmonary tuberculosis, and 24% had disseminated disease (Keane et al. 2001). In contrast, in cases of tuberculosis not associated with HIV infection, about 18% are extrapulmonary and less than 2% are disseminated (Rieder et al. 1990). Another series described the clinical characteristics of 130 infliximab-associated tuberculosis cases reported to the U.S. Food and Drug Administration, and found that 45% had extrapulmonary tuberculosis and 23% had disseminated disease (Raval et al. 2007).

When tuberculosis is diagnosed, prompt treatment should be initiated. Treatment regimens should be based upon local guidelines and the patient's *M. tuberculosis* drug susceptibility

results. Most recommend that TNF- α inhibitor therapy be discontinued, at least temporarily. However, discontinuation of anti-TNF therapy may be associated with a paradoxical worsening of tuberculosis disease. This is felt to be similar to the immune reconstitution syndrome seen in HIV-infected persons who are treated with anti-retroviral therapy. When occurring in the setting of TNF-inhibitor withdrawal, the paradoxical reaction is believed to be due to recovery of TNF-dependent inflammation. The largest series describing such cases retrospectively reviewed charts of patients who developed infliximab-associated tuberculosis from 1999 to 2003 in three Spanish medical centres. They found six cases of tuberculosis, four (67%) of which were associated with a paradoxical reaction (Garcia Vidal et al. 2005). Others have described this paradoxical reaction in association with infliximab withdrawal (Belknap et al. 2005; Arend et al. 2007), etanercept withdrawal (Winthrop et al. 2008), and adalimumab withdrawal (Wallis et al. 2009).

The optimal treatment of the paradoxical reaction is currently unknown. Some recommend corticosteroid therapy (Garcia-Vidal et al. 2009) given favorable results in HIV-infected patients. Other case reports have described the successful re-institution of TNF-antagonist therapy to treat severe tuberculosis paradoxical reactions (Blackmore et al. 2008; Wallis et al. 2009).

Despite these case reports of paradoxical reactions associated with withdrawal of anti-TNF therapy, most experts believe that this phenomenon is relatively uncommon, and that discontinuation of TNF- α inhibitors upon diagnosis of active tuberculosis is advisable. The optimal timing of re-institution of TNF- α inhibitors is unknown, but many experts suggest completing a full course of anti-tuberculosis treatment before re-starting TNF-inhibitors (Solovic et al. 2010).

4. Nontuberculous mycobacterial infections in the setting of TNF- α inhibitors

Nontuberculous mycobacteria (NTM) include species of mycobacteria other than those belonging to the *Mycobacterium tuberculosis* complex and *M. leprae*. They are a large group of ubiquitous environmental organisms that can cause pulmonary and extrapulmonary infections. Pulmonary NTM disease is often associated with underlying structural lung disease, including chronic obstructive pulmonary disease and bronchiectasis. In many other cases, there is no obvious underlying lung disease or overt immune incompetence. The relative proportions of NTM lung disease patients with and without underlying lung disease probably varies by population, but it appears that the majority of cases occur without demonstrable predisposing factors. NTM organisms may be isolated from the sputum in the absence of clinically relevant disease, and thus the diagnosis of pulmonary NTM disease rests on the presence of multiple positive cultures, and clinical (symptoms and radiology) data (Griffith et al. 2007). Extrapulmonary NTM disease is less common than lung disease, and may manifest as a localized infection of lymph nodes, skin, soft tissue, or bone, or may be disseminated. It is diagnosed when biopsy specimens of the involved organ(s) culture the causative organism, or, in the case of disseminated disease, with positive blood cultures (Griffith et al. 2007).

4.1 The risk of NTM disease associated with TNF- α inhibitors

Given the known role of tumor necrosis factor (TNF) in granuloma formation and maintenance, it is likely that TNF- α inhibitors increase the risk of all granulomatous

infections, including NTM infection. However, in comparison to tuberculosis, relatively little has been published on this association. NTM infection is more difficult to study than tuberculosis, since the diagnosis is more complex as it relies on clinical data in addition to positive cultures. Additionally, in many jurisdictions, NTM isolation and NTM disease are not reportable to public health authorities.

