# *Listeria monocytogenes* infection in patients with rheumatic diseases on TNF-alpha antagonist therapy: the Spanish Study Group experience

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## Abstract

### Objective

*The prognosis of patients with rheumatic diseases has improved considerably following the use of biological therapies. However, an increase in the frequency of bacterial infections has been observed in patients receiving these therapies. In the present study we aimed to assess the frequency of Listeria monocytogenes infection in a large series of patients with rheumatic diseases on treatment with tumor necrosis factor (TNF)-alpha blockers because of active disease refractory to conventional therapy, included in the Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER) of the Spanish Society for Rheumatology.*

### Methods

*Assessment of the incidence of infection due to* Listeria monocytogenes *in the Spanish Registry Study (BIOBADASER) per 1000 patient-years and 95% confidence intervals (95% CIs) was performed. Rate from this registry was compared with that from the general population in Europe and with the rate found in patients with rheumatoid arthritis (RA) from the Spanish Rheumatoid Arthritis Registry Cohort Study (EMECAR) that assessed morbidity and clinical expression of RA and included patients treated in most cases with conventional therapies.*

### Results

*Six patients on treatment with TNF-alpha antagonists were diagnosed as having* Listeria monocytogenes *infection. The incidence of this infection per 1000 patient-year (95% CI) was 0.256 (95% CI: 0.115-0.570). This was greater than the incidence observed in the general population from Europe and in the EMECAR study.*

### Conclusion

*Despite the benefits associated to the use of TNF-alpha antagonists, a high level of surveillance is required to reduce the potential risk of infections related to the use of these drugs.*

**Key words**

*Listeria monocytogenes*, rheumatic disease, TNF-alpha blockers.

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## Introduction

Tumor necrosis factor (TNF) is a cytokine mainly secreted by macrophages. It is involved in systemic inflammation and infection (1). The use of anti-TNF-alpha therapies has dramatically improved the outcome of inflammatory rheumatic diseases (2). Clinical trials of the three currently licensed TNF-alpha blocker agents (the chimeric anti-TNF-alpha monoclonal antibody infliximab, the fully human anti-TNF-alpha monoclonal antibody adalimumab and the soluble TNF-alpha receptor fusion protein etanercept) have proved to be effective in patients with chronic inflammatory diseases refractory to conventional therapies (2-5). However, the use of TNF-blockers has also been associated with an increase in the incidence of infections in these patients (6).

Although the occurrence of tuberculosis following TNF-alpha antagonist therapy has extensively been reported (7, 8), little is known about the incidence of other opportunistic infections in patients on treatment with these drugs. Due to this, in the present study we aimed to assess the incidence of *Listeria monocytogenes* infection, a prototype of opportunistic infection, in a large series of patients with rheumatic diseases on treatment with TNF-alpha antagonists due to severe disease refractory to conventional therapy.

To address this issue we have reviewed the data gathered on *Listeria monocytogenes* infection in a large series of patients with rheumatic diseases enrolled in a national longitudinal observational registry study on the effect and outcome of biological therapies.

## Patients and methods

The present study is based on the analysis of the clinical characteristics and outcome of all patients from the BIOBADASER (Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases) prospective registry study who received TNF-alpha blocker therapy and developed *Listeria monocytogenes* infection.

A detailed description of the BIOBADASER registry has previously been reported (9) and is available at http://biobadaser.ser.es/. Briefly, BIOBADASER was set up in February 2000 to study the side effects of biological therapies in rheumatic diseases. All Spanish hospitals with rheumatology Units were invited to take part in the project. The Spanish Society for Rheumatology has been providing its members with information on all the incoming data. Patients included in BIOBADASER have been diagnosed as having different rheumatic diseases, most of them with rheumatoid arthritis or seronegative spondyloarthropathies, and have been treated with biological therapies.

BIOBADASER systematically and prospectively gathers the following information: 1) Characteristics of the center, department or rheumatology unit; 2) Data on the patient: gender, age of birth, diagnosis, date of diagnosis and comorbidity; 3) Type of treatment and dates for onset and discontinuation of the biological therapy, as well as the reasons for that. Information on side effects is also included. In this case the clinical diagnosis of the adverse side effect is registered: type, prognosis and concomitant treatment. An important adverse side effect is defined as an effect that causes the patient's death, puts his/her life in danger, requires prolonged hospitalization or leads the patient to significant or persistent disability. Other serious adverse effects are those that require relevant clinical intervention. Data on the adverse effects are gathered following the recommendations of the MedDRA dictionary (Medical Dictionary for Regulatory Affairs)

*Listeria monocytogenes* infection was considered to be present when this microorganism was isolated in a patient with a compatible specific clinical diagnosis.

