Guidelines for treatment with infliximab for Crohn’s disease

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A B S T R A C T

Infliximab is an accepted induction and maintenance treatment for patients with Crohn’s disease. The effectiveness of infliximab has been demonstrated for both active luminal disease and for enterocutaneous fistulisation. In addition, infliximab can be administered for extraintestinal symptoms of Crohn’s disease, such as pyoderma gangrenosum, uveitis and arthropathy. Maintenance treatment with infliximab is effective and is regarded as safe as long as the necessary safety measures are heeded. Infusion reactions occur in 3 to 17% of the patients and are associated with the formation of antibodies to infliximab (ATi). A reduction in infusion reactions is possible by the concurrent administration of steroids and the use of immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate). Furthermore, immunosuppressants increase the duration of the response to infliximab. For these reasons, the concomitant use of immunosuppressants with infliximab is recommended. Infections and most specifically tuberculosis need to be ruled out before infliximab is administered. Up to now, there are no indications for a connection between an increased risk for malignancies and treatment with infliximab.

K E Y W O R D S

Crohn’s disease, guideline, infliximab

I N T R O D U C T I O N

Infliximab (Remicade®) is a chimeric monoclonal antibody (75% human, 25% mouse) against tumour necrosis factor alpha (TNFα), a cytokine which plays an important role in the development of inflammatory reactions. Increased TNFα concentrations are found, for instance, in patients with Crohn’s disease and rheumatoid arthritis and are associated with increased disease activity. In Crohn’s disease, neutralising TNFα-induced effects with infliximab often result in a rapid reduction in intestinal inflammation with a good clinical response as outcome. Infliximab has been registered in the Netherlands since 1999 for the treatment of serious, active Crohn’s disease in patients who do not respond to an adequate course of treatment with corticosteroids, or to an immunosuppressive therapy (azathioprine, 6-mercaptopurine, methotrexate), or in those with an intolerance to or a contraindication for these therapies. In addition, infliximab is registered for the treatment of draining enterocutaneous fistulas in Crohn’s patients not responding to an adequate conventional therapy.

Since the registration of infliximab for these indications, and the publication of a consensus text about the use of infliximab for Crohn’s patients,³ numerous studies have been carried out on the effects of infliximab on Crohn’s disease. Now that greater insight has been gained into the effectiveness and long-term safety of infliximab for Crohn’s disease, an updated consensus text is desirable. There are, after all, great differences around the country in treatment regimens with infliximab, and greater unequivocalness is needed.
The guideline for induction and maintenance treatment with infliximab for Crohn’s patients is described in this article. The objective of this guideline is to provide more clarity about the indications and safety of infliximab and to present a practical treatment plan. Based on this guideline, local treatment protocols can be developed. The guideline was drawn up by specialists in the field of inflammatory intestinal diseases from all Dutch University Medical Centres (UMCs). Data from the literature as well as the specific experience of a large group of Dutch Crohn’s patients over the past six years form the basis for this guideline. In this article, the following subjects will be discussed in succession: induction treatment of luminal Crohn’s disease, induction treatment of fistula disease associated with Crohn’s, maintenance treatment with infliximab, remaining treatment indications, the safety of infliximab, and practical treatment instructions.

INDUCTION TREATMENT OF ACTIVE LUMINAL CROHN’S DISEASE

Indications
1. Active luminal disease in patients who do not respond or inadequately respond to an adequate dose of corticosteroids, alone or in combination with an immunosuppressive drug. This includes both steroid-resistant and steroid-dependent patients. A patient is regarded as being steroid-resistant when the disease does not respond to intravenous steroids (1 mg/kg, maximum 60 mg). A patient is called steroid-dependent when an exacerbation recurs during the reduction of the steroids (5-10 mg/week to 20 mg thereafter 2.5 to 5 mg/week) or within one month of stopping the steroids.
2. Active luminal disease in patients where corticosteroids or immunosuppressants are contraindicated as a result of a previous history of clinically relevant side effects.

