

# Biological therapies in the treatment of inflammatory disease and cancer: impact on pulmonary infection

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**Abstract:** Biological therapies are increasingly used for the treatment of inflammatory conditions in the realms of rheumatology, dermatology, and gastroenterology due to their ability to target specific cytokines in the inflammatory cascade. The impact of these biologic therapies is immunosuppression leading to an increased risk of infection. This review focuses on commonly used biologic agents in the treatment of inflammatory conditions and cancer and their impact on pulmonary infections. We have summarized potential pathogens in this group of patients. The hope being that this will increase awareness and therefore prevention timely diagnosis and successful treatment of patients receiving biologic therapies. It is also important to note that it is not solely the choice of an agent that predisposes to particular infections. Concomitant factors that might increase an individuals' risk of contracting an infection include the underlying disease, comorbid diseases, increased age, and other medical treatment as well as exposure to opportunistic pathogens. In the treatment of cancers many immunotherapies are being developed. The most notable adverse effects from immunotherapy are due to stimulation of the immune response, and these may mimic infection by causing flu-like symptoms and breathlessness due to pneumonitis. The treatment of this is immunosuppression, further leading to an increased risk of infection. Biologic therapies have been a revolution in the treatment of inflammatory conditions and cancers. They have improved outcomes and quality of life for patients. However, the use of these drugs needs to be balanced against the risk of infection and every patient needs to be assessed on an individual basis.

**Keywords:** Biologics; respiratory infection; pneumonia; immunotherapy; cancer; tuberculosis

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## Introduction

Biological therapies are increasingly used for the treatment of inflammatory conditions in the realms of rheumatology, dermatology, and gastroenterology due to their ability to target specific cytokines in the inflammatory cascade. More recently these compounds have emerged in oncology to target cancer cells directly; stimulate the body's response against the cancer cells, or inhibit pathways that promote

tumour growth. These agents have led to dramatic improvements in treating disease, prolonging life and improving quality of life. However, targeting the immune system with these drugs increases the risk of respiratory infections, which are an important cause of morbidity and mortality in these patients (1). The spectrum of potential pathogens known to cause respiratory infections in these individuals has increased, and to identify the subset of pathogens that may be the culprits of the infection it is

**Table 1** Potential respiratory pathogens according to immune defect

Immune defect	Potential respiratory pathogens
Neutropenia/impaired neutrophil chemotaxis	Gram positive bacteria (e.g., <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Nocardia</i> species)
	Gram negative bacteria (e.g., <i>Klebsiella pneumoniae</i> )
	Fungi (e.g., <i>Aspergillus</i> species, <i>Candida</i> species)
T-cell mediated immunity	Herpesviruses (e.g., herpes simplex virus, Cytomegalovirus)
	Respiratory viruses (e.g., influenza)
	Fungi (e.g., <i>Pneumocystis jirovecii</i> , <i>Histoplasma capsulatum</i> , <i>Cryptococcus neoformans</i> )
	Mycobacteria
	<i>Nocardia</i> species
	<i>Legionella pneumophila</i>
B-cell mediated immunity	Encapsulated bacteria (e.g., <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> )

important to know the nature of the underlying immune defect. This is of paramount importance for prevention, timely diagnosis and successful treatment of patients receiving biological therapies (Table 1). It is also important to note that it is not solely the choice of an agent that predisposes to particular infections. Concomitant factors that might increase an individuals' risk of contracting an infection include the underlying disease, comorbid diseases (e.g., diabetes mellitus), increased age, and other medical treatment (e.g., use of high dose corticosteroids). Exposure to opportunistic pathogens is also increased by living or travelling in endemic areas, or through occupational exposure, contaminated food, soil and water (2,3). Here we provide a concise review of established biological therapies and their impact on respiratory infection. The investigations required for the detection of opportunistic respiratory pathogens and their treatment are not discussed here as they are discussed in detail elsewhere (2,4).

