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CD4 antibody treatment in patients with active Crohn’s disease: a phase 1 dose finding study

A Stronkhorst, S Radema, S-L Yong, H Bijl, I J M ten Berge, G N J Tytgat, S J H van Deventer

Abstract

Background—T cells play an important part in Crohn’s disease. Immunomodulating therapies that target T cell activation may have clinical effects in Crohn’s disease.

Aim—To investigate the toxicity and potential efficacy of anti-CD4 monoclonal antibody therapy in patients with Crohn’s disease.

Patients and methods—A dose escalating pilot study was conducted in three groups of four patients with intractable Crohn’s disease, refractory to steroids. They received 70, 210, or 700 mg of cM-T412, a depleting anti-CD4 monoclonal antibody (mAb).

Results—The mean reduction in Crohn’s disease activity index (CDAI) was respectively 25%, 24%, and 36% at four weeks, and 24% and 52% at 10 weeks in the 210 mg and 700 mg groups. There was only a minor effect on endoscopically evaluated disease activity. Side effects were mild to moderate fever with chills and headache. No signs of opportunistic infection were seen. There was a sustained decrease in CD4 count which lasted at least four weeks in the 70 mg group (76·3 (SD 40·6)% of the baseline value) and 10 weeks in both the 210 mg group (50·8 (SD 60·9)% and the 700 mg group (24·8 (SD 15·4)%). The primary and secondary humoral immune response was not influenced by anti-CD4 mAb treatment.

Conclusion—This study shows the moderate potential efficacy of treatment of patients with Crohn’s disease using a depleting chimeric monoclonal anti-CD4 antibody.

Keywords: Crohn’s disease, T cells, monoclonal antibody treatment, inflammatory bowel disease.

The treatment of steroid resistant Crohn’s disease remains a clinical challenge. Surgery is usually non-curative and immunosuppressive treatment may be associated with substantial toxicity. Immunomodulating therapies that target T cell activation may have a clinical effect in severe Crohn’s disease. Cyclosporin inhibits T cell activation by interfering with the transcription of interleukin-2 (IL-2), which is an early event in activation of CD4 as well as CD8 positive cells. Treatment of patients with active Crohn’s disease with oral cyclosporin resulted in a decrease of disease activity. However, the long term efficacy of cyclosporin in Crohn’s disease is disappointing and is associated with substantial toxicity. An alternative option for treatment of steroid resistant Crohn’s disease might be depletion of certain T lymphocyte subpopulations. Although the specific pathogenic T lymphocyte subpopulations in inflammatory bowel disease have not been characterised, most T lymphocytes in the lamina propria express CD4 and lamina propria CD4+ cells of patients with Crohn’s disease coexpress the activation marker CD25. It has been reported that refractory Crohn’s disease may improve in the course of the development of AIDS, which is characterised by severe depletion of CD4 positive lymphocytes.

Administration of monoclonal antibodies (mAbs) that recognise CD4+ lymphocytes has been reported to have beneficial effects in various animal models of autoimmune disease. The efficacy of anti-CD4 mAbs is in part related to interference in the interaction between the CD4 molecule and the constant regions of HLA class II molecules, thereby preventing effective antigen presentation. In addition, some of these mAbs are depleting, causing an important and prolonged decrease in circulating CD4 lymphocyte counts. Finally, by as yet incompletely characterised mechanisms, treatment with anti-CD4 mAb may result in the development of immunological tolerance.

To investigate the toxicity and potential efficacy of anti-CD4 mAb therapy in patients with intractable, steroid refractory Crohn’s disease, we have conducted an open label, dose escalating study using CM-T412 (Centocor, Malvern, PA, USA), a human-mouse chimeric, depleting, anti-CD4 mAb. Here, we report on toxicity, possible efficacy, and specific immunomodulating effects of this treatment.

