Emergence of *Legionella pneumophila* Pneumonia in Patients Receiving Tumor Necrosis Factor–α Antagonists

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**Background.** Patients treated with tumor necrosis factor–α (TNF-α) antagonists have an increased risk of infection, but infection due to *Legionella pneumophila* has rarely been described in patients receiving such therapy.

**Methods.** A registry involving 486 clinical departments in France was designed by a multidisciplinary group (Recherche Axée sur la Tolérance des Biothérapies [RATIO]) to collect data on opportunistic and severe infections occurring in patients treated with TNF-α antagonists. All cases are reported to RATIO in accordance with national health authorities and validated by infectious disease experts. The legionellosis rate among patients treated with TNF-α antagonists was compared with the rate in France overall.

**Results.** We report a 1-year consecutive series of 10 cases of *L. pneumophila* pneumonia in France in 2004, including 6 cases treated with adalimumab, 2 treated with etanercept, and 2 treated with infliximab. The median patient age was 51 years (range, 40–69 years). Eight patients were treated for rheumatoid arthritis, 1 was treated for cutaneous psoriasis, and 1 was treated for pyoderma gangrenosum. The median duration of TNF-α antagonist treatment at onset of infection was 38.5 weeks (range, 3–73 weeks). Eight patients were receiving concomitant treatment with corticosteroids, and 6 were receiving treatment with methotrexate. The relative risk of legionellosis when receiving treatment with a TNF-α antagonist, compared with the relative risk in France overall, was estimated to be between 16.5 and 21.0. We also report a second episode of confirmed legionellosis following the reintroduction of infliximab therapy.

**Conclusions.** *L. pneumophila* pneumonia is a potentially severe but curable infection that might complicate anti–TNF-α therapy. In patients receiving anti–TNF-α who develop pneumonia, legionellosis should be systematically investigated, and first-line antibiotic therapy should be efficient against *L. pneumophila*.

TNF-α has been shown to play an important role in the pathogenesis of several chronic inflammatory diseases [1–3], and TNF-α antagonists are increasingly used to treat such conditions. TNF-α also plays an important role in host resistance against infectious agents, especially those multiplying intracellularly [4]. This proinflammatory cytokine induces differentiation of monocytes into macrophages, essential in the induction of granuloma, and is important for maintaining the integrity of granuloma [5, 6]. Thus, treatment with TNF-α antagonists is associated with an increased risk of infection, particularly that caused by intracellular microorganisms [7]. Indeed, previous studies have reported infections caused by *Mycobacterium tuberculosis* [8]—and, less frequently, *Listeria monocytogenes* [9],...
Legionellosis often presents as pneumonia and is mainly caused by *Legionella pneumophila* serogroup 1, a ubiquitous, opportunistic, gram-negative intracellular pathogen. To date, to our knowledge, only 4 cases of *L. pneumophila* infection in patients treated with TNF-α antagonists have been reported in the literature, all of which occurred in patients treated with infliximab [14–17].

We report here the first results of the French registry of infections complicating TNF-α antagonist therapy, the occurrence of 10 cases of pneumonia due to *L. pneumophila*, and the increased risk of this infection in patients treated with TNF-α antagonists.

**METHODS**

The French Recherche Axée sur la Tolérance des Biothérapies (RATIO) registry is designed by a multidisciplinary group to collect data on opportunistic and severe bacterial infections in patients treated with TNF-α antagonists. Three TNF-α antagonists are currently available: infliximab for the treatment of Crohn disease, ankylosing spondylitis, and rheumatoid arthritis; etanercept for the treatment of rheumatoid arthritis, including juvenile rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis; and adalimumab for the treatment of rheumatoid arthritis.

