Netherlands
The Journal of Medicine

REVIEW

Infliximab therapy in Crohn's disease: safety issues

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ABSTRACT

Infliximab has become a valuable addition to the therapeutic arsenal for Crohn's disease. Although the rate of adverse events was relatively low in the premarketing trials, several investigators have recently reported experience in large groups of patients. This has shed more light on safety aspects of infliximab therapy, which should change the approach towards patients prior to infliximab infusion. This review discusses some immunological aspects that are relevant for infliximab therapy and provides guidelines for daily practice.

INTRODUCTION

It is only a decade ago that the first patient received anti-TNF antibodies for severe Crohn's disease (CD), demonstrating a remarkable response after a single intravenous gift.[1] Today, more than 300,000 patients, both with CD and with rheumatoid arthritis (RA), have been treated with infliximab. Infliximab can induce and maintain remission of Crohn's disease that is refractory to standard therapy, while reducing or eliminating the need for steroid use. The success of this innovative therapeutic strategy is to a great extent the result of a better understanding of the immunological defects in the gut mucosa.[2,3] Although the addition of infliximab to the therapeutic arsenal in CD has made a substantial impact on the daily life of large groups of patients, it is now known that this therapy is associated with immunosuppression that greatly increases the susceptibility to certain infections. In addition, infliximab is immunogenic, and is associated with the induction of antidouble-stranded DNA (anti-ds-DNA) antibody formation. Moreover, several important questions with regard to the safety of infliximab therapy remain to be answered. These questions include the long-term toxicity of infliximab, assessment of toxicity in patients with comorbid diseases, identifying patients at risk for infliximab toxicity, and evaluation of the effect of drug combinations on toxicity. This review will summarise the current knowledge on the safety profile of infliximab and attempt to bring these facts into a practical framework for physicians frequently treating CD patients.

GENERAL SAFETY ISSUES

Safety issues relating to biotechnologically manufactured drugs have been categorised into four groups.[4]

Group 1: infectious agents

There is a risk of infectious agents originating from the cell lines used in the manufacturing process being transmitted to patients.[5] This concern has been particularly focussed on viral contamination. For this purpose, the hybridoma cell line responsible for the production of the monoclonal antibody as well as the cell bank and end product are extensively screened, and no contaminating viruses have been detected.

Group 2: hypersensitivity

The likelihood that biotechnologically manufactured drugs will produce a host immune response is dependent on the quantity of 'foreign' material. A murine type of antibody will often induce hypersensitivity reactions, whereas with recombinant human antibodies this is not the case. With

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infliximab, these hypersensitivity reactions occur in about 21% of patients, and associated symptoms include headache, nausea, shortness of breath, flushing, dizziness and pruritus (discussed below). Apparently, such reactions are mediated by mast cell release, but the precise mechanism has not been characterised. Infliximab is an engineered IgG1 murine human chimeric monoclonal antibody containing 75% human protein and 25% murine protein.[6] The murine 'business end' of the molecule is immunogenic, and human antichimeric antibodies (HACAs) occur in 28% of patients. HACA formation is associated with an increase in the incidence of infusion reactions, and the formation of immune complexes can give rise to a syndrome that resembles serum sickness.

Three strategies can be employed to minimise these hypersensitivity reactions: first, co-administration of other immunosuppressive drugs has been shown to reduce the risk of sensitisation to therapeutic antibodies. Secondly, desensitisation is a strategy to diminish specific IgE-induced responses towards a specific therapeutic antibody. In general, small but increasing quantities of the antigen-containing antibody are administered over a period of hours or more gradually over weeks or months. As a result, specific IgE levels decrease and possibly specific T-cell tolerance is induced. The role of IgE during infliximab hypersensitivity reactions has not been established, however successful desensitisation has been reported in two Crohn's disease patients.[7] Finally, therapeutic biologicals can be 'humanised' for instance by grafting a complementarity determining region into the variable domain of a human antibody or by producing wholly humanised monoclonal antibodies.[8]

Group 3: opportunistic infections or neoplasm during biological treatment

Integrity of the immune system is essential for defence against infectious organisms and the control of tumour antigens. Although our enthusiasm over the use of targeted immunotherapy is enormous, long-term immunosuppression holds the risk of interfering with the coherence of the immune system. A clear example has been the reactivation of tuberculosis (TBC) in patients treated with infliximab (this will be discussed further in this article). Although the postmarketing surveillance has not shown any increased risk of cancer yet, other biological therapy has been associated with for instance lymphomas.[9]

Group 4: monoclonal antibodies producing cell lysis of activated macrophages and T cells

Antibodies directed against cell surface proteins are capable of inducing cell death either by activation of the complement system or by the induction of apoptosis.[10] A sudden release of cytokines from the targeted immunocompetent cells can result in clinical symptoms of fever, chills and organ dysfunction. This problem can be overcome by only utilising the F(ab)2 fragments of the antibody, thereby retaining the capacity of antigen binding, but eliminating the Fc-fragment's ability to activate complement. Although the mechanism of action of infliximab is thought to be related to induction of apoptosis of T lymphocytes, in contrast to other monoclonal antibodies (OKT3, anti-CD4 antibodies), no cell lysis or cytokine release syndromes are observed after infliximab infusion.

