Non-typhi *Salmonella* infection in patients with rheumatic diseases on TNF-alpha antagonist therapy


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Abstract

Objective

The morbidity and mortality of patients with rheumatic diseases has improved considerably following the use of biologic therapies. However, an increase in the frequency of bacterial infections has been observed in patients receiving these drugs. In the present study we aimed to establish the incidence and clinical manifestations of non-typhi Salmonella infection in a large cohort of patients with rheumatic diseases undergoing TNF-α antagonist therapy due to severe rheumatic diseases refractory to conventional therapies.

Methods

The rate of non-typhi *Salmonella* infection found in the Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER) was compared with that observed in a cohort of rheumatoid arthritis (RA) patients from the EMECAR (Morbidity and Clinical Expression of Rheumatoid Arthritis) Study, who were not treated with TNF-α antagonists. The rate found in the BIOBADASER registry was also compared with that available in a non-RA historic control cohort reported in a population from Huesca (Northern Spain).

Results

Seventeen cases of non-typhi Salmonella infection were observed in the series of patients exposed to anti-TNF-α therapies. The incidence rate of non-typhi Salmonella in BIOBADASER was 0.73 per 1000 patient-years (95% confidence interval [CI]: 0.45–1.17). The incidence rate in the EMECAR cohort was 0.44 per 1000 patient-years. The relative risk for non-typhi salmonellosis in RA patients exposed to TNF-α inhibitors compared to those not treated with biological therapies was 2.07 (95% CI: 0.27–15.73) (p=0.480) whereas the relative risk of non-typhi Salmonella infections in patients with rheumatic diseases undergoing TNF-α antagonist therapy compared with the non-RA Spanish control cohort was 0.63 (95% CI: 0.38–1.04) (p=0.07). Nine of the 17 patients with non-typhi salmonellosis presented a severe systemic infection.

Conclusion

Incidence of non-typhi Salmonella infection is not increased significantly in rheumatic patients undergoing anti-TNF-α therapy when compared with RA patients undergoing conventional DMARD therapy or with the general population. Nevertheless, at least 50% of patients on TNF-α have severe complications once they develop non-typhi Salmonella infection. This fact suggests that anti-TNF-α therapies may predispose to salmonella dissemination rather than to infection.

Key words

Non-typhi *Salmonella* infection, rheumatic disease, TNF-α antagonists.
Introduction
Although a relation between chronic inflammatory rheumatic diseases and infection has long been subject to debate, it is currently well established that patients with chronic inflammatory rheumatic diseases, in particular those with rheumatoid arthritis (RA), suffer more infections than the general population (1-3). A number of factors have been implicated in the increased susceptibility to infections in these patients. Apart from alterations in the immune system due to these chronic inflammatory diseases, the severity of the disease itself, the presence of comorbidities and the use of immunosuppressive drugs have been postulated to be of major relevance in the occurrence of infections in these patients.

Tumour necrosis factor (TNF-α) is a pivotal proinflammatory cytokine involved in systemic inflammation and infection (4). Clinical trials of the three currently licensed TNF-α antagonist agents (the chimeric anti-TNF-α monoclonal antibody infliximab, the fully human anti-TNF-α monoclonal antibody adalimumab, and the soluble TNF-α receptor fusion protein etanercept) proved to be effective in patients with chronic inflammatory rheumatic diseases refractory to conventional therapies (5-9).

TNF-antagonists have improved dramatically the outcome of inflammatory rheumatic diseases. The use of these drugs has been associated with a reduction in the mortality of patients with rheumatic diseases (10), largely due to a decrease in the incidence of cardiovascular complications that has been mediated by a number of mechanisms such as the improvement of insulin resistance (11) and endothelial dysfunction (12), the reduction of biomarkers or endothelial dysfunction (13), and the modulation of some mediators associated with the inflammatory response (14, 15).

However, the use of these biologic therapies has also been associated with an increase in the incidence of infections in these patients (16-18). TNF is essential for maintaining homeostasis against infection, especially against pathogens causing the formation of granulomas (16, 17). Due to this, tuberculosis, salmonellosis, and listeriosis, which are infections caused by intracellular bacteria that require TNF-activation for their elimination might be more common in patients undergoing TNF-α antagonist therapy. In line with the above, an increase in the incidence of tuberculosis has been documented since the introduction of TNF-α antagonist therapy in rheumatic diseases, in particular in RA (17,19). Cases of listeriosis and salmonellosis of varying severity have also been described (20-25). In this regard, we have recently reported an increased incidence of Listeria monocytogenes infection among patients undergoing TNF-α antagonist therapy (26). However, to the best of our knowledge, the actual incidence and relative risk of non-typhi Salmonella infection in patients with rheumatic diseases on treatment with TNF-α antagonists has not been reported. To address this issue, we have reviewed the data gathered on non-typhi salmonella infection in a large series of patients with rheumatic diseases enrolled in the Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER).