A total of 486 medical units in metropolitan France, including 124 internal medicine departments, 72 gastroenterology departments, 67 rheumatology departments, 50 pediatrics departments, 48 dermatology departments, 48 chest medicine departments, 32 hemato-oncology departments, 25 intensive care units, and 20 infectious diseases departments from tertiary care centers and general hospitals participate in the RATIO registry. Beginning on 1 February 2004, clinicians in participating centers were asked to prospectively report to the RATIO registry each case of opportunistic and severe bacterial infection in patients who were currently receiving treatment or who had been treated at any time with a TNF-α antagonist. Clinicians had to complete a standardized case report form that was specific to each type of infection (e.g., legionellosis). To encourage this reporting, clinicians reporting such cases to the registry are not required to report cases to national health authorities via the pharmaco-vigilance regional centers, which is a procedure that is mandatory in France (the reporting instead being performed by the RATIO registry). In addition, all cases reported to the pharmaco-vigilance regional centers are transmitted to the RATIO registry.

In addition, 4 times per year, clinicians involved in the RATIO registry receive a reminder to encourage them to report new cases. All patients with legionellosis were included in the registry if they had received a validated diagnosis of legionellosis by 2 qualified infectious disease physicians (O.L. and D.S.-C.) on the basis of the standardized case report form, the hospitalization summary, and the microbiological and radiological results. The patients described here all had confirmed cases according to a proposed case definition from the US Council of State and Territorial Epidemiologists [18], with the exception of 1 case of *L. pneumophila* serotype 6 that was considered to be suspect.

We calculated reported rates of legionellosis among patients treated with TNF-α antagonists (the number of reported cases divided by the number of treated patients). The numerator was the number of cases of *L. pneumophila* infection reported to the RATIO registry. The denominator was estimated from unpublished data provided by the Health National Authority, the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), based on the number of therapeutic units sold, mean dosage, and treatment duration.

The annual rate of legionellosis in France was provided by the French national public health surveillance system (Institut de Veille Sanitaire), which has surveyed legionellosis since 1987 (with a mandatory clinician- and biologist-based notification) [19]. Thus, we calculated the relative risk for patients in whom *L. pneumophila* infection developed while they were being treated with a TNF-α antagonist, compared with that in France overall. Both rates are drawn from population data and not from a sample. There is no random variation because of sampling. Statistical confidence intervals relying on variable distribution are, therefore, meaningless. Instead, we provide a range corresponding to the 2 boundaries of the data provided by the AFSSAPS.

**RESULTS**

Description of 10 consecutive cases of *L. pneumophila pneumonia*. During the period from 1 February 2004 through 31 January 2005, 10 consecutive cases of confirmed *L. pneumophila* infection associated with TNF-α antagonist treatment in adult patients were reported to the RATIO registry (table 1). The median age of the patients was 51 years (range, 40–69 years); 5 patients were male. Patients were treated with TNF-α antagonists for rheumatoid arthritis in 8 cases (including 1 case of juvenile onset rheumatoid arthritis), severe cutaneous psoriasis in 1 case, and pyoderma gangrenosum in 1 case. Six patients received adalimumab, 2 patients received etanercept (1 patient had previously received infliximab), and 2 patients received infliximab. All patients were being treated with a TNF-α antagonist at the onset of infection, and the median duration of treatment when the infection occurred was 38.5 weeks (range, 3–73 weeks).

