Mayo Clinic Center for Tuberculosis

Biologics and TB

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Disclosure

I have no conflict of interest to declare
Learning Objectives

• Learn about the risk of TB associated with different biologic agents and

• Understand the implications of immuno-suppressive states on tests for latent TB

• Be able to implement appropriate TB screening in patients on biologic agents and give a rationale for the use of different tests

• Know how to follow-up patients on biologic agents for the risk of TB

• Be able to act properly if active TB is suspected
Presentation overview

1. Introduction

2. TB risk associated with biologic agents
   - Drug-specific relative risks of TB
   - TB risk associated with underlying medical condition

3. Performance of screening tests in patients with IMIDS*

4. Screening algorithms and current guidelines

5. Treatment of latent TB

6. Observation during treatment with TNF-alpha inhibitors

7. Tuberculosis in patients on TNF-alpha inhibitors

*IMIDS= immune-mediated inflammatory diseases
Introduction

TUBERCULOSIS ASSOCIATED WITH INFlixIMAB, A TUMOR NECROSIS FACTOR α–NEUTRALIZING AGENT

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ABSTRACT

Background Infliximab is a humanized antibody against tumor necrosis factor α (TNF-α) that is used in the treatment of Crohn’s disease and rheumatoid arthritis. Approximately 147,000 patients throughout the world have received infliximab. Excess TNF-α in association with tuberculosis may cause weight loss and night sweats, yet in animal models it has a protective role in the host response to tuberculosis. There is no direct evidence of a protective role of TNF-α in patients with tuberculosis.

Methods We analyzed all reports of tuberculosis after infliximab therapy that had been received as of May 29, 2001, through the MedWatch spontaneous reporting system of the Food and Drug Administration.

Results There were 70 reported cases of tuberculosis after treatment with infliximab for a median of 12 weeks. In 48 patients, tuberculosis developed after three or fewer infusions. Forty of the patients had extrapulmonary disease (17 had disseminated disease, 11 lymph-node disease, 4 peritoneal disease, 2 pleural disease, and 1 each meningial, enteric, paravertebral, bone, genital, and bladder disease). The diagnosis was

Infliximab (Remicade) is a humanized monoclonal antibody against TNF-α that is approved in the United States and elsewhere for the treatment of rheumatoid arthritis and Crohn’s disease. Infusions of infliximab can be administered in a single dose, a monthly regimen, or on day 0, day 14, day 42, and then every 8 weeks. The half-life of infliximab is 10 days, and its biologic effect persists for up to 2 months. The Food and Drug Administration (FDA) approved infliximab in 1998 for use in patients who do not have a response to other antiinflammatory agents. Approximately 147,000 people throughout the world have received the drug; in the United States, 45,000 patients have received it for rheumatoid arthritis and 76,000 for Crohn’s disease (Table 1). One case of tuberculosis after infliximab therapy was reported in a clinical trial. We evaluated the clinical pattern of disease and the interval between the initiation of infliximab therapy and the onset of disease in 70 reported cases of tuberculosis in patients treated with infliximab. We compared the rate of reported tuberculosis in this group with


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TB risk associated with biologic agents

Indications for biologics
ankylosing spondylitis (AS)
Crohn’s disease (Crohn’s)
juvenile idiopathic arthritis (JIA)
plaque psoriasis (Ps)
psoriatic arthritis (PsA)
rheumatoid arthritis (RA)
ulcerative colitis (UC)

gastroenterology
rheumatology
dermatology
## Drug-specific relative risks of TB

<table>
<thead>
<tr>
<th>Biologic</th>
<th>FDA approved indications (as of Nov 1, 2016)</th>
<th>Relative risk of TB compared to the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>adalimumab</strong></td>
<td>AS, JIA, RA, Ps, PsA, Crohn’s, UC</td>
<td>29.3 (95% CI 20.3–42.4)(3) (standardized for age and sex)</td>
</tr>
<tr>
<td><strong>infliximab</strong></td>
<td>AS, RA, Ps, PsA, Crohn’s, UC</td>
<td>18.6 (95% CI 13.4–25.8)(3) (standardized for age and sex)</td>
</tr>
<tr>
<td><strong>etanercept</strong></td>
<td>AS, JIA, RA, Ps, PsA</td>
<td>1.8 (95% CI 0.7–4.3)(3) based on SIR (standardized for age and sex)</td>
</tr>
<tr>
<td><strong>certolizumab pegol</strong></td>
<td>AS, RA, PsA, Crohn's</td>
<td>no definite increase in RR in pooled data from RCTs (4)</td>
</tr>
<tr>
<td><strong>golimumab</strong></td>
<td>AS, RA, PsA, UC</td>
<td>no definite increase in RR in pooled data from RCTs (5)</td>
</tr>
</tbody>
</table>
## Drug-specific relative risks of TB