Objective
The ultimate goal is to induce a complete clinical and endoscopic remission. When this objective is achieved, the patients are largely free of symptoms, the corticosteroids can be reduced, and surgical intervention may be avoided (see under Maintenance treatment).

Effectiveness
Clinical efficacy of a single induction treatment with infliximab has been demonstrated in a double-blind, placebo-controlled study with 108 therapy-resistant patients with Crohn’s disease. Out of this group, 27 patients were treated with the recommended dose of 5 mg/kg. The higher doses of 10 and 20 mg/kg delivered less positive results. A response was observed within two weeks, with a maximum response after four weeks. After 12 weeks, a response could still be observed in nearly half of the patients. In another placebo-controlled study, it appeared that after four weeks a single infliximab treatment did not only result in a positive clinical response, but also in a significant endoscopic improvement. Histological examination confirmed that a complete reduction in the inflammation infiltrate could only be seen in the patients treated with infliximab.

Dosage
In dose-response studies, a better result was not found at doses higher than 5 mg/kg. A slightly better clinical response was observed after ten weeks at the 5% significance level with a treatment regimen of infusions at 0-2-6 weeks (65%) compared with a regimen which was started with one single infusion (52%). However, this is unlikely to be clinically significant. In most of the patients, infliximab could still be detected in the serum for at least eight weeks after a once-only administration of the recommended dose of 5 mg/kg. For this reason an induction regimen of two or three infusions every eight weeks could also be selected. Arguments which speak in favour of the 0-2-6 week induction regimen are that this regimen appears to result in less infusion reactions, delayed allergic reactions, and decreased formation of antibodies. For this reason, the recommended intravenous dosage regimen for induction treatment is 5 mg/kg at 0-2-6 weeks.
TREATMENT OF ACTIVE FISTULA DISEASE ASSOCIATED WITH CROHN'S DISEASE

Indications
Symptomatic and draining enterocutaneous or perianal fistulas which do not respond or which respond inadequately to an adequate antibiotic course of treatment, alone or in combination with an immunosuppressive.

Objective
The aim is to reduce the number of active draining fistulas and complete or partial closure of the fistulous ducts. Complete radiological healing of fistulous ducts is usually not achievable, but patients in whom healing on MRI is achieved usually do better.\(^7\)\(^9\)

Effectiveness
A rapid effect of infliximab on fistula formation associated with Crohn's disease has been demonstrated in a double-blind, placebo-controlled study of 94 patients who had one or more fistulas in a period of at least three months.\(^10\) These patients received three infusions (with placebo or infliximab) at 0-2-6 weeks. Infliximab in a dose of 5 mg/kg (figure 2)\(^10\) appeared to be more effective than the higher dosage of 10 mg/kg. A response was seen after an average of two weeks. The median duration of the response came to 12 weeks. Closure of all fistulas was achieved in 55% of the patients treated with infliximab 5 mg/kg and in 13% of placebo-treated patients.

Infliximab does not seem to be indicated for enteroenteral fistulas or enterovesical fistulas. These types of complicated intra-abdominal fistulas usually require surgical intervention. The use of infliximab for rectal-vaginal fistulas seems disappointing.\(^7\) However, in an infliximab maintenance study, ACCENT II, rectovaginal fistulas healed well.

Dosage
For the treatment of active fistula disease associated with Crohn's disease, a similar dosage (5 mg/kg infliximab) and treatment regimen can be selected as for luminal disease (see previous comments). Here too, consideration has to be given to the selection of an intensive remission-induction regimen of 0-2-6 weeks, or a series of two to three infusions at an interval of eight weeks.

MAINTENANCE TREATMENT

Indication
Patients with luminal Crohn's disease and fistulising Crohn's disease who, after a successful induction treatment with infliximab and despite an adequate treatment with immunosuppressants, have a rapid exacerbation, an increased risk for this, or whenever the dosage of corticosteroids cannot be reduced or phased out.