Eight patients were receiving concomitant treatment with corticosteroids, with daily doses not exceeding 15 mg of pred-
<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of diagnosis</th>
<th>Age, years</th>
<th>Sex</th>
<th>Anti TNF-α drug regimen</th>
<th>Treatment duration</th>
<th>Indication for use (disease duration)</th>
<th>Concomitant immunosuppressive drugs</th>
<th>Comorbidity</th>
<th>Clinical and radiological features</th>
<th>Community-acquired infection?</th>
<th>Diagnosis (serogroup)</th>
<th>Antibiotic therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 Feb 2004</td>
<td>43</td>
<td>M</td>
<td>ALMB (two 40-mg doses per month)</td>
<td>71 weeks</td>
<td>RA</td>
<td>MTX, prednisone</td>
<td>Diabetes mellitus</td>
<td>BL pneumonia, vomiting</td>
<td>...</td>
<td>LPAg positive (LP1)</td>
<td>FLQ</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>22 Jun 2004</td>
<td>55</td>
<td>F</td>
<td>ALMB (40 mg per month)</td>
<td>26 weeks</td>
<td>RA (30 years)</td>
<td>MTX (7.5 mg per week), prednisone (8 mg per day)</td>
<td>None</td>
<td>UL pneumonia</td>
<td>Yes</td>
<td>LPAg positive (LP1)</td>
<td>Macrolide, rifampicin</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>19 Jul 2004</td>
<td>67</td>
<td>M</td>
<td>Etanercept (two 25-mg doses per week)</td>
<td>16 weeks</td>
<td>RA (3.5 years)</td>
<td>MTX (12.5 mg/week), prednisone (10 mg per day)</td>
<td>Tobacco-related COPD</td>
<td>Ventilator-assisted UL multibacterial pneumonia, ARDS, acute renal failure (hemodialysis)</td>
<td>Yes</td>
<td>Isolate from culture of BAL; LPAg positive (LP1)</td>
<td>Rifampicin, FLQ</td>
<td>Admitted to ICU, recovered</td>
</tr>
<tr>
<td>4</td>
<td>6 Aug 2004</td>
<td>46</td>
<td>F</td>
<td>IFMB (5 mg per kg of body weight by infusion)</td>
<td>73 weeks</td>
<td>Psoriasis (45 years)</td>
<td>Prednisone (10 mg per day), prednisone (7.5 mg per day)</td>
<td>Diabetic mellitus, tobacco-related COPD</td>
<td>BL lower lobes pneumonia, small pleural effusion, ARDS, nausea</td>
<td>Yes</td>
<td>LPAg positive (LP1)</td>
<td>Macrolide, rifampicin</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>25 Aug 2004</td>
<td>58</td>
<td>M</td>
<td>IFMB (5 mg per kg of body weight by infusion)</td>
<td>3 weeks</td>
<td>Psoriasis (45 years)</td>
<td>Sulfasalazine (2 g per day), betamethasone (2 mg per day)</td>
<td>Tobacco-related COPD</td>
<td>No</td>
<td>Community-acquired LPAg positive, PCR-positive sputum samples (LP1)</td>
<td>Macrolide, FLQ</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>25 Aug 2004</td>
<td>40</td>
<td>M</td>
<td>ALMB (two 40-mg doses per month)</td>
<td>34 weeks</td>
<td>RA (4 years)</td>
<td>Prednisone (10 mg per day), prednisone (5 mg per day)</td>
<td>Diabetic mellitus, tobacco-related COPD</td>
<td>Community-acquired UL upper lobe pneumonia, small pleural effusion</td>
<td>Yes</td>
<td>LPAg positive (LP1)</td>
<td>Rifampicin, FLQ</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>30 Sep 2004</td>
<td>45</td>
<td>F</td>
<td>ALMB (two 40-mg doses per month)</td>
<td>36 weeks</td>
<td>RA with juvenile onset (13 years)</td>
<td>MTX (15 mg per week), prednisone (5 mg per day)</td>
<td>Diabetic mellitus, tobacco-related COPD</td>
<td>任意性的肺炎,上気道炎,視覚障害</td>
<td>Yes</td>
<td>LPAg positive (LP1)</td>
<td>Macrolide then FLQ</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>1 Oct 2004</td>
<td>66</td>
<td>F</td>
<td>ALMB (two 40-mg doses per month)</td>
<td>45 weeks</td>
<td>RA (10 years)</td>
<td>MTX (15 mg per day)</td>
<td>Prednisone (5 mg per day)</td>
<td>Community-acquired LPAg positive, PCR-negative (LP6)</td>
<td>Yes</td>
<td>LPAg negative, seroconversion (LP6)</td>
<td>FLQ, ceftriaxone</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>22 Oct 2004</td>
<td>47</td>
<td>M</td>
<td>ALMB (two 40-mg doses per month)</td>
<td>50 weeks</td>
<td>RA (3 years)</td>
<td>Prednisone (10 mg per week)</td>
<td>任意性的肺炎,上気道炎,視覚障害</td>
<td>任意性的肺炎,上気道炎,視覚障害</td>
<td>Yes</td>
<td>LPAg positive (LP1)</td>
<td>Rifampicin, FLQ</td>
<td>Admitted to ICU, recovered</td>
</tr>
<tr>
<td>10</td>
<td>17 Nov 2004</td>
<td>69</td>
<td>F</td>
<td>Etanercept (two 25-mg doses per week); IFMB (3 mg per kg of body weight by infusion)</td>
<td>45 weeks</td>
<td>RA (10 years)</td>
<td>MTX (7.5 mg per week), prednisone (5 mg per day)</td>
<td>任意性的肺炎,上気道炎,視覚障害</td>
<td>任意性的肺炎,上気道炎,視覚障害</td>
<td>任意性的肺炎,上気道炎,視覚障害</td>
<td>Yes</td>
<td>LPAg positive (LP1)</td>
<td>FLQ</td>
</tr>
<tr>
<td>11</td>
<td>13 Sept 2002</td>
<td>27</td>
<td>F</td>
<td>IFMB (250 mg dose by infusion)</td>
<td>1 week</td>
<td>CD (5 years)</td>
<td>Azathioprine 1000 mg per day, prednisone (15 mg per day)</td>
<td>任意性的肺炎,上気道炎</td>
<td>任意性的肺炎,上気道炎</td>
<td>任意性的肺炎,上気道炎</td>
<td>No</td>
<td>LPAg, positive (LP1)</td>
<td>Rifampicin, FLQ</td>
</tr>
</tbody>
</table>