Most literature associating NTM disease with TNF- α inhibitors has been in the form of case reports; a broad range of different NTM species infecting different body sites have been described in association with infliximab, adalimumab, and etanercept therapy (van Ingen et al. 2008). However, incidence studies are scarce. In 2004, Wallis *et al.* reported rates of granulomatous infections in persons treated with infliximab and etanercept. The cases were voluntarily reported to the United States Food and Drug Administration (FDA) Adverse Events Reporting System (AERS) from January 1998 to September 2002. A correction was published soon after (Wallis et al. 2004), which removed erroneously included cases from Europe. This study identified 29 cases of unspecified NTM infections, which translates to a rate of 17 per 100,000 treated persons (Wallis et al. 2004). This is much higher than the background incidence of 4 cases per 100,000 persons, reported in the United States in 1996 (Centers for Disease et al. 1996).

An updated study of the same Medwatch database, extending the time period to 2007, reported 105 confirmed or probable cases of NTM infection associated with TNF- α inhibitors (Winthrop et al. 2009). These cases were most frequently associated with infliximab ($n = 73$, 69%), followed by etanercept ($n = 25$, 24%), and then adalimumab ($n = 7$, 7%). Unfortunately, they did not have information regarding drug exposure, and so were unable to calculate rates of infection.

Interestingly, the original report of the US FDA Medwatch data found that the incidence of NTM infection was significantly lower than the incidence of tuberculosis in patients on TNF- α inhibitors (Wallis et al. 2004). However, a more recent report, based on a survey of infectious disease physicians in the United States, found the opposite; there were more cases of NTM infection than tuberculosis infection associated with TNF- α inhibitors in the United States (32 vs. 17 cases) (Winthrop et al. 2008). This finding is not unexpected, given the low prevalence of tuberculosis in the United States, and the widespread belief that rates of NTM disease are increasing (Griffith et al. 2007), but it highlights the fact that NTM disease is an underrecognized but important complication of TNF-antagonist therapy.

4.2 The presentation, treatment, and prevention of NTM disease associated with TNF- α inhibitors

Similar to tuberculosis, in the setting of TNF- α inhibitor therapy, extra-pulmonary and disseminated NTM disease appear to be more common. In the 2009 report of the US FDA Medwatch data, 56% of the confirmed or probable NTM cases were pulmonary, and 44% were extrapulmonary; 26% involved skin or soft tissue, 9% bone or joint, and 8% were disseminated (Winthrop et al. 2009). In contrast, in the United States during the period from 1993 through 1996, the NTM isolates reported by state public health laboratories were divided as follows; 75% were pulmonary, 5% were from blood, 2% from skin/soft tissue, and 0.4% from lymph node isolates (Centers for Disease et al. 1996).

Patients with rheumatoid arthritis, however, may be more likely than those with other indications for TNF-antagonist therapy to have pulmonary NTM disease. The US FDA Medwatch study showed that compared with patients with extrapulmonary NTM disease, patients with pulmonary NTM disease were 3.6 times more likely to have underlying

rheumatoid arthritis (95%CI 1.5–8.8) (Winthrop et al. 2009). There are several possible reasons for this. For one, rheumatoid lung disease, which can include bronchiolitis and bronchiectasis, occurs in about 10% of people with rheumatoid arthritis, and can predispose to NTM disease (Winthrop et al. 2009). Also, rheumatoid arthritis and NTM lung disease have similar epidemiologic risk profiles, as both occur more commonly in elderly women (Winthrop et al. 2009). Additionally, rheumatoid arthritis is more common in the elderly, who may have comorbidities predisposing to NTM lung disease, such as chronic obstructive pulmonary disease.

NTM disease is associated with a high level of morbidity and mortality when it develops on TNF- α inhibitor therapy. In the report from Winthrop et al., 61% of patients with NTM infections were hospitalized, and 9% died (Winthrop et al. 2009).

A broad range of different NTM species have been described in association with TNF- α inhibitors, including those of high and low pathogenicity (van Ingen et al. 2008). In the US Medwatch study, *M. Avium* was the most common etiologic organism reported (49%), followed by rapidly growing mycobacteria (19%), and *M. marinum* (8%) (Winthrop et al. 2009).

