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EDITORIAL

The Dutch guidelines for treatment with infliximab for Crohn's disease

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In the current issue of the Netherlands Journal of Medicine, inflammatory bowel disease (IBD) specialists from the Dutch University Medical Centres publish their guidelines for the use of infliximab in patients with Crohn's disease.[1] Infliximab is a monoclonal antibody to tumour necrosis factor-alpha (TNF-α) and is the first biological therapy registered and approved for the treatment of this chronic inflammatory gastrointestinal disorder.
In these guidelines, the authors give a detailed and very practical overview of all aspects related to the use of infliximab. The indications and the effectiveness of the drug in each of these indications are given, based on the results from the controlled studies, together with practical guidelines on dosing, interval and monitoring of patients. The second part of the guidelines deals with safety aspects of infliximab. The authors need to be congratulated for this large and detailed piece of work. This manuscript provides very useful and practical flowcharts that will undoubtedly help the (Dutch) gastroenterologist in treating patients with Crohn's disease.

There are a few issues which merit additional attention and maybe some updating since inevitably, new results and additional safety information are gathered on an almost weekly basis.
The first relates to safety and in particular the risk of developing malignancies or infections. TNF plays an important role in host defence and in tumour growth control. Anti-TNF therapies may therefore potentially increase the risk of infections and malignancies. Although I agree with the authors that the safety data from the controlled trials, as well as from post-marketing surveillance and prospective safety registries (TREAT registry in particular), do not support an increased risk for malignancies with use of infliximab, we need to bear in mind that the follow-up for this kind of side effect is still modest and that longer and closer follow-up remains necessary.[2] In this respect, a recent meta-analysis of patients treated with infliximab for rheumatoid arthritis has shown an increased risk for malignancy with a pooled odds ratio (OR) of 3.3 (95% CI 1.2 to 9.1) as well as for serious infections with a pooled OR of 2.0 (95% CI 1.3 to 3.1).[3] The risk of malignancies was dose-dependent and only increased in patients receiving higher (≥6 mg/kg) doses of anti-TNF (OR 4.3; 95% CI 1.6 to 11.8) as compared with patients treated with lower doses (≤3 mg/kg) (OR 1.4; 95% CI 0.3 to 5.7). Although no data in this meta-analysis are given on concomitant therapies or illnesses, nor on subgroups of patients at risk, these figures warrant careful follow-up, also in patients with Crohn's disease treated with infliximab, especially since the dose used (5 mg/kg) is close to the high-dose group described in rheumatoid arthritis. To date, the large prospective TREAT registry has not shown an increased risk for malignancies or serious infections related to the use of infliximab in patients with Crohn's disease.[2] The results of a European registry are expected soon.
The safety concern has also been brought back to attention recently following the report of six cases of hepatosplenic γδ T cell lymphomas (HSTCL) in patients treated with infliximab. HSTCL is a rare and often fatal form of non-Hodgkin's lymphoma that preferentially occurs in children and adolescents receiving azathioprine or 6-mercaptopurin. The six reported cases all occurred in adolescents or young adults (five males, one female, aged 12 to 31 years) who had received between two doses and three years of infliximab in combination with azathioprine. Therefore, safety of anti-TNF remains an important question, especially when the drug is used in combination with immunosuppressive agents such as azathioprine.

Combination therapy with immunomodulators has been demonstrated to reduce immunogenicity to infliximab and this is the main reason to recommend combination therapy at the onset of treatment.[4] Our group recently completed a randomised trial where 80 patients, who had been on combination therapy with infliximab and azathioprine or methotrexate (MTX) for at least six months and were in

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stable clinical remission, were randomised to continuation (n=40) or discontinuation (n=40) of the immunosuppression (Infliximab Maintenance Immunosuppression Discontinuation (IMID) study).[5] After two years of follow-up, continuation of immunosuppressive drugs was not superior in preventing the need for change in dosing interval or loss of response or intolerance to infliximab. Also no differences in infliximab trough levels were observed after discontinuation of the immunomodulators, suggesting that immunomodulators may safely be stopped after a period of six months, provided of course that infliximab is continued every eight weeks to maintain remission.
The recommended dose of infliximab in patients with Crohn's disease is 5 mg/kg. It is still unclear what the ideal induction regimen is. The original evidence to support a 0-2-6 induction regimen is not very convincing and some authors have suggested an induction of two infusions at week 0 and 4.[6] The three doses were launched for commercial rather than scientific reasons. It is our current clinical practice to apply the 0-2-6 induction regimen in patients treated for fistulising disease (following a baseline MRI and examination under anaesthesia, and followed by a repeat MRI at week 10), and for luminal disease to give a single infusion of infliximab at week 0 and reassess the patient after four weeks, with a second infusion at that time if symptoms persist.

A question that is even more difficult to answer at this moment is how long to continue treatment with infliximab? Controlled studies are indeed lacking and at the moment one depends on expert opinion or data from small retrospective, uncontrolled studies. The authors do not provide clear guidelines on this issue either. Instead, they suggest that after induction treatment one should wait to see if relapse occurs. This is probably only true for patients in whom immunomodulation has recently been started, changed or optimised. In patients on a background therapy that is already optimal and has not been changed, starting maintenance therapy immediately after induction should be considered, since relapse is highly predictable.
In a patient in stable clinical remission with infliximab, it is our current practice to treat for at least one year.[7] If, after this period, the patient is in sustained clinical remission without corticosteroids or has complete external healing of fistulas, we may try to discontinue infliximab and continue immunosuppression. This decision may be supported by a repeat MRI (for fistulising disease) to confirm absence of fistula tracks or by repeat colonoscopy or small bowel imaging to confirm mucosal healing. For fistulising disease, Van Assche *et al*. showed that healing on MRI is associated with a better outcome.[8] Therefore, incomplete healing on MRI is an indication for continued treatment, whereas full healing may be a reason to discontinue.
However, the presence of mucosal healing has not yet been shown to guarantee successful discontinuation of infliximab. In any case, if the disease relapses, maintenance infliximab needs to be resumed in the long term. The situation for extraintestinal manifestations of Crohn's disease is slightly different since in the case of skin or eye manifestations, infliximab is given until the signs have disappeared and will then be stopped. Patients with Crohn's disease experiencing arthralgias and/or arthritis need to be treated long term with infliximab every eight weeks.
Prospective inflximab discontinuation studies have just been started and will give us more answers to this question.

In conclusion, the Dutch guidelines provide a good working document for all gastroenterologists, internists and surgeons treating Crohn's patients with infliximab. This drug has lead to a revolution in the treatment of this chronic and often complicated disease by the rapid and sustained induction of remission and mucosal healing. Infliximab is also the first drug that has been shown to heal and close perianal fistulas in a rapid and profound way. However, as always, the benefit of this treatment needs to be balanced against the potential risks of increased infections and possible malignancies. Until then, the use of this drug as first-line therapy in all patients is most likely not justified. Instead, the search for predictive molecular markers of complicated disease is of great importance in selecting the ideal candidates for this therapy and to enable earlier treatment in these high-risk patients.

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