Tuberculosis and infliximab treatment
National surveillance from January 1, 2000, through June 30, 2003

Summary

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Objectives  Analysis of the tuberculosis cases reported in France in patients treated with infliximab since its marketing approval, assessment of the effect of changes in the summary of product characteristics and national guidelines.

Methods  Based on tuberculosis reports from the national post-marketing adverse drug reaction databank of the manufacturer from January 1, 2000 through June 30, 2003, and records from the national multicenter retrospective survey on opportunistic infections with anti-TNFα, we analyzed all cases of tuberculosis and the impact of the changes made in December 2000 in the summary of product characteristics and the guidelines on the prevention and management of tuberculosis in patients treated with infliximab published in February 2002.

Results  56 cases of tuberculosis were reported: the median interval before diagnosis was 12 weeks with a median of 3 infusions. The presence of Koch bacilli was confirmed in 32 patients; 29 patients had extrapulmonary or disseminated forms of tuberculosis. The tuberculosis rate among patients treated with infliximab was greater than among the general population and differed significantly by period (p<0.005).

Conclusion  Tuberculosis can occur within the first 12 weeks of treatment with infliximab. Information for practitioners must be continued, together with surveillance of the tuberculosis cases in France.

Infliximab is a chimeric monoclonal antibody against TNFα that binds to the cytokine’s soluble transmembrane forms and blocks interaction with its receptors. This anti-TNFα may play a role in the onset of infections by impairing immune defenses. On January 1, 1999, European authorities approved marketing of infliximab (Remicade®) for rheumatoid arthritis and Crohn’s disease; in October 2003 it was also authorized for ankylosing spondylitis. It is administered as an intravenous infusion at a dosage of 3 mg/kg at intervals of 2, 6, and then 8 weeks for rheumatoid arthritis and at a dosage of 5 mg/kg for Crohn’s disease and ankylosing spondylitis. Treatment for the latter indications can be continued with infusions at 15 days and then every 8 weeks. One case of tuberculosis (TB) was observed during the clinical trials. From 1998 through May 2001, the US Food and Drug Administration received reports of TB in 70 patients treated with infliximab worldwide, 64 in countries with a low TB incidence. Nine cases were published through 2003, including three in France (all included in this study). An intensive multicenter study of adverse drug reactions in Spain found a TB incidence estimated at 1.8 and 1.1 cases/100,000 patients in 2000 and 2001, respectively. In December 2000, after 28 cases of TB had been reported worldwide, the summary of product characteristics (contraindications, warnings, and precautions) were modified in France to include recommendations for screening (by tuberculin skin testing and chest radiography and specific checking for any history of TB before infliximab treatment) and treating all active TB before starting treatment. In February 2002, national guidelines were issued for the prevention and management of TB after infliximab treatment, at the initiative of the TB and infliximab group (GTI) (see sidebar). At the request of the French drug agency (AFSSA), a national survey began in February 2003 to review the available data in France about TB after infliximab treatment and assess any effect of the national guidelines published a year earlier. The aim of this work was to analyze:
- the number of TB cases reported in France in patients treated with infliximab since its authorization (January 1, 2000, through June 30, 2003);
- the impact of the changes in the summary of product characteristics in December 2000 and the national guidelines in February 2002.

Methods

The analysis examined all cases of TB reported in patients who had received infliximab treatment from January 1, 2000, through June 30, 2003.
Information was collected from:
- spontaneous reports of TB to the regional adverse drug reaction reporting centers from January 1, 2000, through June 30, 2003;
- reports of TB to the manufacturer (Centocor–Schering Plough) over the same period;
- TB cases found during the retrospective national multicenter survey of opportunistic infections during anti-TNFα treatment, conducted by the RATIO (Research of Anti-TNF and opportunistic infections) group between January 1, 2000, and September 30, 2002.

Cases were classified as one of three forms of TB: common pulmonary, extrapulmonary, or disseminated. In the absence of precision about clinical symptoms, the case was classified as “tuberculosis without further details”.

The analysis, essentially descriptive, considered the following items:
- patient characteristics: age, sex;
- risk factors for TB: history of TB, other immunosuppressants;
- treatment characteristics: indication, dosage, number of infusions;
- clinical characteristics of the TB, time to occurrence, course, and outcome;
- compliance with national guidelines: date of occurrence, pretreatment work-up, prophylactic treatment.