Methods

Patients

In this open, phase one, dose finding study we enrolled three groups of four patients with active (Crohn’s disease activity index (CDAI) >150), longstanding, intractable Crohn’s disease. The Table presents the characteristics of the patients. Patient 1 had an adapted CDAI, because he had a colostomy with constant stool production. The diagnosis of Crohn’s disease was made on generally accepted clinical, endoscopical, radiological,
Clinical data for the patients with Crohn’s disease treated with cM-T412 and the effect of this treatment on endoscopically evaluated disease activity

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<th>Week 4</th>
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Patients 1 and 4 were treated for seven consecutive days with 10 mg cM-T412 mAb daily (70 mg group). Patients 5, 8, 9, and 12 were treated with respectively 30 mg (210 mg group) and 100 mg (700 mg group) daily. All patients but number 7 were concomitantly using oral mesalazine. Changes in endoscopy v baseline are: = no change, + minor improvement, ++ moderate improvement, +++ good improvement, ++++ disappearance of inflammatory signs, – minor worsening, — moderate worsening, —— pronounced worsening. (ND=not done).

Follow up

Laboratory variables were assessed immediately before and during the infusions. The assessment continued up to six hours after starting the infusion for the first five treatment days. Follow up examinations were performed on day 8, at four weeks, and at 10 weeks. Crohn’s disease activity, side effects, and endoscopic and immunological variables were monitored. Because two referring physicians reported a beneficial effect in the 70 mg group after 10 weeks, it was decided to extend the observation period from four weeks in the original protocol to 10 weeks in the 210 mg and 700 mg dosage groups.

Endoscopical monitoring

The effect of cM-T412 mAb on mucosal inflammation was endoscopically monitored and registered on videotape. Two independent experienced gastroenterologists judged the videotapes, using the endoscopical score described by Mary and Modigliani. They were blinded for the dosage group and date of the endoscopy. Follow up endoscopy was compared with baseline endoscopy and scored to show no change, minor improvement, moderate improvement, good improvement, disappearance of inflammatory signs, minor worsening, moderate worsening, and pronounced worsening.

Laboratory testing

Blood samples for routine complete blood cell count, platelet count, electrolytes, renal and liver chemistry, and analysis of urine were obtained at inclusion, prior to infusion, and 1, 4, and 10 weeks after the first infusion. An HIV test and a pregnancy test were performed at inclusion.

Immunophenotyping

Immunophenotype analysis was performed by direct immunofluorescence with a panel of commercially available mAbs utilising a single laser FACScan flow cytometer (Becton Dickinson, Mountain View, CA, USA) as described before.14 The absolute number of cells of each subset was calculated by multiplication with the absolute lymphocyte count. The CD4 Ab used had previously been shown to recognise a different epitope than cM-T412.13 The following mAbs were used: CD2 (anti-Leu-5b, IgG2a), CD3 (anti-Leu-4,
TNF.16 Soluble TNF receptors p55 and p75 both free and soluble TNF receptor bound manufacturer’s instructions. This assay detects (Medgenix, Fleurus, Belgium) according to the were determined by immunoradiometric assay tumour necrosis factor (TNF) concentrations U/ml; the detection limit was 20 U/ml. Serum (n=323) 96% had concentrations less than 59 Belgium). Using this assay in normal controls IL-2 receptor (Eurogenetics, Tessenderlo, mAb recognising different epitopes of the sandwich type ELISA using two types of determined with a commercial available soluble IL-2 receptor concentration was stored at –30 temperature) blood at 3000 × g for 20 minutes. The serum was aliquoted in 1 ml cups and stored at −30°C until batchwise assay. The soluble IL-2 receptor concentration was determined with a commercial available sandwich type ELISA using two types of mAb recognising different epitopes of the IL-2 receptor (Eurogenetics, Tessenderlo, Belgium). Using this assay in normal controls (n=323) 96% had concentrations less than 59 U/ml; the detection limit was 20 U/ml. Serum tumour necrosis factor (TNF) concentrations were determined by immunoradiometric assay (Medgenix, Fleurus, Belgium) according to the manufacturer’s instructions. This assay detects both free and soluble TNF receptor bound TNF. Soluble TNF receptors p55 and p75 were measured with enzyme linked immunological binding assays (ELIBAs, Hoffman-La Roche Ltd, Basel, Switzerland) as described previously using TNF binding non-inhibitory mAb against TNF receptors p55 or p75. The intra-assay and the interassay variations were 3%–6% and 5%–10% respectively; the detection limit was 0.1 pg/ml. Concentrations of IL-6 were determined with a commercial available ELISA, in which anti-huIL-6 Ab was coated to polystyrene microtitre wells (CLB, Amsterdam, The Netherlands). The detection limit in our laboratory was 1 pg/ml. Concentrations of sCD27 were measured using CLB-CD27/1-3 mAb. Control subjects had concentrations between 100 and 200 U/ml and interassay and intra-assay coefficients of variation of the ELISA were below 10%. Statistical analysis Clinical and immunological data are expressed as means (SD). The difference in lymphocyte (sub) counts and cytokine concentrations were analysed over time with repeated measures analysis of variance (ANOVA). Comparisons between groups were made by Mann-Whitney U and Wilcoxon rank tests. All reported significance levels are two tailed and α was set at 0.05.

