Fibrotic Strictures and Anti-TNF- α Therapy in Crohn's Disease

Dario Sorrentino^a Giovanni Terrosu^b Salvatore Vadalà^a Claudio Avellini^c

^aChair of Gastroenterology of the Department of Clinical and Experimental Pathology, and Departments of

^bDigestive Surgery, and ^cPathology, University of Udine School of Medicine, Udine, Italy

Dear Sir,

Strictures, both in the small intestine and colon, represent one of the most common complications of Crohn's disease. Although infliximab, an anti-TNF- α monoclonal antibody, is very effective in active Crohn's disease it has been reported to cause stricture development in some patients [1–3]. Although recent studies suggest that these and other results might have been affected by unadjusted analysis [4] it still remains unknown whether infliximab could be safely used to treat an inflammatory process in a patient who *already* has a fibrotic stricture (in the obvious absence of clinical indications for surgery). We describe here a case that may shed light on this important issue. A man affected by ileocecal Crohn's disease presented in March 2003 with weight loss, diarrhea, abdominal pain and tenderness in the right lower quadrant. He had been treated with mesalamine 4 g/day and occasional cycles of prednisone p.o. without much benefit. A complete blood count was normal but ESR and CRP were elevated. A small bowel enteroclysis performed in May showed a tight stricture in the terminal ileum with a prestenotic dilation, in the presence of mucosal alterations (fig. 1). Active inflammatory disease as well as narrowing of the ileal lumen was confirmed by ileocolonoscopy (not shown). Finally, an MRI performed in the same period showed significant enrichment of gadolinium-DTPA in the wall of the affected intestine, a sign confirming the

presence of active inflammation (fig. 2). Thus, the clinical, laboratory, endoscopic and radiologic features of this case indicated the presence of a fibrotic stricture with an inflammatory component of unknown entity in the terminal ileum. After

extensive discussions with the surgeon as well as with the patient, we proposed a careful trial with infliximab to relieve inflammation and as a possible bridge to surgery. Infliximab was started in June 2003 as a slow i.v. infusion (5 mg/kg body weight

Fig. 1. Small bowel enteroclysis, performed before infliximab therapy (May 2003). Note a clear shoe string sign indicating a tight stricture of the last ileal loop as well as a prestenotic dilation (arrow) indicating the presence of a major fixed, fibrotic component in the ileal stricture.

Fig. 2. Magnetic resonance imaging performed before infliximab therapy (May 2003). Note the enrichment of gadolinium-DTPA as intravenous contrast medium in the wall of the stenotic ileal loop (circle) indicating the presence of an inflammatory component.

Fig. 3. Small bowel enteroclysis, performed 1 month after starting therapy (July 2003). Note (compared with figure 1) a clear increase in the lumen of the terminal ileum. However, the affected bowel walls remain scarcely distensible and the prestenotic dilation (arrow), although much reduced, is still present.

with 100 mg i.v. hydrocortisone). The patient received an almost immediate symptomatic benefit with disappearance of pain and diarrhea. ESR and CRP returned to normal. It was then decided to continue infliximab following the standard regimen (two more infusions after 2 and 6 weeks, then every 8 weeks). A small bowel enteroclysis, 1 month after starting therapy showed (fig. 3) a clear increase in the lumen of the affected intestine with a faster transit of barium and disappearance of ulcerations. However, the affected bowel walls remained scarcely distensible and the prestenotic dilation, although much reduced, was still present. Subsequently, blood tests were repeated every 2 months and found always normal. An ileocolonoscopy performed after 1 year failed to show active inflammation. A small bowel enteroclysis repeated after 18 months showed a picture superimposable to that taken 1 month after starting therapy, indicating that the stricture had been long relieved of its inflammatory component and was now

essentially fibrotic. The patient was advised that his disease could not be further cured with medical therapy and that, in the future, further scarring in the intestinal wall could result in complete lumen obstruction. With his consent, surgery was planned and performed in May 2005, 2 years after starting infliximab therapy, in election and with the patient still in excellent clinical conditions.

Discussion

The powerful and rapid healing effect of infliximab in Crohn's disease has been deemed responsible for later development of strictures, due to collagen deposition in the deep layers of the gut wall [1–3]. For this reason, up to this day, the presence of strictures is considered by many a contraindication to infliximab. However, infliximab appears both safe and effective in the presence of an inflammatory stenosis [5], while being predictably ineffective – but not harm-

ful – in the presence of small degrees of fibrosis [6]. In addition, data showing an apparent greater incidence of strictures in infliximab-treated patients (such as those of the TREAT registry) may be affected by unadjusted analysis [4]. If infliximab does not cause formation of strictures and may relieve, if present, the inflammatory component of any stenoses, it may logically follow that this medication should not be contraindicated in the presence of strictures, even those mostly fibrotic. The case described here gave us an opportunity to prove this point. A man affected by ileocecal Crohn's disease had an important narrowing of the terminal ileum with combined clinical, endoscopic, radiological and MRI features suggesting the presence of a high degree of fibrosis in the stricture coexisting with active inflammation in the same site. Infliximab treatment brought about a dramatic improvement in his symptoms and a resolution of the inflammatory component of the stricture without affecting – not even after 1.5 years of therapy – for bet-

ter or for worse, its fixed, fibrotic component. We do not know whether the patient, in time, would have developed a clinical obstruction due to the scarring process. It is tempting to suggest that patients with an advanced disease, such as our patient, were those originally described as developing strictures or obstruction as an apparent complication of infliximab therapy [1–3]. Although this case indicates that infliximab can be used in the presence of strictures, medical therapy should not delay surgery in the presence of an urgent indication, i.e. clinical obstruction. Since we cannot predict with certainty whether and when a fibrotic stricture will completely occlude the lumen, we believe it is mandatory to follow the patient very closely whenever a tight stricture is already present and surgery is postponed.

Indirectly, our study provides evidence that infliximab may be much more effective if given earlier in the course of disease

[7], but it also shows that in selected cases it could also be used as a bridge to surgery – especially in patients unresponsive to steroids. In conclusion, we believe that this case, together with the current literature, indicates that intestinal strictures per se should no longer be regarded as a priori contraindication to infliximab treatment [4–6].

References

- 1 D'Haens G, Van Deventer S, Van Hogeand R, et al: Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology* 1999; 116:1029–1034.
- 2 Vasilopoulos S, Kugathasan S, Saeian K, et al: Intestinal strictures complicating initially successful infliximab treatment for luminal Crohn's disease. *Am J Gastroenterol* 2000; 95:2503.
- 3 Toy LS, Scherl EJ, Kornbluth A, et al: Complete bowel obstruction following initial response to infliximab therapy for Crohn's disease: A series of a newly described complication. *Gastroenterology* 2000;118:A2974.
- 4 Lichtenstein GR, Olson A, Travers S, et al: Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. *Am J Gastroenterol* 2006;101:1030–1038.
- 5 Holtmann MH, Neurath MF: Anti-TNF strategies in stenosing and fistulizing Crohn's disease. *Int J Colorectal Dis* 2005;20: 1–8.
- 6 Sorrentino D, Avellini C, Beltrami CA, et al: Selective effect of infliximab on the inflammatory component of a colonic stricture in Crohn's disease. *Int J Colorectal Dis* 2006;21: 276–281. Epub 2005 Jun 11.
- 7 Sorrentino D, Terrosu G, Avellini C, et al: Prevention of postoperative recurrence of Crohn's disease by infliximab. *Eur J Gastroenterol Hepatol* 2006;18:457–459.