Drugs 2004; 64 (16): 1767-1777
0012-6667/04/0016-1767/$34.00/0

Managing Immunogenic Responses to Infliximab

Treatment Implications for Patients with Crohn's Disease

Peter D. Han and *Russell D. Cohen*

The University of Chicago Medical Center, Chicago, Illinois, USA

Contents

Abstract

Infliximab is a tumour necrosis factor (TNF)-α antagonist that has revolutionised the treatment of Crohn's disease and rheumatoid arthritis. However, infliximab therapy can be complicated by a variety of adverse reactions. Acute infusion reactions occur during or shortly after infusion and typically consist of fever, chills, nausea, dyspnoea and headaches. Delayed reactions, characterised by myalgias, arthralgias, fever, rash, pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache may occur 3–12 days after infusion. Although the mechanisms of these reactions are not yet clearly defined, emerging evidence indicates that these reactions may be associated with the immune response against infliximab and the development of antibodies to infliximab.

A number of studies have identified protective factors that may minimise adverse reactions, presumably related to the immune response against infliximab. Factors that may be protective by helping to establish immune tolerance for the foreign infliximab protein include concomitant administration of immunomodulators or corticosteroids, starting infliximab therapy with a 0, 2, 6-week induction regimen, maintenance dose administration with infusions every 8 weeks or less, and avoiding long periods between infusions.

Infliximab therapy also may have other immunological consequences. There is evidence that infliximab may impede the appropriate immune response to a number of pathogens, prohibiting its use in patients with active infections. In addition, patients should be screened and appropriately treated for tuberculosis

before initiating infliximab therapy. The development of autoantibodies, such as antinuclear antibody or anti-ds-DNA, has also been described with infliximab therapy, although the development of clinical lupus-like syndrome is rare. While there is a theoretical risk of increased rate of malignancies due to antagonism of TNFα, to date there is no clear evidence of such an effect. In addition, cardiac and neurological adverse events associated with infliximab therapy have been described. The mechanism for these adverse events is unclear.

In summary, infliximab therapy can be an effective treatment for Crohn's disease; however, a number of immunological consequences and adverse events may complicate the infusion of this agent. Appropriate prophylaxis and therapy of these adverse reactions will allow infliximab to be used safely in the vast majority of patients.

The introduction of infliximab, an infusible chimeric antibody specific for the pro-inflammatory cytokine tumour necrosis factor (TNF)-α, has led to remarkable improvements in the therapy of Crohn's disease, as well as rheumatoid arthritis. Clinical trials have shown that infliximab is effective in the induction and maintenance of remission in patients with moderate to severe Crohn's disease. Infliximab has also proven effective in healing Crohn's mucosal lesions and closing Crohn's-related perianal, rectovaginal and enterocutaneous fistulas.[1-5] Infliximab has also been shown to be effective as a steroid-sparing agent in patients with steroid-dependent Crohn's disease.[6]

Clinical trials and open-label experience with infliximab for the treatment of Crohn's disease have found that the median duration of remission to a single infusion of infliximab is approximately 8–12 weeks. Repeat infusions are necessary in most patients to maintain remission;[4] thus, there is a growing population of patients who have received multiple infusions of the drug. Numerous studies have described adverse events associated with infliximab infusion, including infusion reactions, delayed reactions, infectious complications, development of autoantibodies or lupus-like syndrome, potential development of malignancy, and cardiac and neurological sequelae of infusion. Emerging evidence links several of these adverse events to the immunological consequences of infusion of a foreign protein. Ongoing research elucidating the mechanisms of these adverse reactions and immunological consequences may guide effective therapy and appropriate prophylaxis against further adverse reactions.

1. Reactions During the Infusion Period (Infusion Reactions)

A number of clinical trials of infliximab in patients with rheumatoid arthritis and Crohn's disease have described adverse events, termed infusion reactions, occurring during infusion or in the immediate period 1–2 hours after infusion.[1,2,7,8] These reactions are typically characterised by symptoms such as fever, chills, nausea, dyspnoea and headache.

Initial clinical trials of infliximab for the treatment of rheumatoid arthritis[7,8] showed that minor infusion-related adverse events (including nausea, headache, cough and malaise) were more common in patients receiving infliximab (82.8%) than patients receiving placebo (57.1%; $p = 0.186$). In a study of 342 patients with active rheumatoid arthritis receiving methotrexate therapy treated with either 3 or 10 mg/kg of infliximab at 0, 2 and 6 weeks and then at 4- or 8-week intervals followed out to 30 weeks, Maini et al.[9] reported that infusion reactions, defined as adverse reactions during infusion or in the hour following infusion, occurred in 16–20% of patients treated with infliximab compared with 10% of patients receiving placebo. Infusion reactions occurred most often with first infusion and most were responsive to slowing of the infliximab infusion. In the group of patients treated

with infliximab, adverse reactions suggestive of an immediate hypersensitivity reaction occurred rarely (hypotension in 8 of 340 [2%] patients and urticaria in 4 of 340 [1%]). Infusion reactions prompted the administration of antihistamines in only 10% of patients, and the majority of infusion reactions were controlled with slowing of the infusion rate. Only 2 of 340 (0.5%) patients were unable to complete infusion because of an infusion reaction (urticaria in one and dyspnoea in one).