NTM disease seems to occur after many months of TNF- α inhibitor therapy. The report of the US FDA Medwatch data showed that the median time between TNF- α inhibitor start date and infection diagnosis was 43 weeks for infliximab (range 2–200 weeks), 35 weeks for etanercept (range 0–288 weeks), and 18 weeks for adalimumab (range 4–94 weeks) (Winthrop et al. 2009). This group therefore surmised that most cases represent newly acquired infection. However, given the natural course of pulmonary NTM disease, which typically is insidious in onset and slowly progressive, the possibility exists that some patients had undiagnosed pulmonary NTM disease before starting TNF-antagonist therapy. The experience of treating NTM disease in the setting of TNF- α inhibitor therapy is limited. Anti-TNF- α therapy should likely be held for an unknown duration. However, one case report described a paradoxical worsening of NTM disease after withdrawal of infliximab (Salvana et al. 2007), similar to the paradoxical reaction sometimes seen with tuberculosis; the clinician should be aware of this complication. Treatment of NTM disease is complicated because different regimens exist for the different NTM species. Furthermore, prolonged antimicrobial therapy is required and results are often disappointing; expert consultation should always be sought.

The best approach to screening and prevention of NTM disease prior to initiation of TNF- α inhibitor therapy is unknown. Unlike tuberculosis, there is no evidence of a latent phase in NTM disease. Additionally, screening is complicated by the possibility of NTM colonization without active disease, and the ongoing environmental inoculation that is likely present. However, given the insidious nature of NTM disease and its slow progression, unrecognized NTM disease may be present in some patients prior to starting TNF-antagonist therapy. Screening for such patients should be considered. Screening should include chest radiography, which must be done for all patients prior to starting TNF- α inhibitors to screen for tuberculosis. However, chest radiographs are not sensitive for detecting bronchiectasis or other parenchymal abnormalities associated with pulmonary NTM disease. Computerized tomography (CT) should therefore be considered in patients suspected of predisposing pulmonary diseases, including those with chronic unexplained cough. If chest CT is suggestive of possible NTM disease, sputum or bronchoscopy specimens should be cultured to rule out active NTM disease prior to initiation of TNF-antagonist therapy (van Ingen et al. 2008; Winthrop et al. 2009).

During therapy with TNF- α inhibitors, patients should be regularly assessed to rule out active infections. With respect to NTM disease, repeated sputum cultures during therapy should be considered in the setting of chest symptoms or co-morbid pulmonary disease, as well as chest radiography or CT scans. Extrapulmonary disease should be thoroughly investigated, and biopsy specimens should be stained for acid-fast bacilli and cultured for mycobacteria (van Ingen et al. 2008).

5. Conclusion

The TNF- α inhibitors, including the four currently available anti-TNF monoclonal antibodies and the soluble TNF receptor, have revolutionized the treatment of rheumatoid arthritis and other chronic inflammatory diseases since their introduction over a decade ago. However, their use is associated with an increased risk of granulomatous infections, including tuberculosis and NTM disease. The biological basis of this infection risk is the critical role played by TNF in the host response to mycobacterial infection, via its role in macrophage activation, cell recruitment, and granuloma formation and maintenance.

The magnitude of the risk of tuberculosis associated with TNF-antagonist therapy appears to be between 1.5 and 30 times above the risk associated with rheumatoid arthritis alone. The risk of tuberculosis differs amongst the various TNF- α inhibitors; the monoclonal antibodies portend more risk and are associated with a shorter tuberculosis onset time than the soluble TNF receptor. These differences may be related to different pharmacokinetic properties of the drugs, differential binding of soluble and transmembrane receptors, and differential effects on immune cell function and death.

All patients should be clinically evaluated for latent tuberculosis infection prior to the initiation of TNF- α inhibitor therapy. This evaluation should include a history, chest radiograph, and either a tuberculin skin test or an IGRA. IGRAs appear to be more specific for latent tuberculosis infection than tuberculin skin tests; they may also be more sensitive but this has not been definitively established. Most national guidelines recommend the tuberculin skin test as the diagnostic tool of choice for latent tuberculosis infection in this setting. The treatment of latent tuberculosis infection prior to the initiation of TNF- α inhibitors has proven benefit. Isoniazid therapy for a duration of 9 months is the most commonly recommended regimen, although some national guidelines recommend other regimens. The duration of therapy required before starting anti-TNF- α therapy is not well established.