The choice to move forward with infliximab maintenance therapy is partially determined by the risk profile of the patient. Risk factors for a rapid exacerbation and a complicated course are earlier resections, a positive family history, smoking, and previous frequent exacerbations despite the use of corticosteroids with immunosuppressants.\(^12\) In patients already on optimal concomitant immunosuppressive therapy, which remained unchanged at the onset of infliximab, maintenance therapy should be strongly considered immediately after induction of remission.

Objective
The aim is to prevent an exacerbation of luminal disease or reoccurring fistulas, the reduction of luminal disease or recurring fistulas, the reduction or obviation of corticosteroid treatment, the reduction or obviation of hospital admissions and surgical interventions.

Effectiveness
The efficacy of infliximab maintenance treatment for Crohn's disease has been demonstrated in three double-blind, placebo-controlled studies:

- After successful induction treatment with a single infusion of infliximab, patients (n=73) with luminal Crohn's disease received an infusion of infliximab (10 mg/kg) or placebo four times at eight-weekly


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intervals. In the infliximab group, 53% remained in remission vs 20% in the placebo group. Most of the patients showed an exacerbation 8 to 12 weeks after the final infliximab infusion, which points to a duration of efficacy of about 8 to 12 weeks.13

- In the ACCENT I study, 573 luminal Crohn’s disease patients were treated with infliximab (5 mg/kg) according to the induction regimen of 0-2-6 weeks.14 Those who showed a response (n=335, 59%) were randomised to maintenance treatment with a placebo or infliximab (5 mg/kg or 10 mg/kg) every eight weeks over a period of 46 weeks. The results (figure 3)14,15 indicate that retreatment with infliximab every eight weeks is effective in preventing exacerbations after successful induction treatment.

- In the ACCENT II study, 195 (out of a group of 306) patients with fistula disease associated with Crohn’s, had a clinical response after an induction treatment with infliximab (5 mg/kg at 0-2-6 weeks).15 This group received maintenance treatment of placebo or infliximab (5 mg/kg) every eight weeks. The results (figure 3)14,15 showed that maintenance treatment with infliximab over a long period (54 weeks) is effective in preventing new active draining fistulas.

In two placebo-controlled studies of luminal Crohn’s disease, the remission percentage was the largest in the group of patients who combined an infliximab maintenance treatment with an immunosuppressant (azathioprine, 6-mercaptopurine, methotrexate).13-14 This possible synergistic effect of infliximab, combined with an immunosuppressant, has already been described for patients with rheumatoid arthritis.

In addition to the clinical effects noted above, it has been demonstrated in various studies that during a maintenance treatment with infliximab (5-10 mg/kg every eight weeks), the corticosteroids can be completely phased out in most patients,14,16,17 the intestinal mucous improves considerably if not entirely cured,14-18 the number of hospital admissions and surgical interventions is significantly reduced for luminal Crohn’s disease18 as well as for fistula disease19 and that the quality of life of these patients improves.20,21

**Dosage**

As maintenance treatment for luminal Crohn’s disease as well as for fistulas associated with Crohn’s disease, infliximab is administered on average every eight weeks in a dosage of 5 mg/kg. This dose may temporarily be increased to 10 mg/kg if loss of response occurs, to make patients responsive to the normal 5 mg/kg dose again.

**Duration of maintenance therapy**

The question when to discontinue maintenance therapy with infliximab is difficult to answer, because evidence is lacking. We believe that in azathioprine or methotrexate refractory patients, infliximab maintenance therapy should be continued after successful induction of remission, because on demand retreatment with infliximab with long intervals in between may increase the formation of anti-infliximab antibodies. In our experience, long-term remissions were observed in patients naive for immunosuppressants, after induction therapy with infliximab together with azathioprine or methotrexate maintenance therapy.