Safety data describing infusion reactions from clinical trials of infliximab used for Crohn's disease are similar to the data from trials in rheumatoid arthritis. In an analysis of 129 patients treated with infliximab for fistulising and luminal Crohn's disease, we described infusion reactions as complicating 5–13% of infusions.[10] In 100 patients with Crohn's disease, given 233 infusions of infliximab, Farrell et al.[11] described 27 infusion reactions (12%) in 25 patients. The most commonly observed reactions were lightheadedness/hypotension, chest pain/palpitations, wheeze/cough/dyspnoea, pyrexia and nausea. Infusions were not completed because of infusion reactions in 5 of 233 (2%) instances. In the ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen) I trial, Hanauer et al.[6] studied 573 patients who received infliximab infusions at weeks 0, 2 and 6, and then every 8 weeks until week 46 compared with a control group that received an infliximab infusion at week 0, and subsequently received placebo. Infusion reactions, generally characterised by headache, dizziness, nausea, injection-site irritation, flushing, chest pain, dyspnoea and pruritus, occurred in 106 of 2026 (5%) infusions compared with 23 of 837 (3%) patients in the control group. Infusion reactions led to discontinuation of study agent in only 12 (0.6%) patients. In a study of 500 patients with Crohn's disease treated with 2211 infusions of infliximab, Colombel et al.[12] noted that acute infusion reactions occurred in 19 patients (4%); 14 (3%) of these reactions were attributable to infliximab.

The mechanism behind immediate adverse reactions is unclear. As described earlier this in section, the incidence of infusion reactions that have symptoms such as hypotension, bronchospasm and rash consistent with IgE-mediated type I hypersensitivity reactions is low – probably complicating fewer than 2% of infusions. Even infusion reactions with characteristic symptoms of type I hypersensitivity reactions may be responsive to decreasing the infusion rate.[13] The observations that: (i) most infusion reactions are responsive to slowing the infusion rate; (ii) a large percentage of infusion reactions occur with the first infusion; and (iii) infusion reactions do not reliably occur with each infusion, even without prophylaxis, suggest that a mechanism in addition to type I hypersensitivity is involved. In fact, Cheifetz et al.[14] examined 11 patients who had 14 'immediate' reactions to infliximab and demonstrated that serum tryptase levels, a substance released upon mast cell degranulation, and total IgE were not elevated, providing further support for a mechanism other than type I hypersensitivity for the majority of infusion reactions.

It has been postulated that some infusion reactions may be similar to the anaphylactoid reactions experienced with the administration of other proteins such as intravenous immune globulins.[15] Although the mechanism of these reactions has not been clearly defined, reactions that were seen in patients treated with immune globulin are thought to be related to an excessive protein load resulting from rapid administration rates and are responsive to decreasing the infusion rate.[15-18] Similar infusion reactions characterised by dyspnoea, arthralgias, fever, chills and angioedema were also reported in patients with other diseases who also receive targeted monoclonal therapy such as rituximab, a chimeric murine/human monoclonal antibody directed against CD20 used in patients with non-Hodgkin's lymphoma,[19-21] and alemtuzumab, a human monoclonal antibody directed against CD52 used in patients with chronic lymphocytic leukaemia.[21-23]

Clinical trials have suggested an association between acute infusion reactions and the development of antibodies targeted against infliximab – termed human antichimeric antibodies (HACAs), or anti-

bodies to infliximab (ATIs) in later studies. For the sake of clarity, these antibodies are all referred to as ATIs in this review. In the ACCENT I trial, Hanauer et al.[6] noted that 42 of 254 (17%) infusions in patients with positive ATIs resulted in infusion reactions, compared with only 55 of 656 (8%) in patients negative for ATIs. In a recent study of 125 patients treated with infliximab, Baert et al.[24] noted that high concentrations of ATIs were associated with a significantly higher rate of infusion reactions as well as a decreased duration of infliximab efficacy (35 vs 71 days; $p < 0.001$). Patients with infusion reactions had shorter responses (38.5 vs 65 days; $p < 0.001$) and lower infliximab concentrations at 4 weeks, suggesting neutralisation of the drug by the induced ATIs.

Concomitant treatment with immunomodulators such as 6-mercaptopurine, azathioprine or methotrexate may be protective against development of ATIs and infusion reactions. In both of the studies discussed in the previous paragraph,[6,24] lower titres of ATIs were noted in patients who were taking immunomodulators such as 6-mercaptopurine, azathioprine or methotrexate. Maini et al.[8] noted that patients receiving higher doses of infliximab (10 vs 3 vs 1 mg/kg) were less likely to form ATIs, and also that concomitant therapy with low-dose methotrexate (7.5mg orally once weekly) greatly diminished the appearance of ATIs. Baert et al.[24] also noted a lower incidence of infusion reactions and higher serum infliximab concentrations in patients taking concomitant immunomodulators.

