Treatment of small bowel subocclusive Crohn's disease with infliximab : an open pilot study

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Abstract

Stricturing subocclusive small bowel Crohn's disease (CD) is often an indication for surgery. We embarked on an open label pilot study to assess the safety and efficacy of infliximab in patients with stricturing subocclusive CD.

Patients and methods : **A cohort of patients with a documented and symptomatic small bowel stricture caused by CD was studied. Patients had to be refractory to corticosteroids and/or immunosuppressives, and not in need for immediate surgery. The patients were treated by a single infusion of infliximab 5 mg/kg and followed up at w1, w2, w4 and w8.**

Results : **After the 6th patients, the study was prematurely discontinued because the predefined safety thresholds of more than 2 surgeries within the first 5 patients was reached. Only two patients completed the 8 weeks study, with a positive response to infliximab and improvement of inflammation confirmed by the CRP and CT scan. Two patients had to be operated early and the last two patients first did well but worsened after one month and were operated 35 and 42 days after infliximab, respectively. No surgical complications occurred in the 4 operated patients.**

In conclusion, a subset of patients with subocclusive small bowel stricturing CD may benefit from infliximab. (Acta gastroenterol. belg., **2007**, 70, **15-19**).

Introduction

Stricture formation is a frequent complication of Crohn's disease (CD). Ten years after diagnosis, approximately one third of the patients develop such intestinal strictures (1). The small bowel, particularly the terminal ileum is the most frequent location of these strictures. The pathophysiology of stricture formation in CD is incompletely understood but involves smooth muscle cells hyperplasia, increased number of submucosal fibroblast and collagen deposition (2). Current medical treatments available for CD have little or no demonstrated effect on these parameters. When these strictures induce occlusions or recurrent subocclusions, the treatment is generally surgical resection of the diseased area. However besides these fibrotic and hyperplastic characteristics, these strictures have also a significant inflammatory component. The mucosa can be ulcerated and oedematous in some cases. Furthermore, even in the absence of important mucosal lesions, the fibrotic submucosa can be infiltrated and the hyperplastic muscularis propria is dissected with a large number of activated immuno-inflammatory cells. Although it has never been studied in controlled trials, steroids seem to have some positive effect on CD strictures (3). However, mid or long term benefit of such steroid treatment is not proven and does not seem to suppress the need for early surgical resection (4,5).

The role of TNF and TNF expressing cells in stricturing CD may be considered as significant. Most of the studies indicate a participation of TNF alpha in fibrotic processes in different organs, including the intestine (6-8). However some results are contradictory, suggesting an anti-fibrotic effect of TNF (9). The impact of anti-TNF treatment on stricturing CD is also controversial. Significant stricturing CD was a contra-indication in the large controlled trials with infliximab (10-11), but since then several retrospective small series or case reports have been published suggesting either positive effect (12,13), no positive effect (14) or even deleterious effect (15) of infliximab on stricturing CD. These discrepancies may be linked to the type of strictures that have been treated. Particularly, a positive effect may be mostly expected in patients in whom the intestinal stricture is associated with a significant local inflammatory reaction contributing to the stricture, while pure fibrotic strictures may not respond (12,13). A recent analysis of a very large number of patients treated with infliximab in the setting of ACCENT 1 trial and the TREAT registry, showed that infliximab was not independently associated with an increased risk of intestinal stenosis, stricture or obstruction (16).

The aim of our study was to assess the safety and efficacy of infliximab treatment on inflammatory strictures of CD in an open pilot trial. As this trial was mainly a feasibility trial for the treatment of stricturing CD with infliximab, the protocol included security thresholds for the requirement of surgery. As this security threshold was reached at the 6th patient, the study was prematurely stopped. We report here the data on the 6 patients finally included.

