Infectious Risks Associated with Biologics

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Abstract

Biologics are generally either custom-designed monoclonal antibodies against specific target cells (e.g. B-cells) or target cytokines (e.g. tumour necrosis factor, TNF) or they are receptor constructs (fusion proteins) based on naturally-occurring cytokine or cell receptors. Biologics are mostly used in adult rheumatology but are increasingly used in paediatrics. There are significant concerns about safety and also about cost. The main safety concerns are about increased risk of infection and malignancy.

The use of TNF antagonists is associated with increased risk of serious infections with intracellular organisms, particularly mycobacteria, but also intracellular bacteria, fungi and Pneumocystis. B-cell antagonists like rituximab can cause progressive multifocal leukoencephalopathy. IL-6 antagonists are associated with increased rates of common bacterial infections and the complement pathway antagonist eculizumab with meningococcal infection.

The risk of some infections associated with biologics can be reduced, by screening patients starting TNF antagonists for latent tuberculosis and giving them cotrimoxazole prophylaxis against Pneumocystis, and by immunising against VZV, hepatitis B, meningococci and pneumococci. However, the risk of the biologics causing serious infection in children is unknown and needs study. Children should not be started on the biologics without careful consideration of the risks and without fully informed consent.

12.1 What is a Biologic?

The US FDA has a Center for Biologics Evaluation and Research which regulates a diverse array of complex products they term biologic agents [1]. The term biologics (or biologicals [2]) can be used to include a wide range of medicinal

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products including vaccines, blood and blood components, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins created by biological processes (as distinguished from chemistry). Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.

However, in most cases, the term biologics is used more restrictively for a class of genetically engineered medications produced by means of biological processes involving recombinant DNA technology. These medications are usually one of three types:

1. Recombinant human proteins. Examples are erythropoetin, growth hormone and biosynthetic human insulin and its analogues (all hormones).
2. Monoclonal antibodies. Custom-designed antibodies (using hybridoma technology or other methods) designed to counteract or block specific targets of the inflammatory response, either target cells (e.g. B-cells) or target cytokines (e.g. tumour necrosis factor or TNF).
3. Receptor constructs (fusion proteins), usually based on a naturally-occurring receptor for a cytokine (e.g. etanercept targets the TNF-alpha receptor) or for a cell receptor (e.g. belatacept blocks T-cell activation by targeting the CD 28/CTAL-4 receptor).

All of the currently used biologics have to be administered parenterally, either sub-cutaneously or by intravenous infusion, anything from daily (anakinra) to every few weeks, with obvious implications for the paediatric population. Most data come from use in adults, but paediatric use is increasing [2].

The biologics, when used in this sense, have arguably had most impact in adult rheumatology and notably in the treatment of rheumatoid arthritis, giving rise to the term biologic disease-modifying agents for rheumatic diseases or bDMARDs. However, they are being used increasingly in a range of fields, to treat inflammatory conditions (e.g. TNF-alpha inhibitors like infliximab for inflammatory bowel disease), malignancy (e.g. trastuzumab or Herceptin for breast cancer), and to treat transplant rejection (e.g. monoclonals directed at B-cells like rituximab). Almost every discipline now uses biologics to treat one or more disease with an immunologic contribution to pathogenesis.

However, the advent of biologic therapeutics has also raised significant concerns about safety and cost. The cost of biologic therapies is dramatically higher than the cost of conventional pharmacological medications. Furthermore, biologics are mainly used to treat chronic conditions such as rheumatoid arthritis or inflammatory bowel disease, or for the treatment of refractory cancer for the remainder of life. Safety concerns include increased risk of malignancy, particularly lymphoma, and worrying reports of demyelination, hepatotoxicity and severe allergic reactions to the biologics. This paper, however, will concentrate on the infectious risks of the biologics.

For all the biologics, the exact degree of increased susceptibility to infection is difficult to quantify. Randomised controlled trials and meta-analyses tend to consider "all infections", "serious infections" and "death" as their outcomes [3]. Most patients on biologics are also taking or were taking corticosteroids, methotrexate and other medications with profound effects on the immune system. Other important variables include underlying disease state, age, and prior and future exposure to pathogenic organisms such as mycobacteria, *Pneumocystis* and fungi.

12.2 Biologics and Infection

Biologics target the immune system. We know that patients with congenital or acquired immune deficiency are at increased risk of infections. Persons with severe congenital or acquired T-cell immune deficiency are also at increased risk of malignancy, particularly lymphoma. It is far from surprising, therefore, that biologics have been shown to be associated with increased risk of infections and of lymphoma.

