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Serum sickness, encephalitis and other complications of anti-cytokine therapy

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The introduction of biological therapies has greatly advanced the therapeutic armamentarium of the inflammatory bowel diseases Crohn's disease and ulcerative colitis. At present, three anti-tumour necrosis factor (TNF) agents (infliximab, adalimumab and certolizumab pegol) and one anti-adhesion cytokine (natalizumab) have been approved and have shown efficacy in luminal and/or fistulizing Crohn's disease and/or in ulcerative colitis. Although the overall benefit/risk ratio for the anti-TNF agents is positive, of particular concern has been the problem of immunogenicity ascribed to the formation of antibodies to these molecules. Antibody formation is associated with allergic reactions and loss of response through decreased trough serum concentrations. Ways to reduce antibody formation include maintenance therapy, the use of concomitant immunomodulators and pre-treatment with corticosteroids. Other safety concerns include the occurrence of opportunistic infections, skin manifestations, and the rare but often lethal hepatosplenic T-cell lymphoma. The alpha-4 integrin natalizumab has been associated with three cases of progressive multifocal leucoencephalopathy and was the reason for which the drug was not approved in Europe, and is available only through a specialised programme in the US. We discuss the safety aspects of the biological agents in this chapter and, where available, give ways to prevent and/or treat them.

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The pathogenesis of the inflammatory bowel diseases Crohn's disease (CD) and ulcerative colitis (UC) is not well understood, but the actual hypothesis of an abnormal immune response of the gut towards the commensal flora in a genetically susceptible host has been widely accepted. In the absence of preventive measures or a cure, the management of irritable bowel disease (IBD) aims at suppressing inflammation and maintaining a healed bowel to prevent complications such as fistulas or strictures. Corticosteroids have been the mainstay of the treatment of IBD for many decades, but do not change the course of the disease and are associated with substantial side effects. The thiopurines azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective for steroid sparing and for maintenance of remission in Crohn's disease, but their efficacy in ulcerative colitis is much less established [1,2]. They also suffer from side effects, of which bone marrow suppression, gastrointestinal symptoms, pancreatitis and hepatotoxicity are the most frequent. Methotrexate has been demonstrated to be effective in inducing and maintaining remission in CD, but again its use in patients with UC is not substantiated by good randomised clinical studies. Side effects include bone marrow toxicity, liver abnormalities, and rare but severe cases of interstitial pneumonia. Furthermore, this drug is under no circumstances to be used during pregnancy, which makes it less attractive in a disease like IBD which frequently occurs in young individuals.

Biological therapies and their mechanism of action

More recent research on the pathophysiology of Crohn's disease has shown the important role of the pro-inflammatory cytokine tumour necrosis factor (TNF) in the inflammatory process, and this cytokine subsequently received a lot of attention as a potential target for therapeutic intervention [3,4]. Several strategies to interfere with the biological effects of TNF have been developed, such as antibodies which directly bind and inactivate TNF, and recombinant soluble receptors targeting TNF. Antibodies in clinical use for IBD include infliximab (Remicade®), an IgG1 chimeric monoclonal antibody, adalimumab (Humira®), a fully human IgG1 monoclonal antibody, and certolizumab pegol (Cimzia®), a pegylated humanised anti-TNF Fab fragment. Infliximab and adalimumab, by means of their Fc portion, bind complement and induce apoptosis of inflammatory cells [5–11]. Crohn's disease has been associated with resistance to apoptosis, and this was long accepted as one of the major mechanisms by which inflammation was perpetuated [12]. Initially it was, therefore, believed that the positive effect of infliximab and adalimumab was explained by apoptosis induction. However, the efficacy of certolizumab pegol in Crohn's disease has reopened the debate on the precise mechanism of action of these drugs, as certolizumab pegol is lacking an Fc portion and does not induce apoptosis (Table 1) [13].

Besides the class of anti-TNF agents, a second class of molecules which block interactions between adhesion molecules on circulating immune cells and their endothelial cell receptors has been developed [14]. Natalizumab (Tysabri®, formerly known as Antegren) is a recombinant humanised IgG4 monoclonal antibody to α_4 integrin that blocks adhesion and subsequent leukocyte migration into the gut. Following one week of natalizumab administration, the total number of circulating leukocytes (including lymphocytes, monocytes, basophils and eosinophils) increases due to inhibition of transmigration out of the vascular space. This therapy does not affect the number of circulating neutrophils. Due to important safety issues (discussed further below), more gut-selective molecules are currently being developed and are under study.

