Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/j.1365-2249.2007.03481.x

Anti-tumour necrosis factor-α therapy for severe enteropathy in patients with common variable immunodeficiency (CVID)

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Accepted for publication 10 July 2007
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Summary

We present three common variable immunodeficiency (CVID) patients with severe inflammatory bowel disease of unknown aetiology, resistant to steroid treatment, treated with infliximab. After exclusion of any infection, infliximab was given at a dose of 5 mg/kg every 4 weeks for a 3 month induction followed by every 4–8 weeks depending on clinical response. Two of these patients had predominantly small bowel disease; they both showed clinical response to infliximab with weight gain and improvement of quality of life scores. The third patient had large bowel involvement with profuse watery diarrhea; this patient improved dramatically within 48 hours of having infliximab treatment. All three patients have been maintained on infliximab treatment for between 5 and 53 months (mean 37 months) with no evidence of increased susceptibility to infections in the patients with small bowel disease, although the third patient developed two urinary tract infections and a herpes zoster infection following therapy. This is the first small case series to show that infliximab is a useful addition to current therapy in this rare group of patients with potentially life threatening enteritis.

Keywords: anti-TNF therapy, CMV, common variable immunodeficiency, inflammatory bowel disease, infliximab

Introduction

Common variable immunodeficiency (CVID) is a primary antibody deficiency disorder, usually of adult onset, requiring treatment with immunoglobulin replacement. CVID patients are susceptible to bacterial respiratory tract infections and often develop bronchiectasis. About 20% of patients have evidence of immune dysregulation, manifesting clinically in a variety of autoimmune conditions including haemolytic anaemia, idiopathic thrombocytopenia, pernicious anaemia, vitiligo and also by sarcoid-like granulomatous disease [1]. The underlying mechanism of the immunodeficiency in most CVID patients is not known, although genetic defects that cause or predispose to CVID have been identified in about 10% of cases [2].

At least 20% of CVID patients have chronic gastrointestinal symptoms including bloating, discomfort, malabsorption and diarrhoea; in 5% the symptoms are severe and are associated with histological evidence of mucosal inflammation [1,3–5]. Although these patients are prone to recurrent infection with giardia or campylobacter [3], no infection can be identified in the majority of patients with persistent symptoms. The management of patients with severe enteropathy has been unsatisfactory. Antibiotics or elemental diet sometimes produce short-term benefit, but only high-dose steroids reduce symptoms in the longer term at the cost of significant side effects [6,7]; there was also a high incidence of small bowel stricturing in two case series [6,7]. We describe three CVID patients with severe enteropathy who were treated with the anti-tumour necrosis factor (TNF) antibody infliximab, which resulted in significant long-term improvement.

Patients and methods

Patient 1

A 53-year-old-woman with CVID and bronchiectasis complained of abdominal cramps, bloating and frequent loose stools with steatorrhoea at age 39 years (Table 1) and has been reported in a previous study [6] (patient 4). At that time her duodenal biopsy showed mild partial villous blunting and nodular lymphoid hyperplasia, the colon showing increased numbers of intraepithelial lymphocytes. Over the next 14 years she was treated with budesonide, prednisolone, elemental and gluten-free diet and pancreatic substitute

Table 1. Clinical features prior to infliximab therapy.

Characteristic	Patient 1	Patient 2	Patient 3
Symptoms	Weight loss, cramps, bloating, steatorrhoea	Weight loss, bloating, diarrhoea steatorrhoea	Severe watery diarrhoea
Age at diagnosis of hypogammaglobulinaemia	32	21	24
Age at onset of enteritis (years)	39	25	53
Duration of symptoms before infliximab (years)	14	11	6
White cell scan	Ileal uptake	Increased uptake in descending colon	Increased uptake throughout colon
Treatment	Budesonide	Budesonide	Budesonide
	Prednisolone	Prednisolone	Prednisolone
	Pancreatin	Cholestyramine	Cholestyramine
	Gluten-free diet	Gluten-free diet	Gluten-free diet
	Elemental diet	Lactobacillus	Mesalazine
			Ganciclovir

(pancreatin), with limited success. At 48 years her condition deteriorated with a weight loss of 10 kg, low serum albumin and evidence of multiple vitamin and iron deficiencies, despite prolonged prednisolone (30 mg once daily) treatment over 18 months. Her duodenal and colon biopsy showed evidence of active inflammation (Table 2). A trial of anti-TNF-α therapy (infliximab) was started 5 months after prednisolone was discontinued.

