Immunogenicity of infliximab : how to handle the problem ?

Filip Baert, Martine De Vos, Edouard Louis and Séverine Vermeire for the Belgian IBD Research Group*

***Appendix** : Belgian IBD Research group members (as of September 2006 and in alphabetical order) : Baert Filip, Caenepeel Philippe, Claessens Christophe, Coche Jean-Charles, Coenegrachts Jean-Louis, De Reuck Marc, De Vos Martine, Dewit Olivier, D'Haens Geert, D'Heygere Francois, Dutre Joris, Ferrante Marc, Fiasse Rene, Fontaine Fernand, Holvoet Jan, Lambrecht Guy, Lammens Pierre, Louis Edouard, Maisin Jean-Marc, Mana Fazia, Mokaddem Fady, Moreels Tom, Muls Vinciane, Noman Maja, Peeters Harald, Pelckmans Paul, Pierik Marieke, Potvin Philippe, Rutgeerts Paul, Schapira Michael, Schoofs Nathalie, Schurmans Piet, Sermeus Alexandra, Staessen Dirk, Terriere Luc, Van Assche Gert, Van De Mierop Frank, Van Gossum Andre, Van Hootegem Philippe, Van Outryve Marc, Vancalck Michel, Vermeire Severine

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, **163-170**).

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 $\geq$ 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 given 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

Author for correspondence : Séverine Vermeire MD, PhD. Department of Gastroenterology. University Hospital Leuven, Herestraat 49, 3000 Leuven Belgium. E-mail : Severine.Vermeire@uz.kuleuven.ac.be.

Submission date : 27.09.2006
Acceptance date : 23.04.2007

Table 1. — **Frequency of the different types of infusion reactions. The numbers represent % of patients with the given condition**

Reference	n	prospective	Acute infusion reactions (%)	Serious acute infusion reactions (%)	Delayed infusion reactions (%)	React resulting in treatment Interruption (%)
Hanauer 2004	573	Yes	23.2	3.8	2.3	2.8
Lamireau 2004	88	No	15.0	NA	NA	NA
Seiderer 2004	100	No	NA	2.0	1.0	NA
Colombel 2004	500	No	NA	3.8	2.8	4.8
Cheifetz 2003	165	Yes	9.7	2.4	1.8	1.2
Kugathasan 2002	86	No	NA	4.7	9.3	NA
Baert 2003	125	Yes	27.0**	NA	NA	NA
Louis 2002	336	No	NA	2.0	0.9	NA
Miele 2004*	34	Yes	23.5	2.0	0.9	0
Crandall 2003*	57	No	38.6	NA	7.0	1.7

* paediatric studies ** all types of infusion reactions grouped.

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 tryptase 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 1 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

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).

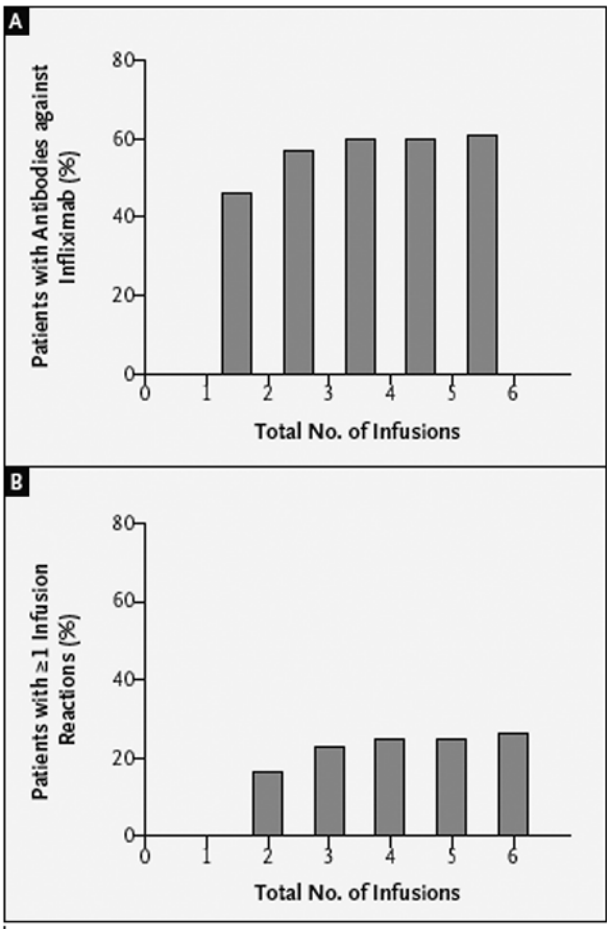

Fig. 1. — Cumulative Incidence of Antibodies against Infliximab (Panel A) and of Infusion Reactions (Panel B) in the Study Cohort (adapted from Baert *et al.*, *NEJM*, 2003, **348** : 601-8).

