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Anti-tumour necrosis factor therapy in Crohn's disease: where are we now?

S J H van Deventer

Controlled trials have confirmed the efficacy of two tumour necrosis factor α (TNF- α) antibodies in active Crohn's disease.¹⁻⁴ In responding patients, the therapeutic effects qualitatively differ from those observed with standard therapy, including corticosteroids and immunosuppressives, and complete clinical remission can be induced in about one third of patients that did not respond to standard treatment. More than 140 000 patients have been treated with infliximab, and in large centres the reported efficacy in Crohn's disease is comparable with data reported in controlled clinical trials. Few would disagree that anti-TNF- α therapy is an important therapeutic addition in the treatment of patients with active Crohn's disease. On the other hand, toxicities related to TNF- α neutralising therapies have emerged. Of 147 000 infliximab treated patients, 70 developed tuberculosis, and 12 subsequently died (four as a direct result of tuberculosis).⁵

The importance of TNF- α for the host defence against *Mycobacterium tuberculosis*,⁶ *Listeria monocytogene*, and other intracellular pathogens is long known, and it should come as no surprise that neutralisation of TNF- α predisposes to (reactivation of) tuberculosis. Indeed, tuberculosis has been reported in etanercept (a TNF receptor II fusion protein) and D2E7 (a human anti-TNF- α antibody) treated patients. In the majority of cases, tuberculosis following treatment with TNF- α blocking proteins is a result of disease reactivation, and in most patients the disease is extrapulmonary. Although the incidence of tuberculosis following infliximab therapy is low (1:2000), prior to administration of TNF- α blocking molecules all patients should have a Mantoux test and a chest x ray. Patients who develop fever during TNF- α blocking treatment should be appropriately assessed for tuberculosis and other opportunistic infections.

For unknown reasons, TNF- α blocking proteins may cause the formation of anti-dsDNA antibodies, and after repeated treatment the cumulative ANA incidence can be as high as 50%.⁷ None the less, infliximab therapy is infrequently associated with lupus-like symptoms. Demyelinating disease and aplastic anaemia have been reported in a small number of infliximab and etanercept treated patients. A major problem of repeated administration of chimeric therapeutic antibodies is immunogenicity, and up to 60% of infliximab treated patients develop human anti-chimeric antibodies (HACAs) which are related to infusion reactions and reduce therapeutic efficacy.^{8,9} It is not completely clear how HACA formation can be prevented but it has been suggested that combined treatment with azathioprine or methotrexate, or infusion of hydrocortisone immediately prior to infliximab infusion, may be beneficial.¹⁰ Clearly, more data are needed.

Forty two women have been treated with infliximab during pregnancy, and the outcome of pregnancy is known

in 35. Of these pregnancies, 26 resulted in live births, and no unexpected teratogenicity has been reported.¹¹ However, this does not indicate that TNF- α blockade is safe during pregnancy and patients should be informed.

Which Crohn's disease patients should be treated with TNF- α blocking proteins? It is necessary to understand the limitations of anti-TNF antibody treatment: anti-TNF antibodies do not cure Crohn's disease, have side effects, and are expensive. Patients who respond to therapy usually need repeated infusions to maintain disease remission. Hence the availability of TNF- α blocking proteins does not discharge the prescribing physician from designing long term treatment plans; surgery remains a good option for selected patients with therapy refractory Crohn's disease. Preliminary data have suggested that immunosuppressive drugs prolong the duration of responses following TNF blocking therapies but this observation needs to be confirmed by controlled clinical trials.

Is infliximab a first, second, or third line therapy? Traditionally, Crohn's disease has been treated using step up (mesalazine-corticosteroids-azathioprine) strategies, and with this strategy most patients can be adequately managed. I believe that at present infliximab should be reserved for patients that have failed adequate medical therapy, including a full course of an appropriately dosed immunosuppressive (azathioprine or methotrexate). Studies in rheumatoid arthritis patients have demonstrated that progression of disease can be stopped by early aggressive combination therapy,¹² and it is conceivable that a combination of anti-TNF antibody treatment with an immunosuppressive is a better approach to treat newly diagnosed patients than repeated courses of corticosteroids. Clearly, this hypothesis needs to be appropriately investigated, and a prospective controlled trial has been initiated.

Infliximab effectively binds and neutralises TNF- α , but how does it really work? An increasing body of evidence suggests that binding of infliximab to target cells that express membrane associated TNF- α causes cell suicide by apoptosis.^{13,14} In view of the known apoptosis defect of lamina propria T lymphocytes in Crohn's disease,¹⁵ this might be a major mechanism of efficacy. These observations predict that combinations of infliximab with drugs that are proapoptotic (such as methotrexate) but not with antiapoptotic drugs (cyclosporin) would be beneficial.

Many questions remain: why are some patients completely resistant to anti-TNF- α treatment, and why is the duration of response so variable? Which cells are responsible for mucosal TNF- α production in Crohn's disease, and why does the number of TNF- α producing mucosal cells massively decrease after anti-TNF treatment? What predicts the response to infliximab therapy?

It is conceivable that small molecules that inhibit the production of TNF- α and other cytokines can have therapeutic effects that are comparable with infliximab. Drugs such as pentoxifylline (derivatives) and thalidomide have only modest TNF- α blocking capacities but inhibitors of signal transduction proteins (mitogen activated protein

Department of Experimental Medicine, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands; S.J.vanDeventer@amc.uva.nl

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(MAP) kinases) that are involved in TNF- α signalling potentially block TNF- α production. In an uncontrolled trial, CNI 1493, an MAP kinase inhibitor that preferentially inhibits JNK, dramatically reduced disease activity in severe Crohn's disease. These data are encouraging but it will take years before the first of these compounds, if proven effective, become widely available.

In conclusion, TNF- α binding proteins (antibodies and fusion proteins) are an important step forward in the treatment of Crohn's disease, and for the coming years this class of compounds will be the standard of medical care for patients who do not respond to medical therapy. Infliximab and CDP571, but not etanercept, have shown therapeutic benefit in active Crohn's disease. TNF- α blocking therapies should be part of a carefully planned long term therapeutic strategy. These immunosuppressive biologicals are associated with a spectrum of specific toxicities, and physicians who prescribe TNF- α blocking proteins should be fully aware of these potential complications.

Conflict of interest: S J H van Deventer served as a consultant for Centocor.

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