**NOTE.** Patients 1–10 are consecutive adult patients with legionellosis complicating TNF-α antagonist therapy; patient 11 is an additional patient with a case of *Legionella pneumophila* pneumonia that occurred before the Recherche Axe´es sur la Tolérance des Biothérapies (RATIO) registry began. ALMB, Adalimumab; ARDS, acute respiratory distress syndrome; AS, ankylosing spondylitis; BAL, bronchoalveolar lavage fluid; BL, bilateral; CD, Crohn disease; COPD, chronic obstructive pulmonary disease; FLQ, fluoroquinolone; ICU, intensive care unit; IFMB, Infliximab; LP1, *L. pneumophila* serogroup 1; LP6, *L. pneumophila* serogroup 6; LPAg, *Legionella* urinary antigen; MTX, methotrexate; RA, rheumatoid arthritis; UL, unilateral.  

*The equivalent of 13 mg of prednisone per day.*  
*The patient received IFMB from April 2002 to January 2004.*
nisone or the equivalent. Of the 8 patients with rheumatoid arthritis, 6 received concomitant treatment with methotrexate (7.5–15.0 mg per week).

All patients presented with pneumonia of recent onset. The clinical and radiological pattern was usual for all patients, and no cases of cavitated pneumonia were reported.

The diagnosis was evidenced by the detection of Legionella antigen in the urine of 9 patients and by seroconversion in 1 patient (1:16 to 1:256). In 2 patients, L. pneumophila was also cultured from samples of bronchoalveolar lavage fluid, and in another patient, the L. pneumophila genome was detected in sputum samples. In 9 patients, L. pneumophila was serogroup 1; in 1 patient, it was serogroup 6.

All patients received antibiotic therapy for L. pneumophila, which mainly consisted of therapy with 2 of the following: fluoroquinolone, rifampicin, and macrolide, and the TNF-α antagonist treatment was immediately stopped. No patient died. Admission to an intensive care unit because of respiratory failure was reported for 3 patients.

These cases of L. pneumophila infection were not clustered with respect to time or place. All cases were community acquired. Only 1 case (occurring in patient 5) could be considered to be part of an outbreak. The other cases were sporadic.

