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## Legionellosis and biologic therapies



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#### **KEYWORDS**

Legionella;
Biologic therapies;
Tumour necrosis
factor alpha
inhibitors;
Infection;
Immunocompromised
patients

#### Summary

*Background*: 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*.

Results: 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.

*Conclusion*: Physicians should be aware of this potentially severe association. Early recognition and treatment would likely result in reduced morbidity and mortality.

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#### Introduction

Biologic agents approved for clinical use include tumour necrosis factor alpha inhibitors (anti-TNF $\alpha$ ) 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, rituximab; a fully human monoclonal antibody that binds to B-lymphocyte stimulator, belimumab; and a monoclonal antibody which binds

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Study name	Type of study	Number of	Associated	Biologic drug	Median	Concomitant	Diagnostic	Treatment	Outcomes
		pts with infection	disease		age (range)	immunosuppressive drugs	method	duration <sup>a</sup> (median, range)	
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 [21]	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	Erytrodermic psoriasis	Infliximab	56	Steroids	Cultures (post mortem diagnosis)	2 weeks	Died
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 [22]	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 [23]	Case report	1	RA	Adalimumab	62	AZA	LAg, cultures	10 weeks	ICU, recovered
Favalli [37]	LOHREN registry, including 1064 pts	1	RA	AntiTNFα	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 TNFα	26	Steroids	LAg	16 months	recovered
Aringer [19]	Case report	1	SLE	Rituximab and	NR	Steroids, AZA, MMF,	NR	8 weeks	Died

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