In a similar study, Farrell et al.[25] examined 53 patients with Crohn's disease who received 199 infusions of infliximab; 19 of 53 (36%) developed ATIs, including all seven patients who had serious infusion reactions, and 11 of 15 patients who reported decreased efficacy with subsequent infusions of infliximab were positive for ATIs, compared with none of 21 who reported continued response to infliximab ($p < 0.0001$). Administration of a second infusion within 8 weeks of the first (odds ratio [OR] 0.13; $p = 0.0007$) or concurrent use of immunosuppressants (OR 0.19; $p = 0.007$) significantly reduced ATI formation.

1.1 Management of Acute Infusion Reactions

Infusion reactions are, in most cases, minor and easily managed with supportive care, without prohibiting future doses (figure 1). Most infusion reactions respond to slowing of the infusion rate or temporarily stopping the infusion. For more serious symptoms such as hypotension, dyspnoea or chest pain that indicate the possibility of a type I hypersensitivity reaction or anaphylaxis, initial measures should include stopping the infusion, starting a saline infusion and frequent monitoring of vital signs including pulse oximetry. Administration of an antihistamine (diphenhydramine 25–50mg intravenously) and paracetamol (acetaminophen) may be helpful, while in severe cases, epinephrine (adrenaline), corticosteroids (prednisone 40mg orally or methylprednisolone 100mg intravenously) or nebulised β-adrenoceptor agonists may be administered, but are rarely necessary. If patients recover after initially halting the infusion, our standard practice in all but the most severe infusion reactions is to restart the infusion at half the previous infusion rate. Almost all patients are able to complete the infusion without further problems.

2. Delayed Reactions

Adverse reactions may also occur more than 24 hours after the infusion. These delayed reactions typically occur between 3 and 12 days after infusion and are characterised by myalgias, arthralgias, fever, rash, pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache. The clinical presentation is similar to Gell-Coombs type III (serum sickness) reactions[26] due to immune complex-mediated reactions where circulating antigen-antibody complexes involving IgM or IgG antibodies are thought to activate the immune response.[27]

In one study of 40 patients with Crohn's disease who were retreated with infliximab after a 2- to 4-year period without treatment,[28] 10 of 40 (25%) patients developed delayed adverse reactions. All of these patients had elevated ATI titres. Available data suggest that delayed reactions are less likely to occur among patients who do not have a long hiatus

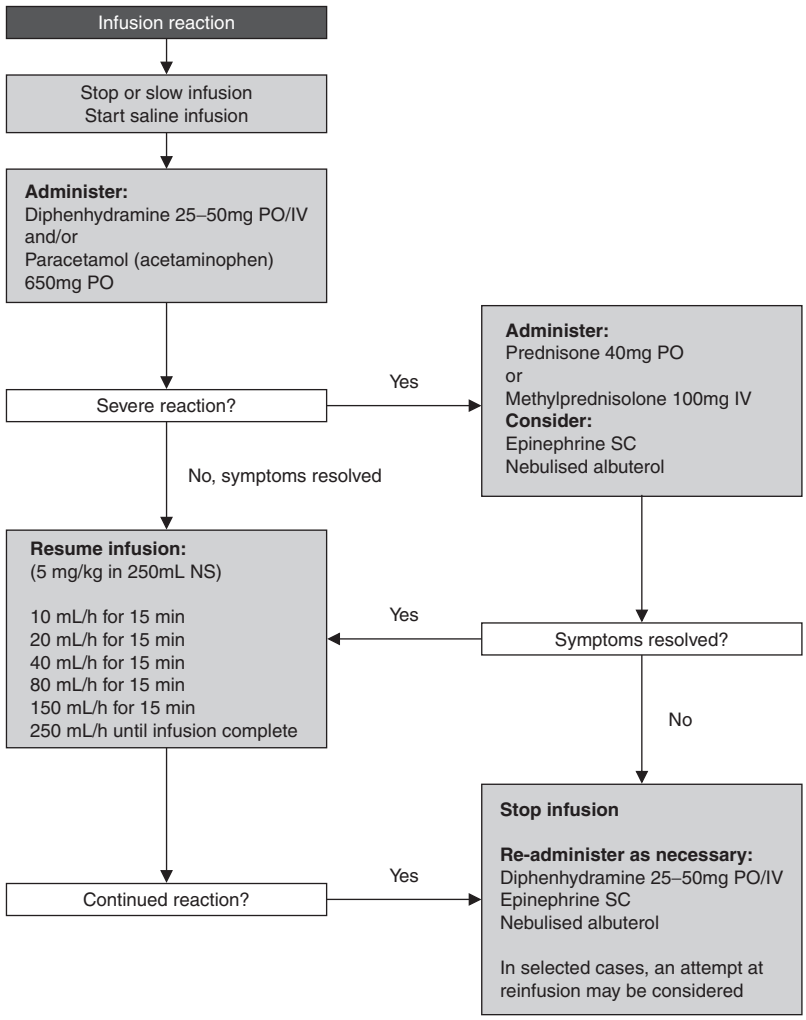

Fig. 1. Algorithm for management of acute infusion reactions to infliximab. **IV** = intravenous; **NS** = normal saline; **PO** = oral; **SC** = subcutaneous.