Results Clinical disease activity after infusion of cM-T412 mAb During the treatment week, the CDAI decreased in nine of 12 patients. Compared with the baseline value, the CDAI had decreased in all but two patients by the fourth week. The mean CDAI reduction at four weeks was 25%, 24%, and 36% in the 70 mg, 210 mg, and 700 mg groups respectively (Fig 1). The CDAI was prospectively calculated at later time points in the two highest dose groups only. At 10 weeks the CDAI had decreased in all eight patients with a mean of 24% and 52% respectively. The reduction of the CDAI in all patients treated with cM-T412 after one week was 9% (p=0.049), at four weeks 26.4% (p=0.004), and at 10 weeks 39% (p=0.012).

Effect of treatment with cM-T412 mAb on the endoscopical score Endoscopy performed immediately after the infusion week and at the fourth week showed minor to moderate improvement in two patients of both the 210 and 700 mg groups

Figure 1: Effect of cM-T412 treatment on Crohn’s disease activity index (CDAI) in the 70 mg (open bar), 210 mg (grey bar), and 700 mg (black bar) groups. The graph represents the means (thick horizontal line) and 25th and 75th percentiles (bar), and error bars indicate 5th and 95th percentiles (thin line). The mean CDAI in patients with Crohn’s disease treated with cM-T412 decreased in all three treatment groups, at all time points compared with baseline. There were no significant differences within or between the groups. Ten out of 12 patients improved at 4 weeks and all eight patients improved at 10 weeks. All patients combind showed a significant decrease in CDAI at one, four and 10 weeks with respectively –9% (p<0.05), –26% (p<0.005), and –39% (p<0.01).
CD4+ subpopulation (Fig 2) decreased rapidly (within one hour) decline in lymphocytes as assessed by Coulter counter (data not shown). This was caused mainly by a major decline in CD3+ and CD4+ lymphocytes and a minor and temporary decrease in CD8+ and CD19+ lymphocytes (data not shown). The CD4+ subpopulation (Fig 2) decreased dramatically within one hour in all three groups to a mean (SD) of 13·7 (4·9)%, 24·3 (6·1)%, and 23·5 (10·8)% of the baseline value. Mean fluorescence intensity of CD4 expression showed a decrease (data not shown). Before the second infusion, the CD4+ lymphocyte count had recovered to preinfusion values in the 70 mg group. There was a partial recovery in the 210 mg group. Repeated infusions led to a sustained decrease in both groups which lasted at least four weeks (maximum follow up period in this group) in the 70 mg group (76·3 (40·6)% of the baseline value) and 10 weeks in the 210 mg group (80·8 (60·9)% of the baseline value). In the 700 mg group no rebound effect was seen, and the number of CD4+ lymphocytes remained significantly decreased during follow up. At 10 weeks the CD4 count in the 700 mg group was still significantly decreased to 24·8 (15·4)% of the baseline value. Hence, the reduction in the CD4 counts after cM-T412 showed a dose-response relation that reached significance (ANOVA; \( p=0.049 \)). The CD8 count combined for all dose groups showed a 50% decrease after the first mAb infusion. CD8 counts recovered before the second infusion, and only minor, non-significant changes occurred during the remainder of the study period. CD19+ lymphocytes showed a minor, non-significant decrease after the infusion of anti-CD4 mAb (data not shown).