The presentation of active tuberculosis in patients on TNF- α inhibitors is different from classically described tuberculosis; it is more likely to be extra-pulmonary and more likely to be disseminated at presentation. Discontinuation of anti-TNF- α therapy may be associated with a paradoxical worsening of tuberculosis disease, but discontinuation of therapy is still recommended in most guidelines.

NTM disease is an under recognized but important complication of TNF-antagonist therapy. Some research has suggested that NTM disease may be more common than tuberculosis in the setting of TNF- α inhibitor therapy, however the magnitude of the risk of NTM disease in this setting is unknown. NTM disease is associated with a high level of morbidity and mortality when it develops on TNF- α inhibitor therapy and may have atypical presentations. The best approach to screening and prevention of NTM disease prior to initiation of TNF- α inhibitor therapy is unknown.

Future research should include prospective studies establishing the magnitude of the risk of NTM disease with TNF- α inhibitor therapy; such studies may guide development of

preventive strategies. Prospective studies estimating the positive predictive value of IGRA responses compared with tuberculin skin test responses for the development of tuberculosis in patients treated with TNF- α inhibitors are also needed. Reports on treatment and outcomes of tuberculosis and NTM disease in the setting of TNF- α inhibitor therapy are also necessary.

6. References

- Anonymous (1982). Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. *Bulletin of the World Health Organization*, Vol. 60, No. 4, pp. 555-64.
- Arend, S. M., Leyten, E. M. S., Franken, W. P. J., Huisman, E. M. & van Dissel, J. T. (2007). A patient with de novo tuberculosis during anti-tumor necrosis factor-alpha therapy illustrating diagnostic pitfalls and paradoxical response to treatment. *Clinical Infectious Diseases*, Vol. 45, No. 11, (Dec 1), pp. 1470-5.
- Askling, J., Forged, C. M., Brandt, L., Baecklund, E., Bertilsson, L., Coster, L., Geborek, P., Jacobsson, L. T., Lindblad, S., Lysholm, J., Rantapaa-Dahlqvist, S., Saxne, T., Romanus, V., Klareskog, L. & Feltelius, N. (2005). Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis & Rheumatism*, Vol. 52, No. 7, (Jul), pp. 1986-92.
- Beglinger, C., Dudler, J., Mottet, C., Nicod, L., Seibold, F., Villiger, P. M. & Zellweger, J.-P. (2007). Screening for tuberculosis infection before the initiation of an anti-TNF-alpha therapy. *Swiss Medical Weekly*, Vol. 137, No. 43-44, (Nov 3), pp. 620-2.
- Bekker, L. G., Freeman, S., Murray, P. J., Ryffel, B. & Kaplan, G. (2001). TNF-alpha controls intracellular mycobacterial growth by both inducible nitric oxide synthase-dependent and inducible nitric oxide synthase-independent pathways. *Journal of Immunology*, Vol. 166, No. 11, (Jun 1), pp. 6728-34.
- Belknap, R., Reves, R. & Burman, W. (2005). Immune reconstitution to Mycobacterium tuberculosis after discontinuing infliximab. *International Journal of Tuberculosis & Lung Disease*, Vol. 9, No. 9, (Sep), pp. 1057-8.
- Blackmore, T. K., Manning, L., Taylor, W. J. & Wallis, R. S. (2008). Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes. *Clinical Infectious Diseases*, Vol. 47, No. 10, (Nov 15), pp. e83-5.
- Brassard, P., Kezouh, A. & Suissa, S. (2006). Antirheumatic drugs and the risk of tuberculosis. *Clinical Infectious Diseases*, Vol. 43, No. 6, (Sep 15), pp. 717-22.
- Brassard, P., Lowe, A.-M., Bernatsky, S., Kezouh, A. & Suissa, S. (2009). Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. *Arthritis & Rheumatism*, Vol. 61, No. 3, (Mar 15), pp. 300-4.
- British Thoracic Society Standards of Care, C. (2005). BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax*, Vol. 60, No. 10, (Oct), pp. 800-5.
- Carmona, L., Gomez-Reino, J. J., Rodriguez-Valverde, V., Montero, D., Pascual-Gomez, E., Mola, E. M., Carreno, L. & Figueroa, M. (2005). Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis & Rheumatism*, Vol. 52, No. 6, (Jun), pp. 1766-72.

