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Infections in patients treated with tumor necrosis factor antagonists: incidence, etiology and mortality in the BIOBADASER registry

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ABSTRACT

Background and objectives: Whether the use of tumor necrosis factor antagonists increases the risk of infection remains a subject of open debate. Developing effective strategies of prevention and empirical treatment entails carefully establishing the etiology and prognosis of the infections.
Patients and methods: Analysis of the Spanish registry BIOBADASER (Feb-2000 to Jan-2006), a national drug safety registry of patients with rheumatic diseases.
Results: 907 episodes of infection occurring in 6,969 patients were analyzed. The infection incidence observed was 53.09 cases/1,000 patients-years (CI 95% 49.69-56.66). The most frequent infections were skin infection (12.18 cases/1,000 patients-yrs), pneumonia (5.97 cases/1,000 patients-yrs), cystitis (3.92 cases/1,000 patients-yrs), tuberculosis (3.51 cases/1,000 patients-yrs) and arthritis (3.76 cases/1,000 patients-yrs). *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella* spp. emerged as important pathogens. *Varicella zoster virus* and *Herpes simplex virus* caused most cases of viral infections. Mucocutaneous candidiasis accounted for most fungal infections. Mortality was increased in infected patients (log-rank test $p < 0.0001$). Pneumonia, sepsis, tuberculosis, abdominal infection and endocarditis were associated with significant attributable mortality.
Conclusions: A significant number of bacterial, viral and fungal infections occurred in patients with rheumatic diseases treated with TNF antagonists. The information of this study can illuminate clinicians globally on how to address infection in this vulnerable group of patients.

Infecciones en pacientes tratados con antagonistas del factor de necrosis tumoral: incidencia, etiología y mortalidad en el registro BIOBADASER

Palabras clave:
Antagonistas del factor de necrosis tumoral
Infección
Etiología
Pronóstico
Enfermedades reumáticas

RESUMEN

Fundamento y objetivo: El aumento del riesgo de infección en la utilización de los antagonistas del factor de necrosis tumoral (TNF) sigue siendo un tema de debate abierto. El desarrollo de estrategias eficaces de prevención y tratamiento empírico implica establecer la etiología y el pronóstico de las infecciones.
Pacientes y métodos: Análisis del registro español BIOBADASER (febrero 2000 a enero 2006), un registro de terapias biológicas en pacientes con enfermedades reumáticas.
Resultados: En los 6.969 pacientes registrados a la fecha del análisis, se produjeron 907 episodios de infección. La incidencia de infección observada fue de 53,09 casos/1.000 pacientes-año (IC 95% 49,69-56,66). Las infecciones más frecuentes fueron las de piel (12,18 casos/1.000 pacientes-año), neumonía (5,97 casos/1.000 pacientes-año), cistitis (3,92 casos/1.000 pacientes-año), tuberculosis (3,51 casos/1.000 pacientes-año) y articulares (3,76 casos/1.000 pacientes-año). Emergen como patógenos importantes *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*

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y *Salmonella* spp. El virus de la varicela zóster y el virus del herpes simple causaron la mayoría de los casos de infecciones virales con germen identificable. La candidiasis mucocutánea fue la más frecuente entre las infecciones fúngicas. La mortalidad fue mayor en los pacientes infectados (p-log-rank < 0,0001). La aparición de una neumonía, sepsis, tuberculosis, infección abdominal y endocarditis se asociaron significativamente con la mortalidad.
Conclusiones: Un número significativo de infecciones bacterianas, víricas y fúngicas se produjeron en pacientes con enfermedades reumáticas tratadas con antagonistas del TNF. La información de este estudio puede suponer un avance para la medicina sobre cómo tratar la infección en este grupo vulnerable de pacientes.

Introduction

Biological agents, including tumor necrosis factor (TNF) antagonists, are used to control some rheumatic and autoimmune diseases.[1–4] There is evidence that some rheumatic patients exhibit a high incidence of infectious complications.[5–7] Although clinical trials and post-market experience have demonstrated the security of TNF antagonists,[8] some cohort studies have exposed an additionally increased risk with the use of TNF antagonists,[9–11] particularly in regard to diseases caused by intracellular microorganism.[12–17]

The primary aim of this study was to characterize the incidence, etiology and prognosis of infectious complications associated with TNF antagonists use in rheumatic patients analyzing a registry of adverse events (BIOBADASER). Such data could be used to dictate prevention policies and empirical treatment recommendations pending microbiological diagnosis.

