Screening for tuberculosis infection before initiation of anti-TNF-α therapy

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Background

Patients receiving anti-TNF-α therapy for rheumatic or chronic inflammatory bowel diseases are at higher risk of developing tuberculosis during treatment than patients with similar diseases not receiving anti-TNF-α therapy or subjects in the surrounding population [1–3]. As most cases appear to be secondary to reactivation from a state of latent infection and not *de novo* infection, screening of patients for tuberculosis and latent tuberculosis infection is recommended before initiating anti- TNF-α therapy [4, 5].

Preventive treatment should be offered to all patients with evidence of latent tuberculosis infection before starting any anti-TNF-α therapy [6], even if it does not appear to offer complete protection [7], while patients with signs of active tuberculosis should be offered a full course of treatment.

Various recommendations and guidelines have been issued on screening for latent tuberculosis infection. They are traditionally based on history, chest x-ray (CXR) and tuberculin skin test (TST). However, TST has several disadvantages. Its specificity is low, false positive results being common in BCG-vaccinated subjects or due to a booster effect [8, 9]. Its sensitivity is also lower in immunosuppressed patients than in healthy subjects [10, 11], and some patients may therefore have false negative TST. Furthermore, TST is poorly reproducible, requires two visits for its performance (for application and reading) and is subject to observer error. Finally, the limit above which the TST is considered positive (i.e. indicative of latent infection) is [illegible] and actually differs between countries and guidelines (5 to 10 mm).

Two *in vitro* tests have been developed which detect gamma-interferon (γ-IFN) released by T-lymphocytes sensitised to specific antigens of *M. tuberculosis*. These tests (Quantiferon-TB® Gold [Cellestis] and T-SPOT.TB® [Oxford Immunotec]) have a better sensitivity than TST in immunocompromised subjects [11–13] and a higher specificity, as they are not influenced by prior vaccination with BCG or contact with non-tuberculous mycobacteria [13, 14]. False-negative and indeterminate results have been observed in rare cases with both tests, but are less frequent than with TST [15, 16]. However, and despite the evidence of better performance of interferon gamma release assays (IGRA) than of TST, neither test has been incorporated into some guidelines for the screening of latent infection before anti-TNF-α therapy [17]. The cost-effectiveness of screening for latent infection with IGRA instead of TST has been demonstrated [18, 19]. The new guidelines of the Swiss Lung Association and the Federal Office of Public Health have defined the indications for IGRA tests for the detection of latent tuberculosis infection [6] (available online at www.tbinfo.ch)

Recommendations

A group of experts in rheumatology, gastroenterology and pneumology met in Berne on 19 September 2006 to evaluate the current arguments in favour of IGRA and their incorporation into recommendations for tuberculosis screening before prescription of anti-TNF-α therapy, and decided to issue Swiss recommendations based on current knowledge and literature and their own experience of using IGRA tests in this setting.

After review of the existing literature, the experts agreed that:

1. A definite risk of tuberculosis exists with anti-TNF agents, and all patients should be screened for tuberculosis and latent tuberculosis infection prior to any anti-TNF-α therapy.
2. The screening should be based on history, chest x-ray and an IGRA test.
   a. History: a detailed history of exposure to or prior treatment for tuberculosis, considering the risk associated with birthplace or country of origin or residence in special environments involving increased risk of TB contact (prisons, shelters).
   b. Chest x-ray: a single PA chest x-ray for detection of past or present tuberculosis.
   c. IGRA test.
3. Use of TST is no longer recommended for screening in view of the limitations mentioned. Even a history of positive TST should be confirmed by an IGRA test.
4. Patients with abnormal x-ray findings suggestive of past tuberculosis should undergo complete clinical and bacteriological testing to rule out or confirm active tuberculosis. Patients with active tuberculosis should receive a full course of antituberculosis treatment. Anti-TNF-α therapy can be resumed once the patient is under antituberculous treatment.
5. Preventive treatment according to the current recommendations of the Swiss Lung Association (isoniazid 300 mg/day for 9 months or rifampicin 10 mg/kg daily for 4 months) [6] should be prescribed for any patient considered to be at significant risk of reactivation of latent tuberculosis infection defined as any of the following:
   a. A positive IGRA test (unanimous opinion)
   b. An abnormal X-ray suggestive of past tuberculosis not adequately treated without current evidence of activity (majority of experts and BTS Recommendations)
   c. A history of significative prior exposure to tuberculosis without adequate treatment (majority of experts and BTS Recommendations) Patients following preventive treatment for latent infection may receive anti-TNF-α therapy. Current practice is to delay introduction of anti-TNF-α therapy for one month following preventive treatment.
6. Screening and preventive treatment do not offer complete protection, and patients under anti-TNF-α therapy should be followed up clinically for signs of tuberculosis reactivation. There are no data to recommend repeated IGRA testing if the result is positive, but they could be useful in suspect cases or if a patient with a negative test result is newly exposed to tuberculosis.
7. In the rare event of an indeterminate test result it is possible that the patient's lymphocytes do not produce interferon-gamma. If the indeterminate result persists despite repetition of the test, the need for preventive treatment is determined solely by history and chest x-ray findings; in this setting a cautious approach is strongly recommended.

Conclusions

Screening for latent tuberculosis infection is indicated prior to the administration of anti- TNF-α therapy. Due to the better sensitivity and specificity of IGRA tests, their incorporation into current recommendations should serve to detect more cases at risk for reactivation of latent tuberculosis infection and to prevent unnecessary prophylaxis with its potentially adverse effects in patients with false-positive TTS.

Participants at the experts meeting

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