### *Statistical analysis*

Listeriosis is rare within the general population in Europe for the purpose of the present study, the incidence of *Listeria monocytogenes* infection 1000 patients/year (95% confidence interval-CI) in this series of patients with rheumatic diseases on treatment with TNF-alpha antagonist therapies was calculated using the incidence of *Listeria monocytogenes* infection in the

**Table I.** Clinical characteristics and outcome of six patients with *Listeria monocytogenes* infection.

| Patient | Age/sex | TNF-alpha blocker | no. of doses | Disease diagnosis | Prednisone* (mg/day) | Methotrexate* (mg/week) | Type of Infection | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 63/F | Infliximab | 24 | PsA | 7.5 | 10 | meningitis/sepsis | Good |
| 2 | 57/M | Infliximab | 6 | PsA | 10 | 15 | meningitis | Good |
| 3 | 69/F | Adalimumab | 3 | RA | No | No | septicemia | Good |
| 4 | 63/F | Infliximab | 21 | RA | 5 | 12.5 | meningitis | Good |
| 5 | 56/F | Infliximab | 7 | RA | 10 | 10 | sepsis/peritonitis | Good |
| 6 | 36/F | Infliximab | 21 | RA | 10 | 10 | endophthalmitis | Bad |

M: Male. F: female; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis.
*At the time of diagnosis of *Listeria monocytogenes* infection.

general population from Europe as a reference (10). Also, incidence rate was compared with the rate found in patients with rheumatoid arthritis (RA) not treated with TNF-alpha blockers from the Spanish Rheumatoid Arthritis Registry Cohort Study (EMECAR) that assessed morbidity and clinical expression of RA and included patients treated in most cases with conventional therapies but not with TNF-alpha blockers (11).

**Table II.** Comorbid conditions in six patients with rheumatic diseases that developed *Listeria monocytogenes* infection following TNF-alpha blocker therapy.

| Patient | |
|---|---|
| 1 | Collagenous colitis, ischemic cardiopathy and hypertension |
| 2 | Inactive hepatitis and hypertensive cardiopathy |
| 3 | None |
| 4 | Amyloidois secondary to RA with renal insufficiency |
| 5 | Chronic hepatitis of unknown etiology, pulmonary fibrosis due to RA<br>Type 2 diabetes and ischemic cardiopathy |
| 6 | None |

## Results

Between May 2001 and July 2007, the total patient-years of follow-up receiving TNF-alpha blocker therapy for several different rheumatic diseases were 23,427. Among them, 15,364 patients/year had been diagnosed with RA and 2,769 patients/year with psoriatic arthritis (PsA). Six of them (4 diagnosed with RA and 2 with PsA) developed *Listeria monocytogenes* infection. The main features of these 6 patients are summarized in Table I. The mean age of patients with this infection was 57.3 years (range 36 to 69 years). Five of them were women. Five patients had received infliximab and 1 adalimumab therapy. In BIOBADASER there are registered 5207 treatments with infliximab, 3422 treatments with etanercept, and 1786 with adalimumab. Besides TNF-alpha blockers, corticosteroids and methotrexate had been administered to 5 of the 6 patients. The clinical diagnosis of these patients is also shown in Table I.

Four presented serious comorbid, concomitant, diseases (Table II).

Apart from the patient who suffered an isolated endophthalmitis that evolved to blindness, the remaining 5 patients had a good outcome as full recovery without physical sequelae was achieved following antibiotic therapy based on microbiological data and antibiogram results (4 patients received ampicillin and 2 erythromycin) (Table I).

The incidence rate of listeriosis per 1000 patient-year of follow-up for the total number of patients with rheumatic diseases undergoing treatment with TNF-alpha antagonist therapy was 0.256 (95% CI: 0.115-0.570). The incidence rate for RA was 0.260 (95% CI: 0.098-0.694) per 1000 patient-year. The incidence rate for patients with PsA on treatment with TNF-alpha blockers was 0.722 (95% CI: 0.181-2.888) per 1000 patient-year. Compared to the incidence rate in the general population from Europe (0.0034 per 1000 person- years) (10), the incidence rate ratio of *Listeria monocytogenes* infection for patients on treatment with TNF-alpha blockers due to different rheumatic disease was 75.3 (95% CI = 33.8-168.0), $p<0.001$.

