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ARTICLE

Listeriosis in patients receiving biologic therapies

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Abstract The evolution of inflammatory diseases has radically changed since the introduction of biologic therapies, such as tumour necrosis factor alpha inhibitors (anti-TNFα). They, therefore, represent a widely used therapeutic modality. Nevertheless, post-marketing studies reveal an increased risk of infection in patients taking these drugs, especially granulomatous infections such as listeriosis. We aimed to evaluate the reported cases of listeriosis in patients treated with biologic treatments. We used the United States Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) from 2004 to 2011. We also perform a literature review of previously reported cases of listeriosis in patients taking biologic therapies. We identified 266 cases of *Listeria monocytogenes* infection associated with biologic therapies. The majority of patients were receiving infliximab (77.1 %), followed by etanercept (11.7 %), adalimumab (9.8 %), rituximab (4.1 %), abatacept (0.4 %) and golimumab (0.4 %). Indications for the use of biologics were as follows: 47.7 % for rheumatologic diseases, 38 % for inflammatory bowel diseases, 3.4 % for haematological diseases and 10.5 % for other indications. Seventy-three percent of the patients were receiving concomitant immunosuppressant drugs, especially steroids (56 %) and methotrexate (31.6 %). The median time to the onset of infection was 184 days. Mortality rates range from 11.1 % in adalimumab-treated patients to 27.3 % in rituximab-treated patients (p=0.7). Listeriosis is common in biologics-treated patients, especially related to infliximab use given concomitantly with other immunosuppressive therapies. Infections after treatment with biologics mostly occurred in the first year after initiating treatment.

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Introduction

Biologic therapies are targeted immune modulators that are increasingly used in the treatment of certain types of immunologic and inflammatory diseases, such as rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus (SLE), demyelinating syndromes and inflammatory bowel disease (IBD). Biologic agents approved for clinical use include tumour necrosis factor alpha inhibitors (anti-TNFα), such as etanercept, infliximab, adalimumab, golimumab and certolizumab pegol; the interleukin (IL)-1 receptor antagonist, anakinra; the T-cell co-stimulation inhibitor, abatacept; the humanised monoclonal antibody targeting the interleukin-6 receptor, tocilizumab; a monoclonal antibody against B-cell-specific CD20 antigen, rituximab; a fully human monoclonal antibody that binds to B-lymphocyte stimulator and inhibits its biological activity, belimumab; and a monoclonal antibody which binds to $\alpha_4\beta_1$ integrin, a protein on the surface of lymphocytes, blocking their union to the endothelial receptor, natalizumab.

The most commonly used biologics are the tumour necrosis factor alpha inhibitors. TNFα is synthesised by macrophages in response to proinflammatory stimuli and acts as a central mediator of inflammation and immune regulation [1–3]. However, TNFα is also important in host defence and plays a role in the immune-mediated response to infection because it induces the release of cytokines and local chemokines, leading to attraction and stimulation of phagocytes, increased T-cell adhesion and enhanced antigen presentation with recruitment and proliferation of T- and B-cells. Furthermore, TNFα is essential for granuloma formation and maintenance, which are key components of host defences against intracellular pathogens (e.g. *Listeria*, *Histoplasma* and *Salmonella*) and, more specifically, *Mycobacterium tuberculosis* [4, 5].

Given the crucial roles of TNFα, IL-1, IL-6, T-cells and B-cells in the immune response to infection, it is likely that biologics could impair the ability to fight infections [6]. Although pre-licensure randomised controlled trials did not show a significantly increased risk of serious infections, in general or any specific infections, some post-marketing studies based on voluntary registries found a causal association between biologics and infections [7–12]. Apart from tuberculosis, the greatest risk was of intracellular microorganisms, such as *Listeria monocytogenes*, a Gram-positive organism that has been recognised as a cause of meningoencephalitis and sepsis in pregnant women, neonates and immunocompromised individuals, causing significant morbidity and mortality [9]. Furthermore, some murine studies have demonstrated an essential role of TNF in resistance to *L. monocytogenes* infection [13, 14]. Moreover, the United States Food and Drug Administration (FDA) identified fatal *Listeria* infections in a review of data regarding laboratory-confirmed infections that occurred in pre-marketing phase 2 and phase 3 clinical trials and from post-marketing surveillance, and has recently added the *Listeria* pathogen to the *Boxed Warning* for the entire class of TNFα blockers.

