Immunogenicity of infliximab: how to handle the problem?

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Abstract

**Background:** The introduction of infliximab has greatly advanced the therapeutic armamentarium of the inflammatory bowel diseases (IBD), Crohn’s disease and ulcerative colitis. Although the benefit/risk ratio for infliximab is positive, of particular concern has been the problem of immunogenicity ascribed to the chimeric properties of the drug. Antibody formation is associated with allergic reactions and loss of response.

**Aims and methods:** A literature search was undertaken on the magnitude of the problem of immunogenicity and on the clinical consequences. A survey was conducted about the clinical practice and management of acute and delayed allergic reactions to infliximab in different centres in Belgium. For this, a questionnaire was sent to all members of the Belgian IBD research group (n = 38 belonging to 29 centers).

**Results and conclusion:** Infusion reactions are important immunologic events induced by the presence of a substantial concentration of antibodies against infliximab (ATI) in the serum. Concomitant immunosuppressive treatment may optimize response to infliximab by preventing the formation of antibodies. Steroid administration prior to an infliximab infusion can further reduce the immunogenicity. Probably the most effective strategy to optimize treatment and avoid immunogenicity is maintenance therapy. If infliximab therapy can be discontinued is yet unclear but when treatment goals have been reached, we feel this should be attempted. In the case of relapse, infliximab should be restarted as maintenance long term. Practical guidelines on how to handle the problem of immunogenicity to infliximab are important for clinicians treating patients with IBD. (Acta gastroenterol. belg., 2007, 70, 195-202).

Introduction

The introduction of infliximab (Remicade®) has greatly advanced our therapeutic options for patients suffering from Inflammatory Bowel Diseases (IBD). Infliximab is a chimeric monoclonal IgG1 antibody against TNF alpha and is indicated for refractory luminal and fistulizing Crohn’s disease (CD). The recent ACT studies have shown that infliximab is also efficacious in patients with ulcerative colitis (UC) who are resistant to standard therapy. All extra-intestinal manifestations related to IBD respond also very well to infliximab.

Infliximab in IBD is administered as an IV infusion at a dose of 5 mg/kg body weight. For luminal disease, one infusion of infliximab or a three-dose induction scheme at weeks 0, 2 and 6 will give response rates of 52 to 65% at 10 weeks respectively (1). Response can be optimized further by concomitant therapy with immunomodulators. For fistulising disease, a three-dose induction with infliximab is associated with 68-69% response (defined as ≥ 50% reduction of draining fistulas) (2-3). However, the majority of patients will relapse if not retreated and therefore a long term treatment plan is necessary. The optimal strategy is systematic maintenance treatment with infliximab every 8 weeks. This has proven to reduce complications, hospitalisations and surgeries, as well as antibody formation (4-5). Indeed, infliximab may induce several types of immune reactions. This phenomenon called immunogenicity is often ascribed to the chimeric properties of the drug. However, antibody formation and the same allergic reactions have also been described against humanized or human proteins. The precise and complete nature of the immune response to infliximab is therefore not completely understood.

Immunogenicity to infliximab: magnitude of the problem

The prevalence of infusion reactions reported in literature is summarized in table 1 and has been relatively similar in uncontrolled experience (5,7-14). Some differences may be explained by the retrospective or prospective character of data collection, by the definition of the reactions and by the mean number of infusions per patient in these reports. In one retrospective study, two thirds of the reactions occurred at the time of the second infusion and the risk was particularly high when this second infusion was realized more than 20 weeks after the first (7). The most reliable and relevant data on the prevalence of infusion reactions following infliximab come from the ACCENT 1 study (1). In this large prospective controlled study, acute infusion reactions occurred in 23% of patients but only 3.8% were classified as severe reactions. The prevalence of delayed hypersensitivity reactions was 2.3%. Some reactions will result in permanent discontinuation of
infliximab. This is mainly the case for some serious acute infusion reactions but overall this represents a small minority of patients (2.8% of patients in ACCENT 1). In all clinical trials with infliximab (including the RA trials) about 20% of patients treated with infliximab compared to 10% of placebo treated patients. Less than 1% of patients experienced a severe infusion reaction. (Centocor data on file).