between infusions, who receive their initial infusion as a series of three, or who are concurrently being treated with an immunomodulator.[28,29]

In the ACCENT I trial where 573 patients with Crohn's disease received infliximab starting with a 0, 2, 6-week induction regimen and then every 8 weeks through 46 weeks, the frequency of delayed hypersensitivity-like reactions was reported as approximately 2%.[6] In a retrospective analysis of patients with Crohn's disease treated with infliximab, Colombel et al.[12] reported that serum sickness-like reactions attributable to infliximab occurred in 14 of 500 patients (3%). Patients with delayed reactions to infliximab have been re-treated safely using premedication regimens described below, including corticosteroids and concomitant immunosuppressant therapy.[30] However, re-treatment of patients with severe delayed reactions may not be appropriate, particularly since high titres of anti-infliximab antibodies that are present in most patients with delayed reactions will limit the efficacy of infliximab in addition to predisposing the

patient to additional risk of a recurrent delayed or acute infusion reaction.[28,31] In patients in whom a delayed reaction is suspected following an infliximab infusion, it may be helpful to check a serum infliximab level 4 weeks after the infusion. If neutralising antibodies are present, infliximab levels will be low, resulting in limited efficacy of the drug.

3. Infectious Complications

Adverse reactions can occur as a result of the potentially immunosuppressive effects of infliximab resulting from antagonism of TNFα. In clinical studies, infections requiring treatment were reported in 35% of infliximab-treated patients compared with 26% of placebo-treated controls.[32] Infectious complications that have been reported include upper respiratory tract infection, urinary tract infection, gynaecological infection, pneumonia, cellulitis, acute diverticulitis, mastitis, herpes zoster, conjunctivitis, influenza and tuberculosis.[1,11,32] In addition, opportunistic infections such as coccidioidomycosis, nocardiosis and cytomegalovirus infection have been reported.[32] In a retrospective analysis, Colombel et al.[12] reported that 41 of 500 patients (8%) treated with infliximab had infectious adverse events that were potentially attributable to infliximab. Despite the large amount of anecdotal evidence, to date there is no controlled study that definitively shows a significantly increased rate of infections in infliximab-treated patients.

Data from clinical trials and epidemiological data strongly suggest an increased susceptibility to reactivation tuberculosis in patients treated with infliximab.[33] Studies in animal models have shown that TNFα is protective against activation of latent tuberculosis. Out of 175 000 infusions given worldwide, the rate of tuberculosis in infliximab-treated patients is generally higher than country-specific background rates. In addition, the pattern of tuberculosis is different from normal. In infliximab-treated patients, the majority of cases (56%) are extrapulmonary and one out of three are disseminated. Patients should be screened and treated for tuberculosis prior to administration of infliximab (figure 2). It is not known how long patients with evidence of tuberculosis infection should be treated before initiation of infliximab. Our practice is to treat patients with latent tuberculosis infection for at least 2 months prior to starting infliximab. Patients with active tuberculosis infection would require more extensive therapy before infliximab treatment can be considered.

4. Autoantibodies and Lupus-Like Syndrome

There have been several reports of the development of antinuclear antibodies (ANA) in patients treated with infliximab for Crohn's disease and rheumatoid arthritis.[32,34-37] Charles et al.[37] examined the development of ANA in patients with rheumatoid arthritis treated with infliximab and noted that ANA were present in 29% of patients before therapy with infliximab. After initiation of treatment, 53% of patients had positive ANA. In clinical trials, approximately 52% of 1261 infliximab-treated patients who tested negative for ANA at baseline developed positive ANA during treatment with infliximab, compared with approximately 19% of 129 placebo-treated patients.[32] Anti-ds-DNA antibodies were newly detected in approximately 17% of 1507 infliximab-treated patients compared with 0% of 162 placebo-treated controls. Development of a lupus-like syndrome, however, was rare. In a retrospective analysis, Colombel et al.[12] reported that 3 of 500 patients treated with infliximab for Crohn's disease developed drug-induced lupus-like syndrome. In a different study, patients receiving concomitant immunosuppressant therapy were less likely to develop ANA and anti-ds-DNA antibodies than those not receiving immunosuppressant therapy.[34]

In a recent study, Vermeire et al.[38] examined 125 consecutive patients with Crohn's disease treated with infliximab for the development of ANA. Patients with luminal disease received one initial dose of infliximab and subsequently as needed, while patients with fistulising disease received three initial doses at 0, 2 and 6 weeks, and then additional doses as needed. Nine of 125 (7%) patients were ANA-positive at baseline consistent with population