We also report another case of specific interest (occurring in patient 11) that occurred before the RATIO registry began, in a 24-year-old woman with severe Crohn disease who was treated with prednisone (15 mg per day) and azathioprine for 4 years; this regimen was replaced by a 250-mg infusion of infliximab, with fair improvement. Eight days after the first infusion of infliximab, pneumonia developed. The patient was admitted to the intensive care unit. A urinary antigen test had results that were positive for L. pneumophila, and cultures of bronchoalveolar lavage fluid samples revealed L. pneumophila serogroup 1. The patient showed clinical recovery, and urinary antigen test results were negative for L. pneumophila 6 months later. Nine months after the first infusion, a flare of the Crohn disease justified a second infusion of infliximab. After 4 days, fever and cough developed, and urinary antigen test results were again positive for L. pneumophila, but cultures of the bronchoalveolar lavage fluid samples showed no growth. The patient received a second course of fluoroquinolone and rifampicin and recovered shortly thereafter.

Estimation of incidence and relative risk, compared with that in France overall. Approximately 1200 cases of legionellosis are reported each year to the French national public health surveillance system (Institut de Veille Sanitaire). The annual incidence rate of legionellosis in France in 2004 was 2 cases per 100,000 population [19].

From data provided by AFSSAPS, 24,000–30,000 patients were treated with 1 of the 3 TNF-α antagonists in France in 2004. In the RATIO registry, 10 cases of legionellosis were reported within 1 year. Therefore, the annual L. pneumophila infection rate among TNF-α-treated patients in France is 33–42 cases per 100,000 population. The relative risk of L. pneumophila infection for patients treated with TNF-α antagonists, compared with that for the overall population, was, thus, between 16.5 and 21.

We also carried out a mail survey of the rheumatology departments of all French teaching hospitals (tertiary care centers) and the other rheumatology departments involved in the RATIO registry: 69 (93.2%) of 74 answered (including all tertiary care centers and all but 5 of the RATIO rheumatology departments). We focused on rheumatology departments, because rheumatoid arthritis is the main indication for use of anti-TNF therapy. Only 1 case of legionellosis in a patient with rheumatoid arthritis not treated with anti-TNF therapy was reported during the period 2004–2005.

**DISCUSSION**

From this study, it seems likely that the risk of L. pneumophila pneumonia is increased in patients receiving TNF-α antagonists, with a relative risk of 16.5–21, compared with that in the overall population in France. As ever, incidence rates might be somewhat underestimated or overestimated because of an imprecise numerator or denominator. Concerning the numerator, passive surveillance data may underestimate the incidence of adverse events; thus, the annual rate of L. pneumophila infection in the RATIO registry might be lower than the true incidence rate [20, 21]. Reporting bias might exist, because physicians caring for patients receiving anti–TNF-α therapy may be more likely to report cases of legionellosis to a central registry or to the national public health surveillance system. The incidence of L. pneumophila infection in the population might be somewhat underreported, which would lower the relative risk of infection for TNF-α–treated patients. However, the reporting of legionellosis is mandatory in France, and the exhaustivity of the data, therefore, is good [19].

For the denominator of the legionellosis rate, we used data provided by the AFSSAPS. These data are derived from the number of therapeutic units sold, mean dosage, and treatment duration, and therefore, they are approximations. To validate these data, we used files from the French National Sickness Insurance Fund for Self-Employed Workers (Caisse Nationale du Régime Social des Indépendants [CNRSI]), which give the number of patients treated with etanercept among the 3 million CNRSI enrollees (i.e., 5% of the French population). Then, we derived the number of patients treated with etanercept in France. This number was similar to that provided by the AFSSAPS. Because prescriptions for infliximab and adalimumab were exclusively from hospitals at that time and, thus, were not
reimbursed by CNRSI, we do not have data for patients using these drugs.