We now report a series of post-marketing infections due to *L. monocytogenes* infection in patients treated with biologic therapies using the FDA Adverse Event Reporting System (AERS) and a literature review of previously reported cases.

Methods

We searched the publicly available AERS database of the FDA for reports of *Listeria* infections with the use of biologic therapies from 2004 through the second quarter of 2011 (30 quarters in total) [15]. AERS is a post-marketing safety database composed of spontaneous adverse event reports to the FDA's Spontaneous Reporting system (SRS) before October 1997 and reports to the AERS from November 1997 up to the present. The AERS database includes post-marketing adverse events spontaneously reported from US sources and attributable post-marketing clinical trial reports from all sources. We also performed a PubMed search using the terms "listeria" and "biologics" or "tumor necrosis factor antagonists" and included all cases reports in our analysis [16–26].

For our analysis, we included the Medical Dictionary for Regulatory Activities (MedDRA) terms: *Listeria* encephalitis, *Listeria* sepsis, listeriosis and *Listeria* meningitis. Biologic therapies included etanercept, infliximab, adalimumab, golimumab, certolizumab pegol, anakinra, abatacept, tocilizumab, rituximab, belimumab and natalizumab. Reports were also examined for concomitant use of immunosuppressive medications. FDA AERS reports meeting these criteria were then imported in ASCII format into SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA) and analytical files were created for the final study database, including demographic data, drug characteristics and outcomes. To compare cases by biologic drugs, we used the Chi-square test with continuity correction for categorical variables and the Student *t*-test and Mann–Whitney *U*-test for continuous variables. The analysis was performed with the stepwise logistic regression model of the SPSS software package (SPSS version 18.0, SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed and the threshold of statistical significance was $p<0.05$.

Results

We identified 266 cases of *Listeria* infections in biologics-treated patients from January 2000 to September 2011, 228 of them from the AERS database and 38 from the literature. The geographic distribution of the cases was 23.3 % from the United States, 11 % from the United Kingdom, 9.8 % from Spain, 7.1 % from France, 7.5 % from Germany, 6.4 % from Japan, 6 % from Canada and 15 % from other countries. In 89.8 % of the reported cases, biologic therapies were the primary suspected drug related to the adverse event, whereas in 8 % and 2.3 %, biologics were described as the secondary and concomitant suspected drug, respectively. Among the cases, 205 cases (77.1 %) were associated with infliximab therapy, followed by etanercept (31 cases, 11.7 %), adalimumab (26, 9.8 %), rituximab (11, 4.1 %), abatacept (1, 0.4 %) and golimumab (1, 0.4 %). Forty-four percent of the cases were described as listeriosis (116 cases), 40.6 % as meningitis or encephalitis (108 cases) and 16 % as *Listeria* sepsis (42). The indications for the use of the biologic were 47.7 % with rheumatologic disease, 38 % with inflammatory bowel disease, 3.4 % with haematological diseases and 10.5 % with other pathologies. The main characteristics of the cases are described in Table 1.

Although data related to the starting date of treatment were only available for 84 cases (31.6 %), the median time from the onset of biologic treatment to the date on which the infection was reported was 184 days (range 1–2,292 days). It is noteworthy that a high proportion of patients were receiving concomitant immunosuppressive medication (73 %), especially steroids (56 %).