**Changes in lymphocyte subpopulations**

Infusion of cM-T412 mAb was followed by a rapid (within one hour) decline in lymphocytes as assessed by Coulter counter (data not shown). This was caused mainly by a major decline in CD3+ and CD4+ lymphocytes and a minor and temporary decrease in CD8+ and CD19+ lymphocytes (data not shown). The CD4+ subpopulation (Fig 2) decreased dramatically within one hour in all three groups to a mean (SD) of 13·7 (4·9)% and 23·5 (10·8)% of the baseline value. Mean fluorescence intensity of CD4 expression showed a decrease (data not shown). Before the second infusion, the CD4+ lymphocyte count had recovered to preinfusion values in the 70 mg group. There was a partial recovery in the 210 mg group. Repeated infusions led to a sustained decrease in both groups which lasted at least four weeks (maximum follow up period in this group) in the 70 mg group (76·3 (40·6)% of the baseline value) and 10 weeks in the 210 mg group (80·8 (60·9)% of the baseline value). In the 700 mg group no rebound effect was seen, and the number of CD4+ lymphocytes remained significantly decreased during follow up. At 10 weeks the CD4 count in the 700 mg group was still significantly decreased to 24·8 (15·4)% of the baseline value. Hence, the reduction in the CD4 counts after cM-T412 showed a dose-response relation that reached significance (ANOVA; \( p=0.049 \)). The CD8 count combined for all dose groups showed a 50% decrease after the first mAb infusion. CD8 counts recovered before the second infusion, and only minor, non-significant changes occurred during the remainder of the study period. CD19+ lymphocytes showed a minor, non-significant decrease after the infusion of anti-CD4 mAb (data not shown).

**KLH and tetanus immunisations**

Patients with Crohn’s disease treated with cM-T412 mAb as well as Crohn’s disease controls were found to have a significantly diminished primary humoral immune response. Healthy control subjects had a mean (SD) 13·7 (9·3)-fold increase in anti-KLH IgG concentration after immunisation, which was significantly higher (\( p<0.001 \)) than the 3·1 (1·6)-fold increase in patients treated with cM-
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Figure 3: Primary and secondary immune response in Crohn’s disease treated with cM-T412 mAb: to test primary keyhole limpet haemocyanin (KLH) and secondary (tetanus) humoral immune response in patients treated with cM-T412 mAb, patients were immunised with KLH, and tetanus toxoid five minutes before initiation of the first cM-T412 mAb infusion. The responses are expressed as the ratio of the IgG antibody concentration 14 days after and immediately before immunisation. Twelve patients with Crohn’s disease (mean CDAI 241·4, range 72–386) and 12 healthy subjects were used as controls. Patients with Crohn’s disease showed significantly decreased primary immune response compared with controls. However, no differences were found between treated and non-treated patients with Crohn’s disease. There was a normal to increased secondary immune response in patients with Crohn’s disease, which was not influenced by cM-T412 treatment.

T412 and a 3·7 (3·4)-fold increase in patients with Crohn’s disease. The secondary humoral immune responses were normal or increased when compared with healthy controls. An 8·8 (8·9)-fold increase in anti-tetanus IgG concentration was found in healthy controls compared with an 81 (144)-fold increase in cM-T412 mAb treated patients with Crohn’s disease (p<0·06) and a 170 (256)-fold increase in non-treated patients with Crohn’s disease (p<0·03). Patients treated with anti-CD4 did not differ in primary or secondary humoral immune response from non-treated patients with Crohn’s disease (Fig 3).

Cytokine responses to infusion of cM-T412 mAb
Infusion of cM-T412 caused TNF release as well as shedding of TNF receptors. Before infusion, TNF concentrations (mean (SD) 12·56 (5·0) pg/ml, range 1·9–19·9 pg/ml) were slightly increased (normal value <5·0 pg/ml) and cM-T412 infusion caused a release of TNF in all patients to reach a peak concentration of 107·27 (46·06) pg/ml (p<0·01; Fig 4). The TNF concentrations increased most in those patients that developed fever after the infusion (open circles in Fig 4). Soluble TNF receptors p55 and p75 showed a similar reaction to the antibody treatment, with normal pretreatment concentrations (mean 1·31 (0·4) ng/ml and 4·57 (2·47) ng/ml respectively) and maximum concentrations three hours after starting the infusion: mean 3·54 (1·34) ng/ml and 12·34 (4·94) ng/ml respectively. Concentrations of soluble TNF receptors remained increased during the cM-T412 mAb infusion week and subsequently returned to baseline (Fig 5).

Figure 4: Response of serum TNFα to cM-T412 infusion. Individual baseline serum TNFα concentrations and the concentrations three hours after starting the first infusion period of cM-T412 mAb. No differences were found between the three dosage groups, but patients responding to the infusion with fever and chills (○) had higher postinfusion concentrations. Infusion of cM-T412 mAb resulted in a significant (p<0·001) increase in the mean (SD) serum TNF concentration from 12·7 (5·6) pg/ml to 107·3 (46·1) pg/ml (horizontal black line).

