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Megacolon in inflammatory bowel disease: response to infliximab

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ABSTRACT

Megacolon is a serious complication of inflammatory bowel disease that often requires a colectomy. Infliximab is a therapeutic alternative when conventional treatment fails, before resorting to surgery. Its use is currently based on the publication of isolated cases. We present a series of 12 patients with megacolon treated with infliximab, five with signs of systemic toxicity. Seventy-five percent of the patients avoided a colectomy during their acute episode after early infliximab treatment, 2.45 days after the megacolon diagnosis. There was a greater risk of surgery among patients with ulcerative colitis and toxicity criteria. Two more patients required follow-up surgery despite long-term infliximab treatment. No patient suffered significant treatment-related adverse effects or significant post-surgery complications.

INTRODUCTION

The development of megacolon in the context of a severe flare-up of ulcerative colitis (UC) or Crohn's disease (CD) is a serious, potentially life-threatening complication. Nowadays, the incidence has decreased thanks to the inclusion of immunomodulatory therapies in the treatment of inflammatory bowel disease (IBD). The need for colectomy as a rescue treatment has also decreased.

Due to the low incidence, a few isolated case reports are the only studies that have evaluated the outcomes of severe flare-ups of megacolon or toxic megacolon (TM) in IBD, where classical therapy fails and infliximab (IFX) treatment is required. The goal of this study was to describe our patient series and analyze the factors that may influence response to treatment.

MATERIAL AND METHODS

This was a retrospective descriptive study of patients with IBD and toxic or non-toxic megacolon, who required infliximab rescue in our hospital between 2007 and January 2015. Treatment efficacy based on the need for colectomy was evaluated in the short and long term.

The following variables were analyzed: demographic characteristics, phenotypic characteristics and evolution time of IBD, flare-up severity according to the Mayo and Harvey-Bradshaw indices, previous treatments, time between symptom onset and the development of megacolon, time between diagnosis and treatment with IFX, the existence of signs of systemic toxicity (based on the criteria described by Jalan et al. [3]) and other analytical parameters such as C-reactive protein (CRP) and albumin. The adverse events attributable to the biological therapy were also described.

Given the small sample size, a comparative statistical study was not performed. Quantitative variables are expressed as the median and range.

RESULTS

Twelve patients were included, five with CD and seven with UC, six of whom were at the first onset of the disease (Table 1). Of the six patients with a diagnosis prior to admission, none were in treatment with immunosuppressants or biological agents and five required steroids and salicylates. One patient with CD did not require any treatment (patient no. 6). None of the patients were active smokers.

On admission, six patients had megacolon and five developed it during their hospital stay. The remaining patient (no. 9) had megacolon at another center before transfer to our unit. There was evidence of systemic toxicity in 5/12 cases (41.7%). The median (range) values for hemoglobin and CRP were 9.8 g/dl (7.7-11.4) and 208 mg/l (28-290), respectively (Table 2). All patients underwent proctoscopy. Six patients showed severe activity, five had moderate activity and the other displayed mild activity. Ten patients were tested for cytomegalovirus (CMV). One was immunohistochemically positive and was treated with ganciclovir. Stool cultures and tests for *Clostridium difficile* toxin were negative in all cases. The Mayo index in UC was 10 points (median, range 8-11) and 12 in CD according to the Harvey-Bradshaw index (range 8-15).

After failure of the usual therapeutic measures, IFX was started at a dose of 5 mg/kg of weight following a delay since diagnosis of 2.45 days (range 0-9). The patient transferred from another center was excluded, as they started IFX after 17 days. All patients except no. 12 were being treated with intravenous corticosteroids at the start of IFX. During admission, nine of the 12 patients (75%) avoided colectomy. Four needed to progress to the second dose of IFX between days 7 and 12 after the initial dose. However, three required surgery, one even after switching to adalimumab 30 days after the second dose of IFX. All of these patients had UC. The delay time between the megacolon diagnosis and the start of IFX in the patients that required surgery was one day in two cases and three days in the other. Only the combination of UC and the presence of toxicity seemed to be associated with therapeutic failure (Table 2). Just one patient (no. 12) displayed side effects attributable to IFX as they developed an asymptomatic CMV reactivation and was treated with antivirals that did not prevent continued IFX treatment. There were no significant adverse effects during the post-operative period of the patients who underwent surgery.

The nine patients whose flare-ups did not require surgical management remained on maintenance IFX for a mean period of 10.91 months (0-61). This was combined with azathioprine (AZA) in 50% of these patients. Two more patients (22.2%) required surgery after a mean follow-up of 70 months (20-121), three and five years after the megacolon, respectively. One of these patients with CD required colonic diversion due to perianal disease. In the other case, surgery was required for treatment-refractory UC.

DISCUSSION

Megacolon is defined as segmental or total dilation of the colon with a diameter greater than 5.5 cm, in the absence of an obstructive mechanical cause. The associated systemic toxicity is more significant than the dilation itself (1,4). In our series, toxicity occurred in 40% of patients who underwent surgery compared to the 14% who did not develop it. However, the small sample size prevents us from drawing definitive conclusions. IBD is not the only condition that causes megacolon. Any serious inflammatory process of the colon can cause it, particularly infections (1,5) that can simulate or coexist with inflammatory processes and lead to an inadequate treatment. The most significant among these is CMV, which was detected in one of our cases, who ultimately required a colectomy despite treatment with ganciclovir. There is no evidence in the literature to suggest that TM can be reversed by antiviral therapy (5).