Patients and methods
The present study is based on the analysis of the clinical characteristics and outcome of all patients from the BIOBADASER prospective registry study who received TNF-α antagonist therapy and developed non-typhi salmonella infection.

A detailed description of the BIOBADASER registry has previously been reported (27) and is available at http://biobadaser.ser.es. Briefly, BIOBADASER was set up in February 2001 to study the long-term safety of biological therapies in rheumatic diseases.

BIOBADASER systematically and prospectively gathers the following information: 1) Data on the patient: gender, age of birth, diagnosis, date of diagnosis and comorbidity; 2) Type of treatment and dates for the onset and discontinuation of the biological therapy, as well as the reasons for that, and concomitant rheumatic disease treatments; and 3) Information on any relevant adverse events, regarding

Competing interests: none declared.
clinical diagnosis by using the terms in the MedDRA dictionary (Medical Dictionary for Regulatory Affairs), type, and outcome, as well as non-rheumatic treatments. The definition of serious adverse was based on the ICH E2E (International Conference on Harmonisation. Post approval safety management: Note for guidance on definitions and standards for expedited reporting. URL:www.emea.europa.eu/pdfs/human/ich/394503en.pdf)

Non-typhi salmonella gastroenteritis was defined if a patient presented with nausea, vomiting, diarrhea, abdominal pain and fever along with isolation of non-typhi Salmonella species from stool specimens of the patient or from samples of individuals involved in food-borne outbreaks. Extraintestinal non-typhi Salmonella infection was defined if non-typhi Salmonella species were isolated from blood samples or from other extraintestinal locations.

We studied all the cases diagnosed as having non-typhi Salmonella infections that were reported to BIOBADASER from the start date of the registry through December 15, 2006. When necessary, the physician that reported the adverse effect to BIOBADASER was contacted to obtain more information about the clinical condition of the patient.

The incidence rate of non-typhi Salmonella infection per 1000 patient-years of exposure to TNF-α antagonists was estimated with 95% confidence intervals (CI). The exposure time elapsed from the date of entry into the registry, considered as the date of first biologic therapy, until whatever date occurred first: Salmonella infection, exit date from the cohort (baseline visit) until whatever date occurred first: Salmonella infection (identical definition as in BIOBADASER), exit date from the cohort due to lack of follow-up, starting date of any biological therapy, or last visit.

To further establish whether the incidence of non-typhi Salmonella infection was increased in patients with rheumatic diseases undergoing TNF-α antagonist therapy, we also compared the incidence found in BIOBADASER with that reported in a study that included patients from the general population of Huesca (Northern Spain) (28).

Results

Between February 2001 and December 2006, there were 7,835 patients registered in BIOBADASER (23,427 patient-years). Of these, 4,842 patients were diagnosed with RA (15,364 patient-years), 1,525 patients with a diagnosis of spondyloarthopathies (3,953 patients-years), including psoriatic arthritis (PsA), and 1,468 patients with other rheumatic diseases. Over half of the patients were women (n=5,010; 64%), with an average age at treatment onset of 50 ± 15 years (mean ± SD), and an average disease duration of 10±8 years. The mean time of treatment with biologics in the BIOBADASER cohort was 2.6±1.8 years.

Between February 2001 and December 2006, 17 cases of non-typhi Salmonella infection were reported to BIOBADASER. As shown in Table 1, there were cases with the three different TNF-antagonist drugs commercially available. Non-typhi Salmonella infection was often limited to diarrhea yielding enterocolitis similar to that caused by other bacterial enteric pathogens. However, 7 patients had bacteremia; in 6 of them it was associated with acute gastroenteritis. Two patients suffered endocarditis and another patient suffered a spondylodiscitis with vertebral abscess (Table 1). Salmonella enteritidis was isolated in 9 cases, Salmonella typhimurium in 2, and in the remaining 6 cases the Salmonella serotype was unknown. When the infection occurred, 9 (53%) of the 17 patients

In the EMECAR cohort (2,270 patient-years of follow-up with no exposure to biological therapy), only 1 patient presented non-typhi Salmonella infection, with an incidence rate of 0.44 per 1000 patient-years (95% CI: 0.06–3.13). The relative risk (incidence rate ratio) of salmonellosis for RA undergoing to TNF-α antagonist therapy compared to RA non-exposed to biologic therapies was 2.07 (95% CI: 0.27–15.73) per 1000 patient-years (p=0.480). The incidence rate of non-typhi Salmonella infection was reported in a study performed in the general population of Huesca (Northern Spain) as 1.16 cases per 1000 inhabitant/years (28). Compared with this series of unselected Spaniards, the risk of non-typhi Salmonella infection in patients with rheumatic diseases undergoing TNF-α antagonist therapy was 0.63 (95% CI: 0.38–1.04) (p=0.07).