Material and methods

Population

The BIOBADASER cohort was described in previous papers.[18–20] The registry protocol and materials of BIOBADASER are available at http://biobadaser.ser.es/biobadaser/eng/index.html and were approved by the Ethics Review Committee (ERC) of the Hospital Ramon y Cajal (Madrid). Essentially, BIOBADASER is a drug safety registry started in February 2000, which monitors rheumatic patients treated with biological agents in one hundred Spanish health centres. For the objective of this study, only patients treated with TNF antagonists were analysed. The information was obtained in accordance with Spanish regulations on personal data protection currently in force. Treatment changes and any relevant adverse effects —including infections— observed during follow-up were recorded.

Patients entering the registry are followed prospectively and evaluated at the time an adverse event (AE) or a change in the biological therapy occurs. The recorded data included patient gender, birth date, baseline disease, diagnosis date, treatment type, and treatment start and end dates. Recorded items related with adverse effects included the appearance date, type and class as per the Medical Dictionary for Regulatory Activities (MedDRA),[21] outcome, concomitant treatment and comorbidity.

All participating centres were constantly asked to supply an updated record of their patients in the cohort. Also, a yearly audit of a 10% random sample was conducted in those centers with more than 20 patients included in the database. Data of centers that did not notify relevant data actively in the last two years detected after random monitoring were censored at the last valid data entry. This study was performed on those patients included in the database until January 2006.

Tuberculosis prevention

From March 2002, patients falling in any of the following categories were given 300 mg/d isoniazid for a minimum of 9 months in order to treat latent tuberculosis infections: (*a*) a history of untreated or only partially treated tuberculosis; (*b*) chest X-ray showing tuberculosis residual changes; (*c*) skin reaction to the purified protein derivate (PPD) $\geq$ 5 mm induration, whether initially or in a second test performed 7-10 days after the first. Interested readers can find further details in a previous paper[19] and in the Clinical Practice Guideline for Rheumatoid Arthritis (GUIPCAR), which is available at the Spanish Society of Rheumatology website (http://www.ser.es/practicaClinica/GUIPCAR_2007/Menu0_Principal.php).

Definition of infection

For the purpose of this study, infections were defined according to the well-known criteria of the Centers for Disease Control (CDC).[22] Thus, for example, the diagnosis of dengue was based on positive serology and a compatible clinical picture, whereas that of brucellosis required either the isolation of *Brucella* spp. or positive serology as determined by agglutination or ELISA. Infectious mononucleosis was defined by the presence of positive heterophil antibodies in the presence of a compatible clinical picture. Prosthetic joint infection was defined clinically and only related to a specific etiological agent if isolated from aspiration or biopsy, but not from fistulae. Finally, mycobacteriosis was assumed if mycobacteria were isolated in significant samples from patients with a compatible clinical picture.

BIOBADASER database included relevant AE (serious and non-serious). A infection was considered relevant when resulted in death, was life-threatening, required inpatient hospitalisation or resulted in prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, or was considered medically important according to the treating physician.[23]

Statistical analysis

Time of exposure is considered from the beginning of therapy with a TNF-antagonist to date of the last administration plus twice the half-life of the TNF-antagonist (three days for etanercept, two months for infliximab, and 14 days for adalimumab). Patients were censored either at the time of their last valid entry, the date they were lost to follow-up or that of database download, whichever occurred first. All treatment cycles were included in the analysis.

Continuous variables were expressed as mean with standard deviation (sd). The infection incidence rate per 1,000 patients per year of exposure and its 95% confidence level (95% CI) were calculated. The time to infection was expressed as the median month plus the 25 and 75 percentiles (P_{25-75}) from treatment start to infection.

Mortality was considered attributable to infection when it was not controlled at time of death. Kaplan-Meier survival curves and the log-rank test were used to compare differences between survival time in patients with a history of infection and in those with none.