**REMAINING INDICATIONS ASSOCIATED WITH CROHN’S DISEASE FOR INFlixIMAB**

Infliximab can be used for Crohn’s disease localised in the mouth, oesophagus, stomach and duodenum, and for extraintestinal manifestations of Crohn’s disease, such as pyoderma gangrenosum, uveitis and arthropathy including spondylitis. Infliximab is not indicated for primary sclerosing cholangitis.

Crohn’s disease of the proximal digestive tract

In 5 to 15% of patients, disease is found in the proximal digestive tract. This is often coupled with distal luminal...
disease. Usually, proximal lesions react in a similar way, i.e. well, to the therapy, which was originally initiated for distal disease. In some cases, proximal lesions of Crohn’s disease persist, such as oral aphtosis or locations in the oesophagus, stomach or duodenum, although administration of infliximab for these localisations apparently has a beneficial effect. Oral aphtosis is a painful condition.

**Extraintestinal manifestations of Crohn’s disease**

Crohn’s disease is often complicated by extraintestinal manifestations, such as inflammations of skin (erythema nodosum, pyoderma gangrenosum), eyes (uveitis), or of joints (arthropathy, enthesiopathy). Controlled studies of infliximab for these indications are still scarce. For pyoderma gangrenosum and psoriasis, a few studies have reported some therapeutic success. A positive result for uveitis after infliximab treatment has also been published, but clinical response may vary greatly. Joint manifestations can be distinguished as peripheral arthropathy, sacroiliitis, Bechterew’s disease, and tendon pain or inflammation. Manifestations such as peripheral arthropathy are commonly associated with luminal activity and generally respond well to remission-induction therapy. Infliximab also showed good results for sacroiliitis and Bechterew’s disease, which run a more independent course. Psoriatic arthritis, Bechterew’s disease and rheumatoid arthritis are now separate registered indications for infliximab. For primary sclerosing cholangitis (PSC), there is no indication at the moment. A controlled study on the effect of infliximab for PSC in ulcerative colitis patients was cancelled (no published data, Hommes et al.) For the above-mentioned proximal lesions and extraintestinal manifestations, a comparable treatment regimen is recommended as for luminal or fistula disease associated with Crohn’s disease.

**Safety of Infliximab Treatment**

There is a lively ongoing discussion about side effects of infliximab, which in rare cases can be very serious. A full understanding of the safety aspects is needed to use infliximab safely.

### Infusion reaction

**Acute infusion reaction**

An acute infusion reaction generally occurs during infusion or within two hours after infusion. In Crohn’s disease, this acute reaction occurs in 3 to 17% of patients treated with infliximab. In 0.1 to 1% there is an issue of a serious infusion reaction (table 1). This is usually an anaphylactic allergic reaction, which is usually IgE-independent. The most common symptoms are headache, nausea, chest pain, dizziness, urticaria, other types of hives or itching, and shortness of breath. Symptoms such as acute urticaria, hypotension and bronchial spasms occur far less frequently, and these events are often based on an IgE-dependent, type I allergic reaction. A rare and serious side effect is anaphylactic shock, larynx oedema and stridor.

**Delayed infusion reaction**

Delayed infusion reactions may occur as early as two days after infusion. For the most part, these late allergic reactions are observed 3 to 12 days after the infusion. The incidence of these ‘serum disorder-like’ reactions after a single infusion treatment, or during a maintenance treatment (an infusion every eight weeks) is 2 to 3%. Typical symptoms of this reaction are artralgia or myalgia with fever, exanthema, facial, hand, or lip oedema, dysphagia, pruritus, headache, and sore throat.