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Patients and methods

Study design

This study was conducted among the centres of the Belgian IBD Research Group. The protocol was approved by the ethical committees of all participating centres and all the patients gave their written informed consent. Eligible patients were patients with proven CD for more than 6 months, aged 18-75, and experiencing symptoms related to a small bowel stricture, including abdominal pain, nausea, intermittent vomiting and/or abdominal distension for more than 2 months. To be included the patients had to be symptomatic despite steroid and/or immunosuppressive treatment since at least three months. They also had to have an elevated CRP (above normal reference value of the routine laboratory), a baseline CT scan with intravenous contrast confirming the small bowel stricture and the absence of peritoneal abscess, as well as no previous infliximab treatment. Exclusion criteria were immediate need for surgery, allergy to contrast agent, other uncontrolled severe disease, recent (< 3 months) or ongoing serious infection, current or recent (< 5 years) malignancy, pregnancy, positive stool culture, cardiac insufficiency, a positive PPD test and/or a chest X-ray suspicious for previous exposure to tuberculosis. At baseline, patients underwent physical examination, blood test with C-reactive protein (CRP) measurement and abdominal CT scan. The CT scan was performed with a standardized procedure on 4 or 16 multidetector CT scanners, including standardized rotation and acquisition time. Acquisition started 75-80 seconds after intravenous contrast injection. Images were built every 0.7-1.25 mm. CT scans were first interpreted in each participating centre by an experienced radiologist to check for inclusion-exclusion criteria. Secondarily, after the end of the study, a centralized reading of all CT scans was performed by an experienced gastro-intestinal tract radiologist (JB), who was blinded for the clinical evolution of the patient. This second reading aimed at looking for factors predictive of clinical response to infliximab treatment. At day 0, before infliximab 5 mg/Kg infusion, CDAI was calculated, and abdominal pain, nausea, vomiting, abdominal distension as well as ability to eat were assessed using a scoring system. Pooling the abdominal pain (0-3), nausea (0-3), vomiting (0-3), abdominal distension (0-3) and ability to eat score (0-3), a global stricturing CD score was established. This score was the sum of all subscores, with a maximum of 15 and a minimum of 0. This score has not been validated before and was used for the first time in the present study. Allowed treatments were concomitant immunosuppressive treatments at stable dose since at least 3 months, steroids, mesalazine and antibiotics at a stable dosage since at least 2 weeks before baseline. All these drugs were kept a stable dosage throughout the study. The patients were given a low fibre diet. Follow up visits were performed at week 1, 2, 4, and a final visit at week 8, with recording of adverse events and calculation of the global stricturing CD score. At week 4 and 8, CDAI was also calculated and CRP measured. The week 8 visit also included a repeat abdominal CT scan. It was planned to enrol 20 patients at 10 hospitals. However security thresholds were also determined as far as the need for surgery. If these thresholds were reached before the 20 patients were recruited, the study would be interrupted. These thresholds for acceptable rate of surgery were as follows : no more than 2 patients among the first five, no more than 3 patients among the first 10 and no more than 4 patients among the first 15.

End points of the study

The primary end point was the proportion of patients developing an occlusion necessitating surgery or endoscopic dilatation, within 8 weeks after infliximab infusion.

The secondary end points were the evolution of the scores for abdominal pain, nausea, vomiting, abdominal distension, ability to eat and the global stricturing CD score, the evolution of CDAI and CRP, and the evolution of the diameter and characteristics of the stricture at CT scanner.

Statistical analysis

Baseline and follow up characteristics were analysed with descriptive statistics, and expressed as mean +/-SD or median (interquartile range) according to their normal or not normal distribution.

Results

Between March and November 2004, 7 patients were screened for this trial. One patient was a screening failure because the CT scan showed a peritoneal abscess associated with severe and diffuse inflammation of the colon and the small bowel. This patient developed peritonitis 15 days after the screening visit, a few days after having the CT scan. Abscess and peritonitis were due to a perforation of CD lesion in the ileum. Characteristics of the other treated patients are shown in table 1.

Among the 6 enrolled patients, 4 had to undergo a surgical resection within 8 weeks after infliximab because of a significant worsening of the medical condition. Since the thresholds of 3 patients within the first 10 patients requiring surgery was passed, the study was prematurely stopped.