REPORTED ADVERSE EVENTS

Data from the first preclinical studies in both RA and CD patients did not reveal major safety concerns, partly because some of the adverse events occurred after a drug holiday. During recent years, numerous studies have been published, reporting on various events including infusion reactions, delayed-type hypersensitivity reactions, formation of HACAs and infections.[11-14] We will review the most important adverse reactions and propose several management guidelines.

Infusion reaction

Definition: An infusion reaction is defined as any adverse event that occurs during or within two hours following an infusion of infliximab.

Type of hypersensitivity: Anaphylactoid (IgE independent).

Signs and symptoms: Most infusion reactions included headache, nausea, chest pain, dizziness, urticaria, dyspnoea, pruritus and flushing. These symptoms are usually self-limiting.

Complication: Severe anaphylaxis including shock, laryngeal oedema and bronchospasm.

Management: To stop infliximab infusion temporarily, and administer antihistamines and corticosteroids intravenously (i.e. 2 mg clemastine i.v. and 25 mg prednisolone i.v.). When symptoms have resolved, restart the infusion at a slower rate. Most patients respond adequately to treatment and can complete the infusion. Patients who have already experienced an infusion reaction should receive antihistamines and corticosteroids intravenously (i.e. 2 mg clemastine i.v. and 25 mg prednisolone i.v.) 30 minutes prior to infusion.

Comment: Infusion reactions develop in approximately 22% of infliximab-treated patients compared with 9% of placebo-treated patients.[15] They are similar to infusion reactions observed during administration of intravenous immunoglobulins.[16] Although severe anaphylactic reaction is rarely observed in infliximab-treated patients,[11] if it does occur infliximab therapy should be discontinued.[7,17,18] Successful desensitisation and therapeutic infusion using parenteral dose escalation in an intensive care unit setting has recently been reported.[7] Infusion reactions are more common in patients who have developed HACAs.[15] The

formation of HACAs occurs in approximately 28% of infliximab-treated patients, although higher rates have also been reported.[19,20] Concomitant therapy with methotrexate, azathioprine or 6-mercaptopurine reduces the incidence of HACA formation,[20] and probably reduces the rate of infusion reactions. The aforementioned premedication does not seem mandatory in patients who did not experience any infusion reaction during previous infusions.[21] We are of the opinion that if the decision has been made to initiate infliximab treatment, be it for remission induction or maintenance therapy, then all patients should at the same time start an immunosuppressive drug (i.e. azathioprine, 6-MP or methotrexate).

Delayed-type hypersensitivity reaction (DTH)
Definition: An immune reaction in which T cell-dependent macrophage activation and cytokine-mediated inflammation cause tissue injury. This type of reaction usually occurs three to 12 days after infliximab infusion in a patient who had previously been treated with infliximab.
Type of hypersensitivity: Type IV hypersensitivity disorder.
Signs and symptoms: Days after the infliximab readministration, patients can develop myalgia, rash, fever, polyarthralgias, pruritus, facial, hand or lip oedema, urticaria, sore throat, dysphagia and headache.[22] The incidence of DTH seems low, and was reported to be 2% in the ACCENT I study.[23]
Complication: A severe DTH reaction resulting in adult respiratory distress syndrome (ARDS) in a patient who received infliximab after a drug holiday of 15 months was recently reported.[24]
Management: In our opinion, the occurrence of a DTH does not exclude patients from future infliximab re-infusion. However, our advice is to administer premedication, similar to that given during infusion reactions, on following infusions. Also, the use of concomitant immunosuppressive medication seems necessary. Naturally, infliximab therapy is discouraged in patients who have experienced a severe episode of DTH requiring hospitalisation.
Comment: Parallel to infusion reactions, the occurrence of DTH is probably more frequent in HACA-positive patients. Again, we would like to underscore the necessity to initiate immunosuppressive drugs alongside the infliximab treatment period. Since the majority of patients will neither experience infusion reactions or DTH, we do not recommend HACA assessment routinely in infliximab-treated patients.