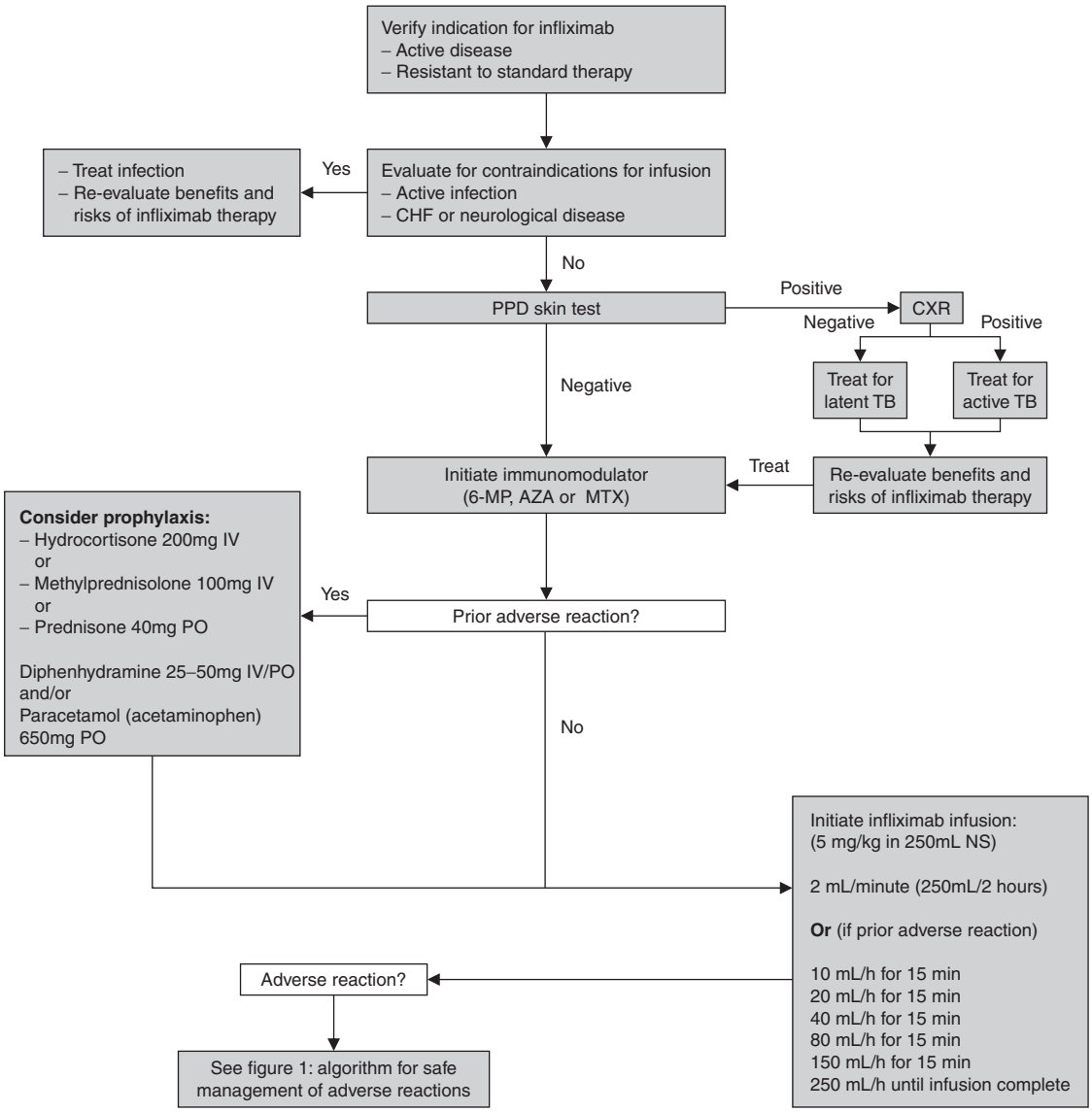

Fig. 2. Suggested algorithm for the administration of infliximab. **6-MP** = 6-mercaptopurine; **AZA** = azathioprine; **CHF** = congestive heart failure; **CXR** = chest radiograph; **IV** = intravenous; **MTX** = methotrexate; **NS** = normal saline; **PO** = oral; **PPD** = purified protein derivative; **TB** = tuberculosis.

averages. After one infusion, 34 of 125 (27%) were positive, and after maximum follow-up (24 months), 71 of 125 (57%) were ANA-positive. The ANA-positive patients were more likely to be female, and 43 of 71 ANA-positive patients had titres of 1 **:** 80 or more; 17 of 43 (39.5%) of these high-titre ANA patients had single-stranded DNA antibodies and 9 of 43 (21%) had antihistone antibodies. During follow-up in patients with positive ANA, 16 of 71 (22.5%) had increasing titres of ANA, 24 of 71 (34%) had stable titres of ANA, and 31 of 71 (44%) had decreasing titres of ANA (15 patients became ANA-negative). Most patients continued to receive infliximab infusions in the follow-up period.

Development of clinical symptoms was uncommon. Two of 71 patients with positive ANA developed a lupus-like syndrome with clinical symptoms of polyarthralgias, myalgias and a clear butterfly facial rash. In both patients, clinical signs and symptoms disappeared quickly after discontinuation of infliximab. One patient developed autoimmune haemolytic anaemia. Because the development of lupus-like clinical symptoms is uncommon in patients with positive ANA and is responsive to discontinuation of infliximab, the development of positive ANA is not a contraindication to treatment with infliximab.