Table I shows the main clinical characteristics of patients with non-typhi Salmonella infection from the BIOBADASER registry. As shown in the table, there were cases with the three different TNF-antagonist drugs commercially available. Non-typhi Salmonella infection was often limited to diarrhea yielding enterocolitis similar to that caused by other bacterial enteric pathogens. However, 7 patients had bacteremia; in 6 of them it was associated with acute gastroenteritis. Two patients suffered endocarditis and another patient suffered a spondylodiscitis with vertebral abscess (Table 1). Salmonella enteritidis was isolated in 9 cases, Salmonella typhimurium in 2, and in the remaining 6 cases the Salmonella serotype was unknown. When the infection occurred, 9 (53%) of the 17 patients
were taking prednisone (mean dose 6.17 mg/day) and 8 (47%) methotrexate (mean dose 13.3 mg/week).

Comorbid conditions such as diabetes mellitus or hypertension were frequently observed (Table I). All the patients required hospital admission due to the infection, with a range of stay in hospital between 5 and 60 days. All of them received broad-spectrum antibiotic treatment (most cases were treated with ciprofloxacin). Besides bed rest, fluid and electrolyte replacement was given to the patients presenting with acute gastroenteritis. Two patients underwent surgery; one for septic aortic pseudoaneurysm (patient no. 3) and another for a paravertebral abscess (patient no. 6). Apart from 1 patient with type 2 diabetes and bacteremia who died due to multiorgan failure, all of the patients recovered without sequelae (Table I).

### Discussion

The generalised use of TNF-α inhibitors has been associated with an increase in the incidence of severe infections (29). In the present study we assessed, for first time, the incidence of non-typhi Salmonella infection in a large cohort of patients with rheumatic diseases undergoing treatment with TNF-α inhibitors. We also compared the incidence rate of non-typhi Salmonella infection in these patients with that observed in a cohort of RA patients not exposed to TNF-α inhibitors and with that found in a Spanish population. According to our results, we cannot say that the incidence of non-typhi Salmonella infection is increased in rheumatic patients undergoing anti-TNF-α therapy when compared with RA patients on conventional DMARD therapy or with the general population. However, the number of severe complications of non-typhi Salmonella infection that appeared in patients on TNF-α therapies called our attention, and this fact suggests that anti-TNF-α therapies may predispose to Salmonella dissemination. These observations are in line with several reports that described an increased risk of severe complications in patients receiving these biologic therapies (24, 25).

In assessing the British National Registry on biological therapies in rheumatic diseases, Dixon et al. highlighted an increase in the frequency of intracellular bacterial infections (16). Gastroenteritis and enterocolitis are the most frequent manifestations of non-typhi Salmonella infection. Approximately 1–4% of the general population with gastroenteritis has been associated with an increase in metastatic infection (30). Of note, 9 of