Response to infliximab

Two patients (patients 1 and 2) responded positively to infliximab with improvement of the global stricturing CD score and had a sustained response until week 8. Evolution of clinical and biological parameters is shown in figure 1. These patients showed also a significant

Table 1. — **Characteristics of the patients at baseline**

	age	gender	Disease location	Main stricture	Previous occlusion	smoking	treatment	CDAI	Abdominal mass	CRP (mg/l)
Patient 1	24	F	Ileocolic	ileal	no	yes	Azathioprine and steroid	369	no	31
Patient 2	35	F	ileal	ileal	yes	no	Azathioprine and steroids	41	no	20
Patient 3	56	M	Jejunoileal	jejunum	yes	no	antibiotics	140	no	22
Patient 4	24	M	ileal	ileal	no	yes	Azathioprine and 5ASA	251	no	100
Patient 5	36	F	ileal	ileal	no	no	azathioprine	235	yes	8
Patient 6	39	F	ileocolic	ileal	no	no	Azathioprine, steroids and antibiotics	236	yes	70

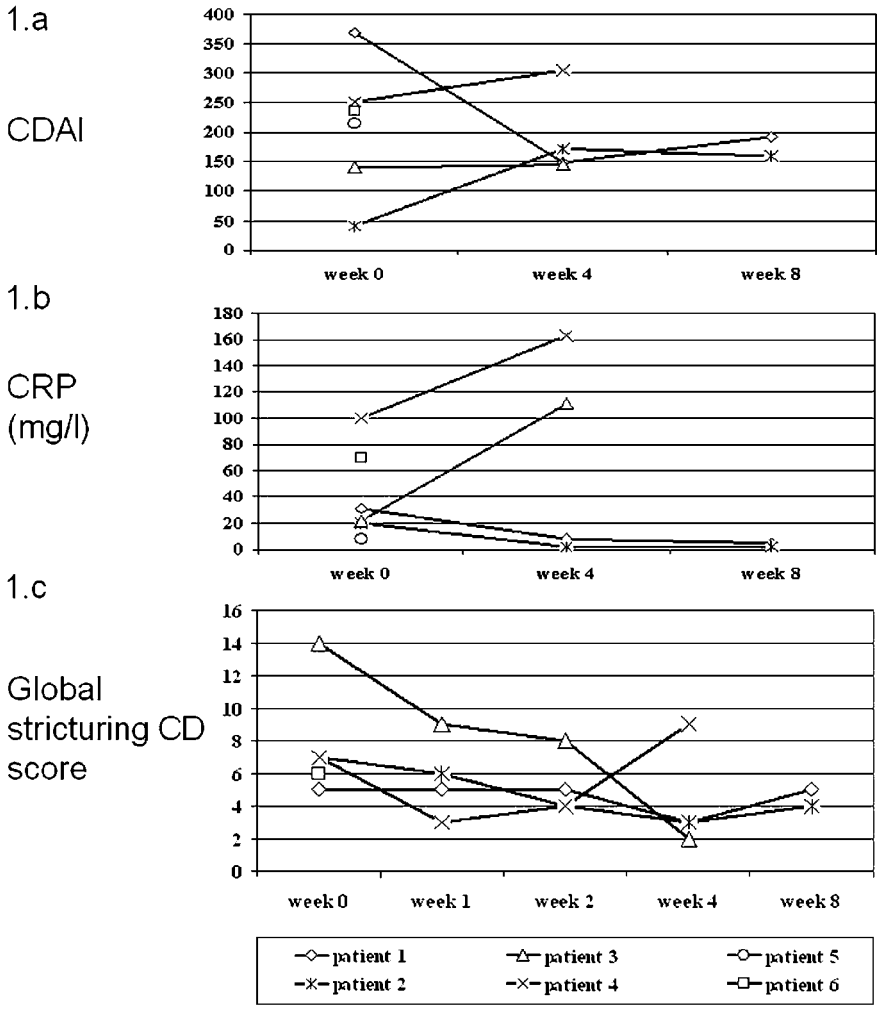

Fig. 1. — Evolution of CDAI (1a), CRP (1b) and global stricturing CD score (1c), after one infusion of infliximab 5 mg/Kg in patients with small bowel stricturing CD. Global stricturing CD score corresponds to the sum of 5 subscores (on a 0-3 scale) for abdominal pain, nausea, vomiting, abdominal distension and ability to eat score.

improvement on CT scan, showing a decrease in the contrast enhancement and widening of the stricture calibre at week 8.

Two patients showed a positive clinical response at week 4 (patients 3 and 4) (Fig. 1), but then worsened and had to be operated 35 and 42 days after infliximab infusion. Interestingly, while the global stricturing score transiently improved in these patients, they had a dramatic increase in CRP at week 4, before clinical worsening (Fig. 1). Patient 3 developed severe abdominal

pain and distension. Surgery showed a stricture and severe infiltration in a jejunal loop, with inflammatory reaction going into the mesentery but no abscess. Patient 4 developed severe abdominal pain, vomiting and anorexia ; surgery showed severe diffuse ileitis with deep lesion and stricture but no abscess. Both patients had an uncomplicated evolution after surgery.