5. Malignancies and Lymphoproliferative Disease

TNFα has been hypothesised to play a role in immune surveillance for cancer. The incidence of malignancies in patients treated with infliximab has been examined in a number of clinical trials. In completed clinical studies of infliximab for up to 102 weeks, 18 of 1678 (11%) patients developed 19 new or recurrent malignancies of various types, such as non-Hodgkin's B-cell lymphoma, and breast, melanoma, squamous, rectal and basal cell cancers.[32] The observed rates and incidences were similar to those expected for the populations studied.[39,40] Colombel et al.[12] reported that 3 of 500 (0.6%) patients treated with infliximab for Crohn's disease developed malignancies that were possibly related to infliximab therapy. No controlled study to date, with the limited follow-up that is available at this time, has shown increased rates of malignancies in patients treated with infliximab.

6. Cardiovascular Adverse Events

Increased levels of TNFα have been noted in patients with heart failure.[41] However, large-scale randomised, placebo-controlled trials of etanercept (a TNFα antagonist) for treatment of heart failure were stopped early because they failed to demonstrate an improvement in clinical heart failure or mortality.[42] Several cases of new-onset heart failure or exacerbation of existing heart failure have been described after infliximab therapy. In an analysis of 500 patients treated with infliximab for Crohn's disease, Colombel et al.[12] reported that one patient developed worsening heart failure that was potentially attributable to infliximab administration. In a case series based on the US FDA's MedWatch adverse event reporting system,[43] 38 patients were identified who developed new-onset heart failure and nine patients developed heart failure exacerbation. Of the patients with new-onset heart failure, ten (26%) were aged <50 years and 19 (50%) had no identifiable risk factors. Following discontinuation of infliximab and initiation of heart failure therapy in the ten patients <50 years of age, three had complete resolution of heart failure, six improved and one died. In a randomised study evaluating infliximab in moderate to severe heart failure (New York Heart Association [NYHA] class III or IV), 150 patients were randomised to receive treatment with three infusions of infliximab 5 or 10 mg/kg at 0, 2 and 6 weeks.[44] Higher incidences of mortality and hospitalisation due to worsening heart failure were observed in patients receiving the 10 mg/kg dose. There were trends towards increased dyspnoea, hypotension, angina pectoris and dizziness in both the 5 and 10 mg/kg infliximab treatment groups compared with placebo recipients. These data suggest that infliximab should be used with caution in patients with congestive heart failure. In particular, alternative therapies should be considered in patients with NYHA class III or IV heart failure.

7. Neurological Events

Exacerbations of multiple sclerosis have been documented with the use of infliximab in patients with rheumatoid arthritis.[45] In a retrospective review of 500 patients treated with infliximab for Crohn's disease, Colombel et al.[12] reported the development of a new demyelination disorder in one patient. A review of the US FDA adverse event report database reported that 17 patients had neurological events including paraesthesias, seizure and optic neuritis following etanercept or infliximab therapy.[46] All of these events showed partial or complete resolution with discontinuation of therapy,

and one patient had recurrent symptoms when rechallenged. Patients should be monitored for the development of neurological symptoms with infliximab therapy. Infliximab should be used with caution in patients with pre-existing or recent-onset central nervous system demyelinating disease or seizure disorder.

8. Proposed Protocol for Administration of Infliximab

Several factors have been identified that may be protective against adverse reactions resulting from infliximab administration. In the ACCENT I trial,[6] the lowest incidence of infusion reactions occurred in patients receiving both corticosteroids and immunosuppressants: 7 of 85 (8%) compared with 17 of 84 (20%) patients receiving only immunosuppressants, 47 of 207 (23%) patients receiving corticosteroids alone and 62 of 197 (31%) patients without corticosteroids or immunosuppressants. In a study of 53 patients with Crohn's disease who received infliximab, Farrell et al.[25] reported that patients treated with hydrocortisone 200mg intravenously before each infusion of infliximab showed a significantly lower titre of ATIs than controls (1.6 vs 3.4 μg/mL; $p = 0.02$) and also a trend towards lower incidence of ATIs (26% vs 42% for placebo-treated patients; $p = 0.06$). However, there was no difference in the incidence of overall infusion reactions between the two groups.

Data from clinical trials also suggest that patients who receive a three-dose induction regimen at 0, 2 and 6 weeks may be less likely to form antibodies to infliximab, or to develop infusion reactions, potentially due to the induction of immunological tolerance to infliximab.[8,47,48] In the ACCENT I trial, 28% of patients who received placebo after their initial infliximab infusion developed ATIs versus fewer than 10% of those who received infliximab for all infusions of the 0, 2, 6-week induction regimen. Farrell et al.[25] also reported that administration of a second infliximab infusion within 8 weeks decreased ATI formation ($p = 0.0007$).