The main hypothesis behind these allergic reactions, acute or delayed and severe or not, is that they are related to some form of immunogenicity against infliximab. However this has not been adequately studied and the only biological marker available to assess immunization against the drug, are the so-called antibodies to infliximab (ATI; formerly called human anti-chimeric antibodies or HACAs). To understand incidence of antibody formation some basic principles have to explained. Technically, in the laboratory, the measurement of ATI interferes with the infliximab concentration in the serum. Whenever there is infliximab detected in the serum, the antibodies cannot be detected for methodological reasons. Therefore a combination assay should always be performed measuring both infliximab concentration and ATIs. As long as infliximab is detected in the serum the results for ATI are called indeterminate. A serum sample can only be called true negative for ATI when no infliximab is detected. To interpret results from clinical trials one has to know at what time points in relation to the (study)drug administration the antibody formation has been assessed. Nowadays most if not all treatments will be with prescheduled regular drug administrations. Therefore in most instances the drug will be continuously present in the serum so that the reported incidences of antibodies will be low.

**Immunogenicity to infliximab: types of allergic reactions**

Acute infusion reactions need to be differentiated from delayed reactions. Acute reactions are defined as reactions occurring during or within 2 hours of an infusion. They can be severe or not. Severe reactions are usually defined as reactions necessitating stop of the infusion due to significant dyspnoea or drop in blood pressure. Mild to moderate acute reactions may include fever, slight decrease in blood pressure, erythema, itching, or shiver.

The spectrum of symptoms can be subdivided in non-immune mediated reactions (nausea, headache, fever) and immune-mediated reactions (urticaria, dyspnea, hypotension, chest pain). The question remains whether these reactions are typical type I hypersensitivity reactions since the majority of the patients can be successfully retreated, which is an uncommon phenomenon in IgE mediated reactions. There are however no or very few studies on the underlying mechanisms of infusion reactions following infliximab. The only study investigating this issue found that there was no significant increase in trypase levels suggesting that they were not classical type 1 IgE-mediated hypersensitivity reactions (6). Tryptase is a mast cell enzyme that is released upon degranulation during type I reaction and is detected in the serum shortly after a reaction. A second argument against a classical type I IgE-mediated reaction is that bronchospasm is almost always absent.

Delayed reactions occur 2 days to 2 weeks after reinfusion of infliximab. The symptoms can be quite severe and usually last 3-5 days. Delayed reactions are usually assimilated to serum sickness like reactions. Possible

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
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<th>Acute infusion reactions (%)</th>
<th>Serious acute infusion reactions (%)</th>
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* paediatric studies  ** all types of infusion reactions grouped.
symptoms include a cluster of features (generalised stiffness, myalgias, arthralgias, fever, and/or rash).

Clinical relevance of immunogenicity to infliximab

In all registration studies with infliximab (e.g. Accent 1 and Accent 2) ATIs have been detected in 4 to 38% of patients (1,3). At the time of publication of these studies it was then told that antibody formation was a rare problem with no clinical importance. In the early post marketing clinical experience where infliximab was used on demand with and without concomitant immunosuppressives up to 25% of patients developed more or less serious infusion reactions as described above. Some of these patients continued to have these reactions when retreated despite a slower infusion rate and despite prophylactic therapy with corticosteroids and anti-histamines before the infusion. In addition the clinical impression was also that patients experiencing severe infusion reactions despite prophylaxis had a shorter duration of response to their infliximab infusion.

Since then we have learned a great deal about the impact of ATI formation on the occurrence of infusion reactions and clinical efficacy. Indeed hallmark studies have shown the relation between ATI and infusion reactions. Most importantly they dramatically changed the way we use infliximab: how to avoid immunogenicity and how to avoid infusion reactions and ensure long and sustained efficacy to infliximab. The study by Baert and Noman et al. examined a cohort of 125 consecutive patients with CD who were treated with on demand infliximab infusions (11). They evaluated the concentrations of infliximab and of ATIs, clinical data, side effects (including infusion reactions), and the use of concomitant medications before and 4, 8, and 12 weeks after each infusion. ATIs were detected in 61% of patients (Fig. 1A). Remarkably, >95% of the patients who developed ATI did so after the first or second infusion. The cumulative incidence of infusion reactions in this cohort of patients was 27 percent. No reactions occurred during the first infusion. Similarly the vast majority of infusion reactions occurred during the second or third infusion (Fig. 1B). There was a strong relation between the concentration of ATIs and the occurrence of infusion reactions. The median concentration of ATI was 20.1 µg/mL (95% confidence interval 3.0 to 22.6) at the time of a first infusion reaction, as compared with 3.2 µg/mL (95% confidence interval, 1.6 to 4.9) among patients without an infusion reaction (p < 0.001). Concentrations of 8 µg/ml or higher predicted a higher risk of infusion reactions (RR 2.40; 95% CI 1.65 to 3.66; p < 0.001).

