Tumour necrosis factor-α inhibitors and the reactivation of latent tuberculosis infection

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Infliximab (Remicade) is a chimeric (part human, part mouse) antibody that targets tumour necrosis factor-α (TNF-α), a potent proinflammatory cytokine implicated in different inflammatory diseases, such as Crohn's disease and rheumatoid arthritis.[1,2] (Cytokines are molecules secreted from cells. Among other things, they play an important role in interactions, modulations and regulation of the immune system. Thus, they play a part in the reactions that cause inflammation and killing of invading microbial agents, including tuberculosis (TB). The cytokines include interleukins, TNF-α and interferon-γ.) Although the role of TNF-α in the human immune response to mycobacteria is incompletely understood, in animal models TNF-α plays a central role in the formation of granulomata and containment of disease (Fig. 1).[3,4]

There are now a large number of reports of TB in close temporal association with the initiation of TNF-α inhibitors and an increased rate of TB among patients treated with infliximab, as compared with available data on background rates.[5–7] Although passive surveillance data do not prove a causal relationship between infliximab and TB (e.g., increased awareness alone could be contributing to diagnoses of TB independent of infliximab therapy), the association is not thought to be coincidental.[5] In most instances, TB appears to be secondary to reactivation of latent TB infection.

In Canada, infliximab is approved for use in the treatment of Crohn's disease or rheumatoid arthritis that is not responding to other anti-inflammatory agents.[1,8–10] Etanercept (Enbrel), a recombinant TNF receptor fusion protein, also targets TNF-

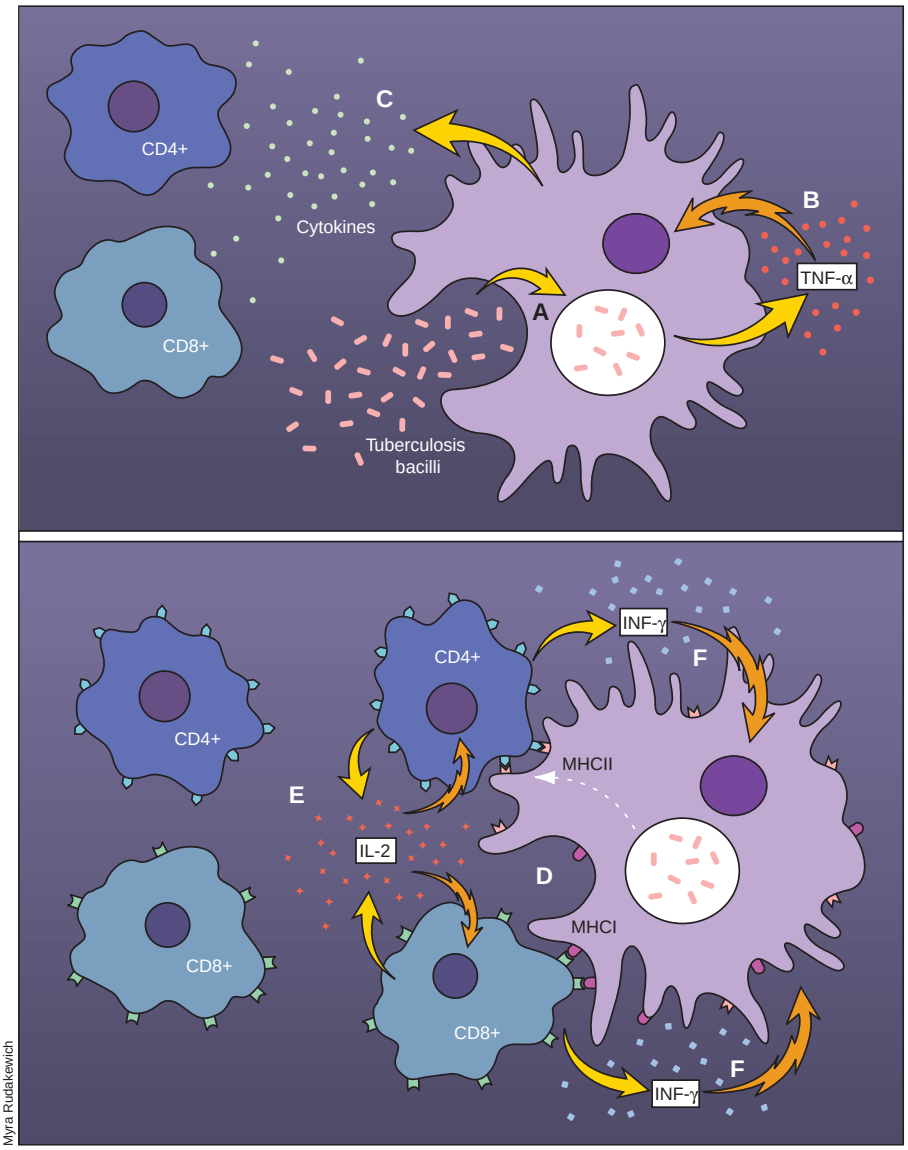

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Fig. 1: The putative role of tumour necrosis factor-α (TNF-α) in the cell-mediated normal human immune response to tuberculosis infection. The macrophage (A) phagocytoses the invading mycobacteria. This results in the release of TNF-α (B) and other cytokines (C), the effect of which is further activation of cell-mediated immunity. The early release of TNF-α enhances the ability of macrophages to phagocytose and kill mycobacteria. Antigen presentation through major histocompatibility complexes (MHC) leads to the release (D) of other cytokines (interleukin-2) with further recruitment of T lymphocytes (E). Lastly, T-lymphocyte release of interferon-γ (F) further activates the macrophage to enhance bacterial killing. Inhibitors of TNF-α such as infliximab interfere with this process at an early stage (B).