An algorithm for appropriate prophylaxis and administration of infliximab is presented in figure 2. Before infliximab administration, the indication for use of the drug should be confirmed, as unnecessary administration of infliximab may result in the development of ATIs, leading to decreased efficacy and predisposition to adverse reactions when infliximab is indicated in the future. The presence of heart failure or active neurological disease should lead to a re-evaluation of the benefits and risks of infliximab administration. Patients should be screened and treated for active infections, and all patients should be evaluated for tuberculosis with a purified protein derivative skin test and chest radiograph as necessary and treated appropriately. Once the decision is made to initiate infliximab therapy, all patients should be started on immunomodulators (such as 6-mercaptopurine, azathioprine or methotrexate) if possible, even if these drugs have not had therapeutic efficacy in the past. The available data support the regimen of a 0, 2, 6-week induction schedule followed by repeat infusions at least every 8 weeks as a way of inducing and maintaining immune tolerance to infliximab. Data show that most patients will need regular doses of infliximab to maintain remission. As described in section 2, a long hiatus from infliximab has been associated with the development of antibodies to infliximab and an increased incidence of delayed reactions. A commercially available assay of infliximab levels and ATI (HACA) titres may be helpful in determining whether patients who have lost response to infliximab have developed neutralising antibodies, reflected in low or absent infliximab levels 4 weeks after infusion.

Patients who have had a previous severe infusion reaction to infliximab or have risk factors for adverse reactions such as a long hiatus (>6 months between infusions) should be premedicated with corticosteroids (intravenous methylprednisolone 100mg or oral prednisone 40mg), or hydrocortisone 200mg intravenously) and antihistamines (diphenhydramine 25–50mg intravenously or orally) prior to infliximab infusion. The infliximab infusion should be started at a lower rate (such as 10 mL/h) and titrated up as tolerated (as detailed in figure 2).

Infliximab therapy should be continued with regular maintenance infusions, unless no longer effective or serious adverse events related to the infusions occur. Unduly long intervals between infusions (>6 months), may put patients at high risk for 'serum-sickness-like' delayed reactions.[28] In addition, early data have suggested that the likelihood of maintaining an infliximab-induced remission is extremely low in the absence of maintenance therapy.[49]

9. Conclusions

The introduction of infliximab has been a significant advancement in the therapy of Crohn's disease. Emerging evidence indicates that administration of the chimeric protein has a number of immunological consequences, including development of antibodies that may lead to acute or delayed reactions, or limit efficacy of the drug. It is important that physicians be cognisant of the wide array of immediate and long-term adverse events associated with infliximab therapy and, when indicated, use strategies to limit the immunogenicity of the drug, such as: (i) concomitant administration of an immunomodulating agent; (ii) use of a 0, 2, 6-week induction regimen; (iii) administration of maintenance infusions every 8 weeks or less; and (iv) avoidance of unduly long intervals between infusions. Although adverse reactions to infliximab are common, most adverse reactions are minor and are easily managed, and the majority of patients should be able to continue with infliximab therapy. Continuing research into the mechanisms underlying adverse reactions promises to lead to further advancements in the safety of administration of infliximab.

Acknowledgements

Dr Russell Cohen would like to declare the following: Speakers' Bureau – Proctor and Gamble, Salix Pharmaceuticals, Shire Pharmaceuticals, Axcan-Scandipharm, Solvay Pharmaceuticals, Centocor, Astra-Zeneca; Research Grants – Centocor, Salix Pharmaceuticals; Consultant Celltech, Centocor, Isis Pharmaceuticals, Elan; Spouse – employee of Centocor, shareholder in Johnson & Johnson.

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease: Crohn's Disease cA2 Study Group. N Engl J Med 1997; 337 (15): 1029-35
2. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 340 (18): 1398-405
3. van Dullemen HM, van Deventer SJ, Hommes DW, et al. Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). Gastroenterology 1995; 109 (1): 129-35
4. Rutgeerts P, D'Haens G, Targan S, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology 1999; 117 (4): 761-9
5. D'Haens G, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. Gastrointest Endosc 1999; 50 (5): 667-71
6. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002; 359 (9317): 1541-9
7. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994; 344 (8930): 1105-10
8. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41 (9): 1552-63
9. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354 (9194): 1932-9
10. Cohen RD, Tsang JF, Hanauer SB. Infliximab in Crohn's disease: first anniversary clinical experience. Am J Gastroenterol 2000; 95 (12): 3469-77
11. Farrell RJ, Shah SA, Lodhavia PJ, et al. Clinical experience with infliximab therapy in 100 patients with Crohn's disease. Am J Gastroenterol 2000; 95 (12): 3490-7
12. Colombel J, Loftus EV, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo Clinic experience in 500 patients. Gastroenterology 2004; 126 (1): 19-31
13. Stephens MC, Shepanski MA, Mamula P, et al. Safety and steroid-sparing experience using infliximab for Crohn's disease at a pediatric inflammatory bowel disease center. Am J Gastroenterol 2003; 98 (1): 104-11
14. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol 2003; 98 (6): 1315-24
15. Duhem C, Dicato MA, Ries F. Side-effects of intravenous immune globulins. Clin Exp Immunol 1994; 97 Suppl. 1: 79-83
16. Bagdasarian A, Tonetta S, Harel W, et al. IVIG adverse reactions: potential role of cytokines and vasoactive substances. Vox Sang 1998; 74 (2): 74-82
17. Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP)