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<tr>
<td>rituximab</td>
<td>Chronic lymphocytic leukemia, Non-Hodgkin lymphomas, Granulomatosis with polyangiitis, Microscopic polyangiitis, RA</td>
<td>no definite increase in RR in pooled data from RCTs (6)</td>
</tr>
<tr>
<td>tocilizumab</td>
<td>JIA, RA</td>
<td>no definite increase in RR in pooled data from RCTs (7)</td>
</tr>
<tr>
<td>vedolizumab</td>
<td>UC, Crohn’s</td>
<td>no definite increase in RR from drug safety data (8)</td>
</tr>
<tr>
<td>ustekinumab</td>
<td>Ps, PsA, Crohn’s</td>
<td>no definite increase in RR from drug safety data (9) first choice in patients with PsA at high infection and TB risk (10)</td>
</tr>
</tbody>
</table>
TB risk associated with underlying medical condition

• increased risk of TB associated with immunosuppressive diseases
  • Relative risk of TB in RA: 2.0, 95% CI 1.2-3.4
    Seong SS et al., J Rheumatol, 2007

• co-morbidities and additional medications that increase risk of TB
  • ↑ risk of TB for TNF-alpha inhibitors combined with methotrexate or azathioprine
    (odds ratio 13.3; 95% CI 3.7-100)
Implications for clinical practice

• Consider the risk of TB reactivation associated with different agents when determining the optimal treatment for your patients.

• If patients have an ongoing risk of TB exposure (e.g. travelling to TB-endemic areas) or could not complete a course of latent TB infection (LTBI) treatment (e.g. due to adverse reaction)

⇒ consider selecting a biologic other than adalimumab or infliximab, which are associated with the highest TB risk
Performance of screening tests in patients with IMIDS

Tuberculin skin test (TST)

Interferon Gamma Release Assays (IGRAs)
Performance of screening tests in patients with IMIDS

- IMIDs as well as treatments for these conditions (e.g., steroids, azathioprine, methotrexate) potentially impact on the performance of diagnostics tests for TB

- Increase of false negative TSTs and IGRAs?
  - controversial results
IGRAs and TST in patients with IMIDS

- IGRAs have higher specificity than TST (unaffected by BCG vaccination)

- Sensitivity of IGRAs at least equal and possibly superior to TST (in particular for T-SPOT)
  

- TST in addition to IGRA can increase sensitivity of LTBI testing and thus the diagnostic yield

  Mariette X, Ann Rheum Dis, 2012
IGRAs and TST in patients with IMIDS

- Discordant results between IGRAs and TST in patients with IMIDs are common

- In patients with inflammatory bowel disease: concordance of 85% (95% CI 77%–90%) between the TST and QFT and 72% (95% CI 64%–78%) between TST and TSPOT

- In patients with rheumatic diseases: concordance of 87.6% between TST and QFT and 91.1% between TST and TSPOT
IGRAs and TST in patients with IMIDS

- Discordant results where patients have a positive IGRA and a negative TST are still not fully understood due to the fact that there is no gold standard to determine if a patient truly has latent TB.
Screening algorithms and current guidelines

• **Screening** for latent (and active) TB before initiation of TNF-alpha treatment is **crucial**

• medical history, physical examination, **TST** and/or **IGRA**

• **chest x-ray** if positive TST or IGRA, clinical history or physical examination consistent with active TB or past TB
Screening algorithms and current guidelines

• Sputum Acid- Fast Bacilli (AFB) smear and TB culture, if there is any suggestion of possible TB on chest x-ray.
Screening algorithms and current guidelines

- single-step TST probably sufficient
  Carmona L, Arthritis Rheum, 2005

- most commonly recommended TST cut-off: 5mm

- TST, IGRA or TST and IGRA (either test positive strategy)?
  - Further research required
  - CDC supports TST or IGRA or a combination of both
Screening algorithms and current guidelines

Patients with high pre-test probability of latent TB (e.g. history of contact to a case of active TB, birth or extended stay in a TB-endemic setting)

Patients with low pre-test probability of latent TB (e.g. US-born, no known TB contact)

Immunosuppressed (poorly controlled IMID, immuno-suppressive treatment)?

