

New Biologic Therapies and the Risk of Tuberculosis in Older People

Richard Long, MD, Professor, Department of Medicine, University of Alberta, Edmonton, AB; Chairman, Tuberculosis Committee, Canadian Thoracic Society.

The incidence of tuberculosis increases with age in Canadians. The prevalence of latent tuberculosis infection (LTBI) may also increase with age in Canadians, though information on the age distribution of LTBI is less precise. Chronic inflammatory conditions that currently constitute the major indications for new biologic therapies (tumour necrosis factor inhibitors), such as Crohn's disease and rheumatoid arthritis, often have an older age onset. Biologic therapies have the potential to cause LTBI to progress to active tuberculosis disease. Their use in older Canadians or other populations that may have a higher than average prevalence of LTBI poses a challenge to tuberculosis control.

Key words: tuberculosis, tumour necrosis factor inhibitors, age, rheumatoid arthritis, Crohn's disease.

Background

In Canada, four groups have been identified as being at increased risk of tuberculosis. These include Aboriginal Canadians, immigrants from high prevalence countries, residents of low socioeconomic status in major Canadian cities and older people. Recently generated age-specific tuberculosis case rates in male and female Albertans demonstrated a high incidence of the disease in those ≥ 65 years of age (Figure 1).¹

The risk of tuberculosis in older people should not be underestimated. The portion of the Canadian population that is currently 50 years or older was born before the advent of effective antituberculosis therapy, when the prevalence of tuberculosis and the chances of becoming infected were high. Having lived longer than other members of their communities, the 50+ population also has a greater cumulative risk of being exposed to tuberculosis. These considerations would not be so important were it not for the fact that the immunological response to tuberculosis infection, even in the fully immunocompetent, does not usually destroy the pathogen. Approximately 5% of those who are newly infected will develop disease within one or two years. In the remaining newly infected individuals, the cellular immune

response successfully contains but does not usually destroy the tubercle bacillus. It survives in the host in a state of "non-replicating persistence". Later, as the individual ages this latent tuberculosis infection (LTBI) may progress to disease.²

Population projections for the next half-century suggest that the proportion of the Canadian population 65 years or older will reach 25% by 2040.³ As successive new cohorts of the Canadian-born reach the age of 65, their risk of having

been exposed to tuberculosis may not be as great as earlier cohorts, simply because the prevalence of tuberculosis in Canada has been decreasing with time. On the other hand, if those reaching the age of 65 or older are Canadian-born Aboriginals (the prevalence of disease has been falling in this group but it is still much higher than in Canadian-born non-Aboriginals), are foreign-born from tuberculosis endemic countries, or are Canadian-born and travelled extensively to tuberculosis endemic countries, they may be at much greater risk of having been exposed to tuberculosis and therefore of having acquired LTBI. A single-step or two-step tuberculin skin test (TST) of ≥ 10 mm in a person 65 years or older is usually interpreted to mean they have LTBI.⁴ However, when the epidemiologic risk of tuberculosis infection is high and the risk of reactivation tuberculosis is high, a TST of ≥ 5 mm is interpreted as LTBI in this population.

If those ≥ 65 years have never been infected with *Mycobacterium tuberculosis* in the past, or were infected but have outlived their infection (i.e., they no longer

