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LEGIONELLOSIS AND BIOLOGIC THERAPIES

Running title: legionella infection related to biologics

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SUMMARY

Biologic therapies are widely used in inflammatory diseases, and they are associated to an increased infection risk, especially to granulomatous and intracellular infections such as *Legionella*. A review of the literature revealed 105 cases of *Legionella* pneumonia in patients taking biologic therapies. Sixty-four patients (65.3%) were treated with infliximab, 23 (23.5%) with adalimumab, 5 (5%) with etanercept and 3 (3%) with rituximab. Seventy-one per cent of the patients were treated for rheumatologic diseases and 16% for inflammatory bowel diseases. The majority of the patients received one or more concomitant immunosuppressive drugs, especially steroids (43%). Overall mortality was 19%. *Legionella* pneumonia might complicate therapy with biologic therapies, especially in patients being treated with infliximab or adalimumab given concomitantly with other immunosuppressive medications during their first 6 months of treatment. Physicians should be aware of this potentially severe association. Early recognition and treatment would likely result in reduced morbidity and mortality.

INTRODUCTION

Biologic agents approved for clinical use include tumour necrosis factor alpha inhibitors (anti-TNF α) such as etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol; the interleukin (IL)-1 receptor antagonist, anakinra; the T-cell costimulation inhibitor, abatacept; the humanised monoclonal antibody targeting the interleukin-6 receptor, tocilizumab; a monoclonal antibody against B-cell-specific CD20 antigen, rituxamab; a fully human monoclonal antibody that binds to B-lymphocyte stimulator, 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.

These biologic therapies are widely used in patients treated for inflammatory diseases. Although the overall infection risk remains a subject of open debate, some studies have reported an increased risk of granulomatous and intracellular infections, such as tuberculosis, listeriosis and legionellosis^{1,2}. The United States Food and Drug Administration (FDA) has added risk of these infections as a Boxed Warning for the entire class of TNF α inhibitors.

TNF α is synthesized by macrophages in response to proinflammatory stimuli and acts as a central mediator of inflammation and immune regulation. However, TNF α 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^{3,4}. Furthermore, murine studies found a protective effect of TNF in experimental *Legionella pneumophila* infections^{5,6}. Its antigenic components, especially, lipopolysaccharide, are a strong stimulus to produce TNF α , which induces a cell-

mediated immune response. Rats infected with *L. pneumophila* and treated with antiTNF α antagonists showed persistent pneumonitis with a higher bacterial load, more infected macrophages and less recruitment of peripheral blood monocytes to the lung compared to control rats^{5,6}.

Given the theoretic increased risk of legionellosis in patients receiving biologic therapies, we aimed to analyse the association between *Legionella* pneumonia among these patients. Our purpose was to characterise the clinical presentation, duration of biologic treatment at onset of infection, the use of concomitant immunosuppressive medication and outcomes of the *Legionella* infection cases in patients treated with biologics.

MATERIAL AND METHODS

We searched the publicly available Adverse Event Reporting System (AERS) database of the FDA for reports of *Legionella* infections with the use of biologic therapies from 2004 through the second quarter of 2011 (30 quarters in total). 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 AERS from November 1997 to 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 "legionella" and "biologics" or "tumour necrosis factor antagonists" and included all cases reports in our analysis^{1, 7-25}.

For our analysis we included the Medical Dictionary for Regulatory Activities (MedDRA) term "Legionella infection". 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, Inc. Chicago, IL) 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.

RESULTS

We found 105 cases of *Legionella* infection, 68 of which were from FDA AERS. Other data were from national registries (19 cases) and isolated case reports (18 cases). The main characteristics of the reported cases are described in table 1. Speciation was not denoted in the FDA AERS reports. In all other cases in which speciation were performed, the species was *L. pneumophila* (30 cases).

Sixty-one per cent of the patients were males. The median age was 52 years (range 25 to 87 years). North America and Europe accounted for the bulk of reported cases. France was the country which reported the most episodes (27), followed by United States (10), Spain (10), Italy (10), the United Kingdom (8), Canada (7) and Germany (6).

Infliximab was the biologic most frequently related to *Legionella* infection (65.3% of reported cases), followed by adalimumab (23.5%), etanercept (5%), rituximab (3%), abatacept (1%) and natalizumab (1%). One patient received a combination of adalimumab and infliximab. Denominator data is not available so the proportion of patients receiving any specific biologic agent was not calculable. The majority of the patients received one or more concomitant immunosuppressive drugs, especially corticosteroids (43%), methotrexate (35.5%), and azathioprine (13%). Rheumatologic diseases were the most frequent indication for administration of biologic therapies (71%). Inflammatory bowel disease patients accounted for 16% of the cases and other systemic autoimmune diseases for 7%.

The median duration of biologic therapy prior to onset of *Legionella* infection was 4 months (range from 0.25 to 32 months). This interval was shorter among patients who received

infliximab versus those who received etanercept and adalimumab (1 vs. 7.6 months; $p < 0.001$). Forty-two percent of all reported cases developed within 90 days of initiating biologic treatment.