α, but is only approved for use in patients with rheumatoid arthritis.[11–13] Neither drug is curative nor currently approved for use in chronic inflammatory conditions other than Crohn's disease and rheumatoid arthritis. Infliximab and etanercept are expensive, which accounts for their current omission from most drug benefit lists or regional formularies.

Although clinical and epidemiological reports are preliminary, there is nonetheless general agreement that patients who are being considered for treatment with infliximab should be screened for active TB and latent TB infection before the introduction of the agent (Box 1).[13–16] It is recommended that patients with proven active disease complete a satisfactory course of antituberculosis drug treatment before infliximab is introduced.[5,14]

Screening for TB in patients with rheumatoid arthritis may be challenging, because the clinical and radiological features of rheumatoid lung disease may overlap with those of TB. Likewise, virtually all of the clinical and radiological features of Crohn's disease are indistinguishable from those of ileocecal TB. A diagnosis of Crohn's disease, especially in patients who are Aboriginal or were born in countries where TB is endemic,[17] should always raise suspicion of ileocecal TB.[7]

Box 1: Screening for tuberculosis (TB) and latent TB infection in individuals for whom infliximab therapy is being considered

1. Exclude active TB
   - Symptom inquiry (persistent cough, fever, weight loss, night sweats)
   - History of TB or TB exposure
   - Chest radiograph
   - Submission of specimens appropriate to the site of suspected disease for acid-fast bacilli smear and culture
2. Determine the adequacy of earlier treatment in those who report having received treatment of active TB or latent TB infection in the past
3. Perform a tuberculin skin test with intermediate-strength purified protein derivative (Mantoux method) unless patient has a past history of TB or a well-documented previous positive tuberculin skin test[15]
   - The tuberculin skin test should be read at 48–72 hours by a health care worker experienced at reading tuberculin skin tests
   - In elderly people (≥ 65 years) and in those in whom annual testing is felt to be justified by high infection rates, a baseline 2-step tuberculin skin test should be considered
   - Latent TB infection is most likely to be discovered in residents of Canada who are already at increased risk of TB, namely, foreign-born patients from countries where TB is endemic, Aboriginal people, inner-city poor and homeless people, and elderly people[16]

Most guidelines for the treatment of latent TB infection recommend that when the pretest probability of a true-positive tuberculin skin test is high, and the risk of reactivation TB is high, then a Mantoux test cut-off point of ≥ 5 mm or more should be indicative of latent TB infection.[18] When the risk of reactivation is judged to be extraordinarily high (for example in people with HIV/AIDS), then a ≥ 5-mm cut-off point is used regardless of the pretest probability of a true-positive tuberculin skin test.[18] Whether infliximab constitutes such an extraordinarily high risk has not been established yet. A conservative approach would be to assume that it does. Routine anergy testing is not recommended.

The management of latent TB infection in candidates for infliximab is controversial and likely to remain so until new information concerning the risk of reactivation in recipients of the agent is available (Box 2). The controversy surrounds the question of whether, in the interest of TB prevention, it is necessary to complete preventive therapy before the introduction of infliximab, or whether it is sufficient to simply initiate treatment of latent TB infection before the introduction of infliximab. Implicit in the first position is the withholding of infliximab for the 9 months that are necessary to complete isoniazid preventive therapy. People with latent TB infection are understood to be harbouring fewer than 100 000 tubercle bacilli.[19] To completely destroy this population of bacilli requires 9 months of isoniazid. Implicit in the second position is the understanding that infliximab may be safely introduced 1 day after the start of preventive therapy. The available clinical literature[5–7] advocates for the first position, imputing to infliximab a degree of acute, electively induced immunosuppression that might result in TB reactivation in the absence of a complete course of preventive therapy.

Those arguing in favour of the second position may cite evidence of isoniazid's efficacy in treating latent TB infection in patients with HIV/AIDS,[20] asserting that infliximab-induced immunosuppression can be no worse than HIV/AIDS-induced immunosuppression (single-dose therapy with infliximab is not associated with changes in major circulating lymphocyte populations[21]). However, the circumstances may not be the same. HIV/AIDS immunosuppression is virally induced and very slowly progressive. At the point of introduction of preventive therapy the patient has not, despite the existing immunosuppression, developed active TB. Deferring a recommendation of treatment of latent TB infection in such a patient is usually not an option. Infliximab immunosuppression, on the other hand, is electively drug induced. Transiently, it may be very potent. Deferring the onset of the immunosuppressed state may be an option, though understandably unattractive from the point of view of management of a patient's Crohn's disease or

rheumatoid arthritis. Newer and shorter-course treatments of latent TB infection may reduce waiting times to the completion of preventive therapy.[18]