Interestingly, in contrast to the increased incidence of *Listeria monocytogenes* infections in patients with rheumatic diseases on treatment with TNF-alpha antagonists, none of the patients from the Spanish Rheumatoid Arthritis Registry Cohort Study (EMECAR) that assessed morbidity and clinical expression of RA in 2269 patients-years from 34 different Rheumatology Units of Spain treated in most cases with conventional therapies but not with TNF-alpha blockers (11) suffered *Listeria monocytogenes* infection.

## Discussion

Isolated cases of bacteremia due to *Listeria monocytogenes* infection in patients with RA on conventional methotrexate therapy have been reported (12). However, with the generalized use of TNF-alpha blockers for the treatment of patients with rheumatic diseases refractory to conventional therapies, tuberculosis and other opportunistic infections has become a matter of growing concern among the rheumatologists (13). Based on a large series of patients with rheumatic diseases undergoing TNF-alpha antagonist therapy, the present study emphasizes an increase in the risk of developing the opportunistic *Listeria monocytogenes* infection following the use of these drugs.

In 2001 the Food and Drug Administration reported through postmarketing studies 12 cases of listeriosis in patients undergoing anti-TNF-alpha therapy (14). Overall, data from different reports show that 38 patients undergoing treatment with TNF-alpha blockers have been diagnosed with listeriosis (14-24). Thirty-two of these patients were on treatment with Infliximab, 4 with Etanercept and 2 with Adalimumab. In our series none of the patients developed *Listeria monocytogenes* infection following etanercept therapy.

Data from the present Spanish registry study on biological therapies support the increase risk of listeriosis in patients receiving TNF-alpha antagonist therapy. This increased incidence of bacteremia due to *Listeria monocytogenes* infection compared to the general population has not been observed in series of patients with chronic rheumatic patients on conventional (standard) drugs but not exposed to biological agents. With respect to this, data retrieved from another Spanish registry, the results from the EMECAR study (Study of Morbidity and Clinical Expression of RA), which encompassed a large series of patients with RA prospectively followed since 1999, most on them on treatment with conventional therapy mainly methotrexate (11), did not show an increase in the incidence of *Listeria monocytogenes* infection. In this regard, none of the RA patients on conventional therapy included in this registry developed *Listeria monocytogenes* infection.

Both age and comorbidity may play a role in the occurrence of listeriosis in patients on TNF-alpha antagonist therapy. With respect to this, the 3 of the 6 patients from the present series were older than 60 years and 4 had severe comorbid diseases.

The mechanisms leading to listeriosis in patients undergoing TNF-alpha therapy have not been clearly established. However, it is known that *Listeria monocytogenes* infection is associated with increased lymphocyte apoptosis (25). Interestingly, besides increased lymphocyte apoptosis, animal models of *Listeria monocytogenes* infection have shown that increased levels of TNF-alpha produced by the macrophages reduce the severity of the infection caused by these bacteria. However, the injection of infected animals with anti-TNF-alpha monoclonal antibodies yields a progression of the infection, leading to the death of the animal (26). Based on these observations, it is possible that the use of TNF-alpha antagonists may counteract the effect of endogenous TNF-alpha and promote the development of listeriosis in patients on periodical treatment with these drugs.

Of particular interest was the development of *Listeria monocytogenes* endophthalmitis in one of our patients on anti-TNF-alpha therapy. Patients with *Listeria monocytogenes* endophthalmitis have a reduction in visual acuity and an increase in intraocular pressure in the anterior chamber (27). The diagnosis of endophthalmitis is made by anterior chamber puncture of the eye (28).

Peritonitis due to listeriosis was another rare form of listeriosis observed in the present series. It has also been observed in immunocompromised individuals (29). In keeping with that, our patient with *Listeria* peritonitis had a chronic hepatopathy of unknown cause accompanied by varicose veins of the esophagus and splenomegaly. The presence of this severe comorbid condition along with the use of the TNF-alpha blocker may have promoted the occurrence of this infectious complication.

In summary, although evidence suggests that the use of TNF-alpha antagonist therapy has been associated with a decrease in the mortality of patients with chronic inflammatory rheumatic diseases, in particular of RA, largely due to a reduction in the incidence of cardiovascular events mediated by different mechanism such as improvement of endothelial function (30) or improvement of insulin resistance (31), clinicians should keep in mind that these biological therapies are associated to an increased risk of developing uncommon opportunistic infections. Due to this, a high level of surveillance, in particular in immunocompromised individuals, is mandatory in patients on TNF-alpha antagonist therapy.

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