The last two patients (patients 5 and 6) worsened after infliximab infusion and had to be operated on early. Patient 5 had increased abdominal pain 2 days after infliximab He was hospitalised 6 days after infliximab with occlusion and operated 4 days later. The surgery showed occlusion on a tight ileal stricture. Patient 6 became generally unwell with nausea and severe abdominal pain already the day after infliximab infusion and had to be operated 10 days later. Surgery showed tight stricture and closed perforation. These two patients fully recovered and had no complication following surgery.

Factors associated with response to infliximab

When looking at clinical or biological baseline characteristics of the patients, the only difference between patients having a sustained response, transient response or no response at all was the presence of an abdominal mass at baseline. Both patients who had no response and underwent early surgery had an abdominal mass before treatment, while none of the other 4 patients had such abdominal mass. Other parameters, particularly baseline CRP, CDAI, and co-treatment, were not different. CT scan also showed interesting features. The patients 1 and 2 who showed a favourable clinical evolution had no signs of local complications apart from the intestinal stricture. The other patients either had an intramural intestinal abscess without real peritoneal abscess (patient 3 in the jejunum and patient 5 in the ileum), or free intrapelvic fluid (patient 6). There was no clear difference between patients as far as other qualitative or quantitative CT scan data (number of strictures, size and calibre, contrast enhancement, vasa recta, aspect of surrounding fat, or upstream dilation).

Discussion

Infliximab induced a sustained clinical response and allowed to avoid surgery in only two out of six patients with inflammatory stricturing subocclusive CD. This suggests that infliximab may be a good option in only a small subgroup of such patients. Globally in these two patients it induced a decrease in the stricturing disease clinical score, an improvement of qualitative and quantitative parameters at CT scan, and a good clinical evolution. Such a good evolution had already been noted in a previous retrospective series (12), but the characterization of the clinical situation before treatment as well as the strict evaluation of the patients was lacking in these retrospective series. An improvement in such situation may correspond to diminution of bowel wall inflammatory mediators, with a decrease in inflammation at CT scan correlating with clinical improvement (13). However, in our study, in a second subgroup of patients (2/6), the situation worsened after a transient improvement. Clinically, these patients were not different at baseline from the ones who had a sustained response. However, at CT scan one of these patients had a jejunal intramural abscess. Furthermore, these patients with transient clinical improvement showed a dramatic increase of CRP at week 4, a few days or weeks before clinical degradation, indicating that CD was not adequately controlled or that a local complication may have developed.

In the last 2 patients, the evolution was unfavourable with a rapid need for surgery. Interestingly, these patients were the only two with an abdominal mass at baseline clinical examination. Furthermore, CT scan showed an intramural ileal abscess in one and intraperitoneal fluid in the other. Physicians must be particularly careful in these cases, and an abdominal mass could be considered as a relative contra-indication for infliximab in this clinical setting. Steroids seem to perform better in this particular case of abdominal mass without detectable intraabdominal abscess. Felder *et al.* reported a series of 24 CD patients with a palpable abdominal mass, treated with high dose steroids (17). In the majority of patients, the mass resolved and short term clinical evolution was favourable. Furthermore, although over the mid and long term, the majority of these patients had to undergo elective surgery, one third of them never required surgery over a mean follow up of 40 months. Results of this uncontrolled trial must be taken with caution since a recent case-control retrospective series describe a high rate of complication, particularly intra-abdominal abscess in such patients treated with corticosteroids (5).

Importantly, in our series, even in the patients with abdominal mass, there were no peri-operative complications. This is in agreement with two large series of patients undergoing surgery shortly after infliximab (19,20). In these series there was no increase of mortality or severe complications.

In conclusion, infliximab treatment in CD patients with small bowel inflammatory strictures causing occlusive or subocclusive symptoms is not beneficial in the majority of the patients and does not seem to avoid surgery. However, in a subgroup of patients without abdominal mass at clinical examination and without signs of local complications on CT scan apart from intestinal stricture, infliximab may be beneficial. A randomised prospective controlled trial comparing steroids to infliximab in this setting would be useful.

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