Serum sickness
Definition: An immune reaction caused by a large dose of protein antigen (i.e. chimeric antibody) resulting in the deposition of antigen antibody complexes in blood vessel walls, especially in the kidneys and joints.
Type of hypersensitivity: Type III hypersensitivity disorder.
Signs and symptoms: Within days to weeks after the infliximab infusion, symptoms of skin rash, fever, myalgias, polyarthritis and even glomerulonephritis develop as a result of immune complex deposition, complement activation and neutrophil-driven inflammation.
Management: Management is similar to that of DTH; if a patient suffers from an episode of serum sickness, premedication is mandatory upon infliximab readministration as well as the use of an immunosuppressant. During such an episode, patients can be treated with a short course of prednisolone. The use of infliximab must be stopped, however, if symptoms have not resolved completely (i.e. renal function, arthralgias).
Comment: The incidence of serum sickness or a serum sickness-like reaction is probably lower than that of DTH. In our experience with 600 infliximab infusions, we observed similar symptoms in two patients. Neither of them required hospitalisation.[12] In the reported cases so far, laboratory investigations showed high titres of HACAs without low levels of complement or active urine sediments.

Tuberculosis and other infections
The rate of infection is higher in infliximab-treated patients (36%) than in those receiving a placebo (26%).[15] Frequently reported infections are upper respiratory infections and urinary tract infections. Serious infections that have been associated with infliximab include TBC, *Pneumocystis carinii* pneumonia, aspergillosis, histoplasmosis, listeriosis and cytomegalovirus.[25-30] The incidence seems to be very low (about 1:2000), but infliximab should not be administered to patients with a known active infection. Active screening for the above-mentioned micro-organisms has not been advised with the exception of TBC, which will be discussed below.
Clinical relevance: TBC has been reported in 101 of approximately 175,000 infliximab-treated patients, of whom 21% suffering from Crohn's disease (data on file, Centocor Inc, Malvern, USA). In virtually all patients, disease was a result of reactivation of latent tuberculosis. Importantly, in most patients the clinical presentation was aspecific and many patients had extrapulmonary disease. Hence, diagnosis of active tuberculosis in infliximab-treated patients requires a high degree of suspicion and extensive diagnostic workup. Most patients were on concomitant therapy (corticosteroids, azathioprine, methotrexate). A higher incidence was seen in patients with rheumatoid arthritis, in female patients and in older patients. In a large Dutch cohort of infliximab-treated CD patients, TBC reactivation was not observed.[12] However, the current recommendations are to screen all patients before infliximab therapy using the purified protein derivative skin test (PPD).[22]
Who is at risk: An increased risk of TBC exists in infliximab-treated patients with latent TBC or with a high risk of tuberculous reactivation. This later is defined as: 1) a history of TBC treated before 1970 or not treated for at least six

months including at least two months on the rifampicin-pyrizinamide combination; 2) in response to an intradermal tuberculin test done more than ten years after the last BCG vaccination, a wheal larger than 10 mm in diameter or a blister, with no history of active TBC or of TBC treatment; 3) residual tuberculous lesions larger than 1 cm^3 in size with no certainty that eradicative treatment was received.[31] TBC screening recommendations: General consensus has been reached over the requirement of a thorough medical history and physical examination together with the PPD test prior to infliximab infusion. French recommendations also include a routine chest X-ray for all patients.[31] Naturally, all PPD-positive patients, or patients who have received TBC immunisation (bacillus Calmette-Guérin), should undergo a chest X-ray. If the chest X-ray is negative in a patient with a positive PPD he or she should be treated for a latent TBC before infliximab can be administered. If the chest X-ray is positive in PPD-positive patients, then patients should be treated for active TBC before infliximab therapy. TBC treatment schedules of either latent or active TBC are beyond the scope of this review.

Miscellaneous

Infliximab-induced lupus: Formation of the autoantibodies, antinuclear antibodies (ANA) and anti-ds-DNA antibodies has been reported in 20 to 40% of infliximab-treated patients.[15] Usually, titres are low and only few patients with autoantibodies develop clinical evidence of lupus. Thus, evidence of autoantibodies does not exclude patients from infliximab therapy; concomitant use of immunosuppressants will reduce the frequency of autoantibody development.

CONCLUSIONS AND RECOMMENDATIONS

In the near future, several biological therapies for inflammatory bowel disease will be added to the therapeutic armamentarium. Infliximab was first registered in the Netherlands, and extensive worldwide infliximab use in large groups of patients has enabled a detailed risk analysis. Most of the safety issues discussed here are relatively predictable and directly related to the mechanism of action of these drugs. Being a chimeric antibody, hypersensitivity reactions and formation of antibodies were likely to appear. Recently published data on frequency and management of adverse events are important for guiding physicians. However, in our opinion, it will also be crucial for all physicians treating these groups of patients to be aware of and understand the fundamental immunological mechanisms that are related with this kind of therapy. Not only will he or she be better prepared for the management of these events, but also the proper use of concomitant immunosuppressive therapy will be promoted. Finally, adequate patient instruction has been shown critical for drug compliance, and thorough knowledge of basic concepts of biological therapy will probably facilitate the doctor-patient information process.

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