Infliximab and pediatric stricturing Crohn's disease : a possible alternative to surgery ? Experience of seven cases

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Abstract

Introduction : **Infliximab (IFX) is one of the treatments of choice for the different phenotypes of pediatric Crohn's disease (CD). Although it was initially feared that anti-TNFα treatment might cause bowel stenosis, recent studies have validated the efficacy of IFX as an anti-stricturing agent.**

Aim : **To assess the efficacy of IFX treatment for pediatric stricturing CD.**

Patients and methods : **Data were obtained on pediatric patients treated at our tertiary level Pediatrics Department (years 2000-2010). Indications for IFX therapy included persistent disease activity (PCDAI > 20) unresponsive to corticosteroids and thiopurines. All patients treated with IFX underwent upper and lower intestinal endoscopy, abdominal ultrasound and magnetic resonance enterography.**

Case series : **Among 44 pediatric CD patients, 21 were treated with IFX. Seven of these cases had luminal strictures and in 6 patients the inflammatory strictures disappeared after treatment with IFX. One child with ileal fibrotic stenosis (MR) required a surgical resection.**

Conclusion : **Our data support the efficacy of IFX in pediatric CD, including the stricturing phenotype.** (Acta gastroenterol. belg., **2012**, 75, **58-60**).

Key words : Infliximab, pediatric Crohn's Disease, stricturing phenotype, magnetic resonance enterography.

Introduction

The onset of strictures in the small bowel and colon is a frequent complication among patients with Crohn's disease (CD) (1). Infliximab (IFX) is among the treatments of choice nowadays for pediatric CD in its various phenotypes (inflammatory, stricturing, penetrating) (2).

Some Authors have suggested in the past decade that anti-TNFα treatment might carry a risk of bowel stenosis and they advised against the use of IFX in clinical practice for patients with previous stenoses (3). This warning stemmed from the consideration that an IFX-induced accelerated mucosal healing process might give rise to fibrosis of the bowel wall's deeper layers (4).

The efficacy of anti-TNFα for treating symptomatic strictures in CD patients has nonetheless been confirmed in the recent literature (5).

Some evidence in support of this treatment has focused on a plausible anti-fibrogenic action of anti-TNFα (6).

No randomized trials have been performed as yet on the effect of IFX therapy on bowel strictures. The aim of our study was to assess 7 cases of stricturing CD treated with anti-TNFα to ascertain the suitability of this approach.

Our case series was divided distinguishing between fibrostenosing CD (described as the B2 phenotype in the Montreal Classification (7)) and pure inflammatory strictures in CD, with a view to discerning any differences in the outcome of anti-TNFα treatment in these two groups.

Patients and methods

Retrospective and prospective descriptive analyses were performed on data obtained on pediatric CD patients treated at our tertiary referral Pediatrics Department during the years 2000 to 2010.

The indications for IFX therapy included failure to respond to therapy with corticosteroids and/or thiopurines (persistent disease activity with PCDAI > 20), steroid dependence, extra-intestinal manifestations and/or perianal disease.

IFX was administered according to a protocol involving 5 mg/kg body weight at weeks 0-2-6, then every 8 weeks.

A diagnosis of stricturing CD was established by upper and lower intestinal endoscopy, abdominal ultrasound (US Technos Esaote, probe LA 523 13-5) and magnetic resonance enterography (MR Philips Achieva, 1.5 Tesla, "body" roll, with gadolinium contrast enhancement), the last of these being used to identify signs of active inflammation as well as complications such as bowel obstruction, fistulas and abscesses.

At endoscopy, "strictures" were identified as bowel tracts hindering or preventing the passage of the pediatric endoscope (Pentax EC - 3470K diameter 11.6 mm).

All strictures were further confirmed on imaging studies (abdominal US and MR enterography) as bowel tracts with a wall thickness measuring > 3 mm and with pre-stenotic bowel dilations of at least 20 mm.

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Table 1. — **Case serie : characteristics of patients, disease phenotype and treatments**

Patients (n°)	1	2	3	4	5	6	7
Sex (M/F)	F	F	M	F	M	F	F
Age at CD onset (years, months)	8.6	7.6	12.6	13	14	10	10.5
Age at CD diagnosis	9.2	8.3	13.6	13.8	14.5	11	11
Follow-up (years, months)	4	8	1.3	4	1	0.8	0.5
PCDAI (pre-IFX)	20.5	20.5	25	25	32.5	35	37.5
CRP (mg/L)	15	18.6	27.4	23.2	33	32.8	33.9
BMI	19	15	20	22	23	17	20
Site of disease (pre-IFX)	Ileum Right colon (L3)	Ileum Colon (L3)	Ileum Colon Upper GI tract (L3 + L4)	Ileum Colon Upper GI tract (L3 + L4)	Ileum Colon Upper GI tract (L3 + L4)	Ileum Colon Upper GI tract (L3 + L4)	Ileum Right colon (L3)
Site of stenosis (pre-IFX)	Ileum, 15 cm from ileum-cecal valve	Pre-pyloric tract	Ileal Multiple Sub-stenoses	Ileum Rectum Anus	Left Colon Sigma	Terminal Ileum	Terminal Ileum
Bowel wall thickening on MR enterography or US (mm)	5	3.5	3.5	3.5	4	3.5	5
Symptoms on diagnosis of stenosis	Abdominal pain Weight loss	Abdominal pain Weight loss Fever	Abdominal pain Weight loss Mucous feces Heartburn	Abdominal pain Weight loss Diarrhea Bloody feces Nausea	Abdominal pain Weight loss Diarrhea Nausea Vomiting Asthenia Arthritis	Abdominal pain Asthenia Weight loss	Abdominal pain Anorexia Asthenia Weight loss Malnourishment
Perianal disease at diagnosis	yes	yes	no	yes	no	no	no
Number of infliximab infusions	6	13	8	6	6	5	5
Associated therapy	EN, 5-ASA, steroids, AZA	EN, 5-ASA, steroids, AZA, antibiotics	EN, 5-ASA, AZA	EN, 5-ASA, antibiotics, AZA	EN, 5-ASA, steroids, AZA	EN, 5-ASA, AZA	EN, 5-ASA, steroids
Post-infliximab stenosis	Yes	No	No	No	No	No	No

Table 1 shows the data collected for each patient. In particular, the Montreal Classification was used as a reference for the site of disease (7), while the Cardiff and Hughes Classification was considered for perianal disease.