<table>
<thead>
<tr>
<th>Table 1. Incidence of side effects after infliximab treatment for Crohn’s patients in various cohort studies</th>
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<tr>
<td><strong>Amsterdam cohort</strong></td>
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<tr>
<td>Number of patients</td>
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<tr>
<td>Acute infusion reactions</td>
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<td>Serious infusion reactions</td>
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<td>Lupus-like syndrome</td>
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<td>Annual serious infections</td>
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<td>Annual malignancies</td>
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<td>Annual mortality</td>
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* p<0.01 (infleximab vs non-infleximab Crohn’s patients).

Anti-infliximab antibodies

Infusion reactions are associated with the presence of anti-infliximab antibodies (ATI, ‘antibodies to infliximab’). High ATI values are associated with lowered serum concentrations of infliximab, and an attenuated and shorter response to infliximab.\(^\text{44,45}\)

Prevention of an infusion reaction

Infusion reactions appear to occur more often after the second or third treatments,\(^\text{38}\) especially if the last treatment occurred more than four months previously.\(^\text{38}\) There are increasing indications that an induction treatment of three infusions at short intervals (at 0-2-6 weeks) diminishes the likelihood of the development of ATI and of an acute or delayed infusion reaction.\(^\text{3}\) A maintenance treatment with an immunosuppressant, started prior to infliximab treatment, also reduces the formation of ATI, so the chance of an infusion reaction is reduced and the extent and duration of the response is increased.\(^\text{5,6}\) The same applies for the administration of an infliximab infusion with hydrocortisone premedication.\(^\text{4}\)

For patients with a previous (delayed) infusion reaction, it is possible that in addition to a maintenance treatment with an immunosuppressive drug, premedication with a corticosteroid and/or an antihistamine can reduce the risk for a second infusion reaction (see under Practical treatment instructions).\(^\text{5,6,38,41}\)

Treating an infusion reaction

If an acute infusion reaction occurs, slowing down or temporarily stopping the infusion is usually sufficient if the adverse reaction is mild.\(^\text{38,41}\) After discontinuing the infliximab infusion, an antihistamine should be administered in combination with corticosteroids; in case of serious anaphylactic problems administration of adrenaline may be necessary.\(^\text{38,41}\)

Mild symptoms of a delayed infusion reaction often disappear spontaneously. For treatment of this type of delayed reaction, an oral antihistamine course of treatment can be given, in combination with acetaminophen.\(^\text{38}\)

For the more serious form of serum disease with myalgia and fever, a course of treatment with steroids can be considered. More details about the treatment of infusion reactions is provided under Practical treatment instructions.

Infection

The use of infliximab in Crohn’s disease patients is associated with an increased risk of infection. The average number of patients in clinical studies who develop an infection after infliximab treatment was 36%, vs 26% after placebo.\(^\text{6}\) This primarily involved uncomplicated upper bronchial tube and urinary tract infections. From various large cohort studies, it appeared that the incidence of serious infections during (maintenance) treatment with infliximab only amounted to 1.3 to 4.0% per treatment-year (table 1). Among other things, this involved fatal sepsis, pneumonia, gastroenteritis and abdominal abscesses. In the ACCENT I and II studies, the incidence of serious infections in the infliximab groups was not elevated in comparison with the placebo group.\(^\text{44,45}\)

The TREAT (Crohn’s Therapy Resource, Evaluation and Assessment Tool) registration, in which data of more than 6000 Crohn’s patients are collected, an increase in serious infections in connection with infliximab treatment was observed (table 1).\(^\text{46}\) That is why it is of utmost importance to rule out abscesses or other ongoing infections before infliximab treatment.