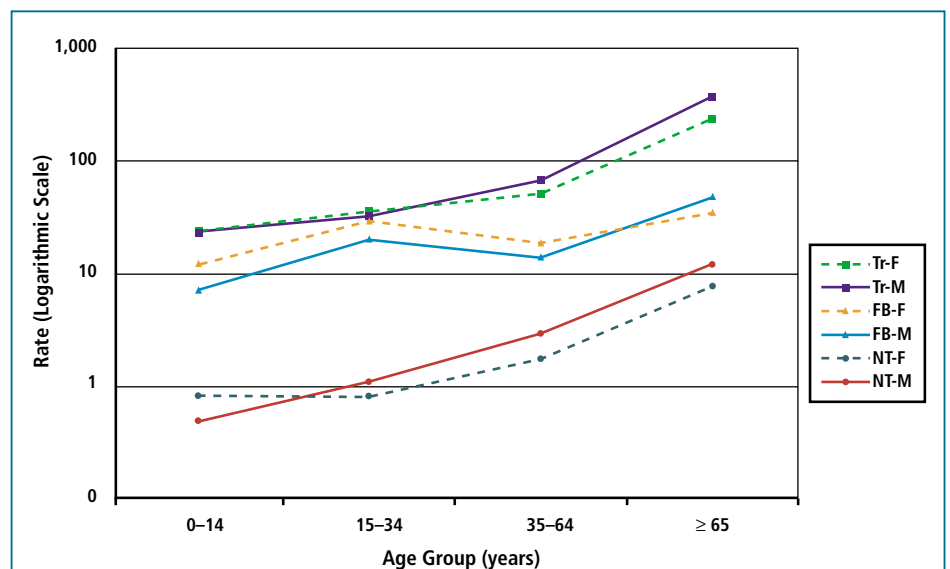


Figure 1: Age-specific tuberculosis case rates per 100,000 person-years for male (M) and female (F) Canadian-born non-Treaty (NT), Canadian-born Treaty (Tr), and foreign-born (FB), for Alberta, Canada, 1989–1998.

Table 1

Risk Factors for the Development of Active Tuberculosis Among Persons Infected with *Mycobacterium tuberculosis*⁸

Risk Factor	Estimated Risk for Tuberculosis Relative to Persons With No Known Risk Factor
High Risk	
Acquired immunodeficiency syndrome	170.0
Human immunodeficiency virus infection	113.0
Transplantation	20–74
Silicosis	30
Chronic renal failure/hemodialysis	10.0–25.3
Carcinoma of head and neck	16.0
Recent infection (< two years ago)	15.0
Abnormal chest X-ray—fibronodular disease	6.0–19
Increased Risk	
Diabetes mellitus	2.0–3.6
Underweight (< 90% ideal body weight)	2.0–3.0
Age when infected (< five years old)	2.2–5.0
Abnormal chest Z-ray—granuloma	2.0
Low Risk	
Infected person, no known risk factor ("low-risk reactor")	1.0

have a positive TST and no longer harbour viable tubercle bacilli), they may be susceptible to new infection, especially in the communal environment of a long-term care facility. This transmission of new infection from a resident with reactivation tuberculosis to a susceptible TST-negative resident living in the same facility, with the subsequent occurrence of primary disease in the second resident, is well described.^{5,6} Most TST-negative older persons remain capable of mounting a T-cell response if newly infected with *M. tuberculosis*.⁵

North American data suggest that age-specific tuberculosis case rates per 100,000 TST-positive persons are higher in older than in younger adults.⁷ It is not known to what extent this heightened risk is attributable to the known risk factors for the development of active tuberculosis among persons infected with *M. tuberculosis* (Table 1).⁸ A certain number of these risk factors are more common among older people.

New Biologic Therapies and the Risk of Tuberculosis

Tumour Necrosis Factor Inhibitors

The most important new biologic therapies are those that inhibit the pro-inflammatory cytokine, tumour necrosis factor (TNF). TNF inhibitors include infliximab, a chimeric antibody approved for use in the treatment of Crohn's disease and rheumatoid arthritis (RA), and etanercept, a recombinant TNF receptor fusion protein approved for use in patients with RA. Their use is limited to patients who are not responding to other anti-inflammatory agents. Neither agent is curative. Related agents, such as adalimumab, approved for use in the treatment of RA patients in the U.S., are expected to become available in Canada in the near future. The number and diversity of indications for TNF inhibitors is expected to increase.