Patient 2

A 36-year-old-man with CVID and recurrent sinusitis started having frequent loose stools with steatorrhoea at age 25 years. A duodenal biopsy showed villous atrophy with a lymphocytic mucosal infiltrate. He was treated with oral budesonide (6–15 mg once daily) for 5 years and then prednisolone (10 mg daily) for 2 years, which partially controlled the diarrhoea. His condition deteriorated aged 32 years when he lost weight, experienced increased bloating and developed multiple vitamin and iron deficiencies which did not respond to increased doses of prednisolone (40 mg daily). Bone densitometry showed osteoporosis. A duodenal biopsy showed similar changes to those seen 11 years earlier and a colonic biopsy showed mild focal inflammatory changes. A radioisotope-labelled white cell scan showed increased uptake in the descending colon. A trial of infliximab therapy was started.

Patient 3

A 59-year-old-woman with CVID and bronchiectasis started having frequent watery loose stools at age 53. She was treated with mesalazine and budesonide (3–6 mg daily). A colon biopsy showed a low-grade active colitis, and a labelled white cell scan showed extensive uptake in the submucosal area of the large bowel. She needed higher doses of budesonide (9 mg daily) for symptom control and 4 years later needed a 4-week course of prednisolone 40 mg daily. A colon biopsy at this stage showed a low-grade active colitis, with a polymerase chain reaction (PCR) test on colonic tissue being positive for cytomegalovirus genome, although no cytome-

Table 2. Histopathological features of small and large intestine before and after infliximab.

	Pre-infliximab		Post-infliximab*	
Patient 1	Duodenum	Villous blunting, crypt hyperplasia, increased number of intra-epithelial and lamina propria lymphocytes with some excess of neutrophils	Duodenum	Villous blunting, increased number of intra-epithelial lymphocytes and lamina propria infiltration of neutrophils
	Colon	Not performed	Colon	Low-grade active colitis
Patient 2	Duodenum	Villous blunting, crypt hyperplasia, increased lamina propria and intra-epithelial lymphocytes	Duodenum	Villous blunting, crypt hyperplasia, increased lamina propria and intra-epithelial lymphocytes
	Colon	Normal architecture, mild focal superficial macrophage and neutrophilic debris	Colon	Minimal crypt distortion, increased intraepithelial lymphocytes, focal mild superficial lymphocytic inflammation
Patient 3	Colon	Low-grade active colitis	Colon	Low-grade active colitis

*Patient 1 had 22 doses of infliximab over 53 months, patient 2 had 17 doses over 53 months and patient 3 had five doses over 5 months.

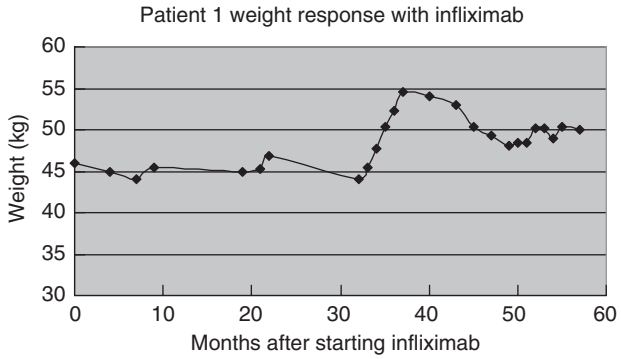

Fig. 1. Patient 1 weight response to infliximab with symbols (◆) indicating infliximab infusions. Deterioration at 40 months was due to campylobacter infection.

galovirus (CMV) inclusion bodies were seen within mucosal macrophages. Treatment with intravenous ganciclovir for 2 weeks followed by oral valganciclovir for 4 weeks resulted in rapid improvement of stool frequency. Within a week of stopping valganciclovir, bowel frequency gradually increased over the next 4 weeks to 16 motions/day. A further 6-week course of oral valganciclovir was associated with a rapid reduction in stool frequency, although this was combined with prednisolone and the anti-malarial, malarone, for the first 2 weeks during a visit to Africa. During the 5th week the valganciclovir was discontinued because of side effects (mouth ulcers and skin rash) but she remained in remission for a further 7 weeks (stool frequency two to three/day). However, her symptoms relapsed and 6 months later she started infliximab therapy.