An important observation is that treatment with infliximab increases the risk of reactivation of latent tuberculosis (TBC). As early as in 2001, 70 cases of TBC were reported among the 147,000 patients treated with infliximab (for rheumatoid arthritis or Crohn’s disease),\(^\text{46}\) while the annual incidence in the American population is normally approximately 6 per 100,000.\(^\text{47}\) Most of the TBC cases manifested during the period of the first three infliximab infusions. Remarkably, 40 of these 70 cases involved extrapulmonary TBC.\(^\text{46}\) In another study,\(^\text{47}\) the incidence of TBC was investigated in a large population of patients with rheumatoid arthritis without and after treatment with infliximab. The TBC incidences amounted to 6.2 per 100,000 per year, vs 32.5 per 100,000 per treatment year, respectively, which is consistent with a clear increased risk of TBC during treatment with infliximab. Therefore, infliximab is contraindicated when there is a manifest presence of latent TBC. For this reason, it should be investigated whether a patient has a higher risk, for example because of previous contact with TBC or TBC treatment, or due to a long-term stay in a country or originating from a country where TBC is endemic (>50 per 100,000 inhabitants) prior to starting a treatment with infliximab. The presence of a latent or manifest TBC must be ruled out before the first infusion. A pretreatment chest X-ray is considered necessary, in addition to a Mantoux skin test.\(^\text{48}\) For patients vaccinated for TBC earlier in their life, the Mantoux skin test is unreliable. Furthermore, there is a change of anergy among patients who are on corticosteroids and/or immunosuppressants. TBC and certainly the extraintestinal form, is difficult to rule out under these circumstances, so a thorough family history and clinical alertness remain important.

Autoimmunity

In various clinical studies, the percentages for antinuclear antibodies (ANA) and double-stranded DNA antibodies (anti-ds-DNA) after infliximab treatment amounted to 46
to 57% and 23 to 34%, respectively. In the placebo groups, these percentages for ANA and anti-ds-DNA were significantly lower (18 to 35%, 6 to 23%, respectively). In rare cases, these elevated ANA values are paired with clinical symptoms which are consistent with the ‘lupus-like’ syndrome, such as polyarthralgia, myalgia, and butterfly-shaped hives on the face (Table 1).

Demelinating diseases and neurological disorders
After treatment with infliximab or other anti-TNFα therapies, new episodes of exacerbations have been described for demelinating diseases and neurological disorders such as multiple sclerosis, myelitis, optic neuritis and Guillain-Barré syndrome, a worrying finding because of the elevated prevalence of demelinating disease in the IBD population. Although no causal relationship has been demonstrated, restraint is advised for patients with these disorders.

Malignancies
There is a concern about an increased risk for malignancy with the use of infliximab, because TNFα may be protective against cancer development. However, up until now, no corroborating epidemiological data support this concern. In clinical studies, over a period of a maximum of 102 weeks, a malignancy developed in 18 of the 1678 patients treated with infliximab (including non-Hodgkin’s lymphoma, breast cancer, skin cancer, rectal adenocarcinoma). On an annual basis, this incidence did not differ statistically from the expected incidence in a comparable population. To make interpretation more complex, it is being debated whether patients with Crohn’s disease have an increased risk for attracting lymphoproliferative disorders or bowel cancer. The use of infliximab in the various controlled studies did not show any increased incidence of any cancer (Table 1). This is corroborated by the results of the TREAT registration, where no statistical difference has been observed in malignancies between patients who were and those who were not treated with infliximab (Table 1). However, longer follow-up of the safety data remains necessary.

Cardiac failure
Because of an increased mortality rate for patients who were treated with infliximab for severe cardiac insufficiency, infliximab is contraindicated in patients with chronic cardiac failure (New York Heart Association class III or IV).

Liver disease
Infliximab has an immunosuppressive effect, which theoretically can result in hepatic, viral inflammation becoming reactivated after the use of infliximab. Furthermore, there are indications that TNFα plays a causal, pathogenetic role in viral hepatitis. In clinical practice, cases have been described where infliximab was safe and effective for Crohn’s disease patients with chronic viral hepatitis. On the other hand, there are reports of patients with Crohn’s disease getting a serious exacerbation of viral hepatitis after treatment with infliximab.