What should intrigue infectious disease physicians is that different biologics are associated with different patterns of susceptibility to different infectious agents. Relating the nature of

Table 12.1 Biologics acting as inhibitors of tumour necrosis factor

Generic name	Trade name	Indications	Technology
Adalimumab	Humira	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's	Humanised monoclonal antibody
Etanercept	Etebrel	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	Recombinant human TNF-receptor fusion protein
Infliximab	Remicade	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's	Monoclonal antibody
Golimumab	Simponi	Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis	Monoclonal antibody

the infections caused by a particular biologic to the target of the biologic should help increase our knowledge of the normal human defences to infection.

A corollary of the previous statement is that there are some congenital immune deficiency diseases which affect a relatively specific part of the immune system and that knowledge of the nature infections experienced by persons with these disorders may predict the nature of the infections likely to be caused by use of a specific monoclonal antibody and vice versa.

12.3 Tumour Necrosis Factor Antagonists

Tumour necrosis factor (TNF), previously called cachectin and then tumour necrosis factor-alpha, is a systemic inflammatory cytokine able to induce apoptotic cell death, to induce inflammation, and to inhibit tumorigenesis and viral replication. It is produced mainly by macrophages, but also by a variety of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts, and neuronal tissue. Large amounts of TNF are released in response to lipopolysaccharide, other bacterial products, and interleukin-1 (IL-1). TNF can bind to two distinct receptors, TNF-R1 (TNF receptor type 1; CD120a; p55/60) and TNF-R2 (TNF receptor type 2; CD120b; p75/80), TNF-R1 being found in most tissues but TNF-R2 only in cells of the immune system [4, 5]. Binding of TNF to receptors leads to activation of a complex array of inter-acting and often conflicting inflammatory responses including enhancement of activated B-cells, pathways involved in cell proliferation and both anti-apoptotic and pro-apoptotic responses. This necessitates a sophisticated signalling system and diverse factors such as cell type, concurrent stimulation of other cytokines, or the amount of reactive oxygen species can shift the balance in favour of one pathway or another. Such complicated signalling ensures that, whenever TNF is released, various cells with vastly diverse functions and conditions can all respond appropriately to inflammation [4, 5]. TNF appears to be important in augmentation of both the adaptive and innate immune systems.

There is no known human state of TNF deficiency, but a "knock-out" mouse model was first developed in 1997, with the genetically engineered mice lacking the gene to produce TNF [6]. TNF-deficient mice or those lacking TNF receptors have markedly increased susceptibility to mycobacterial infection [7] and also to other intra-cellular pathogens including Listeria [8], Salmonella, some viruses but also to some extra-cellular pathogens like *Streptococcus pneumoniae* [9]. Interestingly, in IRAK-4 deficiency in humans, a defect in Toll receptor signal transduction leads to diminished amounts of TNF and other pro-inflammatory cytokines, and patients are susceptible to infections with *S. pneumoniae* and Salmonella. To interfere with TNF in humans seems risky in the extreme, but the important role played by TNF in causing and prolonging inflammation in rheumatic and other auto-immune or inflammatory disorders led researchers to develop a number of different biologics which interfere with TNF. These are shown in Table 12.1.

Table 12.2 Biologics, their targets and their infectious risks

Target	Names of biologics	Technology	Indications	Infectious risks
Tumour necrosis factor	Adalimumab	Humanised Mab to TNF	Arthritis	Mycobacteria
	Etanercept	Receptor fusion protein	Psoriasis	Fungi
	Infliximab	Mab to TNF	Crohn's	Viruses
	Golimumab	Mab to TNF		PCP, listeria
B-cell	Rituximab	Mab to CD20	Transplant rejection, cancer, etc	PML, HepB reactivation
	Epratuzumab	Mab to CD22	Lupus	Unknown
T-cell activation	Abatacept	Fusion protein to CTLA4	Transplant rejection	Unknown
	Belatacept			PML, EBV-related proliferative disease
IL-6	Tocilizumab	Mab to IL-6	Arthritis	Slight increase, no specific organisms
IL-1	Anakinra	IL-1 receptor antagonist	Arthritis	Cellulitis, pneumonia
Complement	Ecalizumab	Mab to C5	PNH	Meningococcus

EBV Epstein-Barr virus, *IL* interleukin, *Mab* Monoclonal antibody, *PCP Pneumocystis carinii* (now *jirovecii*) pneumonia, *PML* Progressive multifocal leucoencephalopathy, *PNH* Paroxysmal nocturnal haemoglobinuria, *TNF* tumour necrosis factor