The number of patients treated with infliximab, based on data furnished by Centocor, served as the denominator for calculating the incidence of TB after treatment. All results with a Gaussian distribution are expressed as the mean ± standard deviation (range) and those with a non-Gaussian distribution as the median (25th and 75th percentiles).

We used a $\chi^2$ trend test to look for a difference in the proportion of patients with TB in 2001, 2002, and 2003.

**Results**

During the study period, 56 cases of TB were reported in patients treated with infliximab (table 1): 8 in 2000, 19 in 2001, 17 in 2002, and 7 between January 1 and June 30, 2003. The exact date was unknown for 5 patients. The patients’ mean age was 54.7 years ± 16.16 (range 12-85 years) and 62% were women.

Examination of risk factors showed:
- history (30 complete files): 4 mentioned recent possible or certain exposure, 7 a history of primary infection and 5 a history of TB disease. None of these patients had received any prophylactic drugs;
- immunosuppressant treatments administered together with infliximab: 29 patients received methotrexate (one patient also received azathioprine), 34 with corticosteroids. Seven patients were not taking methotrexate but other different immunosuppressants (azathioprine, leflunomide, cyclosporin or mercaptopurine), 4 patients had no other immunosuppressants, and 14 files were incomplete.

The reasons for prescribing infliximab were rheumatoid arthritis (37 cases), Crohn’s disease (6), ankylosing spondylitis (7), polymyositis (4), and psoriatic arthritis (2). The median number of infusions before the diagnosis of TB was 3. The median time between the first infusion and the TB diagnosis was 12 weeks for the 44 patients with complete files. The clinical forms of TB were: pulmonary (22 cases), extrapulmonary (12), and unspecified (5). Bacteriological or pathological confirmation was available for 41 patients: samples from 32 patients contained Koch bacillus (Mycobacterium tuberculosis), 4 samples were confirmed with PCR and 5 with a lymph node biopsy. Nine patients had only a pleural or lymph node biopsy. Infliximab treatment was stopped for all patients. Six patients died: 2 of TB, and 4 of other diseases (pneumocystosis, multiple organ failure, pyocyanogenic septicemia, pulmonary embolism). Two other patients had other serious opportunistic diseases: systemic candidiasis and cytomegalovirus in the lung.

Analysis of the impact of the changes in the summary of product characteristics (2000) and national guidelines in 2002 shows that:
- twelve patients began infliximab treatment before the summary of product characteristics was modified in December.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of 56 patients with tuberculosis after infliximab treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td><strong>Value</strong></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>19-85</td>
</tr>
<tr>
<td>25th percentile</td>
<td>44</td>
</tr>
<tr>
<td>Median</td>
<td>57</td>
</tr>
<tr>
<td>75th percentile</td>
<td>67</td>
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<tr>
<td><strong>Time from first dose to diagnosis (weeks)</strong></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-55</td>
</tr>
<tr>
<td>25th percentile</td>
<td>8</td>
</tr>
<tr>
<td>Median</td>
<td>12</td>
</tr>
<tr>
<td>75th percentile</td>
<td>22.5</td>
</tr>
<tr>
<td><strong>Number of injections</strong></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2-11</td>
</tr>
<tr>
<td>25th percentile</td>
<td>3</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>75th percentile</td>
<td>3</td>
</tr>
<tr>
<td><strong>Clinical manifestation of tuberculosis – nb. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>22 (39.3)</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>Disseminated</td>
<td>17 (30.4)</td>
</tr>
<tr>
<td>Not specified</td>
<td>5 (8.9)</td>
</tr>
</tbody>
</table>
National guidelines on the prevention and management of TB during or after infliximab treatment

Look for latent TB
• **Primary infection** (positive reaction or increase of induration diameter to more than 10 mm after contact).
• **Subjects at high risk of reactivation of TB:**
  - subject with past TB but treated before 1970 or not having at least 6 months of treatment including at least 2 months of rifampicin + pyrazinamide;
  - skin test reaction > 10 mm from BCG (> 10 years), or phlyctenula, with no history or treatment of TB;
  - subject with major tubercular sequelae and uncertainty that treatment was completed.