However, regardless of imprecision, the annual *L. pneumophila* infection rate among patients treated with TNF-α antagonists was much higher than the annual rate in the French population overall. From RATIO registry data, we cannot definitely conclude that the increased risk of *L. pneumophila* infection is because of TNF-α antagonist therapy per se or because of the characteristics of patients requiring TNF-α antagonist therapy (e.g., receipt of concurrent immunosuppressive therapy and underlying disease). To take into account the potential effects of uncontrolled confounding variables, such as underlying disease severity, one should compare these rates with the *L. pneumophila* infection rate among patients with rheumatoid arthritis of similar severity but not treated with TNF-α antagonists; however, these data are not available (the Institut de Veille Sanitaire’s data collection form does not extract information on whether patients with *L. pneumophila* infection had an inflammatory disease that could be an indication for anti-TNF therapy and, if so, which immunosuppressive treatment the patient received). However, the mail survey among the French rheumatology centers prescribing anti-TNF therapy in metropolitan France revealed only 1 case of legionellosis in 2 years occurring in a patient with rheumatoid arthritis not treated by anti-TNF therapy (rheumatoid arthritis is the main indication for use of anti-TNF therapy). We cannot eliminate the possibility that use of associated steroids (in 8 patients) or methotrexate (in 6 patients) might have played a role in the infection. However, the dose of steroids was low (<15 mg of prednisone or equivalent per day in the 8 patients), and a low dosage of steroids is unlikely to predispose a patient to infection [22, 23], but whether this fact remains true for patients with long-term use is still debated. Nevertheless, in the literature, the relative risk or hazard ratio of legionellosis associated with use of corticosteroids is estimated to be approximately 1.6–8, even accounting for cumulative dosage or duration of corticosteroid therapy [24–26]. In addition, methotrexate use in rheumatoid arthritis has been shown not to be associated with increased risk of infection, compared with the risk of infection in the general population [24]. Thus, the use of corticosteroids and methotrexate might have played a role in the emergence of legionellosis in our cases, but it is unlikely to explain the entire risk.

Although this nationwide survey design has some limitations (especially the lack of an appropriate control group), it is probably the only way to address these very rare events. Other registries of biologics are cohort studies involving only a part of the focused population and, therefore, will not be able to demonstrate very rare events, and neither will randomized controlled trials [27]. These events are very rare but relevant in clinical practice (legionellosis is curable).

Furthermore, the hypothesis of an increased risk of *L. pneumophila* infection among patients treated with TNF-α antagonists is reinforced by the following considerations. First, in vitro data from mice demonstrate that TNF-α is critical for clearing macrophage infection with the bacterium. Indeed, the major protective immune response against infection with *L. pneumophila* involves both macrophages and T cell–mediated immunity [28]. The addition of TNF-α to macrophage cultures induced resistance of the macrophages to subsequent infection by *L. pneumophila*, and the addition of anti–TNF-α monoclonal antibody restored the susceptibility of the macrophages to the infection [29]. Second, corticosteroids and methotrexate have been used for a long time for inflammatory diseases, such as rheumatoid arthritis or Crohn disease, in a large number of patients, with no alerts about legionellosis in these patients. In the literature, *L. pneumophila* infection is rare among patients with rheumatoid arthritis [30] and Crohn disease [31] who are receiving treatment with agents other than TNF-α antagonists, and this is confirmed by our mail survey of rheumatology departments. Third, in patient 11, who was treated for 4 years with azathioprine, *L. pneumophila* pneumonia developed after the first infusion of infliximab; the patient recovered and experienced a second episode of *L. pneumophila* pneumonia with reintroduction of infliximab, which reinforces the causal role of the TNF-α antagonist in the *L. pneumophila* infection. For this patient, because *L. pneumophila* was not found in cultures during the second episode, we could not determine whether the infection was due to a new environmental contamination or to the intracellular persistence of the bacteria.

In conclusion, *L. pneumophila* pneumonia is a severe and potentially life-threatening—but curable—infected that might complicate TNF-α antagonist therapy. Cases of pneumonia during TNF-α antagonist therapy should be investigated for legionellosis, and antibiotic therapy against *L. pneumophila* infection should be promptly initiated. Our data indirectly confirm the role of TNF-α in *L. pneumophila* infection.

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Potential conflicts of interest. P.R. has received recent research funding from Schering Plough and Abbott. D.S.-C. has received recent research funding from Abbott, is a consultant for Roche and Glaxo Smith Kline, and has been a speaker at symposiums for Bristol-Myers Squibb, Roche,
and Schering Plough. O.L. is a member of the posaconazole speakers bureau for Schering Plough. All other authors: no conflicts.

References