As predicted from the mouse model, use in humans of biologics that target TNF (adalimumab, infliximab) or TNF-receptor (etanercept) has been associated with increased susceptibility to mycobacterial infections, both tuberculosis and atypical mycobacterial infections [3, 10, 11]. Persons with latent TB are at high risk of reactivation, and the Product Information for all the TNF biologics in Table 12.1 states that patients should be screened for latent TB before commencing the biologic. A patient shown to have latent TB (positive tuberculin skin test and/or interferon-gamma release assay, normal physical examination and chest X-ray), should be commenced on chemoprophylaxis with one or more anti-tuberculous drugs. Monotherapy with isoniazid or rifampicin is usual, but it may be advisable to use two or three drugs, depending on risk factors for reactivation, notably the patient's degree of immunosuppression.

For TNF antagonists, as for other biologics, the exact degree of increased susceptibility is hard to quantify. In most of the analysed studies and comparisons, there were no significant differences in safety outcomes between adalimumab and control groups [3, 10]. Serious infections were significantly more frequent in adalimumab patients in only one study [11] with a RR (95 % CI) of 7.64 (1.02–57.18) and a NNH of 30.2. Similarly, based on 4 RCTs (1,231 patients treated with golimumab and 483 with placebo) no significant differences were noted between golimumab and placebo regarding serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events and inefficacy and deaths [12].

On the other hand, there are increasing numbers of reports of serious infections associated with TNF antagonist biologics. These are primarily with intracellular pathogens: tuberculosis and atypical mycobacterial infections, fungal infections and viral infections. The fungal infections have been with Aspergillus, Candida and in the USA with histoplasmosis, coccidiomycosis and blastomycosis, and failure to recognise fungal infections early prompted an FDA warning [13]. Fungal infections are often disseminated rather than localised, have a high mortality (12 of 240 patients died who developed histoplasmosis while taking TNF antagonist biologics and were reported to the FDA) [3] (Table 12.2).

TNF antagonist biologics may be associated with reactivation of chronic hepatitis B infection, and with severe HSV and VZV infections,

including sometimes the macrophage activation syndrome [14].

The pattern of infections with TNF antagonist biologics resembles those of a patient with T-cell deficiency, and there are reports of patients taking infliximab and other TNF antagonist biologics developing *Pneumocystis jirovecii* pneumonia (PJP, PCP) a median of 8 weeks after commencing therapy [15]. In addition, there are individual case reports of patients on infliximab developing Listeria infections.

Patients with T-cell defects may also have increased susceptibility to extra-cellular pathogens and this appears to be the case for TNF biologics, in as much as there are reports of pneumonia, pyelonephritis, septic arthritis and septicaemia in association with their use in adult rheumatology patients [10, 11], although the biologics may be only one of multiple factors contributing to these infections.

12.4 B-cell Antagonists

There is increasing use of rituximab, a monoclonal antibody which targets CD20, a protein found mainly on B-cells, in the treatment of lymphomas, leukaemias, transplant rejection and some autoimmune disorders.

B-cell antagonists can cause hypogammaglobulinaemia with a risk of sinopulmonary infections. While initial reports of the use of rituximab were optimistic regarding safety, there are emerging concerns about reports of reactivation of hepatitis B [16], sometimes leading to fulminant disease, and of the development of progressive multifocal leukoencephalopathy (PML) due to JC virus [17].

The JC virus (JCV) is a human polyomavirus genetically similar to BK virus and SV40. It was discovered in 1971 and named after the two initials of a patient with progressive multifocal leukoencephalopathy (PML). The virus causes PML and other diseases only in persons with immunodeficiency, as in AIDS or during immunosuppressive treatment (e.g. organ transplant patients). The virus is very common in the general population, infecting 40–60 % of humans [18, 19]. Most people acquire JCV in childhood or adolescence. It is found in high concentrations in urban sewage worldwide, leading some researchers to suspect contaminated water as a typical route of infection. PML is a demyelinating disease, affecting the white matter, destroying oligodendrocytes and producing intranuclear inclusions. PML is similar to another demyelinating disease, multiple sclerosis, but progresses much more quickly. In a recent report of 57 cases of PML associated with rituximab, the mortality was 90 % [17].

Epratuzumab, which targets CD22 on human and malignant B-cells, has been used in lupus and in oncology patients. The preliminary data have not suggested any particular infectious risk, but increasing use may reveal a pattern similar to rituximab.

12.5 Interleukin-6 Antagonists

Interleukin-6 (IL-6) is both a pro-inflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response to trauma, especially burns or other tissue damage leading to inflammation. In terms of host response to a foreign pathogen, IL-6 has been shown, in mice, to be required for resistance against *Streptococcus pneumoniae* [20].

