Infections in biological agents used in rheumatic disease

Immunosuppression and biological therapies are being used exponentially to treat inflammatory arthritis and connective tissue diseases. This article discusses the potential infectious complications of these therapies.

Rheumatoid arthritis affects 1% of the UK population. Infections are commonly seen in patients with rheumatoid arthritis (Doran et al, 2002a), although it is not clear whether this is the result of the immunosuppression they receive or the disease itself. Seropositivity, extra-articular manifestations of disease, high erythrocyte sedimentation rate and reduced functional capacity in rheumatoid arthritis are associated with an increased risk of infection (Doran et al, 2002b).

Over the last 20 years, the management of rheumatoid arthritis has changed significantly. Evidence shows that early diagnosis and aggressive reduction of disease activity are vital to prevent long-term damage and disability (Smolen et al, 2010). 'Treating to target', aiming to reduce levels of inflammation by aggressive immunosuppressive therapy, has lead to a large increase in patients receiving these treatments and a drive to explore new therapeutic targets.

The US Food and Drug Administration approved methotrexate in 1998 and infliximab, the first biologic agent for rheumatoid arthritis, was licensed in 2001. Now there are five available anti-tumour necrosis factor alpha (TNFα) agents, in addition to therapies targeting B cells, IL-1, IL-6 and T cell co-stimulation. More recently small molecule immune modulators (kinase inhibitors) have also been developed and are currently in phase III clinical trials for rheumatoid arthritis.

Despite the increasing use of more targeted biological therapies, the risk of infection remains. This article reviews the literature and highlights the reported risks associated with these drugs.

Anti-TNFα therapy

Five anti-TNFα therapies are currently available. Infliximab, the first licensed, is a chimaeric (mouse–human) monoclonal antibody, which is usually given intravenously every 6–8 weeks. Adalimumab and golimumab are fully humanized monoclonal antibodies, given subcutaneously fortnightly or monthly respectively. Certolizumab is a humanized Fab' fragment conjugated to polyethylene glycol to improve drug solubility and reduce immunogenicity, given fortnightly. Etanercept is a fusion of two soluble TNFα receptors. This has the shortest half-life of all the anti-TNFα agents (approximately 70 hours).

The most common indication for their use is rheumatoid arthritis, although they are also licenced for psoriasis, psoriatic arthritis and ankylosing spondylitis. Infliximab and adalimumab also have a UK licence for Crohn's disease and infliximab is the only anti-TNFα currently licenced for ulcerative colitis.

The anti-TNFα therapies appear to have similar efficacy in outcomes for rheumatoid arthritis, although there is a differential risk of infection. Clinical trials and post-marketing surveillance have shown an increased susceptibility to infection, particularly serious infection requiring hospitalization (Curtis et al, 2007). The highest risk is within the first 6 months of therapy (Galloway et al, 2011), and with concomitant corticosteroid use. The risk of any infection is lower with etanercept than the monoclonal antibodies (Salmon-Ceron et al, 2011).

During the first randomized controlled trial of infliximab, one patient developed tuberculosis and one coccidiomycosis (Maini et al, 1999). Subsequently an increased risk of tuberculosis with anti-TNFα therapy has been shown. Reactivation of latent tuberculosis can lead to symptoms within the first 6 months, but can also occur later in the treatment course (Chen et al, 2012). In 2005, the British Thoracic Society published guidelines to ensure all patients are screened for latent tuberculosis infection before starting anti-TNFα therapy. Despite screening there is still an increased risk of tuberculosis compared to the healthy population. This is 3–4 times higher with adalimumab than etanercept. The risk continues after cessation of therapy, and extrapulmonary or disseminated disease is more common (Dixon et al, 2010). To date there have been no cases of drug-resistant tuberculosis emerging from anti-TNFα therapy.

TNFα plays a key role in hepatitis B virus clearance, thus with TNFα inhibition viral replication increases. Reactivation of hepatitis B virus has been seen in carriers of hepatitis B surface antigen (HBsAg), who had not received viral prophylaxis (Vigano et al, 2012). The risk is greater in those receiving infliximab, than adalimumab

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and etanercept. Although cases of hepatitis C reactivation have been reported, this has not caused significant morbidity or mortality, at worst causing elevated liver function tests (Brunasso et al, 2011; Vigano et al, 2012). In comparison, hepatitis B virus reactivation has lead to fulminant liver failure and death. Both hepatitis B and hepatitis C virus serology should be checked before starting anti-TNFα therapy. It is suggested that lamivudine prophylaxis should be given to those with HBsAg and continued for 3–6 months after stopping anti-TNFα therapy (Vigano et al, 2012).