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

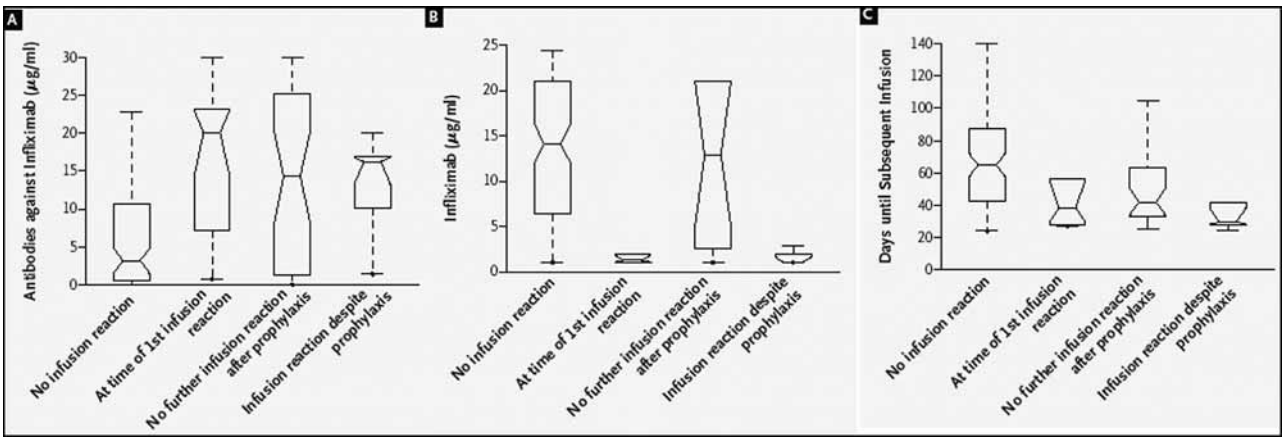

Fig. 2. — Concentrations of Antibodies against Infliximab before an Infliximab Infusion (Panel A), Infliximab concentrations four weeks after the infusion (Panel B), and duration of response (Panel C) according to the occurrence of infusion reactions (adapted from Baert *et al.*, *NEJM*, 2003, **348** : 601-8).

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 μg/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 μg/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 that 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 1 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 1 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 (azathioprine 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

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 centers 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 methylprednisolone (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 reoccurrence of symptoms. After resolution of symptoms, infusion may be restarted at reduced rate (10 ml/hr with gradual increase every 15 minutes) and careful survey of the patient with monitoring of vital signs every 15 minutes. If symptoms re-occur after restarting, the infusion must be stopped.

In the presence of a severe reaction with cardiopulmonary 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 epinefrine (0,1-0,5 ml of a solution 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%) considered that acute infusion reactions precluded further treatment (and then mostly the severe acute reactions). The other centers will re-infuse their patients but with the necessary prophylaxis. In the Mount Sinai experience all patients with mild to moderate reactions were retreated. Three out of 4 patients with severe reactions were retreated with success, one fourth of the patients experienced a new reaction despite prophylaxis (14). In a French study patients in whom treatment was suspended due to infusion reactions were retreated using a systematic tolerance induction regimen. Eleven of fourteen patients were able to be retreated safely of whom about half benefited from these infusions (15). In case of previous history of infusion reaction pretreatment with an antihistamine (oral or IM) and IV hydrocortisone 30 minutes before every infusion is required and the infusion has to be started at a reduced rate (10 ml/hr or four drops/min) and may be gradually increased every 15 minutes.

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. Antihistamines 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 prophylaxis all centers judged that infliximab would best be stopped definitively and that other treatment options need to be seeked. Humanized or human TNF-blockers were judged the first choice when available.