In Table 2, we show the results of a univariate analysis evaluating the risk by type of biologic therapy. Etanercept-treated patients with listeriosis were older compared to those receiving infliximab. There were no statistically significant differences in terms of clinical presentation. However, the median time to infection onset after initiating biologic therapy was significantly shorter in patients receiving infliximab compared to those receiving etanercept, and concomitant immunosuppressive therapies were not used equally. Methotrexate was more frequently used concomitantly with adalimumab,

Table 1 Baseline characteristics of patients with *Listeria monocytogenes* infection

Variable	*n*	%
Median age (IQR)	60	(11–85)
Female rate	135	50.8
Related biologic drug		
Infliximab	205	77.1
Etanercept	31	11.7
Adalimumab	26	9.8
Rituximab	11	4.1
Abatacept	1	0.4
Golimumab	1	0.4
Clinical presentation		
Listeriosis	116	44.3
Meningitis or encephalitis	108	40.6
Sepsis	42	16
Indication for use		
Rheumatologic diseases	127	47.7
Inflammatory bowel diseases	101	38
Crohn's disease	64	28
Ulcerative colitis	25	11
Haematological diseases	9	3.4
Other related diseases	28	10.5
Role for biologics		
Primary suspect drug	239	89.9
Secondary suspect drug	21	8
Concomitant	6	2.3
Median time to onset of infection in days (IQR)[a]	184	(1–2,292)
≤6 months	44	52.4
≤1 year	59	70.2
Mortality rate	43	16.4

[a] Median time from onset of biologic treatment to the date on which the infection was reported

followed by etanercept and infliximab, whilst azathioprine was particularly used by patients receiving infliximab. Furthermore, the indication for the use of biologic therapies followed a heterogeneous distribution. Among the cases, etanercept and adalimumab were mainly used in patients with rheumatologic diseases, infliximab use was equally distributed between inflammatory bowel diseases and rheumatologic diseases, whereas rituximab use was predominantly in patients with haematological diseases.

The overall mortality rate reported from listeriosis in patients receiving biologics was 16 % (43/266), although, in some reports, was not possible to clarify which was attributable mortality. Mortality rates differed depending on the biologic drug, with the highest being in rituximab-treated patients (27.3 %) and the lowest in adalimumab patients (11.1 %), but this difference was not statistically significant ($p=0.7$).

Discussion

This study represents the largest report to date of *Listeria* infections associated with use of the biologic drugs. The FDA AERS identified 228 cases of *L. monocytogenes* infections over an 8-year period. This complements prior publications, which comprise 25 case reports of listeriosis in patients receiving biologics [16–26] and 13 patients reported from registries of biologic use [8, 11, 27].

A deficiency of all of these reports is the lack of denominator or control group data to determine whether they, indeed, represent an increased risk compared to patients with comparable diseases not receiving biologics. Patients receiving biologics are frequently receiving concomitant immunosuppressive drugs. Moreover, in one case–control study performed in solid organ transplant recipients, receipt of high-dose steroids and diabetes mellitus were independent risk factors for this listeriosis [28]. Additionally, *L. monocytogenes* has been found at the site of perforation, and in fissures and cracks in the submucosa of a resected colon from a patient with ulcerative colitis, suggesting that inflammatory bowel disease may be a predisposing factor of listeriosis as well, possibly facilitating the invasion of the bacteria from the gut to the bloodstream [29].

A recent French study has shown a mean annual incidence of listeriosis in France of 0.39 per 100,000 residents [30]. In comparison, they estimated an incidence of listeriosis of 2.71 per 100,000 in rheumatoid arthritis patients, 2.63 in ulcerative colitis and 1.98 in Crohn's disease patients. This represents a risk ratio compared to the population <65 years of age of 56, 54 and 41, respectively for RA, ulcerative colitis and Crohn's disease. Most of these patients were receiving immunosuppressive treatment (90–100 %), although the percentage receiving biologic therapies is unknown [30]. A number of registries of patients receiving biologics have reported *Listeria* infections [7–9, 11, 27] (Table 3). Data from these registries would allow for an estimated listeriosis incidence ranging from 6 to 15.5 cases/100,000 patients receiving biologic treatment and 0.3 cases/1,000 patient-years. This suggests, but does not prove, that there is an increased risk of listeriosis in patients receiving biologics.