Results

Description of the studied population

BIOBADASER included 8,201 starts with TNF antagonist in 6,969 patients, 65% female, mean age 50 (sd = 14). A total of 4,459 (64%) had rheumatoid arthritis, 896 (13%) ankylosing spondylitis, 822 (12%) psoriatic arthritis, 245 (4%) undifferentiated spondyloarthropathy, 212 (3%) juvenile idiopathic arthritis, and 5% other rheumatic diseases. Infliximab was used in 4,525 (55%), etanercept in 2,595 (32%), adalimumab in 1,081 (13%). The mean time of exposure was 2.4 (1.6) yr, median 2.1 (P_{25-75}: 1.0-3.6).

Incidence rate and timeline of infections

Of the 6,969 rheumatic patients in the BIOBADASER, 706 (10%) exhibited a total 907 infections. The overall estimated infection rate was 53.09 cases per 1,000 patient-yrs (95% CI: 49.69-56.66). Such a rate was 85.3 cases/1,000 patient-yrs (95% CI: 72.3-100.7) during the first 90 days of treatment and 75.5 cases/1,000 patient-yrs (95% CI: 66.4-85.7) during the first 180 days. The median time to first infection from start of the TNF antagonist was 8 months (P_{25-75}: 3-17). The incidence and mortality of each particular infection is shown in table 1.

Etiology of infections

A microbiological diagnosis was obtained for 371 infections (41%) (table 2). Bacteria were the most frequent microorganisms (45%), which exhibited a balanced distribution between gram-positive and gram-negative bacteria. *Varicella zoster virus* (VZV), *Herpes simplex virus* (HSV) and *Cytomegalovirus* in combination accounted for 91% of all virus isolates. *Candida albicans* was behind 70% of all fungal infections.

Table 3 shows the etiology of the different infections where more than 40% of etiology was known. As it can be seen, skin infections were caused largely by VZV and *Staphylococcus aureus*.

Majority of infections of the upper respiratory airways had no confirmed etiology (157/165), but there were individual rare cases caused by *Haemophilus influenza* (3/165), followed by *Pseudomonas aeruginosa* (2/165). Stomatitis occurred mostly as oropharyngeal candidiasis or herpetic stomatitis. We observed a case of *Listeria* endopthalmitis in a patient with negative blood cultures at the time of diagnosis and a case of severe VZV keratitis.

Infections of the lower respiratory airways included pneumonia and bronchitis. The etiology of pneumonia was identified in only 24% (25/101) cases. Bacterial pneumonia was caused mainly by *S. aureus* (5/101) and *Legionella* spp. (5/101), *Streptococcus*

Table 1
Frequency, incidence, time of presentation and mortality of 907 infections reported in patients treated with tumor necrosis factor antagonist at BIOBADASER database