Three patients were given inappropriate empirical antibiotic treatment in a total of only 8 patients in whom the initial antibiotic treatment was recorded – two of these three patients died^{9, 13}.

Seventeen deaths were reported from 92 patients in whom outcome was recorded (19%). At least 9 survivors required intensive care unit management.

DISCUSSION

Our study underlines the relationship between biologics and *Legionella* infection. This relationship was first described in 2006 by Tubach et al ⁷. They used data from the French RATIO registry, designed to collect data on opportunistic and severe infections in patients treated with antiTNF α . They described 10 cases of legionellosis among patients with one year follow-up, and estimated an incidence of 33-42 cases per 100,000 patients receiving biologics, and with a relative risk compared with that for overall population in France between 16.5 and 21. The same group recently published a case-control analysis that supports these high incidence rates²⁶. In a review of infliximab adverse events reported to the US FDA up until 2005, the excess risk of infection was quantified by generating a statistic known as the empiric Bayes geometric mean (EBGM) and its corresponding 2-sided 90% confidence interval (CI (EB05,EB95) ²⁷. An EB05 value of 8.7 was discovered, implying that the drug-event pair has been reported 8.7 times as frequently as would be expected if reports involving the drug and reports of the event were independent (that is, no association). In contrast, the EB05 for tuberculosis was 20.9 ²⁷.

Infliximab, which was first approved by the FDA in 2000, was the most commonly reported drug related to *Legionella* infection, followed closely by adalimumab (2002). Only 5 published cases were associated with etanercept, approved in 1998. More data are needed to determine the associated risk of legionellosis in patients receiving newer biologics. It is noteworthy that infliximab and adalimumab have a potentially stronger relationship with legionellosis than etanercept, in line with the study of Lanternier et al²⁶. Some studies have demonstrated higher avidity and better stability of membrane-bound TNF with monoclonal antibodies comparing to TNF receptor fusion molecule therapy. Moreover, this difference is

also observed regarding other granulomatous and intracellular infections such as tuberculosis, which are significantly more frequent in infliximab treated patients compared to etanercept. This gives more feasibility to the difference in risk of infection between these drugs.

Significantly, legionellosis mainly occurred in the first six months after initiating treatment with biologics. This interval was also shorter among patients who received infliximab versus those who received etanercept and adalimumab (1 vs. 7.6 months, $p < 0.001$). Forty-two percent of the cases were reported < 90 days after initiating of treatment. These data are in line with other studies that reported a decline in the infection risk over time in patients treated with biologics. Interestingly, Strangfeld et al analysed the RABBIT German biologic register and found that approximately one-third of the decrease in risk was caused by improvement in the clinical status and reduction of concomitant steroid therapy and the other two-thirds could be explained by selective switching of patients who were at increased risk of infection²⁸.

The fact that most of the analysed cases received other immunosuppressive therapies concomitantly is remarkable. There are certainly other reports that describe legionellosis in immunosuppressed patients who have not received biologic therapies²⁹⁻³². Interestingly, systemic corticosteroids were extensively used among these patients in similar proportions to that in our study, suggesting that it might have played a role in the infection. Furthermore, these studies described a high case fatality rate, ranging from 14.3% in solid organ transplant recipients to 31% in cancer patients, in concordance with our study which reported a mortality of 19%. These rates differ from the ones reported from community-acquired cases in non immunosuppressed patients which are between 2.5- 6%^{33, 34}.

It would have been interesting to know how many cases received inappropriate empirical antibiotic treatment and how long it took to get the diagnosis - and if delays were associated with increased mortality. In our analysis, only 8 cases had this kind of information and 3 of these patients received inappropriate empirical antibiotic therapy, resulting in 2 deaths. Although we do not have enough data to draw conclusions, one of the factors that could contribute our high mortality rate is a delay in diagnosis and consequently in adequate antibiotic treatment.

Legionella infection usually occurs through inhalation of contaminated aerosols produced by water systems such as cooling waters, showers, hot water distribution systems and faucets, causing sometimes community-acquired outbreaks. The clinical manifestations of Legionnaires' disease do not differ much from other types of pneumonia. Diagnosis depends on special laboratory tests, such as the rapid *Legionella* urinary antigen test, with a sensitivity of 0.74 and specificity of 0.99³⁵. Nevertheless, it only detects *L. pneumophila* serogroup 1. Definitive diagnosis is based on cultures of the microorganism from respiratory secretions or pleural fluid. The utility of serology is limited, except for retrospectively proving that an infection has occurred.

Our study has some limitations. First of all, the voluntary nature of physician reports to the FDA AERS may underestimate the real incidence of legionellosis. Secondly, some reports may have been registered in the FDA AERS database and also published or included in national registries, therefore resulting in duplicate information. For example, France was the country that reported most cases, almost 3-fold comparing to United States, Spain and Italy, which were the next countries in order of frequency. It is possible this incidence could be overestimated if some of the cases were reported twice. Furthermore, some information about

case reports is lacking and therefore there is limited statistical power and denominator data is not available so the proportion of patients receiving any specific biologic agent was not calculable.