We are not able to accurately estimate the incidence of listeriosis from the FDA AERS data. Primarily, this is due to the voluntary reporting to the FDA AERS—, hence, underreporting could be likely. Additionally, the heterogeneity of countries that reported events, with differing rates of drug prescriptions and listeriosis incidence in the general population, further complicates the quantitative assessment of risk.

In a review of infliximab adverse events reported to the FDA up until 2005, the excess risk of infection was quantified by generating a statistic known as the empiric Bayes geometric mean (EBGM). An EBGM value of 5 is interpreted to

Table 2 Univariate analysis comparing biologic therapies

	Infliximab, *n* (%)	Etanercept, *n* (%)	Adalimumab, *n* (%)	Rituximab, *n* (%)	*p*-Value
Age (median, IQR)	56 (25–85)	65 (43–83)	–	–	0.001
Clinical presentation					0.07
Listeriosis	85 (41.5)	15 (51.7)	10 (52.6)	6 (54.5)	
Meningitis or encephalitis	93 (45.4)	6 (20.7)	6 (31.6)	3 (27.3)	
Sepsis	27 (13.2)	8 (27.6)	3 (15.8)	2 (18.2)	
Concomitant immunosuppressive therapy	143 (71.1)	23 (82.1)	10 (90.9)	12 (66.7)	0.3
Steroids	108 (53.7)	19 (67.9)	9 (50)	8 (72.7)	0.3
Methotrexate	72 (35.8)	11 (39.3)	9 (50)	0	0.01
Azathioprine	45 (22.4)	1 (3.6)	1 (5.6)	0	0.008
Indication for use					<0.001
Rheumatoid diseases	86 (42.2)	26 (89.7)	14 (73.7)	0	
Inflammatory bowel diseases	96 (47.1)	0	4 (21.1)	0	
Haematological diseases	2 (1)	0	0	7 (63.6)	
Other diseases	20 (9.8)	3 (10.3)	1 (5.3)	4 (36.4)	
Median time from initiating treatment to infection onset in days (IQR)	60	361			0.025
≤1 year	37 (80.4)	9 (50)	10 (66.7)	3 (75)	0.08
≤6 months	31 (67.4)	6 (33.3)	6 (40)	1 (25)	0.03
≤3 months	26 (56.5)	6 (33.3)	4 (26.7)	1 (25)	0.1
Mortality	32 (15.8)	6 (21.4)	2 (11.1)	3 (27.3)	0.7

mean that a drug–event pair has been reported five times as frequently as would be expected if reports involving the drug and reports of the event were independent (that is, no association). For the purposes of signal detection, the authors determined the confidence intervals around the EBGM and used the lower 90 % confidence bound (EB05) as their signal threshold. The EB05 for listeriosis was 20.4, compared to other infections such as *Mycobacterium tuberculosis* (EB05=20.9), *Pneumocystis jirovecii* pneumonia (EB05=9.0) or legionellosis (EB05=8.7) [12].

It is unclear as to whether individual biologic agents pose a greater risk of listeriosis than others. In this evaluation, there were five times as many patients on infliximab developing listeriosis compared to etanercept or adalimumab, and they occurred in the first 6 months after initiating treatment. However, the number of patients receiving the various biologics is not known, so we are not able to determine the relative risk by type of biologic therapy used. Nevertheless, the disproportionate number of cases associated with infliximab in comparison to etanercept, with similar rates of concomitant immunosuppressive drugs and sharing a therapeutic target, may be related to differences between the two in terms of their effects on pre-existing granulomas. Some studies found that infliximab but not etanercept is effective in the treatment of granulomatous chronic inflammatory conditions such as Crohn's disease, sarcoidosis and Wegener's granulomatosis [31, 32]. Furthermore, the mechanisms of TNFα neutralisation are not the same: whereas infliximab is a monoclonal antibody, etanercept