The benefits of accessing a TNF-α inhibitor may outweigh the risks of hepatotoxicity from TB-preventive therapy. Although the incidence of rheumatoid arthritis[13] and the risk of isoniazid-related hepatitis[22] increase with age, the risk to patients with rheumatoid arthritis of isoniazid–induced hepatitis is not prohibitive. Similarly, though hepatobiliary abnormalities may be associated with Crohn's disease,[23] they may not of themselves preclude the use of isoniazid. Under ordinary circumstances, older age alone or pre-existing liver disease, or both, do not represent absolute contraindications to the judicious use of isoniazid. They do, however, dictate the need for careful and systematic monitoring of symptoms and aminotransferase levels. A history of pre-existing liver disease should be sought and baseline aminotransferase levels should be measured before the introduction of isoniazid. Once isoniazid is introduced, patients should be followed for symptoms of hepatotoxicity; 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. If symptoms of hepatitis occur or aminotransferase levels exceed 3–5 times the upper limit of normal, then isoniazid should be withheld.

The half-life of infliximab is 10 days,[24] and its biological effect persists for up to 2 months. Individuals being treated with infliximab who have close contact with patients who have infectious TB should be treated for presumptive latent TB infection. If the TNF-α inhibitor is continued or believed to be active for more than 8–12 weeks after final contact with the TB source case, then preventive therapy should be continued, even when a repeat tuberculin skin test at 8–12 weeks is not indicative of latent infection. Orme and Cooper have proposed that TNF plays a major role in triggering or amplifying the chemokine-driven processes that are central to delayed-type hypersensitivity and the tuberculin skin test.[25] Although this suggests that infliximab could cause a false-negative tuberculin skin test, there is anecdotal evidence that delayed-type hypersensitivity is preserved after infliximab.[26] At the moment, it is not established whether TNF-α inhibition itself will result in a false-negative tuberculin skin test.

During therapy and for a period of at least 6 months post infusion (complete elimination of infliximab may require up to 6 months),[27–29] health care workers who look after patients being treated with infliximab should maintain a high level of suspicion for TB. TNF-α is believed to be responsible for some of the clinical manifestations of TB, including weight loss, night sweats and tissue destruction.[30] Accordingly, its inhibition by infliximab may mask some of the usual signs and symptoms of the disease.

Evidence implicating etanercept, the other currently available TNF-α inhibitor, with TB reactivation is less compelling,[31] perhaps because of differential effects of the 2 agents on monocytes and lymphocytes,[4,32] or perhaps because it was studied in a different patient population.[5] Nonetheless, until more information is available to suggest otherwise, it would be prudent to consider the preceding comments concerning infliximab to be equally applicable to etanercept.

In summary, physicians who prescribe these biological agents need to screen patients for TB and latent TB infection and treat each of these conditions appropriately. Health care providers also need to be vigilant for signs and symptoms of TB among patients with Crohn's disease and rheumatoid arthritis who are taking TNF-α inhibitors.

Box 2: An approach to the treatment of latent TB infection based upon currently available evidence*

1. For individuals who have a positive tuberculin skin test, have not already been treated for TB infection and whose clinical evaluation excludes active TB, the treatment of latent TB infection should be initiated before the introduction of infliximab.
   The same would apply to individuals with a past history of inadequately treated TB disease or latent TB infection.
   The same might also apply to individuals with negative tuberculin skin test results but with evidence of old healed TB on chest radiograph, especially those with a past history of TB exposure. They may, in the judgement of a TB consultant, be candidates for treatment of latent TB infection because the tuberculin skin test may be falsely negative in a systemically ill patient who is already receiving an immunosuppressive drug.
2. If, in the judgement of the treating physician, infliximab therapy could be delayed, then it would be prudent to wait until the full 9 months of isoniazid therapy are complete before the introduction of the TNF-α inhibitor.
3. If, in the judgement of the treating physician, it is necessary to start infliximab therapy sooner, because of the severity of the Crohn's disease or rheumatoid arthritis, it could be started after 1 month of isoniazid therapy (usually by then one will know whether isoniazid is tolerated and safe).
4. In those for whom infliximab is introduced before the completion of treatment of latent TB infection, there may be a continuing risk of TB reactivation.

*Physicians who administer TNF-α inhibitors are encouraged to develop a close working relationship with their local TB control program. This is especially important in the event that patients refuse or do not tolerate treatment of latent TB infection.

Key points

- The reported frequency of TB in association with infliximab therapy is much higher than the reported frequency of other opportunistic infections associated with the drug.
- TB tends to occur after a median of 12 weeks of infliximab therapy.
- Infliximab-related TB frequently manifests as extrapulmonary disease, particularly disseminated disease.
- Many patients with infliximab-related TB are taking concurrent corticosteroids or other immunosuppressants suggesting a possible additive or synergistic effect of infliximab.
- Infliximab may be more potent than other therapeutic agents capable of reactivating latent TB infection.

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