A significant relation was also found between the serum infliximab concentration measured 4 weeks after an infusion and the concentration of ATIs before that infusion (r = 0.34, p < 0.001). The median infliximab concentration four weeks after an infusion was significantly lower among patients with a infusion reaction than among patients who never had a reaction (1.2 µg/ml vs. 14.1 µg/ml, p < 0.001). Once patients had an infusion reaction they received prophylaxis consisting of hydrocortisone and promethazine before subsequent infusions. Among patients who had no further reactions while receiving prophylaxis, infliximab concentrations stayed high at four weeks (median 12.9 µg/ml; 95% CI 1.9 to 21.0). Infliximab concentrations, however, were almost undetectable among patients who had another reaction despite receiving prophylaxis (1.0 µg/mL; 95% CI 1.0 to 1.9; p = 0.01) (Fig. 2).

Once an infusion reaction occurred, the median duration of response to an infusion was shorter: 38.5 days (95% CI 34-51 days), as compared with 65 days (95% CI 56-71 days; p < 0.001). This shortened response persisted during further infusions irrespective of whether infusion reactions could be prevented with prophylaxis (median 42 days; 95% CI 34-56) or not (median 29 days; 95% CI 24-106; p = 0.17). Logistic regression analysis showed that the presence of antibodies against infliximab was independently associated with a shorter duration of response (p < 0.001). Patients who were
taking immunosuppressive agents had a lower incidence of antibodies (43%) than patients who were not taking immunosuppressive agents (75%) ($p < 0.01$). More importantly immunosuppressive agents also protected against a clinical relevant titer of antibodies, e.g. ATI $> 8 \mu g/ml$. The concomitant use of immunosuppressives was the single predictive factor in preventing antibody formation in multivariate analysis. No association between ATIs and sex, location of disease, smoking status, or the use of mesalamine or corticosteroids was found in this study.

The study by Farrell et al. observed similar findings (16). In their initial cohort of 53 patients they found an incidence of ATI of 36%, including all 7 patients with severe infusion reactions. The median ATI concentrations in these patients was 19.6 $\mu g/ml$. Eleven of 15 patients (73%) who lost response to infliximab were ATI positive compared to none of 21 continuous responders. In addition to concurrent use of immunosuppressants, the administration of a second infusion within 8 weeks from the first were protective factors for ATI formation. In a second part of the study they randomised 80 patients to 200 mg of hydrocortisone or placebo before each infusion and found a lower incidence of ATI among steroid pretreated subjects (26 vs 42%). Hanauer et al also showed in a prospective study of patients receiving immunomodulators have lower ATI formation compared with patients receiving infliximab alone (10% and 18%, respectively; $p = 0.02$) (5).

Sequential measurement of ATI levels through the ACCENT I study has shown that ATIs may develop at any time during systematic or episodic retreatment (1). ATI formation is however more pronounced in patients treated episodically than systematically, being around 30% after 72 weeks in the episodic strategy as compared to 10% and 7% in maintenance strategy with 5 mg/kg and 10 mg/kg, respectively. Another important information provided by ACCENT I is that patients positive for ATI at any time point may later become negative, and that globally, the proportion of patients positive for ATI at each time point is not increasing over time, even with episodic strategy.

**Practical approach to immunogenicity of infliximab: results of a national survey**

A survey was conducted about the clinical practice and management of acute and delayed allergic reactions to infliximab in different centres in Belgium. For this, a questionnaire was sent to all members of the Belgian IBD research group ($n = 38$ belonging to 29 centers). The questionnaire was returned by 19 centers (8 university centers and 11 non-academic centers). All centers have a large experience with infliximab of which 11 centers (58%) treat more than 10 patients per year.

Infliximab in most centers is administered as an IV infusion over a period of 2 hours (125 ml per hour). The patient’s signs and symptoms are monitored every 30 min throughout the infusion. The need for monitoring patients longer than 30 minutes after an infusion was questioned and only practiced by 9/19 (47%) of the centres. Since on one hand most of the acute infusion reactions occur very shortly after the start of the infusion or within the first hour of administration and on the other hand symptoms of delayed hypersensitivity only occur after several days, the post-infusion supervision may be short.

The concomitant use of immunomodulators (azathio-prine or methotrexate) to prevent immunogenicity was recommended by all centres. The majority of the centers (84%) treat their patients on a systematic maintenance basis although the interval between infusions may be adapted to the need of the patients varying from 4 to 16 weeks. At the present time, no studies are available about the optimal cost-effective interval. Only information about two strategies can be found in the literature varying from an on-demand strategy with re-infusion in the case of new symptoms versus a systematic treatment
were able to be retreated safely of whom about half ben-

fected from these infusions (15). In case of previous his-
tory of infusion reaction pretreatment with an anti-

management of delayed infusion reactions

Management of delayed infusion reactions

Delayed infusion reactions need to be treated by oral
corticosteroids as agreed upon by all centers although
the duration of treatment varied from 3 to 14 days. The
majority of the centers treats for 5-7 days. Anti-
histamines are given only by 7 centers (36%).