Syndrome	*n* (%)	Incidence per 1,000 patient-yr (95% CI)	Median months (P_{25-75})	Mortality, *n* (%)
Total reported infections	907	53.09 (49.69-56.66)	8 (3-17)	28 (3)
Skin and soft tissue	215 (23.7)	12.59 (10.96-14.39)		
Skin	208 (96.7)	12.18 (10.58-13.95)	9 (3-17)	0 (0)
Soft tissue	7 (3.3)	0.41 (0.16-0.84)	12 (4-22)	0 (0)
Upper respiratory airways	186 (20.5)	10.89 (9.38-12.57)		
Upper airways	165 (88.7)	9.66 (8.24-11.25)	6 (3-12)	1 (1)
Sinusitis	12 (6.5)	0.70 (0.36-1.23)	16 (6-22)	0 (0)
Otitis	9 (4.8)	0.53 (0.24-1.00)	10 (5-17)	0 (0)
Lower respiratory airways	161 (17.8)	9.48 (8.08-11.06)		
Pneumonia	101 (63.0)	5.97 (4.87-7.25)	8 (3-21)	9 (9)
Bronchitis	60 (37.0)	3.51 (2.68-4.52)	8 (5-18)	0 (0)
Urinary tract	89 (9.8)	5.21 (4.18-6.41)		
Cystitis	67 (75.3)	3.92 (3.04-4.98)	7 (3-17)	0 (0)
Pyelonephritis	19 (21.4)	1.11 (0.67-1.74)	14 (8-17)	0 (0)
Prostatitis	3 (3.4)	0.18 (0.04-0.51)	7 (2-12)	0 (0)
Osteoarticular	65 (7.2)	3.81 (2.94-4.85)		
Arthritis	47 (72.3)	2.75 (2.02-3.66)	6 (2-18)	1 (2)
Osteomyelitis	12 (18.5)	0.70 (0.36-1.23)	7 (5-14)	1 (8)
Prosthetic joint infection	6 (9.2)	0.35 (0.13-0.76)	8 (5-20)	0 (0)
Central nervous system	6 (0.7)	0.35 (0.13-0.76)		
Meningitis	4 (66.7)	0.23 (0.06-0.60)	24 (11-33)	0 (0)
Brain abscess	2 (33.3)	0.12 (0.01-0.42)	0 (0-0)	1 (50)
Miscellaneous	185 (20.4)	10.83 (9.33-12.51)		
Tuberculosis	60 (32.4)	3.51 (2.68-4.52)	5 (3-18)	4 (7)
Gastroenteritis	30 (16.2)	1.76 (1.18-2.51)	6 (2-10)	0 (0)
Stomatitis	19 (10.3)	1.11 (0.67-1.74)	7 (3-9)	0 (0)
Oral phlegmon	17 (9.2)	1.00 (0.58-1.59)	14 (4-23)	0 (0)
Sepsis of unknown origin	14 (7.6)	0.76 (0.41-1.30)	6 (4-12)	6 (43)
Intra-abdominal	12 (6.5)	0.70 (0.36-1.23)	4 (4-10)	3 (25)
Genital	12 (6.5)	0.70 (0.36-1.23)	3 (3-9)	0 (0)
Eye	7 (3.5)	0.41 (0.16-0.84)	5 (3-23)	0 (0)
Hepatitis	5 (2.7)	0.29 (0.10-0.68)	6 (0-28)	0 (0)
Endocarditis	4 (2.2)	0.23 (0.06-0.60)	25 (2-35)	2 (50)
Brucellosis	2 (1.1)	0.12 (0.01-0.42)	15 (4-26)	0 (0)
Dengue	1 (0.5)	0.06 (0.00-0.33)	23 (23-23)	0 (0)
Infectious mononucleosis	1 (0.5)	0.06 (0.00-0.33)	4 (4-4)	0 (0)
Unknown	1 (0.5)	0.06 (0.00-0.33)	10 (10-10)	0 (0)

Table 2
Frequency, time of presentation and mortality of 371 pathogens reported at the BIOBADASER database

Microorganism	Cases (%)	Median (P_{25}–P_{75}) (month)	Mortality, n (%)
Gram-positive bacteria	**87 (23.5)**		**4 (4.6)**
Staphylococcus aureus	56 (64)	7 (2-18)	2 (4)
Staphylococcus epidermidis	11 (13)	5 (2-25)	1 (10)
Streptococcus pyogenes	6 (7)	14 (13-23)	1 (20)
Listeria monocytogenes	4 (5)	17 (7-30)	0 (0)
Streptococcus pneumoniae	4 (5)	7 (1-19)	0 (0)
Streptococcus agalactiae	3 (3)	4 (3-6)	0 (0)
Streptococcus bovis	2 (2)	5 (5-5)	0 (0)
Clostridium difficile	1 (1)	0 (0-0)	0 (0)
Gram-negative bacteria	**82 (22.1)**		**4 (4.9)**
Escherichia coli	32 (39)	7 (4-14)	0 (0)
Pseudomonas aeruginosa	12 (15)	8 (3-15)	2 (20)
Salmonella spp.	10 (12)	5 (2-13)	1 (13)
Haemophilus influenzae	6 (7)	6 (3-10)	0 (0)
Legionella spp.	5 (6)	28 (6-45)	1 (25)
Proteus mirabilis	5 (6)	12 (10-23)	0 (0)
Serratia marcenses	2 (2)	38 (38-38)	0 (0)
Klebsiella pneumoniae	2 (2)	11 (1-22)	0 (0)
Brucella spp.	2 (2)	15 (4-26)	0 (0)
Citrobacter freundii	1 (1)	3 (3-3)	0 (0)
Morganella morgagni	1 (1)		0 (0)
Yersinia enterocolitica	1 (1)	16 (16-16)	0 (0)
Neisseria meningitidis	1 (1)	31 (31-31)	0 (0)
Providencia retgeri	1 (1)		0 (0)
Pseudomonas putrida	1 (1)	1 (1-1)	0 (0)
Viruses	**117 (31.5)**		**0 (0)**
Varicella zoster	80 (68)	8 (4-17)	0 (0)
Herpes simplex	22 (19)	3 (3-13)	0 (0)
Cytomegalovirus	5 (4)	8 (8-17)	0 (0)
Hepatitis C	3 (3)	17 (17-28)	0 (0)
Hepatitis B	2 (2)	0 (0-0)	0 (0)
Epstein Barr	1 (1)	4 (4-4)	0 (0)
Dengue	1 (1)	23 (23-23)	0 (0)
Pox	1 (1)	4 (4-4)	0 (0)
Papilloma	1 (1)	15 (15-15)	0 (0)
Influenzae A	1 (1)	22 (22-22)	0 (0)
Mycobacteria	**60 (16.2)**		**4 (6.6)**
Mycobacterium tuberculosis	59 (98)	5 (3-17)	4 (7)
Atypical mycobacteria	1 (2)	38 (38-38)	0 (0)
Fungi	**23 (6.2)**		**1 (4.3)**
Candida albicans	16 (70)	7 (2-10)	0 (0)
Aspergillus fumigatus	4 (17)	31 (31-31)	1 (33)
Malassezia furfur	2 (9)	11 (7-14)	0 (0)
Pitirosporum ovale	1 (4)	30 (30-30)	0 (0)
Parasites	**2 (0.5)**		**0 (0)**
Leishmania spp.	2 (100)	16 (16-16)	0 (0)