TNF inhibitors have recently been implicated in the reactivation of tuberculosis.⁹ Presumably, they allow organisms that were once contained (LTBI) to begin

to replicate and cause disease. *In-vitro* studies have shown that TNF increases the ability of macrophages to phagocytose and kill mycobacteria.^{10,11} TNF production is also a requirement for formation of granulomas, which sequester mycobacteria and prevent their dissemination.¹² Finally, TNF assists in containing mycobacterial growth by inducing apoptosis of presumably ineffective macrophages, thus depriving the organism of an intracellular sanctuary (Figure 2).^{13,14}

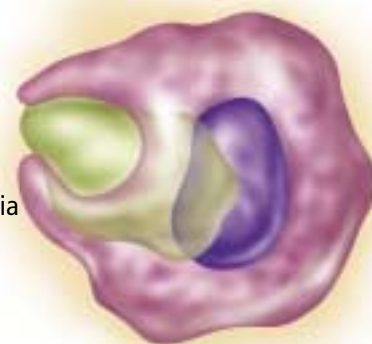
Risk of LTBI Reactivation

The magnitude of the risk of reactivation of LTBI that TNF inhibitors pose has not been precisely quantitated, but available *in vitro* and epidemiological evidence suggests that it is high, especially with infliximab.^{15,16} Cases of tuberculosis that occur in close temporal association with the administration of TNF inhibitors are believed to be the result of reactivation of remotely acquired LTBI. However, it is also possible that these cases may be the result of rapid progression of recently acquired LTBI. The rapid progression of recently acquired infection is known to occur in patients with advanced HIV/AIDS.¹⁷

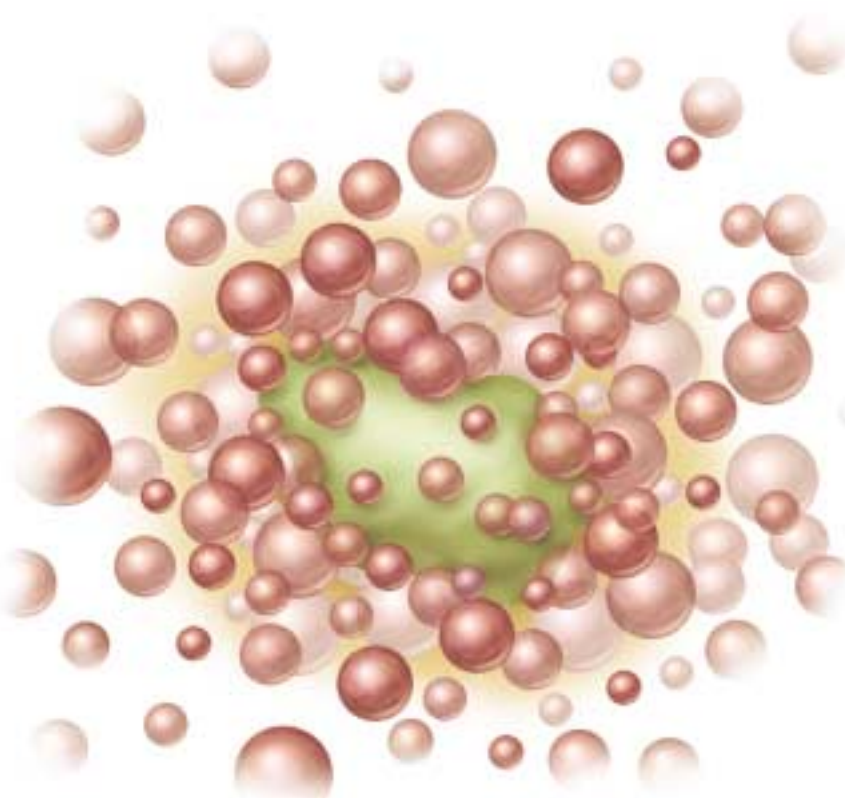
Not surprisingly, many of the RA and Crohn's disease patients who are being considered for TNF inhibitors are older and therefore at greater risk of LTBI. Both RA and Crohn's disease may have an older age onset. For RA, the age distribution is unimodal between the fourth and sixth decades; for Crohn's disease the age distribution is bimodal in the second and third and the sixth and seventh decades.^{18,19} The tuberculosis risk that TNF inhibitors pose to these patients is a function of the immunomodulating effect of the particular therapy and their chances of being infected at the time the agents are introduced, or of acquiring infection during the period when the agents are active. It is thus very important to screen all those being considered for TNF inhibitor therapy for active tuberculosis and LTBI before introduction of the agent. Those with active disease should complete a satisfactory course of antituberculosis drug treatment before the TNF inhibitor is introduced; those with LTBI