The (IL-6) antagonist tocilizumab has been used mainly in adults with rheumatoid arthritis and currently has a benign safety profile. A Cochrane meta-analysis of eight randomised controlled trials (3,334 participants; 2,233 tocilizumab and 1,101 controls) found that the tocilizumab group was a non-significant 1.18 times more likely to have any infection or infestation [21]. However, a non-Cochrane systematic review of six studies found that the higher but usual dose of 8 mg/kg was associated with a significant increase in risk of infection (Odds Ratio of any infection = 1.30, of serious infection = 1.78) [22]. There was no clear pattern to the infections incurred by the tocilizumab group in either meta-analysis.

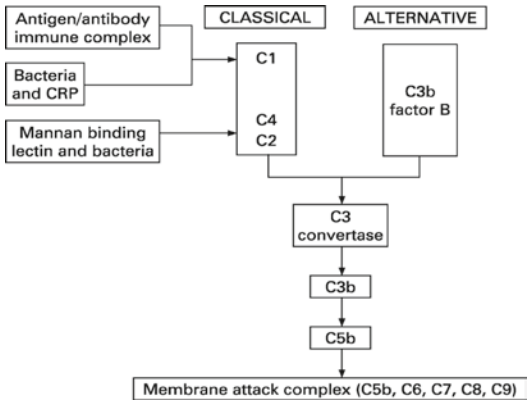

Fig. 12.1 Diagrammatic representation of the complement cascade

12.6 Interleukin-1 Antagonists

Interleukin-1 (IL-1) is produced in response to inflammatory stimuli including infection and mediates various physiological responses, including inflammatory and immunologic reactions, notably lymphocyte proliferation and fever. Anakinra (Kineret) is an IL-1 receptor antagonist, used in rheumatoid and sometimes in juvenile idiopathic arthritis. A Cochrane systematic review found 2,876 patients in trials, but the incidence of serious infections was only reported for 1,900 patients. The incidence of serious infections was "clinically higher", but not statistically different, in the anakinra (25/1,366 patients, 1.8 %) versus the placebo group (3/534 patients, 0.6 %). The pattern was mainly bacterial infections (cellulitis, bone and joint infections and pneumonia) [23].

12.7 Complement Pathway Antagonists

The monoclonal antibody eculizumab is being used increasingly to treat adult patients with paroxysmal nocturnal haemoglobinuria, whose red cells are susceptible to complement-mediated lysis. Eculizumab targets the C5 component of the complement cascade. We know that there are familial disorders that can cause deficiency of any of the terminal components or membrane attack complex of the complement cascade (C5 to C9). The complement cascade occurs on the bacterial cell surface and the membrane attack complex punches a hole in the bacterial cell surface (see Fig. 12.1). Congenital deficiency in C5, C6, C7, C8 or C9 predisposes to meningococcal or gonococcal infections [24]. It is not surprising, therefore, that 3 of 196 adult patients receiving eculizumab developed meningococcal infection [25], and that meningococcal immunisation is strongly recommended for all patients starting eculizumab.

12.8 T-cell Activation Antagonists

Two drugs have been developed that block T-cell activation. Abatacept and belatacept are fusion proteins composed of an immunoglobulin linked to the extracellular domain of CTLA-4, which is a molecule crucial for T-cell co-stimulation, selectively blocking the process of T-cell activation. Abatacept and belatacept differ by only two amino acids. They are intended to provide extended graft survival. Preliminary studies have not reported significant infections with abatacept, but there have been concerning reports that belatacept has been associated with cases of PML and of EBV-related lymphoproliferative disease. The FDA has warned that concurrent use of abatacept and TNF antagonist appears to increase the risk of serious infection compared with TNF antagonists alone.

12.9 Diagnosis and Treatment

It is obviously critical to consider infections, including opportunist infections, in any patient who develops compatible symptoms when taking a biologic, and to follow the usual infectious disease practice of trying to obtain tissue to make a microbiological diagnosis.

12.10 Prevention

Appropriate preventative measures will depend on the nature of the biologic and the pattern of infections anticipated.

1. Screening for tuberculosis with Tuberculin Skin Test and/or interferon-gamma release assay: most relevant for TNF biologics, but also recommended for anakinra and tocilizumab.
2. *Pneumocystis* prophylaxis: consider with TNF biologics
3. Immunisation
   a. Meningococcal conjugate vaccine: all taking eculizumab, consider for B-cell biologics
   b. Pneumococcal conjugate vaccine: all taking biologics
   c. Hepatitis B: TNF biologics, B-cell antagonists (rituximab).

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