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Diagn.</th>
<th>TNF-α blockers</th>
<th>Doses</th>
<th>Clinical manifestations</th>
<th>Subtype</th>
<th>Sepsis</th>
<th>Prednisone mg/day</th>
<th>Methotrexate mg/week</th>
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<tr>
<td>1</td>
<td>67</td>
<td>F</td>
<td>AS</td>
<td>IFX</td>
<td>5 mg/kg/ 8 weeks</td>
<td>AG + Sepsis</td>
<td>S. typhimurium</td>
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<tr>
<td>2</td>
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<td>RA</td>
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<td>3 mg/kg/ 8 weeks</td>
<td>AG + Sepsis</td>
<td>S. enteritidis</td>
<td>Yes</td>
<td>–</td>
<td>15</td>
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<td>3</td>
<td>76</td>
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<td>RA</td>
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<td>3 mg/kg/ 8 weeks</td>
<td>Endocarditis and aortic pseudoaneurysm</td>
<td>S. enteritidis</td>
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<td>–</td>
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<tr>
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<td>M</td>
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<td>3 mg/kg/ 8 weeks</td>
<td>Endocarditis</td>
<td>Salmonella sp</td>
<td>–</td>
<td>12</td>
<td>15</td>
<td>–</td>
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<tr>
<td>5</td>
<td>72</td>
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<td>RA</td>
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<td>3 mg/kg/ 8 weeks</td>
<td>AG</td>
<td>Salmonella sp</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
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<td>Death</td>
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<td>6</td>
<td>66</td>
<td>F</td>
<td>RA</td>
<td>IFX</td>
<td>3 mg/kg/ 8 weeks</td>
<td>Spondylodiscitis with vertebral abscess</td>
<td>Salmonella sp</td>
<td>Yes</td>
<td>5</td>
<td>22.5</td>
<td>Hypertension, Depression</td>
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</tr>
<tr>
<td>7</td>
<td>62</td>
<td>M</td>
<td>RA</td>
<td>ADA</td>
<td>40 mg/14 days</td>
<td>AG</td>
<td>S. enteritidis</td>
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<td>Salmonella sp</td>
<td>–</td>
<td>–</td>
<td>7.5</td>
<td>Hypertension, Anticoagulation for atrial fibrillation</td>
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<td>AG</td>
<td>S. enteritidis</td>
<td>–</td>
<td>–</td>
<td>10</td>
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<tr>
<td>12</td>
<td>46</td>
<td>F</td>
<td>RA</td>
<td>IFX</td>
<td>3 mg/kg/ 8 weeks</td>
<td>Salmonella sp</td>
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<td>7.5</td>
<td>7.5</td>
<td>–</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>F</td>
<td>RA</td>
<td>ADA</td>
<td>40 mg/14 days</td>
<td>S. enteritidis</td>
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<td>–</td>
<td>Hypertension</td>
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<tr>
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<td>62</td>
<td>F</td>
<td>RA</td>
<td>IFX</td>
<td>3 mg/Kg/ 8 weeks</td>
<td>S. enteritidis</td>
<td>–</td>
<td>5</td>
<td>12.5</td>
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<td>ETN</td>
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<td>S. enteritidis</td>
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<td>–</td>
<td>–</td>
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<td>Salmonella sp</td>
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<td>–</td>
<td>–</td>
<td>–</td>
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<td>M</td>
<td>USpA</td>
<td>IFX</td>
<td>5 mg/kg/ 8 weeks</td>
<td>S. typhimurium</td>
<td>–</td>
<td>5</td>
<td>–</td>
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the 17 patients from the BIOBADASER registry receiving anti-TNF-α therapy experienced a bacteremia. This high proportion of patients with non-typhi Salmonella infection presenting with severe complications supports a potential role for the anti-TNF-α therapy as responsible for the development of disseminated Salmonella infection. Salmonella reaches the intestinal epithelial barrier and, after an active endocytic process, invades the macrophages. This ability to invade and proliferate within the macrophages is essential for the dissemination of the disease. A decrease in the dendritic cell receptor-toll-like receptor 4 (TLR4) has been observed in RA patients on TNF-α therapy who developed sepsis due to Salmonella (25). TLR4 is responsible for the lipopolysaccharide recognition of Salmonella. However, in patients under TNF-α antagonist therapy the ability to neutralise these microorganisms in the intestinal wall is reduced. Furthermore, both macrophage activation and production of several of cytokines, such as IFN-gamma, IL-12 and TNF-α, has been observed in mice with Salmonella infection once this bacteria is found in the intestinal wall. As a consequence of the TNF-α blockade, this physiological response may be impaired. Finally, elimination of the bacteria requires the recruitment of CD4 T lymphocytes and the production of specific antibodies to Salmonella by the B cells (31, 32). However, considering the mechanism of action of TNF-α antagonists, it is not surprising to see an alteration in this line of defense leading to a systemic Salmonella infection. Additionally, in experimental studies, conducted in most cases in mice in which the TLR4 response was altered or the genes that codify IFN-gamma, IL12 or TNF-α were manipulated, an increased susceptibility to Salmonella infection was also found (32-42). In keeping with that, immunocompromised individuals with alterations in the cellular immunity, such as HIV patients, also have an increased risk of systemic Salmonella infection. Taking into account all these consideration, the possibility of an increased risk of disseminated Salmonella infection in patients undergoing TNF-α antagonist therapy is plausible. On the other hand, some serotypes such as Salmonella enteritidis or typhimurium have enhanced hematogenous dissemination, since they are able to survive inside macrophages better than other serotypes. Furthermore, Salmonella enteritidis and typhimurium have genes that codify surfactant proteins, which allow for enhanced binding virulence and avidity with intestinal epithelial cells (43).

In the present study there are several limitations that deserve to be discussed. First of all, we do not know whether the incidence of non-typhi salmonella infection is different in the non-rheumatic population of Northern Spain from that of the rest of Spain. Also, it is not clear whether the incidence of non-typhi salmonella infection in patients with RA may be directly compared to a referent non-RA population. Additional comparisons with patients suffering from conditions associated with immunosuppression should be also considered. However, we do not have available data on non-typhi salmonella infection in these specific individual groups.

In conclusion, the use of TNF-α antagonists does not seem to be associated with an increased risk of Salmonella infection. However, it is possible that these drugs may predispose to severe disseminated Salmonella infection.

### BIOBADASER and EMECAR study groups

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