How to screen a patient at risk
• **By detailed questioning** that includes:
  - existence and date of BCG vaccination (previous skin test results);
  - history of personal exposure;
  - general exposure (lived or hospitalized in a country with pandemic levels);
  - personal history of TB;
  - previous treatment of TB.
• **By looking for clinical signs of TB disease** (general pulmonary or extrapulmonary signs).
• **By a chest radiograph and a skin test at 10 IU.**

Management of latent TB
• Patients requiring anti-TB prophylactic treatment before beginning infliximab:
  - 10 mg/kg/day of rifampicin + 20 mg/kg/day of pyrazinamide for 2 months, or
  - 10 mg/kg/day of rifampicin + 4 mg/kg/day isoniazide for 3 months, or
  - 4 mg/kg/day of isoniazide for 9 months.
• **Primary infection** (positive result or skin test diameter increased to more than 10 mm after contact with a person with bacilliaceous TB).
• **History of TB treated before 1970 or treated incompletely.**
• **Tuberculin skin test > 10 mm from BCG (> 10 years) or phlyctenula.**
• **Major tubercular sequelae, uncertainty that treatment was completed.**

Management of active diagnosed TB before or during infliximab treatment
• **Test for Koch bacillus for 3 consecutive days** in sputum or by intubation, skin test reaction, radiograph ± MRI.
• **Other samples if necessary** (bacteriologic testing of urine, etc.).
• **Combined treatment:** rifampicin (10 g/kg/once daily), isoniazide (4 g/kg/d), pyrazinamide (20 g/kg/day for 2 months, then rifampicin + isoniazide (or Rifater® one tablet per 12 kg for the first 2 months then Rifinah®, 2 cp./day for 4 months.
• **Duration of treatment:** 6-9 months for pulmonary or single-node TB and 9 months for disseminated or multinodular TB, 12 months for bone or neuromeningeal TB, with sputum monitoring helpful around the 15th day.


2000: they did not have a complete pretreatment work-up (chest radiograph and tuberculin skin test);
- twenty-four patients began treatment between December 2000 and February 2002: 2 (10%) had a complete pretreatment work-up, 5 an incomplete work-up (skin test or chest radiograph), 3 no work-up, and 14 files did not include the information;
- fifteen patients began treatment after the summary of product characteristics was modified a second time and the national guidelines issued; 5 (one-third) had a complete pretreatment work-up, 1 an incomplete work-up, and records for 9 were incomplete.
The incidence of TB in patients treated with infliximab was estimated at 23/10,000 in 2000, at 14/10,000 in 2001, and at 8/10,000 in 2002 and thus diminished significantly over time.

**Discussion**

The incidence of TB in the general population in France is assessed at 1.1/10,000 and has been stable for three years. Incidence in patients treated with infliximab is thus much higher, since it is estimated at 8.24/10,000, depending on the year. Thus, even though adverse drug reactions may be underreported, these data reveal that TB is much more frequent in patients treated with infliximab than in the general population. Unfortunately, we have no data for France about TB incidence in patients with rheumatoid arthritis, Crohn’s disease or ankylosing spondylitis who are not receiving infliximab. Such data have been reported, however, for Spain and the US. In Spain, the relative risk of TB in patients with RA and treated with infliximab compared with patients not exposed to this product was 19.9 (95% CI: 16.2-24.8) in 2000 and 11.7 (CI 9.5-14.6) in 2001. In the United States, the incidence of TB in the general population was 6.4 cases/100,000 in 1999 and 8 in 2000. Of 10,782 patients with rheumatoid arthritis not treated with infliximab, the incidence of TB was 6.2 cases/100,000 patients, that is, near that of the general population. Of 16,460 patients treated with infliximab, the incidence of TB was 52.5/100,000 patients. In our study, the pulmonary form represented 39% of the cases, similar to the data in the studies by Keane et al. (31%), by Gomez-Reino et al. in Spain (35%) and by Wolfe et al. (33%). The mean time between the start of treatment and TB diagnosis was similar in our study (3 months) and the Spanish study (3 months in 59% of cases); particularly attentive monitoring is therefore needed around the third infusion. Statistical calculations cannot assess compliance with guidelines, given the limited number of records including information on the pretreatment work-up (questioning about TB history, skin test, and chest radiograph) and the lack of information about the exact number of patients treated between December 1, 2000, and February 18, 2002. Latent TB should have been suspected for 8 patients in our study and 7 in the Spanish study from their history and possible (old or recent) exposure, radiologic sequelae or positive tuberculin skin tests; they should have received prophylactic treatment before infliximab administration began.

**Conclusion**

Infliximab treatment increases the risk of TB. This study did not permit us to assess the effect of the national guidelines to look for and treat active or latent TB before beginning infliximab treatment. Thorough clinical surveillance of patients and monitoring for signs suggestive of TB must be reinforced around the third infusion. It appears necessary to continue informing physicians about the current guidelines.