This table shows only the pathogens that were reported or identified by the investigators. Not all infections were microbiologically diagnosed.

pneumoniae (3/101) and *P. aeruginosa* (2/101). Viral pneumonia was caused mainly by *Cytomegalovirus* (3/101), and fungal pneumonia by *Aspergillus fumigates* (4/101). Finally, bronchitis was most often due to gram-negative bacteria (particularly *P. aeruginosa* and *H. Influenza* [6/60]).

Cystitis was caused mainly by *Escherichia coli, Proteus mirabilis* and *Klebsiella pneumoniae*. Pyelonephritis was caused largely by *E. coli*, *S. aureus* and *P. mirabilis*. Genital infections were of fungal (*C. albicans*) or viral (HSV, Papillomavirus) origin.

There were 59 cases of tuberculosis (*M. tuberculosis*) and 1 of atypical mycobacteria *(Mycobacterium avium-intracelulare)*. The incidence of tuberculosis was reduced by 78% by a prophylactic treatment with isoniazid in March 2002; thus, it fell from 522 cases/10^5 patient-yrs (IC 95% 369-738) in March 2002 to only 117 cases/10^5 patient-yrs in 2006 (IC 95% 29-470).[19]

All cases of arthritis and osteomyelitis were due to bacteria (particularly *S. aureus*). *Salmonella* spp. emerged as a cause of osteomyelitis. All prosthetic infections were due to gram-positive bacteria (*S. aureus* and *Staphylococcus epidermidis* [2/6]).

Salmonella spp. and *Cytomegalovirus* emerged as causes of gastroenteritis. Two cases of intra-abdominal infections were caused by *Listeria monocytogenes* and *Providencia retgeri*, respectively. Viral hepatitis was caused by Hepatitis C and Hepatitis B virus.

Non-focal sepsis due to known pathogens exhibited a high frequency and was largely due to *E. coli* and *S. aureus. Salmonella* spp. emerged as a cause of endocarditis.

Mortality

Attributable mortality was 3% (28 cases). Mortality according to infection and etiology is shown in tables 1 and 2. Figure 1 shows the survival curves for the BIOBADASER cohort depending on whether the patient presented an infection or not during follow-up (log-rank test $p < 0.0001$).

Discussion

There is a debate whether TNF blockers increase the risk of infection.[11,24] Although randomized studies have shown that they provide clinical benefits without major complications, some post-marketing studies indicate that they could increase the risk of infection. The overall incidence of infections in the BIOBADASER cohort (53.09/1,000 patient-yrs) was similar to those observed in other studies such as those of Listing et al (64/1,000 patient-yrs)[9] or Dixon et al (53.20/1,000 patient-yrs).[10]

It is also important that, when a relevant infection occurs, it has an impact on mortality. Based on our results, mortality was higher among infected patients; this conclusion, however, should be taken cautiously since our mortality analysis included all reported «relevant infections», whether severe or mild.[25] The particular infectious syndromes associated with significant mortality included pneumonia, sepsis, tuberculosis, abdominal infection and endocarditis.