Table 1
Differences in mechanisms of action of anti-tumour necrosis factor (TNF) agents in clinical use for Crohn's disease.

	Infliximab	Adalimumab	Certolizumab pegol
Structure	IgG1	IgG1	Pegylated Fab fragment
	Chimeric	Human	Humanised
Neutralisation of soluble and membrane TNF	Yes	Yes	Yes
Induction of apoptosis	Yes	Yes	No
Complement-dependent cytotoxicity (CDC)	Yes	Yes	No
Antibody-dependent cell-mediated cytotoxicity (ADCC)	Yes	Yes	No
Necrosis of neutrophils	Yes	Yes	No
Inhibition of lipopolysaccharide- (LPS-) driven cytokine production (IL1b)	Yes	Yes	Yes

Toxicity of biological therapies: general principles

Toxicities related to biological therapy can be classified into three categories (Table 2). Side effects may be *disease-specific*, e.g., the occurrence of abdominal sepsis associated with Crohn's disease of the bowel. Other adverse events may be *class-specific*, as for instance the risk of intracellular infection (tuberculosis), demyelinating disease, worsening of congestive heart failure, or lymphoma with the anti-TNF agents. Finally toxicity may be *molecule-specific*. For example, it is known that IgG1 antibodies are more associated with autoimmunity than IgG4 antibodies. Also the problem of immunogenicity associated with antibody therapy seems more important for chimeric than for humanised or human antibodies. The rare IgE-mediated allergic reactions are drug- and host-specific.

A second aspect to consider when studying safety reports is the phase of clinical development of the drug. The assessment of safety during drug development is difficult. Clinical trials have the advantage of including placebo-treated control groups, and meta-analysis of trials is mostly able to pick up increases in rather common events such as infusion reactions and upper respiratory tract infections (Table 3). However, controlled trials involve only relatively few patients, with strict inclusion criteria and with limited follow-up (ranging in general from one to three years). In contrast, post-marketing surveillance has the advantage that large numbers of patients are treated for a variable duration of time. Moreover, patients usually not included in trials, such as children or elderly patients, become exposed to drugs post-marketing. The disadvantage of this type of adverse event reporting is that there is no control population or denominator, and that reporting rates and accuracy are highly variable. Nevertheless, post-marketing surveillance is more likely to pick up serious but low-background events. The best example was that of tuberculosis during and after development of infliximab [15].

Finally, the problem of cumulative toxicity when combining multiple immunosuppressive therapies needs attention. The risk of sepsis, opportunistic infections, malignancies and myelosuppression is much greater if biologicals are administered against a background of glucocorticosteroids and/or immunosuppression [16]. Therefore, in the absence of clear data showing superior efficacy with combination therapy, monotherapy is probably the way to go. However, the recent short-term (26 weeks) results of the double-blind placebo-controlled SONIC study in patients with early Crohn's disease, in which 508 patients were randomised to azathioprine monotherapy ($n = 170$), infliximab monotherapy ($n = 169$), or the combination of both ($n = 169$) showed significant higher remission and mucosal healing rates in patients treated with a combination of infliximab and azathioprine than in the infliximab monotherapy arm, and this arm again showed superiority over the azathioprine monotherapy arm [17]. These results need close follow-up to learn whether combination therapy is also more efficacious beyond six months, although adverse events will also need to be taken into account.

Indications and contraindications of biological agents in IBD

Infliximab and adalimumab are approved and reimbursed for active Crohn's disease refractory to 'standard therapy', corticosteroid dependence, relapses in spite of immunosuppression, and fistulizing Crohn's disease. Certolizumab pegol is approved for the same conditions in the US and in Switzerland, and is only available in the rest of Europe through a Compassionate Use Programme, while an additional randomised controlled trial requested by EMEA is ongoing. The ACT studies have furthermore shown that infliximab is also efficacious in patients with ulcerative colitis (UC) who are resistant to standard therapy [18]. Studies with adalimumab in UC are ongoing. Besides luminal and fistulizing CD,

Table 2

Classification of toxicities related to biological therapy.