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 monotherapy, (4) infliximab maintenance every 8 weeks together with concomitant immunosuppression 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 pretreatment 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, concomitant 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

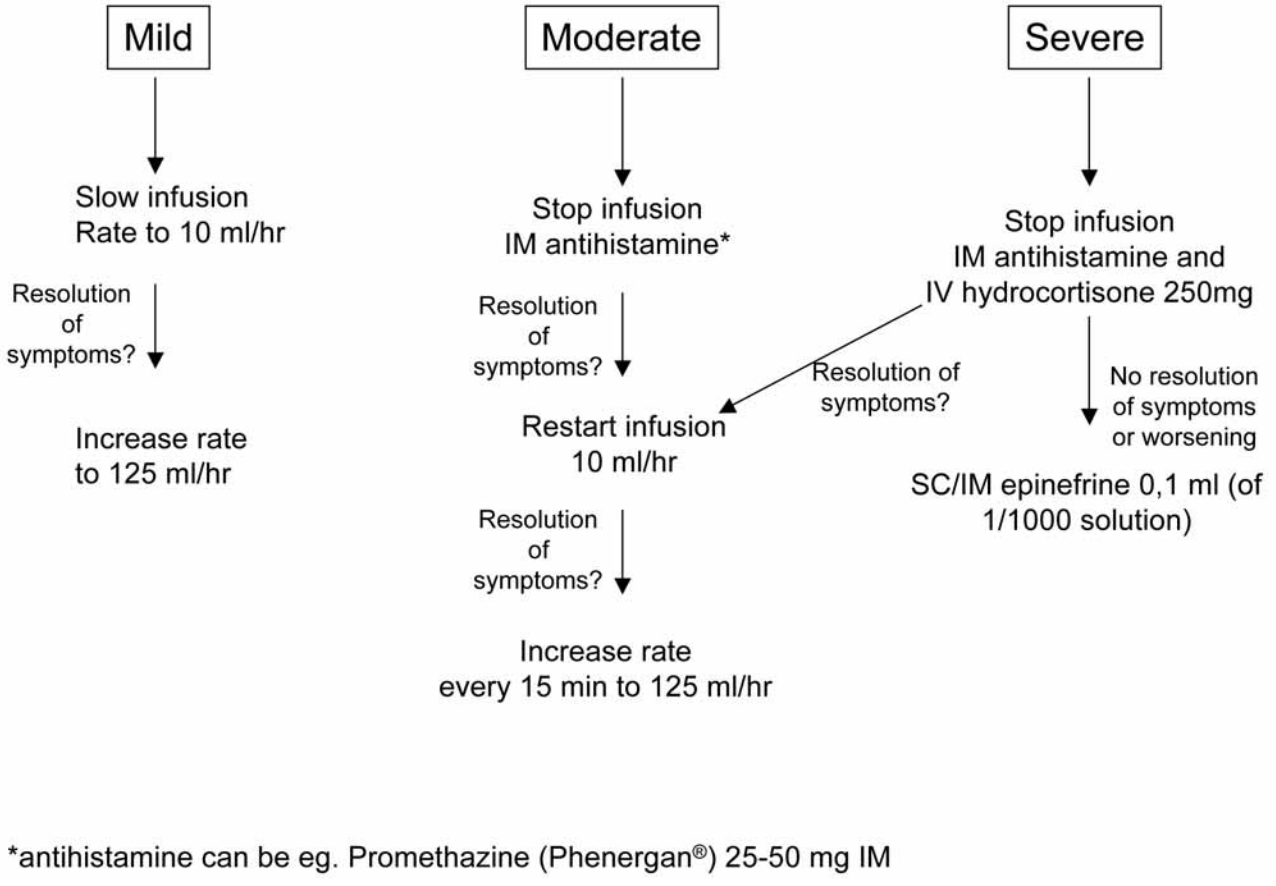

Fig. 3. — Flow chart showing the management of acute infusion reactions

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.