Only 5 centers (26%) considered the occurrence of
delayed hypersensitivity reactions as a reason to stop
treatment definitively. The other centers re-infuse their
patients but after pre-treatment with methylprednisolone
orally (1 mg/kg) 2-3 days before infusion and 3-7 days
after infusion. In the case of recurrence of delayed
immune-mediated infusion reactions despite prophylax-

Avoiding immunogenicity: maintenance or episodic treatment?

Infliximab can be used in different settings long-term.
These include (1) infliximab on demand (episodic) in
monotherapy; (2) infliximab on demand (episodic)
together with concomitant immunosuppression; (3)
infliximab maintenance every 8 weeks in monother-

When it comes to immunogenicity, it is clear from the
large RCTs and cohort studies that maintenance therapy
is preferred over episodic therapy to reduce the risk of
antibody formation. Also the concomitant use of
immunosuppression (azathioprine or MTX) and pre-
treatment with an antihistamine may be administered
(romethazine, clemastine or diphenhydramine).
Administration of hydrocortisone (250 mg) or methyl-
prednisolone (125 mg) IV can be considered but has a
delayed effect. Its major advantage is a shortening of the
duration of reaction and a prevention of a later reoccur-
rence of symptoms. After resolution of symptoms, infu-

Prevention of antibody formation (ATIs)

Infliximab can be used in different settings long-term.
These include (1) infliximab on demand (episodic) in
monotherapy; (2) infliximab on demand (episodic)
together with concomitant immunosuppression; (3)
infliximab maintenance every 8 weeks in monother-
apy, (4) infliximab maintenance every 8 weeks together
with concomitant immunosuppressives (20%), or (5) infliximab
as a bridge to immunosuppression.

When it comes to immunogenicity, it is clear from the
large RCTs and cohort studies that maintenance therapy
is preferred over episodic therapy to reduce the risk of
antibody formation. Also the concomitant use of
immunosuppression (azathioprine or MTX) and pre-
treatment with steroids reduce the risk of ATIs and of
infusion reactions as previously mentioned. Which of
these strategies will optimally protect the patient is
unclear, although steroid pre-treatment appears to be
inferior to concomitant immunosuppressives. Moreover,
in the ACCENT I study the lowest incidence of infusion
reactions occurred among patients receiving both
steroids and immunosuppressives (8%) compared with
patients receiving only immunosuppressives (20%), or
only steroids (23%) (1).

When infliximab is administered episodically, con-
comitant immunosuppression with azathioprine or MTX
should always be given. In this respect, both MTX and
azathioprine seem equally effective in reducing the
immunogenicity (17). On the other hand, episodic
treatment with infliximab in monotherapy is not

systematic treatment with infliximab is not

every 8 weeks. It is clear that the systematic retreatment
is superior over on demand therapy for various reasons
explained below.

Systematic pre-medication with IV hydrocortisone
100-500 mg before every infusion is used by 11/19
(58%) of the centres. After a drug holiday of more than
14 weeks pre-treatment with hydrocortisone (250 mg)
as well as initiation at a slow infusion rate (80 ml/hr) is
recommended by all centres although some prefer a
longer pre-treatment (oral methylprednisolone 32 mg
daily 2 to 4 days prior to the infusion) in case of longer
drug holiday (> 4-6 months). Systematic administration
of antihistamines before each infusion is not common
practice and only done in 3 centres.

Management and prophylaxis of acute infusion
reactions (Figs. 3-4)

The majority of acute infusion reactions are mild and
will resolve after slowing the infusion rate and/or
administration of acetaminophen. In the presence of a
moderate reaction or if symptoms persist, infusion must
be stopped and an antihistamine may be administered
(promethazine, clemastine or diphenhydramine).
Administration of hydrocortisone (250 mg) or methyl-
prednisolone (125 mg) IV can be considered but has a
delayed effect. Its major advantage is a shortening of the
duration of reaction and a prevention of a later reoccur-
rence of symptoms. After resolution of symptoms, infu-

the infusion needs to stopped, normal saline infused, the
airway maintained and oxygen given if necessary.
Antihistamines should be administered IM together with
IV hydrocortisone promptly. In case that the allergic
signs and symptoms do not subside with these measures
slow administration of epinephrine (0,1-0,5 ml of a solu-
tion 1/1 000 (1 mg/ml) SC or IM may be considered
under strict monitoring and eventually repeated every
5 minutes. If symptoms re-occur after restarting, the
infusion must be stopped.