Disease-specific	Class-specific	Molecule-specific
Abdominal sepsis	Intracellular infection Demyelinating disease Congestive heart failure Lymphoma	Autoimmunity Immunogenicity Allergies

Table 3
Adverse event reporting and safety in drug development.

	Advantage	Disadvantage	Detects
Clinical drug trials	Controls Meta-analysis	Few patients Limited follow-up Selected groups	Increases in common events
Post-marketing surveillance	Many patients Variable duration Population subsets	No controls or denominator Variable reporting	Serious low-background events

all extra-intestinal manifestations related to IBD (erythema nodosum, pyoderma gangrenosum, arthritis, uveitis, episcleritis) respond also very well to anti-TNF [19–23]. The optimal strategy of all anti-TNFs is induction therapy followed by systematic maintenance treatment. This has proved to reduce complications, hospitalisations and surgeries, as well as antibody formation in the case of infliximab [24,25].

A number of precautions are necessary before an anti-TNF agent is started. Clear contraindications for the use of anti-TNF as a class include obstructive stenosis in patients with Crohn's disease, active infections such as tuberculosis, the presence of abscesses in patients with fistulizing disease, demyelination of the central nervous system as in multiple sclerosis, and congestive heart failure. The results of a randomised study [26] evaluating the use of infliximab in patients with heart failure – New York Heart Association (NYHA) functional class III/IV – suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been rare post-marketing reports of new-onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer anti-TNF to patients with heart failure, they should be closely monitored during therapy, and the drug should be discontinued if new or worsening symptoms of heart failure appear.

Safety of biological therapies in IBD

Serious infections, malignancy and mortality associated with anti-TNF agents

The rate of *serious infections* in clinical trials in Crohn's disease and rheumatoid arthritis in patients treated with infliximab (6.2%) was not higher than in patients treated with placebo (6.8%), according to the Periodic Safety Update Report (PSUR7). The mortality rate in the clinical trials with three years' post-study follow-up was 1.7% for patients treated with infliximab and 4.2% for placebo-treated patients.

Reactivation of latent tuberculosis is a severe complication with all anti-TNF strategies [15]. By February 2003, active TB was reported in 350 of more than 400,000 patients treated with infliximab, a cumulative incidence of 0.46 per 1000 patient-years. Most cases occurred within the first two months after initiation of therapy. The cumulative mortality amounted to nine percent. Therefore, all patients who will undergo treatment with an anti-TNF agent should be evaluated for latent tuberculosis with a tuberculin skin test and chest X-ray. Treatment of latent tuberculosis should be initiated prior to therapy. Recommendation for screening for TB and treatment are proposed by national scientific organisations, and authorities and physicians should consult their national guidelines.

Our group recently assessed the long-term safety in all patients treated with infliximab for IBD in our hospital over a 14-year period [27]. By reviewing medical records of 743 infliximab- and 666 not-infliximab-treated IBD patients – median follow-up of 58 (IQR: 33–88) months and 144 months (IQR: 83–163), respectively – a total of 113 severe adverse events (SAE) occurred in 93 (13%) of the infliximab patients and 157 SAE in 126 (19%) of the control patients ($P = 0.45$). There was no difference between the two groups in terms of mortality, malignancies and infection rates. An important observation was

that concomitant therapy with steroids came out as the only independent risk factor for infections in infliximab-treated patients, with a 2.69-fold (95% CI: 1.18–6.12) increased risk in case of co-administration of corticosteroids together with infliximab ($P = 0.018$).

Infliximab and other anti-TNF agents have been associated in rare cases with optic neuritis, seizure, and new-onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system *demyelinating disorders*, including multiple sclerosis [28]. As pointed out before, if these signs are present already before start, anti-TNF should not be initiated. If signs suggestive of demyelination appear during anti-TNF therapy and are confirmed by imaging, the drug should be discontinued and not restarted.

The use of anti-TNF agents has been associated with *autoimmunity* and the formation of antinuclear antibodies (ANA) and antibodies to double-stranded DNA [29]. However, drug-induced lupus reactions without end-organ damage occur rarely. Antinuclear antibodies are associated with female sex and with the occurrence of papulosquamous or butterfly rash [29]. Patients with these antibodies can be safely retreated with infliximab without increased risk of complications, and at present there are no data to support routine ANA monitoring in clinical practise during anti-TNF therapy.