Pregnancy
The first publications suggest that the possible risks of infliximab treatment during pregnancy outweigh the risks of active Crohn’s disease during pregnancy. In the TREAT, registration data of 98 pregnant Crohn’s disease patients were recorded (59 treated with infliximab and 39 not treated with infliximab); no children with deformations were registered and the percentages of miscarriages and neonatal complications were equal in both groups. Formal recommendations, however, are premature, and a restrictive approach is advised.

PRACTICAL TREATMENT INSTRUCTIONS
Based on the previously discussed insight into the effectiveness and safety of infliximab for Crohn’s disease, practical treatment instructions are outlined below (see relevant chapters above for further comments).

Selection of patients
Infliximab is indicated for luminal Crohn’s disease and fistula disease associated with Crohn’s disease in patients who do not respond or who respond inadequately to an adequate therapy with a conventional immunosuppressive treatment.

Diagnostic examination
Symptoms of irritable bowel disease frequently occur in quiescent Crohn’s disease. When in doubt about the nature of the symptoms, the disease activity needs to be assessed by endoscopy for localisation in the colon or terminal ileum, or with imaging of the small intestine and duodenoscopy for more proximal localisations. Determination of C-reactive protein levels is advised.

Precautions
Liver function needs to be checked before treatment and infliximab must be stopped in patients who develop jaundice or liver function problems (≥3 times the normal values) after treatment with infliximab. Patients who smoke react significantly less favourably to infliximab. Patients with Crohn’s disease are strongly advised not to smoke.

Contraindications
An anaphylactic shock, the occurrence of stridor, or serious hypotension (or reduction in blood pressure of more than 40 mmHg) with a previous infusion of infliximab are a contraindication for repeating infliximab infusions. The presence of serious infections such as sepsis, abscesses and TBC needs to be ruled out before starting treatment with infliximab. For patients with fistulas associated with Crohn's disease, abscesses must be ruled out, preferably by means of local ultrasound or MRI of the perianal region or with an ultrasound/CT for enterocutaneous localisation.

Before the start of infliximab treatment, latent or manifest TBC must be ruled out with at least:
- Extensive history to detect possible prior TBC contacts
- Mantoux test
- X-ray of the thorax

For a proper interpretation of the Mantoux test, it is important that the previous history of the patient is well documented: here attention needs to be paid to factors which could influence the outcome of the test, such as previous contact with TBC, a long-term stay in (or origin from) a country where TBC is endemic (>50 per 100,000 residents), use of immunosuppressive drugs and risk factors such as diabetes mellitus, kidney insufficiency, and haematological disorders. During infliximab treatment, it is important to be alert for TBC when the patient complains of fever (nocturnal transpiration), coughing, unexplained stomach complaints and weight loss.

Dosage
In general, the following dosage is used for the various indications:
- induction regimen: 5 mg/kg at 0-2-6 weeks, usually followed by:
- maintenance treatment: 5 mg/kg every eight weeks, when response is inadequate increase to 10 mg/kg on strict verified indication.

A good clinical assessment as to whether the remission-induction regimen is effective is essential, preferably within four weeks. With the initiating regimen of 0-2-6 weeks, it may prove difficult to decide within four weeks whether the therapeutic effect is adequate, and waiting until four weeks after the 2nd infusion is an option. If there is no clear and clinically significant response at that time, there is no indication for continuing further infusions or elevating the dosage to 10 mg/kg.

Optimising infliximab treatment
The use of immunosuppressants (azathioprine, 6-mercaptopurine of methotrexate):
- prevents the formation of antibodies against infliximab (ATI) and thus the risk of an infusion reaction;
- increases the likelihood of an adequate response to infliximab;
- increases the duration of the response and with it, the infusion interval.

For an optimal effect, treatment with infliximab should be combined with the use of an immunosuppressive.

The optimal effect of an induction treatment with infliximab (using the 0-2-6 week regimen), combined with a concurrently started treatment with an immunosuppressant, is only noticeable about eight weeks after the third infusion. Because the effective duration of infliximab is an average of 12 weeks, while immunosuppressants such as azathioprine and methotrexate only become effective after about three months, the eventual synergistic effect of this combination can only be evaluated after this period of three months.