In the presence of a severe reaction with cardiopul-
monary symptoms (chest pain, dyspnoe, hypotension)
the infusion needs to stopped, normal saline infused, the
airway maintained and oxygen given if necessary.
Antihistamines should be administered IM together with
IV hydrocortisone promptly. In case that the allergic
signs and symptoms do not subside with these measures
slow administration of epinephrine (0,1-0,5 ml of a solu-
tion 1/1 000 (1 mg/ml) SC or IM may be considered
under strict monitoring and eventually repeated every
5 minutes.

Only about half of the centers (10/19; 53%) consid-

retreatment is suspended due to infusion
reactions were retreated using a systematic toler-
ance induction regimen. Eleven of fourteen patients
were able to be retreated safely of whom about half ben-

recommended, since this is clearly associated with increased immunogenicity. Therefore every patient intolerant to immunosuppressive treatment should be started on systematic infliximab retreatment.

After induction of remission with infliximab, a maintenance strategy with infliximab 5 mg/kg every 8 weeks is the optimal regimen for patients. Maintenance therapy has proven superior to episodic treatment for various reasons, which are summarized in Table 2. The most important advantages of systematic therapy over episodic treatment include better response and remission rates, more thorough mucosal healing, better quality of life and reduced number of disease-related surgeries and hospitalizations. Especially the latter is very important to bear in mind since an often-heard argument to advocate episodic treatment is the lower cost. When looking at the various studies however where episodic therapy is used it appears that the mean interval between episodic infusions is between 9 and 14 weeks in patients that need re-treatment. This is not so very different from the 8 weeks used in the systematic maintenance schedule. On the other hand, the decreased cost resulting from episodic therapy is frequently counterbalanced by the problems of infusion reactions, loss of response with the necessity to increase the dose of the drug or (and) to decrease the dosage interval. Moreover successful therapy with infliximab may decrease the direct as well as the indirect costs of the disease.

The role of concomitant immunosuppression with systematic q8 weeks infliximab after initial successful therapy with the combination is yet unknown. A recent study from Belgium randomized CD patients successfully treated for at least 6 months with a combination of immunosuppressives and infliximab 5 mg/kg to either discontinue or continue immunosuppressives with systematic infliximab retreatment q8 wks (18). Preliminary results showed no difference in response or infusion reactions between both groups. The continuation of immunosuppressives beyond 6 months in patients receiving systematic infliximab maintenance therapy therefore does not seem to offer a clear benefit, although the full results of this study need to be awaited.

**Conclusion**

Infusion reactions are important immunologic events induced by the presence of a substantial concentration of antibodies against infliximab (ATI) in the serum. After an infusion reaction, infliximab disappears quickly from serum and is undetectable four weeks after an infusion.
Once an infusion reaction occurred, the duration of the response to subsequent infusions is decreased. Concomitant immunosuppressive treatment may optimize response to infliximab by preventing the formation of antibodies, thus reducing the incidence of infusion reactions and increasing the duration of response. Since antibodies develop soon after the first infusion in most patients, immunosuppressive therapy should be instituted before or at the same time infliximab therapy is started. Steroid administration prior to an infliximab infusion can further reduce the immunogenicity. Probably the most effective strategy to optimize treatment and avoid immunogenicity is maintenance therapy. If infliximab therapy can be discontinued is yet unclear but when treatment goals have been reached, we feel this should be attempted. In the case of relapse, infliximab should be restarted as maintenance long term. The risk of infusion reaction in such patient having transiently interrupted after a prolonged infliximab treatment in not clearly known but is suspected to be low.

**Table 2.** — Comparison of episodic versus maintenance therapy on response and remission, immunogenicity, mucosal healing, hospitalizations and surgeries (adapted from Rutgeerts et al., Gastroenterology 2004, Hanauer et al., Lancet 2002, Hanauer et al., Clin Gastroenterol Hepatol 2004)

<table>
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<th>Episodic therapy</th>
<th>Maintenance therapy</th>
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<td>Remission week 30</td>
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<td>Steroid free at week 30</td>
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<td>47% (10 mg/kg)</td>
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<td>% patients needing hospitalizations</td>
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<td>24%</td>
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<td>% patients needing surgery</td>
<td>7.4%</td>
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<td>ATI formation</td>
<td>28%</td>
<td>9% (5 mg/kg)</td>
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References


5. PRESENT D.H., RUTGEERTS P., TARGAN S., HANAUER S.B., WAGNER C., BALA M.