The development of *lymphoma* in chronic inflammatory conditions has been a topic of great interest. A large French population-based study, CESAME, suggested a doubling of the risk of lymphoma in patients with IBD, with the majority of cases occurring in association with immunosuppressive therapy [30]. Earlier, a meta-analysis already concluded that the risk of lymphoma is increased fourfold in patients with IBD on thiopurine treatment (azathioprine and 6-mercaptopurine) compared to those not receiving such therapy [31]. Although these analyses cannot demonstrate causation, and of course it is possible that an increased lymphoma risk relates to more active underlying disease rather than thiopurine therapy, they warrant caution. In the CD and RA trials with infliximab six lymphomas were diagnosed for a follow-up of 4148 patient-years versus zero for 691 placebo-patient-years. All lymphomas occurred in patients treated with concomitant immunosuppression. Four of these lymphomas occurred in patients with RA. In RA, the background incidence of lymphoma is increased in comparison to that in the general population. By February 2003, lymphoma was reported spontaneously in 71 cases (45 in RA and 20 in CD) with approximately 365,000 patients treated.

The most recent cases have been of hepatosplenic T-cell lymphomas (HSTCL) reported in mostly young patients under anti-TNF and/or immunomodulator therapy [32]. A total of 17 of these HSTCL under anti-TNF have been documented. They are a rare form of non-Hodgkin's lymphomas and typically have a very aggressive to lethal course. Whereas most cases occurred in patients under combination therapy with anti-TNF and azathioprine or 6-MP, some have also been described in patients treated with anti-TNF in monotherapy [33].

Serious infections, malignancy and mortality associated with natalizumab

The large phase-III studies with natalizumab, ENACT 1 and 2 (Evaluation of Natalizumab as Continuous Therapy), showed clear efficacy in inducing and also maintaining response and remission in Crohn's disease. The combined safety data for natalizumab in clinical studies showed that the drug was well tolerated, and it even received a fast track for registration with the FDA. However, natalizumab was voluntarily withdrawn from the market in February 2005 after two cases – one fatal and one non-fatal – of progressive multifocal leucoencephalopathy (PML) were found in 1869 patients given natalizumab in combination with interferon β_{1a} (Avonex) over a two-year period for multiple sclerosis [34,35]. A second PML death attributed to natalizumab involved a patient with CD who died in December 2003 from PML [36]. This patient received eight doses of natalizumab over an 18-month period and had received multiple immunosuppressant agents and suffered from chronic lymphopenia. Although the few cases of PML were very concerning, a detailed review on >3000 patients who had received natalizumab for multiple sclerosis, CD, or rheumatoid arthritis found no new cases of PML and suggested a risk of PML of about one per 1000 patients treated with natalizumab for a mean duration of 17.9 months [37]. Following this report, Tysabri was reintroduced to the market for MS and is now also approved in the US for CD. Because of the risk of PML, natalizumab is available only through a special restricted distribution programme called the MS-TOUCH™ Prescribing Programme. A similar

programme (CD-TOUCH™) is available for patients with Crohn's disease (www.elan.com). The drug is not approved for Crohn's disease in Europe. Recently (August 2008) two new cases of PML have been diagnosed in patients treated with Tysabri monotherapy for MS in Europe.

Nevertheless, anti-migration strategies remain very attractive for the treatment of IBD, and in particular antibodies which are gut-specific will be preferred in the future if equal efficacy and better safety can be demonstrated. They might even get an important place in the treatment of IBD, as this treatment would allow treatment of patients who present with primary or secondary failure to anti-TNF agents. If effective and safe, these gut-selective therapies would also have their place as primary biological therapy and would expand our therapeutic possibilities. Several of these molecules have been developed and are currently being studied in various phases of RCTs.

Immunogenicity of biological agents: types of reactions and magnitude of the problem

Biological therapies may induce several types of allergic reactions, a phenomenon called immunogenicity. The main hypothesis behind allergic reactions, acute or delayed and severe or not, is that they are related to the formation of some form of antibody to the biological agents. Although first and most often described for chimeric proteins, antibody formation and the same allergic reactions have also been described against humanised or human proteins, although to a lesser extent (Table 4) [38].