Figure 5: Response of soluble TNF receptors. Mean (SD) soluble TNF receptor p55 and p75 concentrations in all patients treated with cM-T412 mAb combined showed a significant increase during the first infusion. The values remained increased during the infusion week, but returned to normal at week four. (p<0·001 for t=1, t=3, t=6, and t=24 compared to baseline, and p<0·05 for t=168).
increased soluble TNF receptors during the complications that occurred in the follow up period (up to 10 weeks). The circulating IL-6 concentration rapidly increased after cM-T412 mAb infusion, reaching maximal concentrations three hours after initiation of the infusion (mean 17·99 (31·11) pg/ml; p<0·01). In all patients except patient 5 the IL-6 concentrations returned to baseline after the cM-T412 mAb infusion period. Serum concentrations of both soluble IL-2 receptor and soluble CD27 showed no significant changes after the anti-CD4 Ab treatment (data not shown).

Discussion
This study in patients with Crohn’s disease refractory to steroids was designed to investigate the potential efficacy and safety of anti-CD4 mAb treatment and to determine an effective dosage scheme. Daily infusion of the chimeric (human/mouse) mAb cM-T412 during seven consecutive days at total doses of 70, 210, and 700 mg resulted in a dose dependent reduction in the circulating CD4 count. After the initial infusion, the CD4+ lymphocyte counts recovered in both lower dosage groups, but finally remained depressed after the seven day course. Infusion of 100 mg cM-T412 mAb daily immediately caused long term depression of the CD4 count. Despite the low CD4 counts, which in patients with HIV infection are considered a potential risk for opportunistic infections, none of these infections occurred in our patients, which is in line with the experience from other clinical studies using murine or chimeric anti-CD4 mAb.19,20 One patient infused with cM-T412 had a complicated course (see results) which was complicated by bacterial sepsis. Despite very low CD4+ lymphocytes she was able to fight the abdominal sepsis, and intermittent pneumonia, and repeated surgery. She eventually recovered.

Anti-CD4 mAb infusion may interfere with the measurement of circulating CD4+ cells using flow cytometry. This possibility was excluded, however, in this study. Firstly, the antibody used for CD4+ cell count assessment has been reported to recognise the CD4 molecule even after binding of cM-T412 mAb.15 Furthermore, the decrease in CD3 counts matched the decrease in CD4 counts. This finding suggests that CD4 and CD3 positive cells are actually depleted from the circulating lymphocyte pool, and makes mere modulation or coating of the CD4 molecule less likely. However, the decrease in mean fluorescence intensity on the remaining CD4 positive cells indicates that modulation or coating occurred as well, as has been reported previously.21 The CD4 depletion after infusion of cM-T412 mAb in the present study is comparable with findings after cM-T412 mAb treatment of patients with refractory rheumatoid arthritis,13 in whom lower doses of cM-T412 mAb caused longer lasting CD4+ cell depletion. The apparent differences in sensitivity to cM-T412 mAb between patients with Crohn’s disease and those with rheumatoid arthritis remain to be explained, but it should be noted that in the present study no concomitant immunosuppressive drugs were given. By contrast with our study population, many patients with rheumatoid arthritis treated with cM-T412 mAb were treated with methotrexate. After the first infusions of cM-T412 mAb, there were transient changes in the CD8+ and CD19+ cell counts. However, after seven days of treatment these cell counts had returned to baseline, and both the CD8 and CD19 (B cell) counts remained unchanged at later time points. Infusion of cM-T412 mAb caused a mild cytokine release syndrome, of which at least TNFα may have contributed to the initial decreases in CD8+ and CD19+ cell counts.22 Shortly after the first infusion, increases in IL-6, TNF, and sTNF receptor concentrations were found, that seemed to cause the febrile reaction that occurred in seven of 12 patients. The cause of this immunostimulatory effect of anti-CD4 remains unknown. Possible explanations include complement activation induced by bound cM-T412, direct cross linking, and stimulation of T cells, Fc receptor mediated stimulation, or by removal of CD4 coated cells by phagocytic cells. Both complement activation and Fc receptor mediated stimulation are less likely in treatment with a chimeric mAb. Others13 26 also found transient increases in IL-6, but not in TNF concentrations. Possibly the time of sampling (three hours after the first infusion in our study versus two weeks in the study of Moreland et al13) and the determination method contribute to this difference. Although cM-T412 mAb caused release of TNF and IL-6, its toxicity seemed minor when compared with OKT3 infusion. Treatment with OKT3 is usually accompanied by high fever, chills, and multiple other side effects, which may be attributed to complement activation.27