Yes

Use TST and IGRA (sequentially), interpret result as positive if any test is positive

No

Use IGRA only

Hewitt RJ, Eur Respir J, 2015
Treatment of Latent TB

- treatment of latent TB in patients on TNF-alpha inhibitors is effective
  
  Carmona L, Arthritis Rheum, 2005

- Commonly recommended treatment regimens: daily isoniazid for 6 to 9 months as well as rifampin and isoniazid for 3 months

- Time on latent TB treatment before TNF-alpha-inhibitor therapy can be started? Unclear, CDC recommends ideally treatment completed, many other guidelines recommend minimum of 1 month
## Summary of CDC recommendations

<table>
<thead>
<tr>
<th>Latent TB screening tests</th>
<th>Treatment regimen for latent TB</th>
<th>Anti-TNF alpha starting delay</th>
<th>Repeat testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST or IGRA, combined use of TST and IGRA supported Positive TST: ≥5mm</td>
<td>9 months of isoniazid</td>
<td>no definite recommendation, completion of latent TB treatment before anti-TNF-alpha therapy, if possible</td>
<td>only in individuals at increased risk for TB infection</td>
</tr>
</tbody>
</table>
Observation during treatment with TNF-alpha inhibitors

- Monitor for **signs and symptoms** of TB, at least until **6 months after cessation** of treatment
- **No need** for routine chest x-rays
- If patient had abnormal chest x-ray at the time of initial TB screening or a past history of TB or TB treatment, but were deemed to have had previous adequate treatment by their TB specialist
  \[\Rightarrow\] chest x-ray three months after commencing anti-TNF-therapy
Observation during treatment with TNF-alpha inhibitors

• No routine repeat TST/ IGRA testing necessary

• CDC and the American College of Rheumatology only recommend annual TB testing in individuals at increased risk for TB infection while they continue on anti-TNF-alpha treatment

• If TST/IGRA were previously positive ⇒ repeat tests are unhelpful, assess new exposure risk to TB and monitor for clinical signs and symptoms of active TB
Travel to TB endemic areas while on TNF-alpha inhibitor treatment

• Case reports of travellers who developed TB

• No guideline recommendations regarding chemoprophylaxis

• Inform patients on anti-TNF-alpha treatment of the risk related to travelling to TB-endemic areas.

• Consider repeat screening for TB infection after travel to areas with a high incidence of TB.
Tuberculosis in patients on TNF-alpha inhibitors

- Increased risk for poor outcomes (e.g., meningitis, disseminated disease, fulminant disease, death)
- anti-TB treatment needs to be initiated as soon as a clinical diagnosis of TB is suspected, even if patients previously tested negative for latent TB!
- Most authorities recommend that anti-TNF-alpha therapy be discontinued at the time of TB diagnosis, at least temporarily
Tuberculosis in patients on TNF-alpha inhibitors

• A TB specialist should be consulted early on if TB is suspected in a patient on TNF-alpha inhibitor treatment

• Complex decisions around pausing/ restarting TNF-alpha inhibitor treatment, risk of immune reconstitution inflammatory syndrome (IRIS)
Take home messages

- The risk of TB varies for different TNF-alpha inhibitors
- IGRAs perform likely better than the TST in this situation
- Consider combining TST and IGRA for screening for latent TB in “high risk” patients
Take home messages

• Increasing the screening sensitivity is important because of the increased risk of TB reactivation and poor outcome (fulminant TB, death from TB)

• Only repeat testing in individuals at ongoing/new TB risk, in line with CDC recommendations
Test your knowledge

- The anti-TNF-alpha monoclonal antibodies adalimumab and infliximab are associated with a lower risk of TB compared to other TNF-alpha receptor therapy (e.g. etanercept) true/false

- IGRAs are at least as sensitive (or more) than TSTs in patients with IMIDs true/false

- All patients on TNF-alpha inhibitors should have annual IGRA or TST testing true/false
Thanks!

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