Immunogenicity and antibody formation is associated with acute or delayed allergic reactions. Acute reactions are defined as reactions occurring during or within 2 h of an infusion. They can be severe or not. Severe reactions are usually defined as reactions which necessitate stopping 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 into non-immune-mediated reactions (nausea, headache, fever) and immune-mediated reactions (urticaria, dyspnoea, hypotension, chest pain). The question remains whether these reactions are typical type-1 hypersensitivity reactions, since the majority of the patients can be successfully retreated, which is an uncommon phenomenon in IgE-mediated reactions. The only study investigating the mechanism of infusion reactions found that there was no significant increase in tryptase levels, suggesting that they were not classical type-1 IgE-mediated hypersensitivity reactions [39]. Tryptase is a mast-cell enzyme that is released upon degranulation during type-1 reactions 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 typically occur two days to two weeks after reinfusion of infliximab. The symptoms can be quite severe and usually last 3–5 days. Delayed reactions are usually attributed to serum sickness-like reactions. Possible symptoms include a cluster of features (generalised stiffness, myalgias, arthralgias, fever, and/or rash). Severe serum sickness-like reactions have been mainly observed in Crohn's disease patients 3–12 days after infliximab when this therapy was reinstituted after a long drug holiday.

The prevalence of acute infusion reactions to infliximab is summarised in Table 5 and has been relatively similar in uncontrolled experience [24,40–48]. Some differences may be explained by the retrospective or prospective character of the data collection, by the definition of the reactions, and by the mean number of infusions per patient in these reports. The most reliable and relevant data on the prevalence of infusion reactions following infliximab come from the ACCENT 1 study [49]. 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

Table 4
Immunogenicity induced by biological therapies.

	Murine	Chimeric	Human
Negligible immunogenicity (<2%)	9%	33%	55%
Tolerable (2–15%)	7%	27%	36%
Marked (>15%)	84%	40%	9%

Table 5

Frequency of the different types of infusion reactions to infliximab. 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 et al, 2004 [24]	573	Yes	23.2	3.8	2.3	2.8
Lamireau et al, 2004 [40]	88	No	15.0	NA	NA	NA
Seiderer et al, 2004 [41]	100	No	NA	2.0	1.0	NA
Colombel et al, 2004 [42]	500	No	NA	3.8	2.8	4.8
Cheifetz et al, 2003 [43]	165	Yes	9.7	2.4	1.8	1.2
Kugathasan et al, 2002 [44]	86	No	NA	4.7	9.3	NA
Baert et al, 2003 [45]	125	Yes	27.0 ^b	NA	NA	NA
Louis et al, 2002 [46]	336	No	NA	2.0	0.9	NA
Miele et al, 2004 ^a [47]	34	Yes	23.5	2.0	0.9	0
Crandall et al, 2003 ^a [48]	57	No	38.6	NA	7.0	1.7

^a Paediatric studies.

^b All types of infusion reactions grouped.

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 rheumatoid arthritis trials) about 20% of patients treated with infliximab experienced infusion reactions compared to 10% of placebo-treated patients.

We previously found a significant relationship between the serum infliximab concentration measured four weeks after an infusion and the concentration of ATIs before that infusion ($r = 0.34$, $P < 0.001$) [45]. The median infliximab concentration four weeks after an infusion was significantly lower among patients with an infusion reaction than among patients who never had a reaction (1.2 µg/mL versus 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: 1.9–21.0). Infliximab concentrations, however, were almost undetectable among patients who had another reaction despite receiving prophylaxis (1.0 µg/mL; 95% CI: 1.0–1.9; $P = 0.01$). 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; $P < 0.001$) (Fig. 1). Patients who were taking immunosuppressive agents had a lower incidence of antibodies (43%) than patients who were not taking immunosuppressive agents (75%) ($P < 0.01$). The concomitant use of immunosuppressives was the single predictive factor in preventing antibody