- Carmona, L., Hernandez-Garcia, C., Vadillo, C., Pato, E., Balsa, A., Gonzalez-Alvaro, I., Belmonte, M. A., Tena, X. & Sanmarti, R. (2003). Increased risk of tuberculosis in patients with rheumatoid arthritis. *Journal of Rheumatology*, Vol. 30, No. 7, (Jul), pp. 1436-9.
- Centers for Disease, Control & Prevention (1996). Nontuberculous Mycobacteria Reported to the Public Health Laboratory Information System by State Public Health Laboratories United States, 1993-1996, cdc.gov/ncidod/dastlr/mycobacteriology.htm (no longer available).
- Centers for Disease, Control & Prevention (2001). Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations--United States, 2001. *MMWR - Morbidity & Mortality Weekly Report*, Vol. 50, No. 34, (Aug 31), pp. 733-5.
- Centers for Disease, Control & Prevention (2004). Tuberculosis associated with blocking agents against tumor necrosis factor-alpha--California, 2002-2003. *MMWR - Morbidity & Mortality Weekly Report*, Vol. 53, No. 30, (Aug 6), pp. 683-6.
- Combe, B., Landewe, R., Lukas, C., Bolosiu, H. D., Breedveld, F., Dougados, M., Emery, P., Ferraccioli, G., Hazes, J. M., Klareskog, L., Machold, K., Martin-Mola, E., Nielsen, H., Silman, A., Smolen, J., Yazici, H. & Hazes, J. M. W. (2007). EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Annals of the Rheumatic Diseases*, Vol. 66, No. 1, (Jan), pp. 34-45.
- Comstock, G. W., Baum, C. & Snider, D. E., Jr. (1979). Isoniazid prophylaxis among Alaskan Eskimos: a final report of the bethel isoniazid studies. *American Review of Respiratory Disease*, Vol. 119, No. 5, (May), pp. 827-30.
- Diel, R., Hauer, B., Loddenkemper, R., Manger, B. & Kruger, K. (2009). [Recommendations for tuberculosis screening before initiation of TNF-alpha-inhibitor treatment in rheumatic diseases]. *Pneumologie*, Vol. 63, No. 6, (Jun), pp. 329-34.
- Dixon, W. G., Hyrich, K. L., Watson, K. D., Lunt, M., Galloway, J., Ustianowski, A., Symmons, D. P. M. & Register, B. S. R. B. (2010). Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Annals of the Rheumatic Diseases*, Vol. 69, No. 3, (Mar), pp. 522-8.
- Elliott, M. J., Maini, R. N., Feldmann, M., Kalden, J. R., Antoni, C., Smolen, J. S., Leeb, B., Breedveld, F. C., Macfarlane, J. D., Bijl, H. & et al. (1994). Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet*, Vol. 344, No. 8930, (Oct 22), pp. 1105-10.
- Fonseca, J. E., Canhao, H., Silva, C., Miguel, C., Mediavilla, M. J., Teixeira, A., Castelao, W., Nero, P., Bernardes, M., Bernardo, A., Mariz, E., Godinho, F., Santos, M. J., Bogas, M., Oliveira, M., Saavedra, M. J., Barcelos, A., Cruz, M., Santos, R. A., Mauricio, L., Rodrigues, M., Figueiredo, G., Quintal, A., Patto, J. V., Malcata, A., da Silva, J. C., Araujo, D., Ventura, F., Branco, J. & Queiroz, M. V. (2006). [Tuberculosis in rheumatic patients treated with tumour necrosis factor alpha antagonists: the