## Biological therapy in autoimmune and inflammatory diseases

### Tumour necrosis factor (TNF) inhibitors

TNF is a pleiotropic pro-inflammatory cytokine central to many aspects of the immune response during disease and in the host's response to infection. When present in excessive concentrations it is responsible for the destructive inflammatory processes that result in bystander tissue damage and consequently is a target in the treatment of various inflammatory diseases. The pharmacological class of

TNF inhibitors includes: (I) etanercept, a soluble p75 TNF receptor fusion protein; (II) infliximab, a chimeric anti-TNF antibody; (III) adalimumab, a fully human monoclonal anti-TNF antibody; (IV) certolizumab, an antigen-binding fragment (Fab') of a humanized monoclonal antibody coupled to polyethylene glycol; and (V) golimumab, human anti-TNF-alpha monoclonal antibody.

TNF stimulates macrophages to produce cytotoxic metabolites, thereby increasing phagocytic killing activity. Consequently, inhibition of TNF impairs macrophage phagocytosis that predisposes to infection. Although the mechanism is not clear anti-TNF therapy also results in significant neutropenia (5). Overall, this results in the inability to eliminate pathogens and increases the risk of developing serious infections requiring hospitalisation, which is seen with the use of all TNF inhibitors. However, it is important to note that in a meta-analysis including >50,000 participants conducted in 2011 a statistically significant increased risk was demonstrated only for certolizumab [odds ratio (OR) 3.51, 95% CI: 1.59–7.79] (6). More recently, a 2015 meta-analysis of patients with rheumatoid arthritis, who received biologic drugs, found that all the classes of TNF inhibitors increased the risk of serious infections compared to traditional disease-modifying anti-rheumatic drugs (DMARD) (6). The risk was higher when high doses were used compared to standard doses (OR 1.90, 95% CI: 1.50–2.39 vs. OR 1.31, 95% CI: 1.09–1.58) (7), suggesting that the risk of infection may be dose dependent. Other risk factors which are demonstrated to increase the possibility of infection in patients receiving TNF inhibitors include age  $\geq 65$  years, concomitant use of

immunosuppressants and co-morbidities such as chronic obstructive pulmonary disease (8). Furthermore, the risk of infection is deemed highest when starting the TNF inhibitor (9). The British Society for Rheumatology Biologics Register reported that the risk of infection is 4.6 (95% CI: 1.8–11.9) times greater in the first 90 days (10), highlighting that during this initial period of therapy caution is required in patients developing symptoms and signs of infection.

In the first randomised controlled trial of Infliximab, one patient developed tuberculosis and another coccidioidomycosis (11). Since then there has been increased recognition of the association between the use of TNF inhibitors and the development of active infection, especially with opportunistic pathogens (3). Notably, due to loss of cellular and humoral immunity with anti-TNF therapy, individuals are also predisposed to infections with pathogens that normally cause infection in healthy individuals such as the respiratory viruses and *Streptococcus pneumoniae*, and in these cases, the ongoing use of TNF inhibitors can result in invasive infection. Likewise, TNF inhibitors increase the risk of infection with *Legionella pneumophila*, with a relative risk of Legionnaire's disease in rheumatoid arthritis patients treated with anti-TNF inhibitors estimated to be between 17 to 21 in comparison with the overall risk in France (12).

Of the respiratory infections associated with anti-TNF therapy infection with *Mycobacterium tuberculosis* is the most notable, with a 25-fold increased risk of reactivating latent *M. tuberculosis* following initiation of treatment (13). The risk is increased because TNF together with IFN- $\gamma$  plays a major role in elimination of mycobacteria and confines mycobacteria to granulomas, which keeps the disease in a latent state (14). The risk of reactivation is greater with the use of infliximab and adalimumab compared to etanercept (15,16). Furthermore, anti-TNF therapy increases the risk of non-tuberculous mycobacterial infections, including *M. avium complex*, *M. chelonae*, *M. marinum* and *M. abscessus* (14). Therefore, current recommendation is to screen individuals for active and latent *M. tuberculosis* infection by taking a detailed history, performing a physical examination, obtaining an interferon gamma release assay (IGRA) and/or tuberculin skin test (TST), and a chest radiograph in those with a positive TST/IGRA or if symptoms suggest active disease. In most cases, an IGRA is sufficient for screening, but in individuals with significant risk factors for previous tuberculosis exposure, the TST should also be carried out if the initial IGRA is negative. If latent tuberculosis infection

is diagnosed then treatment should be commenced before initiating anti-TNF therapy (17).