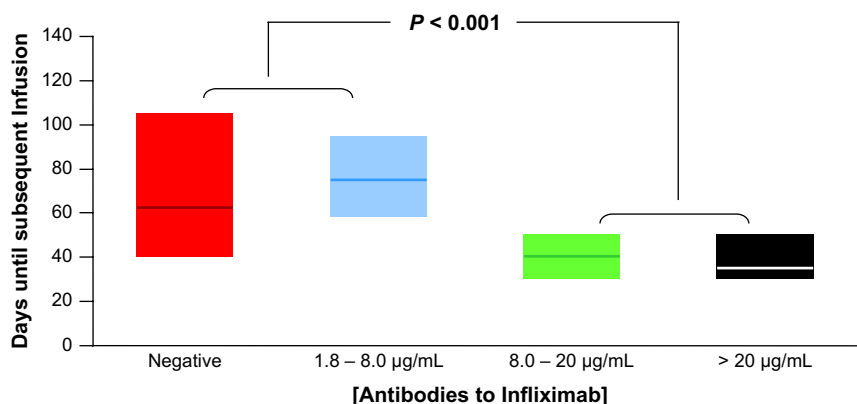


Fig. 1. Duration of response to infliximab by antibody status.

formation in multivariate analysis. No association between ATIs and gender, location of disease, smoking status, or the use of mesalamine or corticosteroids was found in this study.

Therefore, prevention of antibody formation is very important, and ways to do this include systematic maintenance therapy, concomitant use of immunomodulators (with no difference between azathioprine, 6-MP or MTX) and pre-treatment with corticosteroids [49,50]. It is still our clinical practise to maintain the immunosuppressant (azathioprine, 6-MP or MTX) at the start of infliximab for six months. We recently conducted a study where patients in stable remission under combination of azathioprine and infliximab were randomised to either continuation or discontinuation of the purine analogue and continuation of infliximab in maintenance [51]. The results from this IMID (Infliximab Maintenance Immunosuppression Discontinuation) study showed that discontinuation of immunomodulators after at least six months of combined treatment and continuation with systematic infliximab maintenance does not affect long-term efficacy, although the patients who discontinued azathioprine had lower IFX trough levels in their serum. It is, therefore, our current policy to stop the immunomodulators after six months of combined therapy. Again, as previously stated, the long-term results of the SONIC study beyond six months, as well as the analyses of the trough infliximab levels in the different randomised groups in this study, will demonstrate whether this practise needs amendment.

For adalimumab, results of the CHARM and CLASSIC II studies have shown antibody formation to the drug in only 2.8% of patients during the open-label phase, and this did not differ between patients on or not on concomitant immunomodulators [52]. Also the clinical efficacy did not differ between those patients receiving adalimumab in monotherapy and those receiving concomitant immunomodulators. Therefore, we feel adalimumab can be administered in monotherapy, which will also impact on safety.

Management and prophylaxis of acute infusion reactions

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) (Fig. 2) [53]. Administration of hydrocortisone (250 mg) or methylprednisolone (125 mg) intravenously can be considered, but this 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 a reduced rate (10 mL/h with gradual increase

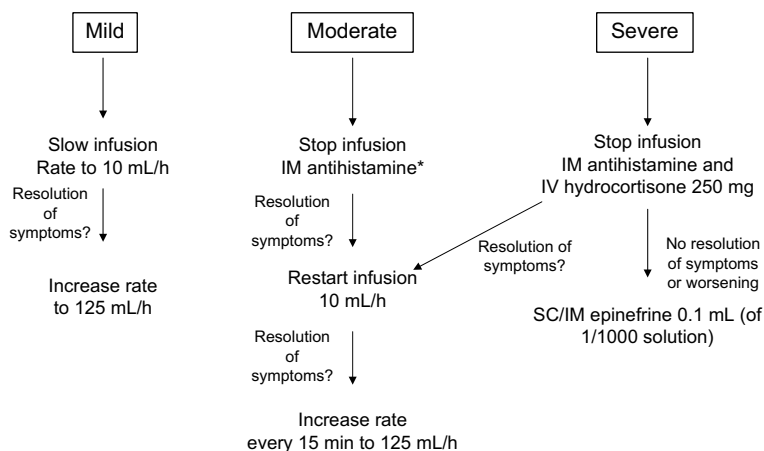


Fig. 2. Flow chart showing the management of acute infusion reactions. *Antihistamine can be, e.g., promethazine (Phenergan®) 25–50 mg intramuscularly (IM).