The most frequent infections with anti-TNFα agents are common bacteria causing pulmonary or soft tissue infections. However, there is also an increased risk of opportunistic infection. The French registry data, RATIO, have shown increased bacterial infections (listeria, nocardia, atypical mycobacteria and non-typhoid bacteriaemic salmonellosis), viral infections (herpes simplex, varicella zoster and disseminated cytomegalovirus), fungal infections (pneumocystosis, invasive aspergillosis and cryptococcosis) and parasitic infections, including legionella (Salmon-Ceron et al, 2011). This is also reflected in the UK registry data (British Society of Rheumatology Biologics Register) (Dixon et al, 2006).

Anti-TNFα therapy has been used in a small number of patients with inflammatory arthritis and HIV, who were resistant to standard therapy. Those with CD4 counts >200/mm^3, viral load <60 000 copies/mm^3 and concurrent use of highly active anti-retroviral therapy had safe outcomes in terms of infection, and no adverse effect on their CD4 count (Cepeda et al, 2008).

Anti-B cell (CD20) therapy

Rituximab (anti-CD20 therapy) was first used as a treatment for non-Hodgkin's lymphoma in 2007. Since then, there has been extensive testing for autoimmune diseases such as systemic lupus erythematosus, Sjögren's syndrome, vasculitis, idiopathic immune thrombocytopaenia and myositis.

CD20 expressing B cells produce pro-inflammatory cytokines such as TNFα and IL-6, the anti-inflammatory cytokine IL-10 and autoantibodies. These play a vital role in the aetiopathogenesis of rheumatoid arthritis and other connective tissue diseases.

In the first 2–6 months following rituximab therapy, there is a rapid depletion of early and mature B cells, while leaving long-lived plasma and stem cells untouched. Serum immunoglobulin levels may fall, although the rates of serious infection do not significantly increase during this time (Covelli et al, 2010). Concomitant use of corticosteroids and older age may contribute to increased infection risks. Long-term effects of B cell depletion, subsequent reduction of serum immunoglobulins and the risk of infection remain unclear.

There have been serious infections reported during the phase III clinical trials, most commonly upper respiratory tract and urinary tract, a few of which have been fatal. As with anti-TNF, this is more common in the first few months following treatment. However, the risk is not significant compared to placebo (Fleischmann, 2009).

There were no cases of reactivation of hepatitis B or tuberculosis from the initial clinical trials. However, the data from lymphoma trials have previously reported reactivation of hepatitis B (Sera et al, 2006) and C (Ennishi et al, 2008) viruses. There have been a few reported cases of opportunistic infections such as *Pneumocystis jirovecii* pneumonia and progressive multifocal leukoencephalopathy (Covelli et al, 2010).

Progressive multifocal leukoencephalopathy is a subacute degeneration of the CNS, caused by reactivation of the JC virus. This occurs in immunosuppressed people, most commonly those infected with HIV. However, it has been reported in association with rituximab treatment cases of haematological malignancies, systemic lupus erythematosus and rheumatoid arthritis. The worldwide prevalence of progressive multifocal leukoencephalopathy in patients with rheumatoid arthritis and B cell depletion is approximately 4 per 100 000 (Palazzo and Yahia, 2012).

IL-6 antagonists

Tocilizumab is a fully humanized monoclonal antibody to both soluble and membrane IL-6 receptors. It is given intravenously on a monthly basis. It was first licensed in the UK in 2009 for rheumatoid arthritis. It has also been used in Castleman's disease and systemic onset juvenile idiopathic arthritis. There are ongoing trials to use this drug in Crohn's disease and systemic lupus erythematosus. It has also been used off licence in a number of chronic inflammatory diseases including Takayasu's arteritis and polymyalgia rheumatica.

Clinical trials have shown the most likely adverse event is infection, with an increased incidence of serious infection (Nishimoto et al, 2010). A review of patients receiving tocilizumab in a German rheumatology clinic showed the infection risk was higher than previously observed (Lang et al, 2011). Predictors of serious infection included concomitant therapy with prednisolone or leflunomide, previous rituximab exposure or active rheumatoid arthritis (with high disease activity score)(Lang et al, 2011). No increase in reactivation of hepatitis or tuberculosis has been seen. Tocilizumab is seldom associated with neutropaenia, although this does not appear to be associated with an increased risk of infection (Nishimoto et al, 2010).

IL-6 induces the expression of acute phase proteins by hepatocytes, including C-reactive protein. In infection, tocilizumab may prevent a rise in C-reactive protein levels and can mask clinical symptoms and signs. This can make diagnosis more challenging. Therefore a thor-

ough history, examination and clinical judgment are required, more than relying on biochemical results or typical clinical signs (Fujiwara et al, 2009).

Several cases of herpes zoster and herpes simplex have been reported from the phase III clinical trials (Nishimoto et al, 2009). There have also been several cases of non-tuberculous mycobacteria, which may have been identified inadvertently (Mori et al, 2011).

Despite these risks, a Cochrane review did not conclude a significant increase in infections compared to placebo (Singh et al, 2011).