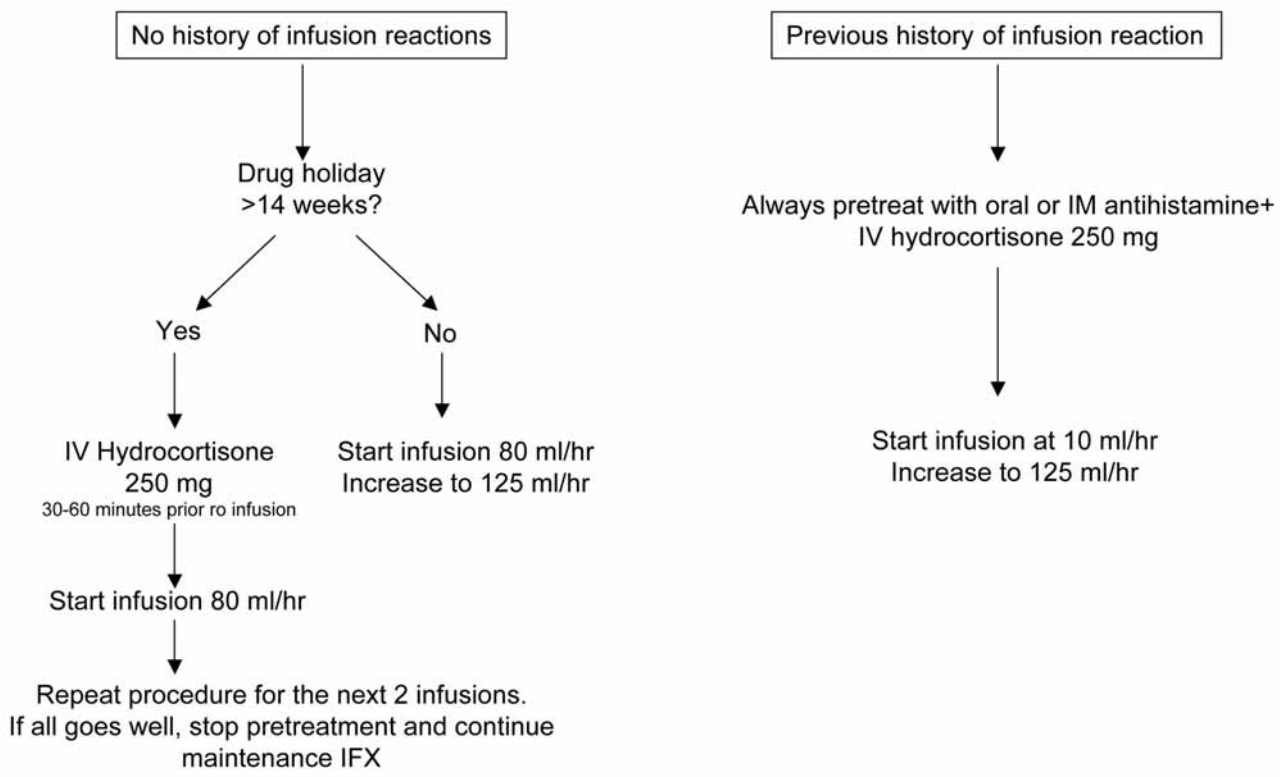

Fig. 4. — Prophylaxis of infusion reactions

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)**

	Episodic therapy	Maintenance therapy	p value
Response week 30	52%	62%	0.024
Remission week 30	32%	40%	0.07
Mucosal Healing	18%	44%	0.041
Normal quality of life (IBDQ > 170)	30%	40%	0.012
Steroid free at week 30	29%	44% (5 mg/kg) 47% (10 mg/kg)	0.03 0.01
% patients needing hospitalizations	38%	24%	0.014
% patients needing surgery	7.4%	2.8%	0.01
ATI formation	28%	9% (5 mg/kg) 6% (10 mg/kg)	< 0.0001 < 0.0001

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.