TNF also plays a key role in the containment of other granulomatous infections including fungal infections, particularly in endemic areas, where fungal infections are a recognised complication of treatment with TNF inhibitors, particularly with infliximab (18,19). Of concern is that many cases of pulmonary and disseminated histoplasmosis, coccidioidomycosis and blastomycosis are missed in these individuals and treatment initiation is delayed, which can result in poor outcomes (20). A high index of suspicion is required in the presence of dyspnoea, fever, and malaise, as well as radiological features of interstitial pneumonitis, mediastinal granulomatous lymphadenitis and mediastinal fibrosing mediastinitis (21). In endemic areas for coccidioidomycosis, despite most infections occurring *de novo*, it is best to perform a chest radiograph and coccidioidal serologic tests prior to the initiation of TNF inhibitors as re-activation of latent infection can occur (19). Due to neutropenia associated with TNF inhibitors, infections with *Aspergillus* species (e.g., *A. fumigatus*), which are ubiquitous environmental fungi, are also of concern particularly in the presence of other immunosuppressants (22). Pneumocystis jirovecii pneumonia is also reported in individuals receiving infliximab, especially within the first month of receiving the infusion (23) and when used concomitantly with high doses of glucocorticoids (24). Consequently, patients receiving both high dose corticosteroids and TNF-inhibitor should be considered for PCP prophylaxis.

TNF also plays a key role in the immune response against viral infections, and respiratory infections with respiratory viruses (respiratory syncytial virus, parainfluenza, influenza, adenovirus, metapneumovirus, coronavirus and rhinovirus) are relatively common in individuals treated with TNF-inhibitors. Re-activation of latent infections with viruses from the *Herpesviridae* family (e.g., human herpes virus, cytomegalovirus, and Epstein-Barr virus) are not frequently seen, but a high index of suspicion for these is required. In immunocompromised individuals, these viral infections can be severe and fatal if not identified early so that TNF inhibitor therapy can be withheld and anti-viral treatment commenced (3,25).

### **Rituximab**

Rituximab is a chimeric/humanised monoclonal antibody that acts on CD20<sup>+</sup> cells and leads to B cell depletion via apoptosis and complement activation before these cells

develop into plasma cells (26-28). In addition to B-cell depletion, rituximab results in hypogammaglobulinemia, which predisposes to recurrent respiratory infection and may require treatment with intravenous immunoglobulin replacement therapy (29). It is, therefore, crucial to obtain baseline serum immunoglobulin levels (IgG, IgA, and IgM) prior to initiation of rituximab therapy and periodic monitoring to identify persistent immunoglobulin deficiencies before the onset of severe infections. In a large study of rheumatoid arthritis patients that received rituximab, serious infections were encountered in 7% of individuals with most having pneumonia, especially when low IgM levels were encountered (30). With the immunoglobulin deficiency, patients receiving rituximab will not mount adequate responses to vaccines, particularly polysaccharide vaccines such as that against *S. pneumoniae*. Therefore, to prevent against pneumococcal pneumonia in this high-risk group the pneumococcal vaccine should be administered before initiation of rituximab treatment.

Unlike with TNF inhibitors there is no need to screen individuals for *M. tuberculosis* infection, but it is important to bear in mind that the risk of re-activation of latent tuberculosis infection is heightened when used concomitantly with other immunosuppressive agents such as high dose corticosteroids (31).

### **Belimumab**

B-lymphocyte stimulator (BLyS) is a transmembrane protein which is a B-cell activating factor and therefore promotes maturation of B-cells into plasma cells and the production of antibodies (32). Belimumab is a human monoclonal antibody that binds to soluble human B-lymphocyte stimulator protein (BLySS) to inhibit its biologic activity in patients with systemic lupus erythematosus (SLE) (33). It increases the development of serious respiratory infections during the first year of treatment, with particular reports of coccidioidomycosis and cytomegalovirus pneumonia. However, in a randomised clinical trial patients treated with belimumab did not have rates of serious infection greater than those treated with placebo (34).