and review of the literature. Haematologica 1993; 78 (6 Suppl. 2): 35-40

18. Misbah SA, Chapel HM. Adverse effects of intravenous immunoglobulin. Drug Saf 1993; 9 (4): 254-62
19. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16 (8): 2825-33
20. Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994; 83 (2): 435-45
21. Dillman RO. Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. Cancer Metastasis Rev 1999; 18 (4): 465-71
22. Osterborg A, Dyer MJ, Bunjes D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia: European Study Group of CAMPATH-1H Treatment in Chronic Lymphocytic Leukemia. J Clin Oncol 1997; 15 (4): 1567-74
23. Osterborg A, Fassas AS, Anagnostopoulos A, et al. Humanized CD52 monoclonal antibody Campath-1H as first-line treatment in chronic lymphocytic leukaemia. Br J Haematol 1996; 93 (1): 151-3
24. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003; 348 (7): 601-8
25. Farrell RJ, Alsahli M, Jeen YT, et al. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology 2003; 124 (4): 917-24
26. Weiss ME. Drug allergy. Med Clin North Am 1992; 76 (4): 857-82
27. O'Connor M, Buchman A, Marshall G. Anaphylaxis-like reaction to infliximab in a patient with Crohn's disease. Dig Dis Sci 2002; 47 (6): 1323-5
28. Hanauer SB, Rutgeerts PJ, D'Haens G, et al. Delayed hypersensitivity to infliximab (Remicade) re-infusion after 2-4 year interval without treatment [abstract]. Gastroenterology 1999; 116: A731
29. Kam LY, Vasiliauskas EA, Abreu MT. Attenuation of response to multiple retreatment infliximab infusions for active Crohn's disease: potential factors that minimize decreased response [abstract]. Gastroenterology 2000; 118: A65
30. Panccione R. Overcoming 'delayed-type hypersensitivity reactions' in patients receiving repeated doses of infliximab: a report of 5 cases [abstract]. Gastroenterology 2002; 122 (4 Suppl. 1): A613
31. Sandborn WJ, Hanauer SB. Infliximab in the treatment of Crohn's disease: a user's guide for clinicians. Am J Gastroenterol 2002; 97 (12): 2962-72
32. Remicade (infliximab) for IV injection [package insert]. Malvern (PA): Centocor Inc., 2003
33. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001; 345 (15): 1098-104
34. Hanauer SB. Review article: safety of infliximab in clinical trials. Aliment Pharmacol Ther 1999; 13 Suppl. 4: 16-22
35. Klapman JB, Ene-Stroescu D, Becker MA, et al. A lupus-like syndrome associated with infliximab therapy. Inflamm Bowel Dis 2003; 9 (3): 176-8
36. Schaible TF. Long term safety of infliximab. Can J Gastroenterol 2000; 14 Suppl. C: 29C-32C
37. Charles PJ, Smeenk RJ, De Jong J, et al. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum 2000; 43 (11): 2383-90
38. Vermeire S, Noman M, Van Assche G, et al. Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. Gastroenterology 2003; 125 (1): 32-9
39. Bernstein CN, Blanchard JF, Kliewer E, et al. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001; 91 (4): 854-62
40. Jones M, Symmons D, Finn J, et al. Does exposure to immunosuppressive therapy increase the 10 year malignancy and mortality risks in rheumatoid arthritis? A matched cohort study. Br J Rheumatol 1996; 35 (8): 738-45
41. Levine B, Kalman J, Mayer L, et al. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990; 323 (4): 236-41
42. Louis A, Cleland JG, Crabbe S, et al. Clinical trials update: CAPRICORN, COPERNICUS, MIRACLE, STAF, RITZ-2, RECOVER and RENAISSANCE and cachexia and cholesterol in heart failure. Highlights of the Scientific Sessions of the American College of Cardiology, 2001. Eur J Heart Fail 2001; 3 (3): 381-7
43. Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med 2003; 138 (10): 807-11
44. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003; 107 (25): 3133-40
45. Weisman MH. What are the risks of biologic therapy in rheumatoid arthritis? An update on safety. J Rheumatol Suppl 2002; 65: 33-8
46. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001; 44 (12): 2862-9
47. Wagner C, Olson A, Ford J, et al. Effects of antibodies to infliximab on safety and efficacy of infliximab treatment in patients with Crohn's disease [abstract]. Gastroenterology 2002; 122 (4 Suppl. 1): A613
48. Kugathasan S, Levy MB, Saeian K, et al. Infliximab retreatment in adults and children with Crohn's disease: risk factors for the development of delayed severe systemic reaction. Am J Gastroenterol 2002; 97 (6): 1408-14
49. Tuvlin JA, Schaefer KG, Sane NP, et al. Infliximab is not a bridge to immunomodulators in Crohn's disease [abstract]. Gastroenterology 2003; 124 (4 Suppl. 1): A518

Correspondence and offprints: Dr *Russell D. Cohen*, University of Chicago Hospitals – Section of Gastroenterology, MC 4076, 5841 S. Maryland Ave, Chicago, IL 60637, USA. E-mail: rcohen@medicine.bsd.uchicago.edu