Case series

Among 44 pediatric patients with CD followed up at our Center during the decade considered, 21 were treated with IFX. Seven of these IFX-treated patients, 2 males and 5 females (Table 1), had luminal strictures. At the time of starting treatment with anti-TNFα, their median age was 12.8 years and they had a mean follow-up of 2.8 years. The mean interval between the diagnosis of their CD and starting the treatment with IFX was 1.2 years.

Stictures (located as stated in Table 1) were detected in all cases before anti-TNFα therapy was administered. When the strictures were found, all patients had a PCDAI (Pediatric Crohn's Disease Activity Index) > 20.

Six patients with inflammatory strictures (identified on US and MR enterography) were given anti-TNFα treatment with periodic control investigations (once-a-year imaging ; mean follow-up : 8 months). The disappearance of the stricture was ascertained on MR enterography (Fig. 1) and endoscopy in all cases.

Surgical resection was required for one child, with a prior severe fibrotic strenosis at the terminal ileum (identified on MR enterography) and with a persistent disease activity (Patient 1, Table 1) after 6 infusions of IFX. The patient's IFX treatment was discontinued. There was no evidence of the luminal stricture worsening (on abdominal US and MR enterography) during the period of time

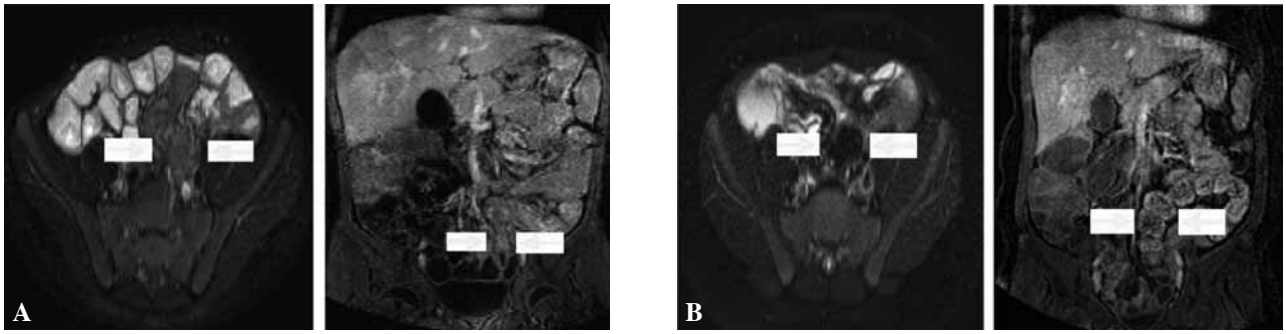

Fig. 1. — Contrasted MR enteropgraphy showing an inflammatory stricturing tract before (A) and after (B) treatment with Infliximab.

elapsing between the diagnosis of the stenosis and the resection surgery.

Patient 2 was a girl with CD since the age of 8 years. Treatment with an exclusively polymeric diet, corticosteroids and azathioprine was administered at diagnosis. In the following months, the child suffered frequent relapses. Abdominal MR excluded any bowel strictures. A year later, upper tract endoscopy identified a prepyloric stricture, confirmed by US as a wall thickening of 3.5 cm. A wireless capsule became lodged inside the stomach because of the stricture, making upper endoscopy necessary for its removal. A course of IFX was administered and further control endoscopies during the follow-up showed that the stricture had disappeared.

Discussion

The distinction between inflammatory and fibrotic strictures is not obvious because the two types of stricture may also coexist (8). US with an oral contrast agent can be useful but only in the hands of an experienced operator. Endoscopy can hardly detect this distinction, because of collagen deposition in the deeper layers of the bowel wall, thus far from the bioptic sample. MR enterography with oral polyethylene glycol as a contrast agent for the bowel lumen, and with i.v. gadolinium is useful for ascertaining the inflammatory component of a stricture : the accumulation of the contrast agent on the wall is a sign of inflammation, while its absence indicates fibrosis.

No randomized trials have been performed as yet on the effect of IFX treatment on bowel strictures. Our description of 7 pediatric cases was conceived with a view to comparing our findings with previously-described adult cases.

A strength of our study lies in the homogeneity of the instrumental methods used to select our CD patients with bowel strictures, and to assess them during the follow-up.

A limitation of our case series lies in its small size, and in the partially retrospective nature of the data collection. A multi-center randomized controlled study should be conducted in a larger sample of cases.

As anticipated, but not yet fully validated by the 2005 ESPGHAN Porto Criteria (9), the use of MR enterography (Fig. 1) in our cases was able to shed light on the accuracy of this method in detecting bowel strictures, which can be used instead of barium enema in this field (10).

In conclusion, our (albeit limited) data confirm that IFX is an effective option for the treatment of inflammatory strictures and also support the ability of this treatment to modify the predictable time course of Crohn's disease when it is administered in the early phase of active disease.

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