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.

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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

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 a serious adverse was based on the ICH E2E (*International Conference on Harmonisation. Post approval safety data 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 S*almonella* 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 registry due to lack of follow-up, or December 15, 2006.

The rate of non-typhi *Salmonella* infection in patients exposed to TNF-α antagonists was compared to the rate in RA patients non-exposed to these. The control population was that of the EMECAR cohort (Study of the comorbidity and clinical expression of RA in Spain), a historic RA control from the period (1999-2005) constituted by patients not receiving biologic therapies (10). Patients enrolled in the EMECAR cohort were patients with RA selected by random sampling from 34 Rheumatology Services. It included 789 patients, at any stage of the illness, representative of the entire spectrum of clinical condition and severity. EMECAR collected prospectively for 5 years data on clinical expression of RA and on co-morbidities. For the purpose of comparison with BIOBADASER, we considered as observation lag the time elapsed from the date of entry into 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 individuals 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). It included 4,842 patients diagnosed with RA (15,364 patient-years), 1,525 patients with a diagnosis of spondyloarthropathies (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 (Detailed description in Table I). In patients exposed to TNF-α antagonists the incidence rate of non-typhi *Salmonella* infection was 0.73 per 1000 patient-years (95% CI: 0.45–1.17). The incidence rate did not vary substantially between patients with RA (0.9; 95% CI: 0.5–1.5) or those with spondyloarthropathies (0.7; 95% CI: 0.2–2.3). 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).

The relative risk in the series of patients with RA on biologic therapies included in the BIOBADASER registry compared to that found in the control population from Northern Spain was 0.78 (95%CI: 0.46–1.34) (p=0.36). The relative risk in the series of patients with spondylorartopathies on biologic therapies enrolled in the BIOBADASER registry compared to that found in the control population from Northern Spain was 0.65 (95%CI: 0.21–2.03) (p=0.45).

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 I). *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 multiorganic 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 caused by *Salmonella* develops bacteremia, and 10% develops a localised metastatic infection (30). Of note, 9 of

Table I. Clinical manifestations and prognosis in 17 patients with chronic inflammatory rheumatic diseases undergoing TNF-α blocker therapy who had non-typhi *Salmonella* infection.

Patients	Age	Sex	Diagn.	TNF-α blockers	Doses	Clinical manifestations	Subtype	Sepsis	Prednisone mg/day	Methotrexate Mg/week	Comorbidity	Prognosis
1	67	F	AS	IFX	5 mg/kg/ 8 weeks	AG + Sepsis	*S. typhimurium*	Yes	5	–	Hypertension	Good
2	57	F	RA	IFX	3 mg/kg/ 8 weeks	AG + Sepsis	*S. enteritidis*	Yes	–	15	–	Good
3	76	F	RA	IFX	3 mg/kg/ 8 weeks	Endocarditis and aortic pseudoaneurysm	*S. enteritidis*	Yes	–	–	Hepatitis B	Good
4	54	M	RA	IFX	3 mg/kg/ 8 weeks	Endocarditis	*Salmonella* sp	–	12	15	–	
5	72	F	RA	IFX	3 mg/kg/ 8 weeks	AG	*Salmonella* sp	Yes	–	–	Type 2 diabetes	Death
6	66	F	RA	IFX	3 mg/kg/ 8 weeks	Spondylodiscitis with vertebral abscess	*Salmonella* sp	Yes	5	22.5	Hypertension, Depression	Good
7	62	M	RA	ADA	40 mg/14 days	AG	*S. enteritidis*	Yes	5	–	Diabetes II, HTA, Depression	Good
8	64	F	RA	ETN	50 mg/kg/ day	AG	*S. enteritidis*	Yes	5	–	Hypertension	Good
9	41	M	AS	IFX	5 mg/kg/ 8 weeks		*S. enteritidis*	Yes	6	15	–	Good
10	78	F	RA	IFX	3 mg/kg/ 8 weeks	AG	*Salmonella* sp	–	–	7.5	Hypertension, Anticoagulation for atrial fibrillation	Good
11	25	F	RA	IFX	3 mg/kg/ 8 weeks	AG	*S. enteritidis*	–	–	10	–	Good
12	46	F	RA	IFX	3 mg/kg/ 8 weeks	AG	*Salmonella* sp	–	7.5	7.5	–	Good
13	67	F	RA	ADA	40 mg/14 days	AG	*S. enteritidis*	–	–	–	Hypertension	Good
14	62	F	RA	IFX	3 mg/Kg/ 8 weeks	AG	*S. enteritidis*	–	5	12.5	Type 2 diabetes	Good
15	75	F	RA	ETN	50 mg/ week	AG	*S. enteritidis*	–	–	–	–	Good
16	74	F	RA	IFX	3 mg/kg/ 8 weeks	AG	*Salmonella* sp	–	–	–	–	Good
17	58	M	USpA	IFX	5 mg/kg/ 8 weeks	AG	*S. typhimurium*	–	5	–	–	Good

F: female; M: male; RA: rheumatoid arthritis; AS: ankylosing spondylitis; USpA: undifferentiated spondyloarthropathy; IFX: infliximab; ADA: adalimumab; ETN: etanercept; AG: acute gastroenteritis.

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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