A decrease in the CDAI at four weeks was noted in 10 out of 12 patients and at 10 weeks all eight evaluated patients improved. The mean CDAI decreased from baseline 265 to 216 (four weeks) in the 70 mg group, from 221 to 166 (four weeks) and 163 (10 weeks) in the 210 mg group, and from 348 to 221 and 174 in the 700 mg group. These data should be interpreted cautiously, because of the open label design of the study, the small number of patients, and the well known occurrence of spontaneous remissions in patients with Crohn’s disease. In only two of eight patients the CDAI decreased below 150, which is considered to indicate a complete remission. Hence, our results contrast with the previously reported beneficial effect of cM-T412 treatment on Crohn’s disease.24 Treatment with cM-T412 had only a minor effect on the endoscopic appearance of the involved bowel, as scored by the Modigliani index using videotapes, and the endoscopic appearance did not correlate with the CDAI. Although depletion of CD4+ cells did not cure Crohn’s disease, this finding does not exclude an important role for CD4 positive cells in the pathogenesis of Crohn’s disease.
The infusion of the CD45RBhigh subset of CD4 positive cells from normal BALB/c mice causes inflammatory bowel disease in B-17 scid mice. A combined infusion of CD45RBhigh and CD45RBlow BALB/c CD4+ lymphocytes does not induce disease in scid mice, however, indicating the differential pathogenic importance of specific phenotypic subpopulations within the CD4 compartment. If these findings can be extrapolated to humans, they may explain why depletion of all CD4+ lymphocytes has only minor therapeutic effect in patients with active Crohn’s disease.

Anti-CD4 mAbs inhibit primary and secondary antibody responses to antigens in animal experiments. The effect of cM-T412 mAb treatment on “B cell” response was investigated by vaccination with KLH and tetanus toxoid. The already diminished primary humoral immune response in patients with Crohn’s disease compared with healthy controls seemed not to be affected. Both treated and control patients with Crohn’s disease had diminished primary antibody responses to KLH when compared with normal controls. The secondary humoral immune reactivity in patients with Crohn’s disease showed a scattered pattern and was significantly increased in the patient group compared with healthy controls. Treatment with cM-T412 mAb seemed not to affect this response, indicating at least a normal memory cell function. These data suggest that anti-CD4 mAb in the tested doses left both primary and secondary immune responses unimpaired, at least when immunisation was carried out in the early phase of treatment. However, it is conceivable that a diminished response might occur when patients are immunised after therapy has started. Our data also suggest that despite depleting CD4+ cells for 90% or more in some patients, the secondary immune response remains intact in CD4+ memory cells are resistant to depletion by cM-T412 mAb. Patients can therefore fight previously encountered agents and recover, for instance, from sepsis. However, this means that in patients with Crohn’s disease the immune response to such a previously encountered antigen in the bowel persists. To cure our patients we have to delete all memory cells that mediate the immune response in Crohn’s disease. Therefore the responsible antigen(s) have to be known.

In conclusion, this pilot study demonstrates the feasibility of treatment of patients with Crohn’s disease using a depletion chimeric monoclonal anti-CD4 antibody. Treatment resulted in a dose-dependent reduction in the CDAI and circulating CD4 count. Controlled studies with high dose cM-T412 mAb are necessary to evaluate further the efficacy of anti-CD4 treatment in Crohn’s disease.

We thank Centocor, Malvern, PA, USA, for the supply of cM-T412 mAb and A Oll. Laboratory of Clinical Immunology of the Academic Medical Centre, Amsterdam, for determining the blood and KLH concentrations in the animal experiments. This work has appeared in abstract form as: Stronkhorst A, Yong SL, Radema SA, ten Berge I, Tytgat GN, van Deventer SJH. Phase 1 study of cM-T412 (Anti CD4) antibodies in Crohn’s disease. Preliminary data. Gastroenterology 1992; 102: A702.


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