A potential increased risk of infection will not restrict the use of these drugs wherever they are indicated. Consequently it seems reasonable to develop a consensus on prevention and empiric treatment of infections in patients treated with anti-TNF antagonists. Accordingly, the essential objective of this study was to describe the reported infections for developing effective strategies on prevention and empirical treatment based on the best scientific knowledge.

Clinicians taking care of patients treated with TNF antagonists should be aware of skin infections. Other studies had provided similar results.[9,10,26–28] Skin infections by HSV and VZV resulted in substantial morbidity. It would be interesting to determine the potential efficacy of appropriate prophylactic measures. As occurred in the general population, gram-positive microorganisms are frequently involved in bacterial cellulitis; therefore, the empirical therapy should be aimed at it.

As occurs in other immunosuppressed patients, stomatitis is usually caused by *Candida albicans* or HSV; therefore, the clinical observation of oral lesions should guide the treatment.

Pneumonia is a very important complication since it was related with a relevant mortality (9%) that could be reduced by an early and appropriate empirical treatment. As occurs with the rest of infections in this study, the fact that we have not applied the same prospective protocol to diagnose all cases of pneumonia, identifying the etiology in only 23% of cases, may restrict our conclusions. The microorganisms that were identified as cause of pneumonia were typical of immunocompromised patients (particularly *S. aureus*, *Legionella* spp., *S. pneumoniae*, *P. aeruginosa*, *Cytomegalovirus* and *A. fumigatus*). This confirms that pneumonia

Table 3
Known etiology (> 40%) of reported infections at BIOBADASER database

Infections, n (%)	Skin	Mouth	Cystitis	Pyelonephritis	Genital	Arthritis	Bone	Gastroenteritis	Sepsis	Meningitis	CNS abscess	Endocarditis
Etiology: unknown	81 (38.9)	4 (21.1)	38 (56.7)	8 (42.1)	3 (25)	18 (38.3)	7 (58.3)	18 (60)	5 (38.5)	1 (25)	1 (50)	1 (25)
Etiology: known	127 (61.1)	15 (78.9)	29 (43.3)	11 (57.9)	9 (75)	29 (61.7)	5 (41.7)	12 (40)	8 (61.5)	3 (75)	1 (50)	3 (75)
Citrobacter freundii			1 (1.5)									
Clostridium difficile								1 (3.3)				
Escherichia coli	1 (0.5)		21 (31.3)	7 (36.8)					2 (15.4)			
Klebsiella pneumoniae			2 (3)									
Leishmania spp.	2 (1)											
Listeria monocitogenes									1 (7.7)	1 (25)		
Morganella morgagni			1 (1.5)									
Neisseria meningitidis										1 (25)		
Proteus mirabilis			3 (4.5)	2 (10.5)								
Pseudomonas aeruginosa	2 (1)					1 (2.1)			1 (7.7)			
Salmonella spp.							1 (8.3)	6 (20)				2 (50)
Serratia marcenses	1 (0.5)					1 (2.1)						
Staphylococcus aureus	20 (9.6)	1 (5.3)		2 (10.5)		19 (40.4)	4 (33.3)		2 (15.4)	1 (25)	1 (50)	
Staphylococcus epidermidis	2 (1)					4 (8.5)						1 (25)
Streptococcus agalactiae						2 (4.3)			1 (7.7)			
Streptococcus bovis			1 (1.5)						1 (7.7)			
Streptococcus pyogenes	4 (1.9)					2 (4.3)						
Yersinia enterocolitica								1 (3.3)				
Cytomegalovirus								2 (6.7)				
Herpes simplex virus	12 (5.8)	6 (31.6)			2 (16.7)			1 (3.3)				
Papilloma virus					1 (8.3)							
Pox virus					1 (8.3)							
Varicella zoster	78 (37.5)											
Candida albicans	2 (1)	8 (42.1)			5 (41.7)			1 (3.3)				
Malassezia furfur	2 (1)											
Pitirosporum ovale	1 (0.5)											