### **Tocilizumab**

Tocilizumab is a humanised monoclonal antibody targeting the interleukin (IL)-6 receptor and blocks the downstream signalling effects of IL-6 on the function of neutrophils, T cells, B cells, and monocytes. Additionally, IL-6 is a potent

inducer of the hepatic acute phase response and secretion of c-reactive protein and is an endogenous pyrogenic (35). Therefore, inhibition of IL-6 may predispose to the development of severe infection in the absence of a febrile and pro-inflammatory response, which may lead to diagnostic and therapeutic delays. Tocilizumab can lead to neutropenia, but the adverse effect is usually transient. However, there remains an increased risk of respiratory infection comparable to that seen with TNF inhibitors and there is a requirement to screen for latent *mycobacterium tuberculosis* infection prior to initiation of treatment (36). The risk is particularly increased in those >65 years of age, with underlying co-morbid respiratory disease, on >5 mg/day corticosteroids, or on a concomitant DMARD (34-37).

### **Abatacept**

Abatacept is a soluble fusion protein of human IgG1 to CTLA4, which is a T-cell surface receptor. The CTLA4 binds to the B cell thus preventing B cell activation, and T cell mediated cytokine release (38). Respiratory infections with opportunistic pathogens were reported with abatacept therapy (9) but overall the available data do not suggest a significantly increased risk of serious infections compared to placebo. The risk for reactivation of *M. tuberculosis* associated with abatacept therapy is currently unclear, but the manufacturer recommends screening for latent infection before treatment initiation (9,32).

### **Tofacitinib**

Tofacitinib is a Janus kinase (JAK) inhibitor that influences multiple downstream signalling pathways. The risk of infections with tofacitinib is similar to that of DMARDs. However, the rate of serious infections with tofacitinib is 3/100 patient years and increases in advanced age, those with diabetes mellitus and with concomitant use of corticosteroids (39). The greatest risk with tofacitinib appears to be with infection with herpes zoster and vaccination is recommended prior to initiation of treatment (40).

### **Eculizumab**

Eculizumab is a humanized monoclonal antibody that binds to the C5 component of complement, inhibiting terminal complement activation (32,41). Eculizumab increases the risk of life-threatening neisserial infections, including *N. meningitidis* and the manufacturers prescribing

information includes a boxed warning describing the risk, the need for meningococcal vaccination at least two weeks prior to treatment, and the importance of monitoring for meningococcal infection (42). Since Eculizumab inhibits complement activation it will also increase the risk of respiratory infection with other encapsulated pathogens such as *S. pneumoniae* and *H. influenzae* (43).

### **Anakinra**

The IL-1 receptor antagonist (IL-1Ra) is a naturally occurring glycoprotein inhibitor of IL-1 by binding to the IL-1 receptor and anakinra is the recombinant human IL-1Ra that functions through competitive binding to the IL-1 receptor (44). The risk of serious infections with anakinra is significantly increased compared to placebo with an OR 4.05 (95% CI: 1.22–16.8) (6). This increases with combination etanercept, and therefore the use of anakinra in combination with other biological therapies is not recommended (45). Regarding the reactivation of latent *M. tuberculosis* there is one case report in the literature (46) and overall the data does not suggest that anakinra significantly increases the risk of developing tuberculosis (6).

### **Ustekinumab**

Ustekinumab is a human IgG1 kappa monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23, preventing the binding of the pro-inflammatory cytokines IL-12 and IL-23 to their cell surface receptor. It results primarily in impairment of natural killer (NK) cell activation, as well as CD4+ T-cell differentiation and activation. Moreover, it interferes with the expression of monocyte chemotactic protein (MCP)-1, TNF, interferon-inducible protein-10 (IP-10), and IL-8. Due to the significant effect on pro-inflammatory cytokine signalling and impairment of adaptive immunity, there is concern that ustekinumab may increase the risk for infections, but to date, the available data is limited to case reports (47) and current studies have not demonstrated a significantly increased risk of pneumonia. However, the incidence of nasopharyngeal infections is increased by up to 10% (48). As many trials of ustekinumab were in individuals previously screened for latent *M. tuberculosis* infection, there is no demonstrable increased risk of tuberculosis reactivation, and the manufacturer continues to recommend that patients are screened for latent *M. tuberculosis* infection before initiation of treatment (49).