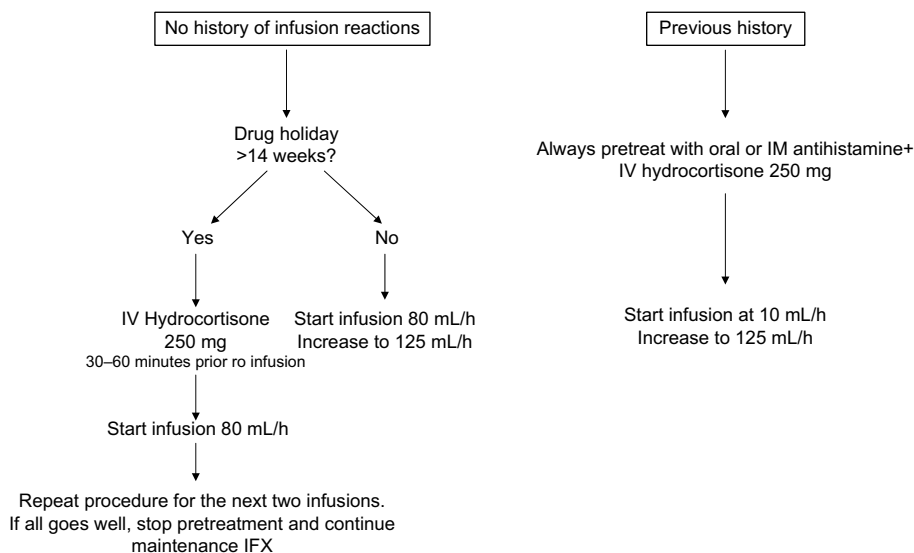


Fig. 3. Prophylaxis of infusion reactions. IFX, infliximab.

every 15 min) and careful survey of the patient and monitoring of vital signs every 15 min. If symptoms recur after restarting, the infusion must be stopped.

In the presence of a severe reaction with cardiopulmonary symptoms (chest pain, dyspnoea, hypotension) the infusion needs to be stopped, normal saline infused, the airway maintained, and oxygen given if necessary. Antihistamines should be administered intramuscularly, together with prompt intravenous hydrocortisone. In the case of allergic signs and symptoms not subsiding with these measures, slow administration of epinephrine (0.1–0.5 mL of a solution 1/1000 (1 mg/mL)) subcutaneously or intramuscularly may be considered under strict monitoring, and eventually repeated every 5 min.

In the case of previous history of infusion reaction, pre-treatment with an antihistamine (oral or intramuscular) and intravenous hydrocortisone 30 min before every infusion is required, and the infusion has to be started at a reduced rate (10 mL/h or 4 drops/min) and may be gradually increased every 15 min (Fig. 3).

Management of delayed infusion reactions

Delayed infusion reactions are controlled only by high doses of intravenous or oral glucocorticosteroids for a period of 5–7 days, and this schedule needs to be repeated around each next scheduled infusion of infliximab. However, with adalimumab and certolizumab pegol on the market, most patients are switched to these therapies, given their lower immunogenicity.

Conclusion

The safety profile of biological therapies for IBD is generally positive, given their good efficacy. One of the early safety issues has been the problem of immunogenicity ascribed to the formation of antibodies to these molecules. Immunogenicity has been greatly reduced over the years thanks to the insights gained into the importance of maintenance therapy, and/or the use of concomitant immunomodulators in the case of infliximab. More recent safety concerns for the anti-TNF agents have included the occurrence of opportunistic infections, skin manifestations, and the rare but often lethal hepatosplenic T-cell lymphoma. The α_4 integrin natalizumab has been associated with three cases of

progressive multifocal leucoencephalopathy and was the reason for which the drug was not approved in Europe and is only available through a specialised programme in the US.

Practice points

After reading this overview, physicians should be able to:

- know the contraindications for use of biological agents in IBD
- appreciate the different classes of toxicities observed with biological therapies
- understand why safety reports from randomised controlled trials, as well as from post-marketing surveillance, are necessary to fully understand the safety profile of a drug
- get a general overview of the safety issues related to anti-TNF agents and anti-adhesion molecules
- understand the problem of immunogenicity related to biological therapies and how to prevent and/or treat it

Research agenda

The following aspects related to the use of biological therapy in IBD have not been adequately understood and need further investigation:

- Is there a correlation between drug serum levels of biological molecules and/or the cumulative dose and the occurrence of complications?
- The phenomenon of loss of response to anti-TNF therapy is only partly explained by antibody formation and immunogenicity; other factors, including individual differences in pharmacokinetics, are likely to play a role and need further study

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