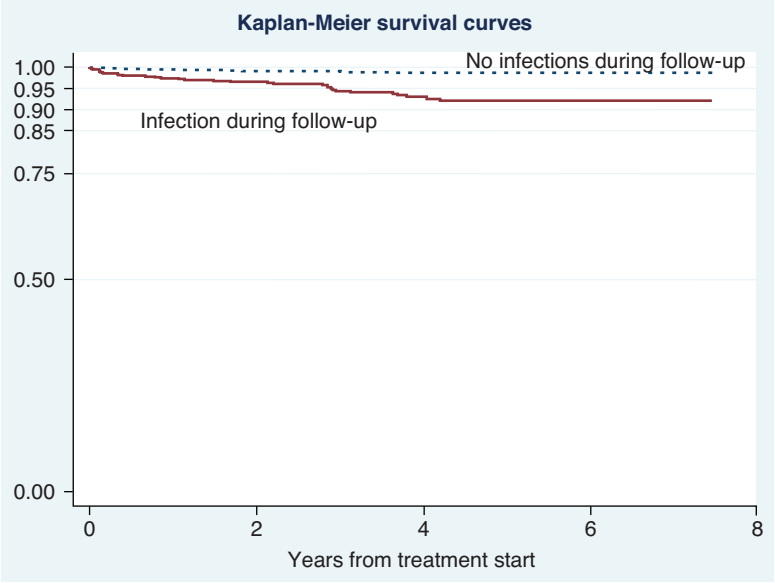

Figure 1. Survival curves for patients on tumor necrosis factor antagonists as a function of whether they developed some infection during follow-up (log-rank $p < 0.0001$).

constitutes a serious disease in this particular population indicating that it should be managed as pneumonia «associated with medical care».[29–31] The policy of vaccination against *S. pneumoniae* and *H. influenzae* should be revised.

Tuberculosis is known to be important in patients under biological therapy.[15,32,33] Our results confirm previously reported data and suggest that it may be associated with substantial mortality (7%). We should stress that isoniazid prophylaxis can dramatically decrease its incidence.[19,34,35] Our patients also exhibited other opportunistic granulomatous infections such as listeriosis, brucellosis and aspergillosis. The mechanism by which TNF-alpha blocking can alter the granulomatous response has been widely documented.[16,17,36]

In our study sepsis was related with significant mortality (43%) stressing the need to implement the management recommendations of the *Sepsis Surviving Campaign*.[37] The empirical treatment should be early and both, gram-positive and gram-negative bacteria, must be covered.

Salmonella spp. emerged as a significant pathogen. Our results confirm the importance of intracellular bacterial infections in patients treated with TNF antagonists.[11,38,39] It flags investigators in the field to look how immunity against these organisms might well be influenced by TNF blockade.

We should note that *S. aureus* caused one-third of all bacterial infections. The importance of this microorganism was previously noted by other authors.[40,41] In centers with high incidence of methicillin-resistant *S. aureus* (MRSA) the utility of detecting nasal carriages in order to be decolonized with nasal mupirocin and clorhexidine washing should be explored.

In other immunosuppressed individuals such as transplanted patients, infections appear according to a well-defined timing, which facilitates their diagnosis and empirical treatment. This was not observed in our patients.

Our study has important limitations. It lacks internal comparators for infectious disease rates. It described «relevant infections» that include serious and less serious infections. Although we did a great effort to reduce the underreporting, it can occur in a registry based in case reporting. The study of the aetiology of infection did not follow the same protocol in all patients. It was only identified in 23% of the cases. There can be differences in assessing the underlying organisms. Infections diagnosed by clinical features –as it is the case with *Candida* as causing organism of genital or oral infections– are easily detected. Some other organisms can only be detected with complex microbiologic studies and could be underdetected.

In conclusion a significant number of bacterial, viral and fungal infections occurred in patients with rheumatic diseases treated with TNF antagonists. Clinicians taking care of these patients should be aware of the infections reported in this study. We think that the information of this report can illuminate clinicians globally on how to address infection in this vulnerable group.

Conflict of interest

The BIOBADASER registry is supported by the Sociedad Española de Reumatología and by the Agencia Española de Medicamentos y Productos Sanitarios. Starting year 2006, BIOBADASER is also supported by grants of similar quantity from Schering-Plough, Wyeth, Abbott Immunology, Roche Farma, and Bristol-Myers Squibb, Spain.

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MAD and MJPS have no competing interest.

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