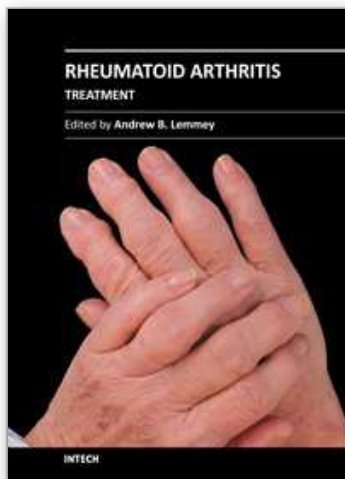
- Portuguese experience]. *Acta Reumatologica Portuguesa*, Vol. 31, No. 3, (Jul-Sep), pp. 247-53.
- Fonseca, J. E., Lucas, H., Canhao, H., Duarte, R., Santos, M. J., Villar, M., Faustino, A. & Raymundo, E. (2006). [Recommendations for the diagnosis and treatment of latent and active tuberculosis in patients with inflammatory joint diseases treated with tumour necrosis factor alpha inhibitors]. *Acta Reumatologica Portuguesa*, Vol. 31, No. 3, (Jul-Sep), pp. 237-45.
- Garcia-Vidal, C., Rodriguez-Fernandez, S., Teijon, S., Esteve, M., Rodriguez-Carballeira, M., Lacasa, J. M., Salvador, G. & Garau, J. (2009). Risk factors for opportunistic infections in infliximab-treated patients: the importance of screening in prevention. *European Journal of Clinical Microbiology & Infectious Diseases*, Vol. 28, No. 4, (Apr), pp. 331-7.
- Garcia Vidal, C., Rodriguez Fernandez, S., Martinez Lacasa, J., Salavert, M., Vidal, R., Rodriguez Carballeira, M. & Garau, J. (2005). Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. *Clinical Infectious Diseases*, Vol. 40, No. 5, (Mar 1), pp. 756-9.
- Gomez-Reino, J. J., Carmona, L. & Angel Descalzo, M. (2007). Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis & Rheumatism*, Vol. 57, No. 5, (Jun 15), pp. 756-61.
- Gomez-Reino, J. J., Carmona, L., Valverde, V. R., Mola, E. M. & Montero, M. D. (2003). Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis & Rheumatism*, Vol. 48, No. 8, (Aug), pp. 2122-7.
- Griffith, D. E., Aksamit, T., Brown-Elliott, B. A., Catanzaro, A., Daley, C., Gordin, F., Holland, S. M., Horsburgh, R., Huitt, G., Iademarco, M. F., Iseman, M., Olivier, K., Ruoss, S., von Reyn, C. F., Wallace, R. J., Jr. & Winthrop, K. (2007). An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *American Journal of Respiratory & Critical Care Medicine*, Vol. 175, No. 4, (Feb 15), pp. 367-416.
- Kavanagh, P. M., Gilmartin, J. J., O'Donnell, J. & O'Flanagan, D. (2008). Tumour necrosis factor-alpha and tuberculosis: guidance from the National TB Advisory Committee. *Irish Medical Journal*, Vol. 101, No. 1, (Jan), pp. 6-7.
- Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N. & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *New England Journal of Medicine*, Vol. 345, No. 15, (Oct 11), pp. 1098-104.
- Keystone, E., Heijde, D. v. d., Mason, D., Jr., Landewe, R., Vollenhoven, R. V., Combe, B., Emery, P., Strand, V., Mease, P., Desai, C. & Pavelka, K. (2008). Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study.[Erratum appears in Arthritis Rheum. 2009 May;60(5):1249]. *Arthritis & Rheumatism*, Vol. 58, No. 11, (Nov), pp. 3319-29.
- Listing, J., Strangfeld, A., Kary, S., Rau, R., von Hinueber, U., Stoyanova-Scholz, M., Gromnica-Ihle, E., Antoni, C., Herzer, P., Kekow, J., Schneider, M. & Zink, A.