## **Biological therapy in cancer**

Biological therapies, also known in this context as immunotherapies, have emerged as game changers in the treatment of various types of cancer (e.g., haematological, skin, gastric, breast, renal, urothelial and lung malignancies). Although many of these drugs are new, others have long been established in the treatment of cancer; For example, the FDA approved Bacillus Calmette-Guérin (BCG) in 1990 for the intravesical treatment of bladder cancer. These therapies mainly aim to alter the host's immune response so that it can detect and eliminate the cancer cells or inhibit tumour growth. Immunotherapies largely consist of (I) monoclonal antibodies that target antigens on the cell surface enabling the immune system to destroy them (e.g., alemtuzumab); (II) monoclonal antibodies that inhibit checkpoint molecules to prevent cancer cells from evading the immune system (e.g., nivolumab); (III) monoclonal antibodies that inhibit cancer growth factors (e.g., bevacizumab); (IV) immunoconjugates containing antibodies that target specific antigens and deliver cytotoxic or radioactive substances (e.g., ado-trastuzumab emtansine); (V) cytokines that stimulate the immune system and induce cell apoptosis (e.g., interferons); and (VI) cancer vaccines that contain cancer-associated antigens to stimulate T-cells to kill cancer cells (e.g., sipuleucel-T).

The most notable adverse effects from immunotherapy are due to stimulation of the immune response, and these may mimic infection by causing flu-like symptoms and breathlessness due to pneumonitis. In a study of patients receiving checkpoint inhibitors, the incidence of pneumonitis was 5–10% with the highest frequency seen in those receiving combination treatment with anti-PD1 and anti-CTLA4 inhibitors (50). In these cases, infectious aetiologies need to be excluded before initiation of treatment. The management of immune-related adverse events is with immunosuppressants (e.g., high dose corticosteroids, mycophenolate mofetil or TNF inhibitors) and these drugs will increase the risk of subsequent respiratory infection in particular with pathogens such as *M. tuberculosis*, *P. jirovecii*, *A. fumigatus* and the herpes viruses (2,4,51,52). In a study of 740 patients receiving checkpoint inhibitors for the treatment of melanoma bacterial pneumonia, *P. jirovecii* pneumonia and invasive pulmonary aspergillosis were identified in 1.8%, 0.4% and 0.3% of patients respectively (53), suggesting that although rare, a high index of suspicion is required to identify these culprit pathogens. Like the PD-1 inhibitors, the PD-L1 inhibitors

(e.g., atezolizumab, avelumab) are also associated with pneumonitis and development of severe respiratory infection in up to 5% of patients (54,55). Other commonly used biologicals that are reported to increase the risk of respiratory infections include the monoclonal antibodies targeting CD20 (e.g., rituximab, ofatumumab, obinutuzumab, tositumomab, ibritumomab tiuxetan), that lead to B-cell depletion and toxicity causing neutropenia (56-58), monoclonal antibodies targeting CD52 (e.g., alemtuzumab) that cause B-cell lysis, T-cell depletion and neutropenia (59), and monoclonal antibodies targeting CD33 (e.g., gemtuzumab) that results in myelosuppression (60). Use of the cytokine IL-2 (aldesleukin) is also associated with an increased risk of respiratory infections due to neutrophil dysfunction (61). Importantly, the risk of respiratory infections with biological agents in the treatment of cancer is further augmented by their use in combination with immunosuppressive chemotherapeutic agents that frequently result in cytopenia.

Most of these infections can be prevented with prophylactic medication, but the frequency currently remains too low to justify their routine use and further research using larger cohorts are needed to demonstrate their cost-effectiveness. It is also important to note that discontinuation of the biological agent may not lead to rapid cessation of immunosuppression due to the long half-life of most monoclonal antibodies. Furthermore, in the presence of active infection discontinuation of immunosuppressive agents may lead to paradoxical worsening as the recovering immune system reacts to the pathogen, as seen in immune reconstitution inflammatory syndrome seen in the treatment of human immunodeficiency virus infection.

## Conclusions

Biological therapies represent a revolution in the treatment of chronic inflammatory diseases and cancer, especially in cases refractory to conventional treatment modalities. They offer significant benefits in disease control and improving quality of life. As with all immunosuppressant agents, it is important to be aware and vigilant for signs of infection, as these therapies confer a significantly increased risk of respiratory infections.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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