Figure 2.
Role of Tumour Necrosis Factor (TNF)

1 TNF increases the ability of macrophages to phagocytose mycobacteria



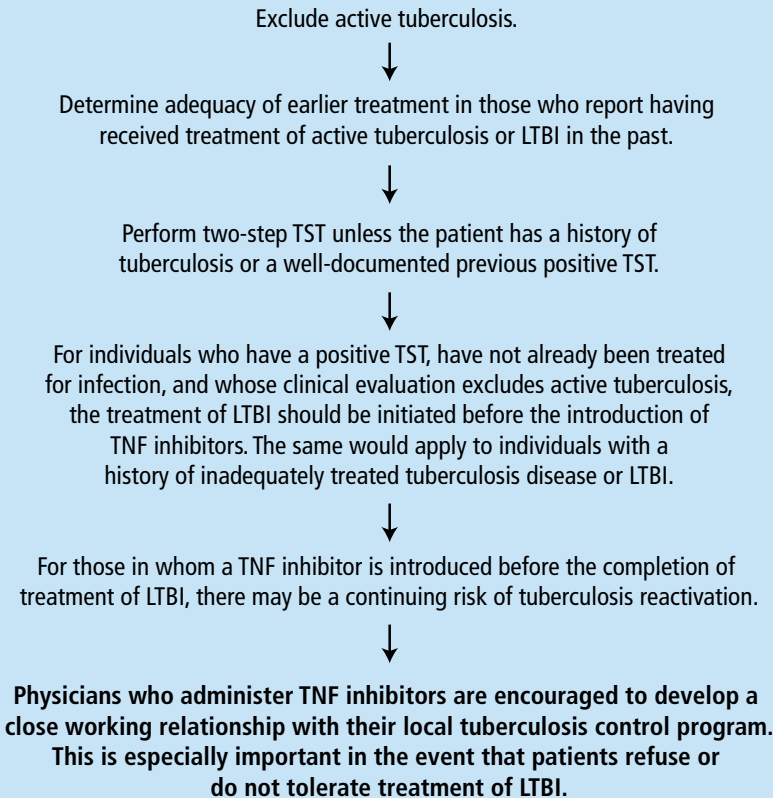
2 TNF production is needed for the formation of granulomas, which sequester mycobacteria, thereby preventing their dissemination.



3 TNF induces apoptosis of ineffective macrophages, depriving the organism of an intracellular sanctuary.



Figure 3: Management of Tuberculosis Risk in Older Patients Being Considered for TNF Inhibitor Therapy



Adapted from Long R, Gardam M, 2003.

should have a minimum of one to two months of treatment of LTBI before the introduction of the TNF inhibitor (Figure 3).^{15,16,20} Because older people may be less able to tolerate tuberculosis or its treatment and may be living in a communal environment where transmission is more apt to occur, the prevention of tuberculosis or its prompt diagnosis is that much more important.