Infliximab trial

In all three patients, gut infection and thyroid abnormalities were excluded as causes of enteropathy; chest radiography was performed with no evidence of tuberculosis (TB) infection before starting treatment. Infliximab, a chimeric anti-TNF antibody, was given as an intravenous infusion over 2 h. Our regimen uses infliximab at a dose of 5 mg/kg every 4 weeks for a 3-month induction followed by every 4–8 weeks depending on clinical response. Patients 1 and 2 had two short courses (three infusions in each) of infliximab 1–3 years before the above regimen was started.

All three patients were monitored carefully throughout infliximab therapy with regular measurement of weight, renal and liver function, C-reactive protein (CRP) and vitamins A, D, E, B12. Iron and red cell folate were measured regularly in the patients with malabsorption; patients completed a daily symptom diary and a quality of life questionnaire [the Inflammatory Bowel Disease Questionaire (IBDQ)]. We considered a mean IBDQ score increase of 40 points as a significant improvement; this was based on the improvement seen in the ACCENT I trial [8] on infliximab for Crohn's disease. Bowel biopsies were taken before and after a significant period of infliximab treatment and were assessed by a histopathologist who was blinded to the patient's condition or treatment.

Results

Patient 1

Following improvement during two short courses of infliximab 4 years previously, it was decided to give more prolonged regular treatment. Figures 1 and 2 show evidence of clinical improvement after treatment; an episode of campylobacter enteritis was associated with a temporary deterioration of symptoms until treated with antibiotics (Fig. 1). After 1 year of infliximab treatment there was a weight gain of 5 kg and an IBDQ score improvement of 50 (Figs 1 and 2). There was no clear evidence of a change in her bowel frequency after treatment, which remained at two to four motions daily.

Patient 2

Patient 2 showed a IBDQ score increase of 47 points, a decrease in stool frequency (three to seven motions/day), but no improvement in weight 1 year after of infliximab (Fig. 2). During this period the prednisolone dose was decreased from 40 mg to 5 mg daily within 7 months. It was difficult to assess whether vitamin or iron absorption improved in either patients 1 or 2, although serum levels of some vitamins increased. Furthermore, repeat bowel histology 2 years into the treatment showed no significant change (Table 2). Attempts to increase the interval between infliximab infusions to 8 weeks led to clinical deterioration in both patients and the 4-weekly regimen was reinstated.

Patient 3

Patient 3 responded rapidly to infliximab with a dramatic reduction of her stool frequency from 14 motions/day to

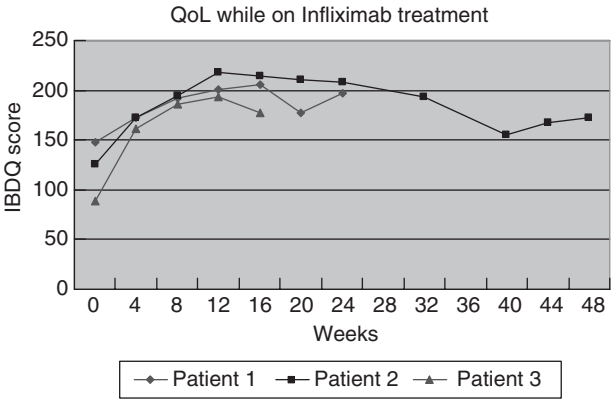

Fig. 2. Inflammatory Bowel Disease Questionaire scores for the three patients with markers representing infliximab infusion. The scoring was started in patient 1 after she had already had nine treatments of infliximab.