Pathophysiologically, megacolon involves a severe inflammation that ultimately causes dystonia of the muscle layer (1,6). This would explain why megacolon develops during the initial stages of the disease (half of our patients at first onset) as the scar tissue caused by the disease would make dilation difficult in more advanced phases. This could also be the reason why all the patients that underwent surgery during an acute flare-up in our series suffered UC, as CD is more likely to cause fibrous strictures. Early diagnosis and treatment are essential because they prevent the development of complications, especially perforation, which is the main mortality-related factor (4). However, it was not detected in any of our patients.

The initial management of megacolon involves support measures, parenteral nutrition, antithrombotic prophylaxis, broad-spectrum antibiotic therapy and intravenous corticosteroids. Nasogastric tube aspiration is also recommended (1,4,7). Before the era of biologicals, calcineurin inhibitors, mainly ciclosporin, were used as rescue therapy (4,8). The development of biological drugs, especially IFX, was a major advance in the treatment of moderate to severe IBD that responds poorly to conventional treatment. However, very few case reports of megacolon or TM treated with IFX have been published. The first cases of severe UC with TM treated with IFX were published in 2004 and 2007. In fact, the first case involving a female patient with ileocolonic CD was reported in 2012. Colectomy was avoided in all cases (9-11). The good results described in our series are possibly determined by the speed at which IFX therapy was started, with a median of less than 72 hours following the diagnosis of megacolon. Nevertheless, the severity of some flare-ups was associated with an IFX-refractory fulminant course, as occurred in three of our patients. We highlight the safety of treatment in patients in a poor clinical and nutritional status, as there were no significant adverse events in our series that could be attributed to IFX.

IFX was maintained as a monotherapy or in combination with AZA once the initial flare-up had been controlled in nine of the non-surgical patients. Despite this, another two patients underwent surgery during the course of the disease. Therefore, great caution should be taken when simplifying treatment in these patients.

With this series of 12 patients, we hope to show the efficacy and safety of IFX in resolving megacolon, with or without associated toxicity. Using this approach, colectomy was avoided during the acute flare-up in 75% of cases, with few adverse effects. We consider the long-term maintenance of treatment with IFX necessary, although prospective studies would be required to define whether it could be suspended under any circumstances.

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Table 1. Baseline and clinical characteristics. Medical treatment and surgery after the development of megacolon

No.	*Gender*	*Age*	*IBD*	*First onset*	*Ø (cm)*	*Toxicity*	*T to IFX*	*Intensified*	*Flare-up Sx*	*T Sx*
1	Female	17	UC	No	6.4	Yes	3	Yes	Yes	30
2	Female	47	CD L2	No	6	No	3	Yes	No	-
3	Male	56	UC	No	6.5	Yes	9	Yes	No	-
4	Male	52	UC	Yes	7	Yes	1	No	Yes	16
5	Male	19	CD L3	Yes	6.5	No	1	No	No	-
6	Female	36	CD L2	No	7	No	4	No	No	-
7	Male	24	CD L3	Yes	7.7	No	0	No	No	-
8	Female	59	UC	Yes	7	No	3	No	No	-
9	Male	22	CD L2	No	6	No	17	No	No	-
10	Male	50	UC	Yes	6	Yes	0	No	No	-
11	Male	33	UC	No	10.5	No	1	Yes	Yes	41
12	Female	19	UC	Yes	5.5	Yes	2	No	No	-

Ø: colon diameter; T to IFX: time (days) elapsed from development of megacolon to start of infliximab; flare-up Sx: colectomy during megacolon flare-up; T Sx: time (days) from megacolon diagnosis to flare-up surgery; Subs. IFX/AZA/IQ: follow-up treatment with infliximab, azathioprine or surgery. *Sx: Discharge colostomy due to perianal pathology.

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Table 2. Influence of baseline, phenotypic, analytical and therapeutic factors on the need for colectomy during an acute flare-up

		Surgery (n = 3)	*No surgery (n = 9)*
Gender	Male (n = 7)	2 (29%)	5 (71%)
	Female (n = 5)	1 (20%)	4 (80%)
IBD type	Ulcerative colitis (n = 7)	3 (43%)	4 (57%)
	Crohn's disease (n = 5)	0 (0%)	5 (100%)
Extraintestinal manifestations	Yes (n = 3)	1 (33%)	2 (66%)
	No (n = 9)	2 (22%)	7 (78%)
First onset	Yes (n = 6)	1 (17%)	5 (83%)
	No (n = 6)	2 (33%)	4 (67%)
Previous treatment	None (n = 7, 6 first onset)	1 (14%)	6 (86%)
	Corticosteroids (n = 5)	2 (40%)	3 (60%)
	Immunosuppressants and/or biologicals (n = 0)	---	---
Age*	Years	34 (17-52)	36.89 (19-59)
IBD evolution time*	Months	15 (0-41)	35.67 (0-250)
T. symptoms-IFX*	Days	32.33 (23-37)	44.56 (18-67)
T. megacolon-IFX*	Days	1.67 (1-3)	2.75 (0-9)[†]
TM criteria	Yes (n = 5)	2 (40%)	3 (60%)
	No (n = 7)	1 (14%)	6 (86%)
Blood chemistry*	Hemoglobin (g/dl)	8.3 (7.7-11.0)	9.35 (8.1-11.4)
	Leukocytes	11,240 (7,920-13,920)	12,030 (8,140-13,620)
	CRP (mg/l)	279 (28-290)	198 (127-217)
	Potassium (mEq/l)	3.4 (3.3-3.7)	3.35 (2.4-4.7)
	Albumin (g/dl)	2.1 (2-2.1)	2.25 (1.6-2.3)

*Median (range). [†]Patient 9 excluded.