Challenges of Tuberculosis Diagnosis

The diagnosis of tuberculosis disease in older patients with RA or Crohn's disease may be very challenging. At any age, the clinical and radiological features of rheumatoid lung disease and Crohn's disease may overlap with those of pulmonary tuberculosis and ileocecal tuberculosis, respectively. Even without the confusion that RA and Crohn's disease

may render, age alone may alter the presentation of tuberculosis. In a meta-analytical review of the effect of aging on pulmonary tuberculosis, patients ≥ 60 years were found to have a lower prevalence of fever, sweating, hemoptysis, cavity disease and a positive TST, as well as lower levels of serum albumin and blood leukocytes, compared to younger patients.²¹ Older patients also had a greater prevalence of dyspnea and concomitant conditions such as cardiovascular disease, diabetes and malignancy.²¹ When older people are recently infected with tubercle bacilli, they may present with radiologic features of primary disease. These may include mid- and lower-lung zone infiltrates or an isolated pleural effusion, findings that may not immediately call to mind tuberculosis in adults.^{5,6}

Once TNF inhibitors have been started, the ability to detect the presence of

active tuberculosis may become yet more challenging. In addition to the problems cited above, TNF inhibitors may mask some of the symptoms and signs of tuberculosis disease; specifically, those symptoms and signs that are believed to be secondary to TNF itself, including weight loss, night sweats and tissue destruction.²² The fact that many of the cases of tuberculosis attributed to the TNF inhibitor infliximab were disseminated at the time of diagnosis⁹ is problematic for older persons because the diagnosis of disseminated tuberculosis is often delayed or not made during life in these patients.²³

Since their tuberculosis infection may have been acquired in the remote past, the capacity of an older person's immune system to remember having previously met mycobacterial antigens may have waned, and the diagnosis of LTBI may require the performance of a two-step TST (Table 2). In the performance of a two-step TST, a single standard test is first administered. If it is negative, a second standard test is administered seven to 21 days later. If the patient has been infected in the past and still has immunity, the first TST will have induced an anamnestic response, such that the second TST will be positive.²⁴ The time restriction (7–21 days) between the first and second tests applies because there is insufficient time in this period for the patient to have become infected and to have converted their TST.²⁴ Patients whose TST is only positive on a second step may in fact be less likely than those with a positive first step to develop tuberculosis in the future.^{6,25} However, for practical purposes a positive first or second step TST should be managed the same.

Management of Active Tuberculosis

While the treatment of active tuberculosis is virtually always mandatory, the treatment of LTBI is not. It is unknown whether the tuberculosis risk posed by TNF inhibitors is so high that patients with untreated LTBI or those unable to tolerate treatment of LTBI should be denied TNF inhibitors. Although the risk of hepatotoxicity from antituberculosis drugs used to treat LTBI may increase

Table 2

Suggested Tuberculin Skin Test Criteria for Patients Receiving TNF Inhibitors^{8,14,18}

TST (mm induration)	Patient Characteristics for which Preventive Therapy is Recommended
0–4mm [†]	Major immune suppression (e.g., anti-TNF therapy with other immunosuppressive medications) with additional significant risk factors for tuberculosis progression, such as: – fibronodular disease on chest radiograph – recent close contact with an infectious case
5–9mm	Anti-TNF therapy with epidemiologic risk factors, such as: – foreign born from an endemic country – Inuit or Treaty Status Aboriginal – abnormal chest radiograph – known contact with an active case
10mm	All others receiving anti-TNF therapy

[†] The decision to treat latent infection in such cases should be made on an individual basis in conjunction with a tuberculosis specialist.

with age, this risk is not considered prohibitive and should be weighed against the potential benefits of a TNF inhibitor.²⁶ Once preventive treatment is introduced, patients should be followed for symptoms of hepatotoxicity. Older patients—especially those at increased risk of hepatotoxicity, such as patients with pre-existing liver disease or alcohol addiction or individuals who are already receiving a hepatotoxic drug—should have serial measurements of aminotransferase levels.

Summary

Physicians who prescribe the new biologic therapies need to screen patients for tuberculosis and LTBI and treat each of these conditions appropriately. Physicians, nurses and other health care providers need to be vigilant for symptoms and signs of tuberculosis among patients who are taking TNF inhibitors. These recommendations are especially important in older patients. ♦

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