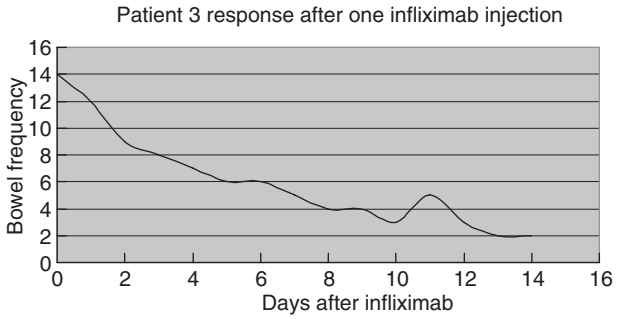

Fig. 3. Patient 3 bowel frequency response to a single infliximab infusion.

six motions/day within 7 days (Fig. 3). Her IBDQ score increased from 89 to > 200 within 4 months (Fig. 2). However, she had two serious urinary tract infections requiring intravenous antibiotics; as a result infliximab treatment was stopped as a precaution. Three months later she developed a serious *Herpes zoster* reactivation, needing intravenous aciclovir. Despite consistent symptomatic improvement, an endoscopy after 6 months of treatment still showed evidence of inflammation in the colon.

When her symptoms relapsed within 4 months of stopping infliximab, a new regimem was started by halving the previous dose to 2·5 mg/kg and giving this when stool frequency was greater than seven motions/day with aciclovir prophylaxis (200 mg twice daily for 2 weeks). This regimen had a similar dramatic response (Fig. 3), allowing a time interval of 3–4 months between treatments. To date she has had three courses using the new regimen without infections.

Histopathology

Despite clinical and symptomatic improvement, no significant change in the histopathological appearance of any of the patients' biopsies was noted following at least 6 months' treatment. The features are summarized in Table 2, and examples of the histopathological appearance are shown in Fig. 4.

Discussion

The mechanism of severe chronic enteropathy in CVID patients is not known, and so far there have been no clear hypotheses to explain this complication [6,7]. There are two types of enteropathy, one affecting exclusively the large bowel and the other predominately the small bowel with malabsorption. In the former, patients presented with frequent watery motions with few systemic effects, apart from episodes of dehydration and electrolyte loss, particularly in hot weather (unpublished personal observation). Patient 3 demonstrates the extreme end of a spectrum of this type of large bowel enteropathy, milder forms probably being relatively common in CVID [5]. Despite the profuse diarrhoea, the histology of the colon usually shows only a mild chronic active colitis in severe cases, with a minimal excess of intraepithelial lymphocytes in milder cases. Despite our patient having less than 40 copies/ml of CMV DNA in her

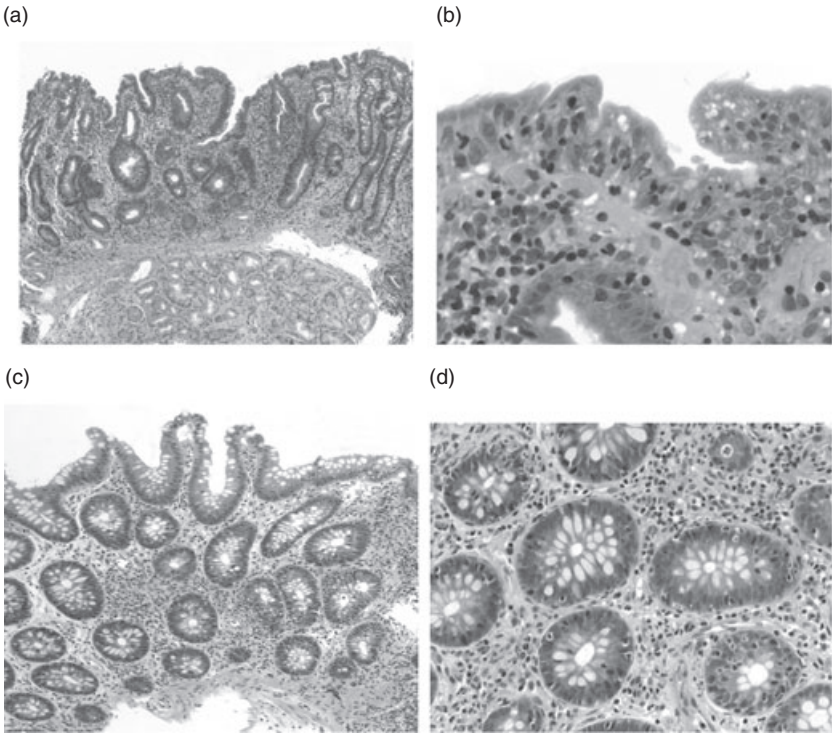

Fig. 4. Small and large bowel inflammation of patient 1 (before infliximab). (a) Low (× 25 magnification) and (b) high (× 200 magnification) power images of the duodenal biopsy show features similar to coeliac disease, with flattened villi, crypt hyperplasia and an increase in lamina propria chronic inflammatory cell infiltrate and epithelial lymphocytes. (c) Low (× 50 magnification) and (d) high (× 100 magnification) power images of the colon biopsy show mild crypt distortion and a patchy chronic inflammatory cell infiltrate. Focal active inflammation (cryptitis) is demonstrated in the top left gland on higher power (d).