For the protocol for administration of infliximab see figure 4 and for the protocol for treatment of acute infusion reaction see figure 5.

Conclusion
Without doubt, infliximab is the most spectacular medicine in recent years for Crohn’s disease patients. It is obvious that this drug has a significant place in current treatment, where the roles of mesalazine and corticosteroids are increasingly being discussed. Even quite recently, it has become clear that Crohn’s disease may be treated without corticosteroids, as the combination of azathioprine with infliximab has proved effective and safe as primary therapy for recently diagnosed patients.

However, infliximab can also be a dangerous drug if the correct measures are not taken to prevent side effects and (serious) complications. This guideline attempts to produce clarity about these precautionary measures for the purpose of optimising the result of a treatment with infliximab. Pharmacoeconomic considerations have shown a reduction in both direct and indirect costs in various Western countries, some of which can be compared with the Netherlands. It is therefore remarkable that reimbursement for this expensive drug is still not sufficiently taken care of by the government and health insurance companies in the Netherlands.

Acknowledgement
We wish to thank Mrs E.P. van ’t Hof for her assistance in preparing this manuscript.
**Figure 4. Algorithm for the administration of infliximab**

1. **Verify indication:**
   - active Crohn's disease?
   - therapy resistant?

2. **Check contraindications:**
   - serious, active infection?
   - previous anaphylactic shock?
   - chronic cardiac failure (CHF)?
   - neurological disorders?
   - liver function disorders?

3. **Treat manifested or latent TBC with (prophylactic) tuberculostatics**

4. **Start immunosuppressant**
   - (AZA, 6-MP, MTX)

5. **Anamnesis**
   - Mantoux test
   - X-ray thorax

6. **Start infusion:**
   - 5 mg/kg in 250 ml
   - 2 ml/minute (250 ml/2 hour) or
     (when previous infusion reaction):
     - 10 ml/hour (15 min)
     - 20 ml/hour (15 min)
     - 40 ml/hour (15 min)
     - 80 ml/hour (15 min)
     - 150 ml/hour (30 min)
     - 250 ml/hour to the end

7. **Infusion reaction?**
   - See figure 5

8. **No**

9. **Yes**

10. **Previous infusion reaction?**
    - Yes
    - No

For patients who are not yet using an immunosuppressant. 6-Mp = 6-mercaptopurine; AZA = azathioprine; MTX = methotrexate.

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**REFERENCES**


**Figure 5. Algorithm for the treatment of an acute or delayed infusion reaction**

<table>
<thead>
<tr>
<th>Acute infusion reaction (during or within 2 hours)</th>
<th>Delayed infusion reaction (2-14 days after infusion)</th>
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</thead>
<tbody>
<tr>
<td><strong>Stop infliximab infusion,</strong> give iv:</td>
<td><strong>Give antihistamine tablet, possibly with paracetamol tablet</strong></td>
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<tr>
<td>- 2 mg clemastine and</td>
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<td>- 25 mg prednisolone/Di-Adreson-F</td>
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<td>- 200 mg hydrocortisone</td>
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<td>- adrenaline for serious reaction</td>
<td></td>
</tr>
</tbody>
</table>

**Serious reaction?**
- e.g. shock, stridor, serious hypotension (drop >40 mmHg)

**Symptoms disappeared?**
- Yes
- No

**Start infusion again at lower speed:**
- 10 ml/hour (15 min)
- 20 ml/hour (15 min)
- 40 ml/hour (15 min)
- 80 ml/hour (15 min)
- 150 ml/hour (30 min)
- 250 ml/hour to the end

**Stop infusion treatment**
- Ye
- No

*With mild complaints, one can also consider switching over to a reduced infusion speed.*

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