- (2005). Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis & Rheumatism*, Vol. 52, No. 11, (Nov), pp. 3403-12.
- Menzies, R. & Vissandjee, B. (1992). Effect of bacille Calmette-Guerin vaccination on tuberculin reactivity. *American Review of Respiratory Disease*, Vol. 145, No. 3, (Mar), pp. 621-5.
- Mines, D. & Novelli, L. (2007). Antirheumatic drugs and the risk of tuberculosis. *Clinical Infectious Diseases*, Vol. 44, No. 4, (Feb 15), pp. 619-20; author reply 620-1.
- Mohan, V. P., Scanga, C. A., Yu, K., Scott, H. M., Tanaka, K. E., Tsang, E., Tsai, M. M., Flynn, J. L. & Chan, J. (2001). Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. *Infection & Immunity*, Vol. 69, No. 3, (Mar), pp. 1847-55.
- Pai, M., Zwerling, A. & Menzies, D. (2008). Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Annals of Internal Medicine*, Vol. 149, No. 3, (Aug 5), pp. 177-84.
- Ponce de Leon, D., Acevedo-Vasquez, E., Sanchez-Torres, A., Cucho, M., Alfaro, J., Perich, R., Pastor, C., Harrison, J. & Sanchez-Schwartz, C. (2005). Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis. *Annals of the Rheumatic Diseases*, Vol. 64, No. 9, (Sep), pp. 1360-1.
- Raval, A., Akhavan-Toyserkani, G., Brinker, A. & Avigan, M. (2007). Brief communication: characteristics of spontaneous cases of tuberculosis associated with infliximab. *Annals of Internal Medicine*, Vol. 147, No. 10, (Nov 20), pp. 699-702.
- Rieder, H. L., Snider, D. E., Jr. & Cauthen, G. M. (1990). Extrapulmonary tuberculosis in the United States. *American Review of Respiratory Disease*, Vol. 141, No. 2, (Feb), pp. 347-51.
- Roach, D. R., Bean, A. G. D., Demangel, C., France, M. P., Briscoe, H. & Britton, W. J. (2002). TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *Journal of Immunology*, Vol. 168, No. 9, (May 1), pp. 4620-7.
- Saag, K. G., Teng, G. G., Patkar, N. M., Anuntiyo, J., Finney, C., Curtis, J. R., Paulus, H. E., Mudano, A., Pisu, M., Elkins-Melton, M., Outman, R., Allison, J. J., Suarez Almazor, M., Bridges, S. L., Jr., Chatham, W. W., Hochberg, M., MacLean, C., Mikuls, T., Moreland, L. W., O'Dell, J., Turkiewicz, A. M. & Furst, D. E. (2008). American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis & Rheumatism*, Vol. 59, No. 6, (Jun 15), pp. 762-84.
- Saliu, O. Y., Sofer, C., Stein, D. S., Schwander, S. K. & Wallis, R. S. (2006). Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. *Journal of Infectious Diseases*, Vol. 194, No. 4, (Aug 15), pp. 486-92.
- Salmon, D., GTI & AFSSAPS (2002). Recommendations about the prevention and management of tuberculosis in patients taking infliximab. *Joint, Bone, Spine: Revue du Rhumatisme*, Vol. 69, No. 2, (Mar), pp. 170-2.
- Salvana, E. M. T., Cooper, G. S. & Salata, R. A. (2007). Mycobacterium other than tuberculosis (MOTT) infection: an emerging disease in infliximab-treated patients. *Journal of Infection*, Vol. 55, No. 6, (Dec), pp. 484-7.