blood, a colonic biopsy was positive by PCR for CMV and she responded rapidly to ganciclovir. This patient had evidence of a vigorous T cell immune response to CMV, and immunological studies on her and other CVID patients have been reported recently by Raeiszadeh *et al*. [9]. Our current hypothesis, which complements those expressed by others [10], is that this type of enteropathy is associated with an inappropriate local T cell inflammatory reaction to CMV causing release of inflammatory cytokines, particularly TNF-α from $CD8^+$ T cells, which increases large bowel permeability. The trigger for attracting CMV-specific T cells into the mucosa may be common enteric infections or even commensal colonic bacteria which have penetrated the mucosa because of the underlying antibody deficiency. The finding that infliximab therapy led to a rapid improvement in bowel frequency and quality of life supports this hypothesis. TNF has been shown to increase CMV replication in pro-monocytic cell lines *in vitro* [11], so infliximab may have the capacity to inhibit CMV reactivation *in vivo*.

The other two patients (1 and 2) suffered from small bowel involvement with malabsorption. This is a more commonly recognized type of enteropathy in CVID, and there have been a few published case series [6,7]. Some workers have considered this complication to be Crohn's disease because the ileum is often involved and stricturing can occur [7], while others have shown subtle differences in the local cytokines released between CVID enteropathy and classical Crohn's disease [12]. Although one of our patients was infected with CMV (as shown by the presence of specific circulating T cells) it is not clear if this type of enteropathy is associated with persistent viral infection. The response to infliximab was less marked in these patients, but careful monitoring of quality of life and weight over many months showed clear benefit.

In our study there was little correlation between the histological features in the bowel and symptomatic improvement. Even in patient 3, the colon did not return to normal after infliximab despite dramatic clinical improvement. This may be due to patchy involvement of the gut and difficulty in obtaining a representative sample, or that infliximab has no influence on the mucosal damage.

All three patients were diagnosed with CVID in their 20s and had been receiving regular immunoglobulin infusions for many years, and the diarrhoea preceded the infliximab treatment by more than 5 years. Their immunological profiles were similar, in that all had low or absent memory-switched B cells with intact T cell subsets. All had splenomegaly and mild liver inflammation, indicating a more widespread inflammatory process that occurs in about 20% of CVID patients. Of interest is the normal CRP level in this complication, which in contrast to Crohn's disease cannot be used as a marker of relapse or improvement [13]; nevertheless, CRP levels do rise during acute bacterial infection in CVID patients.

By analogy with Crohn's disease it could be argued that the appropriate second-line therapy for our patient should have been azathioprine [14]. However, many patients with CVID have been shown to have functional T cell defects [3] and there is concern that azathioprine may result in severe T cell dysfunction. There is also potential that anti-TNF therapy will increase susceptibility to infection in already immunocompromised patients with CVID. Patient 3 was hospitalized on three occasions during therapy with severe infections, although the other two patients experienced no serious problems. Mycobacterial infection is a recognized side effect with infliximab therapy for Crohn's disease and rheumatoid arthritis [15], but it has been suggested that CVID patients are resistant to mycobacteria because of an underlying up-regulation of interleukin (IL)-12 and interferon (IFN)-γ production [16].

In conclusion, our data suggests a useful role for infliximab therapy in CVID patients with severe enteropathy. However, patients need to be monitored carefully for increased susceptibility to infection, and side effects can probably be minimized by adjusting the dose and frequency of therapy to individual patients. Our results in this small case series should encourage a larger trial to confirm our results.

Acknowledgements

We thank our nurses Cilia Freud and Irene Wahlberg, and Dr Bridget Heelan for helping to manage the patients.

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