Table 3 Summary of other studies reporting *Listeria* infections in patients taking biologic therapies

Study name	Year	Number of patients included	Drugs analysed	Number of cases	Estimated incidence
Slifman et al. (FDA) [9]	2003	~186,500	Infliximab, etanercept	15 (+11)[b]	6.1 cases/100,000
Peña-Sagredo et al. (Biobadaser) [27]	2008	6,969	Infliximab, etanercept, adalimumab	6	0.3 cases/1,000 patient-years
Dixon et al. (BSRBR) [8]	2006	7,664	Infliximab, etanercept, adalimumab	3	0.3 cases/1,000 patient-years
Salmon-Ceron et al. (RATIO) [11]	2010	~24,000–30,000	Infliximab, etanercept, adalimumab	4	6.9 cases/100,000
Wallis et al. (FDA) [7]	1998–2002	~346,000	Infliximab and etanercept	38	15.5 cases/100,000 (infliximab) and 1.8 cases/100,000 (etanercept)

[a] The investigators reported 11 additional cases of listeriosis occurring by the time the study was completed

is a fusion protein [33]. It is noteworthy that rituximab, abatacept and golimumab were all associated with cases of *Listeria* infection, although the number of cases with each was low.

Even though listeriosis is a relatively rare disease, the overall mortality is estimated to be between 15 and 30 %, being highest among newborns with infection acquired from their mothers [34]. Our results showed similar mortality rates compared to outcomes from *Listeria* infections in the general population. A Finnish study which compared listeriosis among patients with and without immunosuppressive therapy showed that the percentage of patients with meningitis and with a fatal outcome did not significantly differ [35]. In our series, the highest mortality rates were observed in rituximab-treated patients (27 %), probably reflecting the severity of the underlying disease of those patients, most of whom had haematological malignancies and receiving concomitant chemotherapy.

Given the risks of listeriosis in patients with inflammatory diseases in general, and receiving biologics in particular, how can the infection be prevented in this patient population? *L. .monocytogenes* is found widely in the environment in soil, decaying vegetation and water, and may be part of the faecal flora of many mammals, including healthy human adults. It represents a particular concern with respect to food handling and consumption because it can grow at refrigerator temperatures (4 to 10 °C) and freezing has little detrimental effect. Moreover, failure to reach the desired temperature during the pasteurisation process can allow the organism to survive; food can also be contaminated after processing by the introduction of unpasteurised material, for example, during cheese preparation. Ready-to-eat food products that require storage at refrigerated temperatures for long periods have a high risk of *Listeria* contamination [36]. Recommendations to patients receiving biologics include avoiding soft cheeses, unpasteurised milk products, refrigerated pâtés and smoked seafood or ready-to-eat foods, unless they are reheated until steaming hot. In addition to the recommendations listed above, consideration may be given to antibiotic prophylaxis in selected groups of patients during the first few months of initiating treatment. Trimethoprim–sulfamethoxazole has a long track record of prophylactic use in other immunocompromised populations and has efficacy as a protective factor against listeriosis [28]. Nevertheless, further studies are needed in order to assess which groups are most likely to benefit from prophylaxis.

We conclude that *Listeria* infections are relatively common in patients receiving biologic therapies, especially in infliximab-treated patients given other concomitant immunosuppressive drugs and during the first year after initiating treatment. Apart from giving dietary advice to patients and being aware of early disease symptoms, further research in prevention is needed, because the number of patients taking biologic drugs is increasing, especially in the elderly (a population that, in itself, is a risk factor for listeriosis). The risk of listeriosis is unknown with novel biologic agents which have recently been approved and this should be prospectively evaluated.

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Conflict of interest The authors declare that they have no conflict of interest.

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