T cell co-stimulation blockade (CTLA-4 antagonists)

For T cells to activate, they require co-stimulatory signals from antigen-presenting cells. The best characterized pathway is the engagement of the CD28 cell surface marker on T cells with CD80/86 on antigen-presenting cells. CTLA-4 antagonists (abatacept) bind to the CD80/86 to prevent T cell activation (Kremer et al, 2003). Activated T cells orchestrate the pro-inflammatory cascade in rheumatoid arthritis.

Abatacept has a UK licence for severe refractory rheumatoid arthritis, but only after an adverse event with rituximab. It has also been used off licence in psoriatic arthritis, ankylosing spondylitis and systemic lupus erythematosus. It is currently given monthly, intravenously, although a subcutaneous alternative will be available soon.

Phase III trials have shown an increased rate of bacterial infections with abatacept compared to placebo (Weinblatt et al, 2006), although the rate of serious infections is not increased (Salliot et al, 2009). However, abatacept has the best safety rating of all the biologics at present (Singh et al, 2011), with no increased rates of opportunistic infections or tuberculosis (Salliot et al, 2009).

IL-1 antagonists

Anakinra is a recombinant protein that blocks IL-1 signaling by binding to the IL-1 receptor. It is given as a daily subcutaneous injection.

This has regulatory approval for rheumatoid arthritis, but is not approved in the UK by the National Institute for Health and Clinical Excellence. It is used off licence in systemic onset juvenile idiopathic arthritis, chronic gout and autoinflammatory diseases such as familial Mediterranean fever.

Individual phase III trials and 3-year open label data following the randomized controlled trials have not shown an increased safety signal for infection. Meta-analyses have not shown significant rates of infection compared to other biologics (Singh et al, 2011), although the risk is higher compared to abatacept and rituximab (Salliot et al, 2009).

Single case reports have associated anakinra use with reactivation of tuberculosis, visceral leishmaniasis, varicella infections and *Moraxella catarrhalis* causing septic arthritis.

Janus and spleen tyrosine kinase inhibitors

Janus kinase and spleen tyrosine kinase inhibitors are novel oral 'small molecule' therapies. They play a critical role in meditating the intracellular signal transduction of cytokines involved in immune regulation. Although they are currently being used in phase III trials for rheumatoid arthritis, they have not yet been licensed.

Janus kinase inhibitors, e.g. tofacitinib and VX-509, target cytoplasmic transmembrane cytokine receptors, altering transcriptional factors such as STAT. These are critical for production of interleukins that activate lymphocytes and affect their proliferation and function.

Spleen tyrosine kinase inhibitors modulate immune signaling in cells bearing complement crystallisable g-activating receptors including B cells, mast cells, macrophages, neutrophils and synoviocytes. Fostamatinib is a prodrug that inhibits downstream activations intracellular signaling, such as MAP kinases, ultimately leading to production of pro-inflammatory cytokines including IL-6.

Phase III trials are currently ongoing. There does not seem to be any increased rate of opportunistic infections, although an increased rate of respiratory and urinary tract infection is noted compared with placebo (Weinblatt et al, 2010).

Biologic therapies in combination

Only small numbers of patients have been treated with combinations of biologic therapies, because of the safety concerns of potential serious infections.

A randomized controlled trial added rituximab to either etanercept or adalimumab therapy (Greenwald et al, 2011). The study did report an increased number of serious infections (mostly upper or lower respiratory tract), although there were no opportunistic infections. The rates are considered consistent with the results of clinical trials of rituximab in combinations with methotrexate.

Abatacept used in combination with etanercept showed a higher frequency of serious infections compared to etanercept with placebo (Weinblatt et al, 2007), without any additional clinical benefit for rheumatoid arthritis. Similar outcomes were seen when combining anakinra with etanercept (Genovese et al, 2004).

Abatacept has also been added to anakinra in the treatment of systemic onset juvenile idiopathic arthritis in four cases, and there did not seem to be an increase in number of infections (Record et al, 2011).

Conclusions

Biologic therapies are now flooding the market for chronic inflammatory diseases. They have transformed management of many conditions, previously resistant to standard therapy.

In general, biologic therapies have an excellent side-effect profile, with only a modest increase in the risk of infections. The first 6 months of therapy is associated with the highest risk. Combinations of biologic agents

with corticosteroids do increase rates of infection and further studies need to be performed to establish the risks of mixing biologic agents.

There are specific infections associated with each of the biologic therapies. All physicians need to be aware of these, especially in patients presenting with unexplained symptoms. It is imperative that relevant screening and prophylaxis protocols are followed. BJHM

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KEY POINTS

- The risk of infections is increased in patients with rheumatoid arthritis.
- Anti-TNF alpha therapy increases the risk of reactivation of tuberculosis, thus patients should be screened before therapy.
- Although biologic agents have an excellent side-effect profile, there is a modest increase in risk of infections.

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