References

1. HANAUER S., WAGNER C., BALA M. *et al.* Incidence and importance of antibody responses to infliximab after maintenance of episodic treatment in Crohn's disease. *Clin. Gastroenterol. Hepatol.*, 2004, **2** : 542-553.
2. PRESENT D.H., RUTGEERTS P., TARGAN S., HANAUER S.B., MAYER L., VAN HOGEZAND R.A., PODOLSKY D.K., SANDS B.E., BRAAKMAN T., DEWOODY K.L., SCHAIBLE T.F., VAN DEVENTER S.J. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N. Engl. J. Med.*, 1999, **340** : 1398-1405.
3. SANDS B.E., ANDERSON F.H., BERNSTEIN C.N. *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N. Engl. J. Med.*, 2004, **350** : 876-85.
4. RUTGEERTS P., FEAGAN B.G., LICHTENSTEIN G.R., MAYER L.F., SCHREIBER S., COLOMBEL J.F., RACHMILEWITZ D., WOLF D.C., OLSON A., BAO W., HANAUER S.B. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology*, 2004, **126** : 402-13.
5. HANAUER S.B., WAGNER C.L., BALA M., MAYER L., TRAVERS S., DIAMOND R.H., OLSON A., BAO W., RUTGEERTS P. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin. Gastroenterol. Hepatol.*, 2004 Jul, **2** (7) : 542-53.
6. LAMIREAU T., CEZARD J.P., DABADIE A., GOULET O., LACHAUX A., TURCK D., MAURAGE C., MORALI A., SOKAL E., BELLI D., STOLLER J., CADRANEL S., GINIES J.L., VIOLA S., HUET F., LANGUEPIN J., LENAERTS C., BURY F., SARLES J., FRENCH-SPEAKING GROUP FOR PEDIATRIC GASTROENTEROLOGY NUTRITION. Efficacy and tolerance of infliximab in children and adolescents with Crohn's disease. *Inflamm. Bowel Dis.*, 2004, **10** : 745-50.
7. SEIDERER J., GOKE B., OCHSENKUHN T. Safety aspects of infliximab in inflammatory bowel disease patients. A retrospective cohort study in 100 patients of a German University Hospital. *Digestion*, 2004, **70** : 3-9.
8. COLOMBEL J.F., LOFTUS E.V. Jr., TREMAINE W.J., EGAN L.J., HARMSEN W.S., SCHLECK C.D., ZINSMEISTER A.R., SANDBORN W.J. The safety profile of infliximab in patients with Crohn's disease : the Mayo clinic experience in 500 patients. *Gastroenterology*, 2004, **126** : 19-31.
9. KUGATHASAN S., LEVY M.B., SAEIAN K., VASILOPOULOS S., KIM J.P., PRAJAPATI D., EMMONS J., MARTINEZ A., KELLY K.J., BINION D.G. 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** : 1408-14.
10. BAERT F., NOMAN M., VERMEIRE S., VAN ASSCHE G., D' HAENS G., CARBONEZ A., RUTGEERTS P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N. Engl. J. Med.*, 2003, **348** : 601-8.
11. LOUIS E., RUTGEERTS P., WESTHOVENS R., DE VOS M., VEYS P., VAN GOSUM A., MALAISE M., PESCATORE P., FIASSE R., PELCKMANS P., REYNAERT H., VAN DEN BOSCH F., D'HAENS G., BELAICHE J. Short and long term safety of remicade (infliximab) in Crohn's disease and rheumatoid arthritis. *Gastroenterology*, 2002, **122** : W1347.
12. MIELE E., MARKOWITZ J.E., MAMULA P., BALDASSANO R.N. Human antichimeric antibody in children and young adults with inflammatory bowel disease receiving infliximab. *J. Pediatr. Gastroenterol. Nutr.*, 2004, **38** : 502-8.
13. CRANDALL W.V., MACKNER L.M. Infusion reactions to infliximab in children and adolescents : frequency, outcome and a predictive model. *Aliment Pharmacol. Ther.*, 2003, **17** : 75-84.
14. CHEIFETZ A., SMEDLEY M., MARTIN S., REITER M., LEONE G., MAYER L., PLEVY S. The incidence and management of infusion reactions to infliximab : a large center experience. *Am. J. Gastroenterol.*, 2003, **98** : 1315-24.
15. DUBURQUE C., LELONG J., IACOB R., SEDDIK M., DESREUMAUX P., FOURNIER C., WALLERT B., CORTOT A., COLOMBEL J.F. Successful induction of tolerance to infliximab in patients with Crohn's disease and prior severe infusion reactions. *Aliment Pharmacol. Ther.*, 2006 Sep 1, **24** (5) : 851-8.
16. FARRELL R.J., ALSAHLI M., JEEN Y.T., FALCHUK K.R., PEPPERCORN M.A., MICHETTI P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease : a randomized controlled trial. *Gastroenterology*, 2003, **124** : 917-924.
17. NOMAN M., VERMEIRE S., VAN ASSCHE G., BAERT F., D'HAENS G., MARCELETTI J., DO J., SMITH K.M., RUTGEERTS P. The effectiveness of immunosuppression to suppress the formation of antibodies to infliximab in Crohn's disease. *Gastroenterology*, 2004, **126** : A-54-55.
18. VAN ASSCHE G., PAINTAUD G., D'HAENS G., BAERT F., VERMEIRE S., NOMAN M., WATIER H., MAGDELAINE C., RUTGEERTS P. Continuation of immunomodulators is not required to maintain adequate infliximab efficacy in patients with Crohn's disease but may improve pharmacokinetics. *Gastroenterol.* Suppl, 2006, **130** : A-142.