Finally we conclude that as biologic therapies are increasingly used to treat some inflammatory diseases we should be aware that they may increase susceptibility to cause certain infections such as *Legionella* pneumonia. The highest risk appears to be in patients treated with infliximab or adalimumab given concomitantly with other immunosuppressive medications during their first months of treatment. A high index of suspicion must be maintained if this is considered a potential cause for the patient's clinical presentation and a urinary antigen test should be collected as soon as possible. Rapid diagnosis and treatment is mandatory because the presentation of legionellosis in immunocompromised patients can be fulminant and severe.

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DECLARATION OF INTEREST

All authors declare any conflict of interest.

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Table 1: Main characteristics of the reported cases

Study name	Type of study	Number of pts with infection	Associated disease	Biologic drug	Median age (range)	Concomitant immunosuppressive drugs	Diagnostic method	Treatment duration* (median, range)	Outcomes
FDA AERS ³⁶	Voluntary registry	68	49 rheumatologic diseases, 9 IBD, 10 other.	Infliximab (47), adalimumab (14), etanercept (3), rituximab (2), natalizumab (1)	52 (25-85)	Steroids (21), MTX (22), AZA (5), other (5)	NR	4.6 months (<1-30)	11 deaths
Tubach ⁷	French registry (RATIO)	10	1IBD, 9 rheumatologic diseases	Adalimumab (6) Etanercept(2) Infliximab(2)	51 (40-69)	Steroids (8) MTX(6)	9 LAg, 1 seroconversion, 2 cultures.	38.5 weeks (3-73)	3 required ICU, all recovered
Perez-Sola ⁸	Spanish registry(BIODABASER) ,including 6969 pts	5	Rheumatic diseases	Infliximab, Etanercept, adalimumab	NR	NR	NR	28 months	1 death
Hofmann ⁹	Case report	2	IBD	infliximab	42.5 (26-59)	Steroids (2/2)	2 LAg	4 weeks	Both required ICU, 1 died.
Ramos-Casals ¹⁰	Registry, including 1370 pts	1	Systemic autoimmune diseases	infliximab	NR	NR	NR	NR	NR
Beigel ¹¹	Case report	1	IBD	infliximab	58	Steroids, AZA	LAg, PCR	NR	ICU. Recovery
Kohn ³⁷	Case report	1	IBD	infliximab	27	Steroids, AZA	PCR	11 days	Died from a septic shock
Dixon ¹	British registry (BSRBR) including 9868 pts	2	RA	infliximab	54	NR	NR	72 weeks	NR
Eisendle ¹³	Case report	1	Erythrodermic psoriasis	infliximab	56	Steroids	Cultures (post mortem)	2 weeks	Died

							diagnosis)		
Li Gobbi ¹⁴	Case report	1	RA	infliximab	38	MTX	LAg	2 weeks	recovered
Mancini ¹⁵	Case report	1	Behcet's disease	infliximab	30	MTX	NR	4 weeks	recovered
Albert ³⁸	Case report	1	RA	infliximab	73	Steroids, MTX	Culture	13 months	recovered
Wondergem ¹⁶	Case report	1	RA	infliximab	43	Steroids, AZA	LAg	3 weeks	recovered
Jinno ¹⁷	Case report	1	RA	adalimumab	67	Steroids, AZA	LAg	2 years	ICU, recovered
Wuerz ³⁹	Case report	1	RA	adalimumab	62	AZA	LAg, cultures	10 weeks	ICU, recovered
Favalli ⁴⁰	LOHREN registry, including 1064 pts	1	RA	AntiTNF α	NR	NR	NR	NR	NR
Kaku ¹²	Case report	1	RA	adalimumab	65	MTX	LAg	2 years	Died
Epping ¹⁸	Case report	1	Crohn's disease	Anti TNF α	26	Steroids	LAg	16 months	recovered
Aringer ¹⁹	Case report	1	SLE	Rituximab and infliximab	NR	Steroids, AZA, MMF, cyclophosphamide	NR	8 weeks (infliximab)	Died
Kroesen ²⁰	Retrospective study	1	Psoriasis	infliximab	49	MTX	LAg	NR	recovered
Vinter ⁴¹	Case report	2	Crohn's disease and Psoriasis	infliximab	53.5	NR	LAg, PCR	4.5 years	1 died
Novas ⁴²	Case report	1	RA	abatacept	73	Steroids, MTX	LAg	3 weeks	recovered

*Treatment duration: median duration of biologic therapy prior to onset of *Legionella* infection. LAg: *Legionella* antigen in the urine. NR: no reported. IBD: inflammatory bowel disease. MTX: methotrexate. AZA: azathioprine. MMF: mycophenolate. RA: rheumatoid arthritis. AntiTNF α : tumor necrosis alpha antagonists. SLE: systemic erythematosus lupus.

Conflict of interest statements

As the conflict of interest statements could not be viewed correctly, as a workaround, the statements have been uploaded as supplementary material.

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