- Sandborn, W. J., Feagan, B. G., Stoinov, S., Honiball, P. J., Rutgeerts, P., Mason, D., Bloomfield, R. & Schreiber, S. (2007). Certolizumab pegol for the treatment of Crohn's disease. *New England Journal of Medicine*, Vol. 357, No. 3, (Jul 19), pp. 228-38.
- Scallon, B., Cai, A., Solowski, N., Rosenberg, A., Song, X.-Y., Shealy, D. & Wagner, C. (2002). Binding and functional comparisons of two types of tumor necrosis factor antagonists. *Journal of Pharmacology & Experimental Therapeutics*, Vol. 301, No. 2, (May), pp. 418-26.
- Seong, S.-S., Choi, C.-B., Woo, J.-H., Bae, K. W., Joung, C.-L., Uhm, W.-S., Kim, T.-H., Jun, J.-B., Yoo, D.-H., Lee, J.-T. & Bae, S.-C. (2007). Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. *Journal of Rheumatology*, Vol. 34, No. 4, (Apr), pp. 706-11.
- Smolen, J., Landewe, R. B., Mease, P., Brzezicki, J., Mason, D., Luijckens, K., van Vollenhoven, R. F., Kavanaugh, A., Schiff, M., Burmester, G. R., Strand, V., Vencovsky, J. & van der Heijde, D. (2009). Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Annals of the Rheumatic Diseases*, Vol. 68, No. 6, (Jun), pp. 797-804.
- Solovic, I., Sester, M., Gomez-Reino, J. J., Rieder, H. L., Ehlers, S., Milburn, H. J., Kampmann, B., Hellmich, B., Groves, R., Schreiber, S., Wallis, R. S., Sotgiu, G., Scholvinck, E. H., Goletti, D., Zellweger, J. P., Diel, R., Carmona, L., Bartalesi, F., Ravn, P., Bossink, A., Duarte, R., Erkens, C., Clark, J., Migliori, G. B. & Lange, C. (2010). The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *European Respiratory Journal*, Vol. 36, No. 5, (Nov), pp. 1185-206.
- Spohn, G., Guler, R., Johansen, P., Keller, I., Jacobs, M., Beck, M., Rohner, F., Bauer, M., Dietmeier, K., Kundig, T. M., Jennings, G. T., Brombacher, F. & Bachmann, M. F. (2007). A virus-like particle-based vaccine selectively targeting soluble TNF- α protects from arthritis without inducing reactivation of latent tuberculosis. *Journal of Immunology*, Vol. 178, No. 11, (Jun 1), pp. 7450-7.
- Tubach, F., Salmon, D., Ravaud, P., Allanore, Y., Goupille, P., Breban, M., Pallot-Prades, B., Pouplin, S., Sacchi, A., Chichemanian, R. M., Bretagne, S., Emilie, D., Lemann, M., Lortholary, O., Mariette, X. & Research Axed on Tolerance of Biotherapies, G. (2009). Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry.[Erratum appears in *Arthritis Rheum.* 2009 Aug;60(8):2540 Note: Lortholary, O [corrected to Lortholary, O]]. *Arthritis & Rheumatism*, Vol. 60, No. 7, (Jul), pp. 1884-94.
- van Ingen, J., Boeree, M. J., Dekhuijzen, P. N. R. & van Soolingen, D. (2008). Mycobacterial disease in patients with rheumatic disease. *Nature Clinical Practice Rheumatology*, Vol. 4, No. 12, (Dec), pp. 649-56.
- Wallis, R. S. (2008). Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. *The Lancet Infectious Diseases*, Vol. 8, No. 10, (Oct), pp. 601-11.
- Wallis, R. S., Broder, M., Wong, J. & Beenhouwer, D. (2004). Granulomatous infections due to tumor necrosis factor blockade: correction. *Clinical Infectious Diseases*, Vol. 39, No. 8, (Oct 15), pp. 1254-5.

- Wallis, R. S., Broder, M. S., Wong, J. Y., Hanson, M. E. & Beenhouwer, D. O. (2004). Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clinical Infectious Diseases*, Vol. 38, No. 9, (May 1), pp. 1261-5.
- Wallis, R. S., van Vuuren, C. & Potgieter, S. (2009). Adalimumab treatment of life-threatening tuberculosis. *Clinical Infectious Diseases*, Vol. 48, No. 10, (May 15), pp. 1429-32.
- Winthrop, K. L., Chang, E., Yamashita, S., Iademarco, M. F., LoBue, P. A., (2009). Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. *Emerging Infectious Diseases*, Vol. 15, No. 10, (Oct), pp. 1556-61.
- Winthrop, K. L., Yamashita, S., Beekmann, S. E. & Polgreen, P. M. (2008). Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the Emerging Infections Network. *Clinical Infectious Diseases*, Vol. 46, No. 11, (Jun 1), pp. 1738-40.
- Wolfe, F., Michaud, K., Anderson, J. & Urbansky, K. (2004). Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis & Rheumatism*, Vol. 50, No. 2, (Feb), pp. 372-9.
- Yamada, T., Nakajima, A., Inoue, E., Tanaka, E., Hara, M., Tomatsu, T., Kamatani, N. & Yamanaka, H. (2006). Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. *Annals of the Rheumatic Diseases*, Vol. 65, No. 12, (Dec), pp. 1661-3.

IntechOpen



Rheumatoid Arthritis - Treatment

Edited by Dr. Andrew Lemmey

ISBN 978-953-307-850-2

Hard cover, 366 pages

Publisher InTech

Published online 18, January, 2012

Published in print edition January, 2012

The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 17 chapters, with contributions from numerous countries (e.g. UK, USA, Canada, Japan, Sweden, Turkey, Bosnia and Herzegovina, Slovakia), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Treatment will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sarah K. Brode and Theodore K. Marras (2012). Mycobacterial Infections Associated with TNF- α Inhibitors, Rheumatoid Arthritis - Treatment, Dr. Andrew Lemmey (Ed.), ISBN: 978-953-307-850-2, InTech, Available from: <http://www.intechopen.com/books/rheumatoid-arthritis-treatment/mycobacterial-infections-associated-with-tnf-inhibitors>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen