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CASE REPORT

Infliximab stopped severe gastrointestinal bleeding in Crohn's disease

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Abstract

To report the result of rapid ulcer healing by infliximab in Crohn's patients with severe enterocolic bleeding. During 2005 and 2010, inflammatory bowel disease database of King Chulalongkorn Memorial and Samitivej hospitals were reviewed. There were seven Crohn's disease (CD) patients (4 women and 3 men; mean age 52 ± 10.4 years; range: 11-86 years). Two of the seven patients developed severe gastrointestinal bleeding (GIB) as a flare up of CD whereas the other five patients presented with GIB as their first symptom for CD. Their mean hemoglobin level dropped from 12 ± 1.3 g/dL to 8.7 ± 1.3 g/dL in a 3-d period. Median packed red blood cells units needed for resuscitation was 4 units. Because of uncontrolled bleeding, surgical resection was considered. However, due to the poor surgical candidacy of these patients (n = 3) and /or possible development of short bowel syndrome (n = 6), surgery was not pursued. Likewise angiographic embolization was not considered in any due to the risk of large infarction. All severe GIBs successfully stopped by one or two doses of intravenous infliximab. Our data suggests that infliximab is an alternative therapy for CD with severe GIB when surgery has limitation or patient is a high risk.

Key words: Crohn's disease; Gastrointestinal bleeding; Complications; Infliximab; Biologic agents

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INTRODUCTION

Although severe gastrointestinal bleeding (GIB) is an uncommon complication of inflammatory bowel disease (IBD), severe GIB occurs in 0.1% of ulcerative colitis[1] and 1.2%-1.3% of Crohn's disease (CD)[1,2]. This in turn sometimes progresses to a potential life-threatening condition. Approximately one third of CD patients developed GIB as a flare up and another one fourth of CD patients presented with GIB as an initial symptom[3]. Bleeding sources were mostly found in the colon (50%-85%) and the small bowel (15%-50%). Unfortunately, one third of CD related GIBs were severe and surgery was required because of refractory bleeding especially after failed conventional medical and endoscopic treatment[1,3]. Therefore treatment for severe hemorrhage in IBD remains a challenge. Recently, there has been only a handful of case reports of severe CD related GIB controlled with tumor

necrosis factor (TNF)-α antibody (infliximab). We report the largest number (n = 7) of CD patients presenting with severe GIB who were successfully treated with infliximab without the need for surgery.

CASE REPORT

There were seven CD patients (4 women and 3 men; mean age 52 ± 10.4 years; range: 11-86 years). Two of the seven patients developed severe GIB as a flare up of CD whereas the other five patients presented with GIB as their first symptom for CD (Tables 1 and 2).

In a group with flared CD (n = 2), one patient was diagnosed as colonic CD for 2 mo. She was steroid dependent who required oral prednisolone 35 mg/d and azathioprine 1.5 mg/kg per day. She was admitted because of severe bleeding per rectum and developed orthostatic hypotension. She required 4 units of pack red cell for resuscitation during those 3 d of hospitalization. Another patient was diagnosed as ileocolonic CD for 7 mo. She had been taking budesonide 9 mg/d and mesalamine 2 g/d to control her CD before admission. She developed acute abdominal pain, fever and severe hematochezia. Her hemoglobin (Hb) dropped from 12 to 10 g/dL within 2 d. A unit of pack red cell was required to maintain hemoglobin level.

In patients who presented with hematochezia as their first CD symptom (n = 5), three of the five patients had had abdominal pain and watery diarrhea for 10-14 d prior to the present of hematochezia. The other two presented initially with hematochezia without prior warning gastrointestinal (GI) symptoms. All of those denied the use of non-steroidal anti-inflammatory drugs (NSAIDs) prior to the presentation. Skin signs and symptoms that suggestive of Behçet's disease were not recognized in any.

The average baseline Hb was 12 ± 1.3 g/dL in all patients. Coagulogram and platelets count were normal. The average C-reactive protein level was high (mean 14 ± 18 mg/L; normal 0-6). Endoscopy and ileo-colonoscopy were performed as the initial investigations. One patient with suspected proximal ileal bleeding underwent a double balloon enteroscopy. Endoscopic findings showed multiple discrete deep ulcers with either active oozing or visible vessel in all seven patients. Of these, two patients with visible vessel found on the ulcer underwent endoscopic hemostasis with hemoclipping. However, recurrent hematochezia developed in both and repeat endoscopy failed to indentify other source of bleeding despite the inactive status of previously clipped vessels. Bleeding sources located in the small bowel and mainly in the ileum without colonic source in five patients, while the other had pure colonic lesion. One patient had ulcers in both ileum and colon. Biopsies from Ileum and colon were done in all patients and they revealed acute and chronic inflammation. No granuloma was identified. All specimens were negative for inclusion body and *Mycobacterium tuberculosis* (by polymerase chain reaction).

Despite, an intravenous dexamethasone 5 mg was given at every 6 h for 3-5 d, all patients still had persistent hematochezia. Their mean Hb level dropped from 12 ± 1.3 g/dL to 8.7 ± 1.3 g/dL in a 3-d period. Median packed red blood cells units needed for resuscitation was 4 units. Because of uncontrolled bleeding, surgical resection was considered. Due to the poor surgical candidacy of these patients (n = 3) and/or possible development of short bowel syndrome (n = 6), surgery was not pursued. Likewise angiographic embolization was not considered in any due to the risk of large infarction from multiple areas of embolization. Then infliximab (5 mg/kg) was infused instead. Infliximab rapidly stopped bleeding definitely within 24 h in 6 patients. Another patient developed recurrent bleeding after 3 d of the first dose of infliximab. Subsequently, bleeding ceased promptly after the second dose of infliximab that administered at day tenth. Median doses of infliximab were two. All underwent a follow-up ileo-colonoscopy that revealed a significant improvement of ileal and colonic ulceration (Figures 1 and 2). At the 30-d follow up, no patients reported recurrent bleeding.

DISCUSSION

In our case series, we identified CD patients with severe GIB presented as either the first manifestation or a flare up of disease. None of our patients had histories or findings suggestive of NSAIDs induced ulcers or Behçet' s disease. The common location of ulcers in our series involved ileum, ileocolic region, colon and a combination of all areas. The most common endoscopic findings were extensive multiple deep ulcers with or without active oozing. Infliximab was used as a last resort for controlling bleeding after failure of standard treatments. In fact, surgical treatment was considered in all cases, but it was not opted as mentioned earlier. Almost all patients responded promptly within 24 h after a single dose of infliximab. Only one patient with ileocolonic CD needed the second dose to achieve definite hemostasis after the recurrent bleeding.

Management of severe GIB in CD is problematic since there are multiple lesions with the possibility of bleeding from multiple sites. Endoscopy should be attempted in all patients, but only a quarter of patients that the bleeding sites could be precisely identified[3]. Medical therapies such as steroids, azathioprine and mesalamine also have been reported to control bleeding, but the prompt response is uncertain. Surgical resection is also a crucial therapy[4-6]. Recurrent bleeding was significantly lower in surgically treated patients (5.7%) compared with medically treated patients (38.5%). However, there is a significant rate of post operative and perioperative mortality at 6.9%[7]. In addition, the risk of developing short bowel syndrome after resection should be considered because these patients may have an extensive small bowel involvement[8-10]. Radiological intervention, one of the alternative treatments for small bowel bleeding[11], can accidentally contribute to small bowel infarction after multiple area of embolization. From those five series reported on GIB related to CD (n = 101), an angiographic embolization

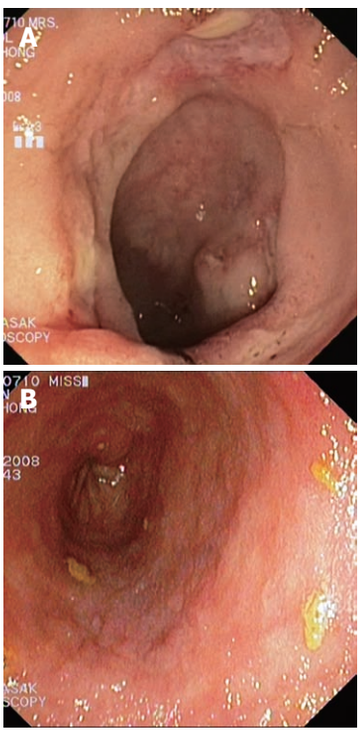

Figure 1 Deep ileal ulcer (A) and completely healed ileal ulcer 6 wk after infliximab (B).

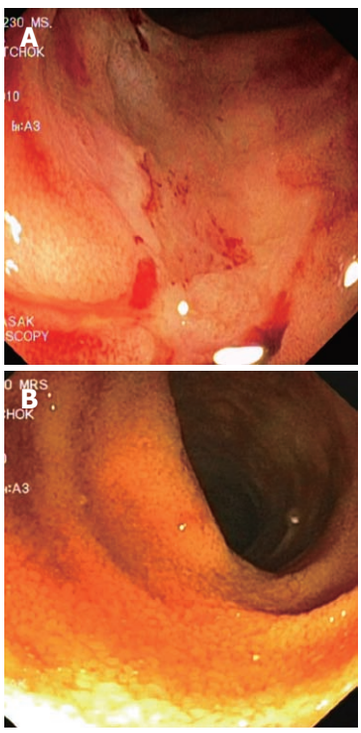

Figure 2 Ileal ulcer with hemoclips (A) and healing ileal ulcer 6 wk after infliximab (B). Note the clips still presented.

Table 1 Clinical characteristics and outcomes of infliximab treatment in 2 Crohn's disease patients with severe gastrointestinal bleeding as a flare-up disease

No.	Age (yr)	Sex	Duration of CD	Location	Current treatment	Presenting symptom	Dropped rate of Hb (g/dL)	PRBC (unit)	Characteristic of lesion	Infliximab therapy	Bleeding controlled in	Follow-up (mo)
1	11	F	2 mo	Colon	Prednisolone 35 mg/d azathioprine	GIB (1 d)	from 11 to 8 in 3 d	4	Multiple deep colonic ulcers without oozing	Infliximab 5 mg/kg (single dose)	1 d	12
2	19	F	7 mo	Ileocolon	Budesonide 9 mg/d 5-ASA	GIB (1 d)	from 12 to 10 in 3 d	1	Multiple ileal and colonic ulcers with oozing	Infliximab 5 mg/kg (d0, d10)	10 d	10

CD: Crohn's disease; GIB: Gastrointestinal bleeding; Hb: Hemoglobin; 5-ASA: 5-aminosalicylates; PRBC: Packed red blood cell; F: Female.

Table 2 Clinical characteristics and outcomes of infliximab treatment in 5 Crohn's disease patients with severe gastrointestinal bleeding as a first presentation

No.	Age (yr)	Sex	Presenting symptom	Dropped rate of Hb (g/dL)	PRBC (unit)	Location	Characteristic of lesion	Infliximab therapy	Bleeding controlled in	Follow-up (mo)
1	59	M	Diarrhea and abdominal pain (10 d) GIB (1 d)	from 10 to 8 in 3 d	6	Ileum	Multiple ileal ulcers with oozing and one visible vessel	Infliximab 5 mg/kg (d0, week 2)	1 d	24
2	86	M	GIB (1 d)	from 12 to 8.5 in 4 d	7	Ileum	Multiple ileal ulcers with oozing	Infliximab 5 mg/kg (d0, week 2)	1 d	36
3	71	F	Diarrhea and abdominal pain (10 d) GIB	from 13 to 10 in 3 d	3	ileum	Multiple ileal ulcers with oozing	Infliximab 5 mg/kg (d0, week 2)	1 d	12
4	50 yr	F	Diarrhea and abdominal pain (14 d) GIB (1 d)	from 14 to 10 in 3 d	2	Ileum and jejunum	Multiple ileal and jejunum ulcers with oozing	Infliximab 5 mg/kg (d0, week 2)	1 d	36
5	71 yr	M	1st episode GIB from ileal ulcer (1 mo) Recurrent GIB (1 d)	from 11 to 6.5 in 5 d	6	Ileum	Multiple ileal ulcers with oozing and one visible vessel	Infliximab 5 mg/kg (single dose)	1 d	24

CD: Crohn's disease; GIB: Gastrointestinal bleeding; Hb: Hemoglobin; 5-ASA: 5-aminosalicylates; PRBC: Packed red blood cell; M: Male; F: Female.

Table 3 Successful control severe lower gastrointestinal bleeding in Crohn's disease with infliximab

Study	Sex	Age (yr)	Location	Duration of disease	Current treatment	Presenting symptom	PRBC (unit)	Characteristic of lesion	Infliximab therapy	Bleeding controlled in	Follow-up (mo)
Belaihe *et al*[26], 2002	F	28	Ileocolon CD	3 yr	Budesonide azathioprine	Lower GIB	5	Multiple deep ulcers at colon without bleeding stigmata	Infliximab 5 mg/kg (d0, week 2, week 6)	14 d	5
	F	59	colon CD	9 yr	Prednisolone, metronidazole, ciprofloxacin	Lower GIB	4	Multiple deep ulcers at colon without bleeding stigmata	Infliximab 5 mg/kg (single dose)	4 d	4
Papi *et al*[7], 2003	M	50	Ileocolon CD S/P resection and ileocolonic anastomosis due to bleeding	9 mo	Prednisolone azathioprine	Lower GIB with hypovolumic shock	NA	Deep ulcers at ileocolon anastomosis without bleeding stigmata	Infliximab 5 mg/kg (d0, week 2, week 6)	NA	12
	M	68	Ileum CD S/P ileal resection due to stricture	24 yr	Mesalamine	Melena	4	Large ulcer at ileocolon anastomosis without bleeding stigmata	Infliximab 5 mg/kg (d0, week 2, week 6)	NA	3
Tsujikawa *et al*[25], 2004	M	31	Ileocolon CD S/P ileocolectomy due to ulcer bleeding	12 yr	Salazosulfapyrimidine	Lower GIB	NA	Multiple ulcers at ileocolon anastomosis and ileum without bleeding stigmata	Infliximab 5 mg/kg (d0, week 2, week 6)	NA	4
Ando *et al*[22], 2009	F	16	Colonic CD	1 yr	Mesalamine prednisolone	Lower GIB with hypovolumic shock	6	Multiple deep ulcers at colon with diffuse mucosal inflammation without bleeding stigmata	Infliximab 5 mg/kg (d0, week 2, week 6)	3 d	12
Meyer *et al*[24], 2009	F	19	Ileocolonic CD	6 yr	Mesalamine prednisolone	Lower GIB with hypovolumic shock	4	Multiple ulcers at terminal ileum without bleeding stigmata	Infliximab 5 mg/kg (d0, week 2, week 6)	NA	6
Julián Gómez *et al*[23], 2010	M	44	Ileocolon CD S/P total colectomy with ileostomy due to toxic megacolon	NA	NA	Postop small bowel resection due to obstruction bleeding	10	Multiple deep ulcers at small bowel without bleeding stigmata	Infliximab 5 mg/kg (d0, week 2, week 6) and maintenance dose	5 d	3
Alcalde Vargas *et al*[21], 2011	M	27	Ileocolon CD	2 yr	Mesalamine	Massive lower GIB	8	Multiple ulcers entire colon and abundant dark red blood at terminal ileum	Infliximab 5 mg/kg (single dose)	4 d	NA
	F	36	Colon and perianal CD	NA	Amoxicillin-clavulanate metronidazole	Massive lower GIB	12	Multiple deep ulcers entire colon and blood clots	Infliximab 5 mg/kg (single dose)	6 d	NA
	M	24	Colon CD	1 mo	Prednisolone	Massive lower GIB	5	Multiple deep ulcers entire colon and spontaneous bleeding mucosa	Infliximab 5 mg/kg (single dose)	4 d	NA

CD: Crohn's disease; GIB: Gastrointestinal bleeding; PRBC: Packed red blood cell; M: Male; F: Female; NA: Not available.

was attempted only in one patient[1-3,12,13]. Unfortunately, that such patient subsequently necessitated surgery due to small bowel infarction after an ileocecal artery embolization[3]. Angiography with intra-arterial vasopressin infusion in case where embolization is not possible has previously been proven to be successful in two CDs related GIB[14,15]. However, many side effects and complications could develop from this technique including hypertension, coronary vasoconstriction, cardiac arrhythmia, and bowel infarction. To decrease the risk for bowel infarction, it is advisable to use superselective angiographic embolization[16]. Although the risk of bowel infarction may be decreased, this serious complication cannot be ignored. In experienced centers, bowel infarction still developed in 5%-24% of lower GIB patients who treated with superselective mesenteric arterial embolization[17,18].

The pathogenesis of hemorrhagic type CD remains unclear. One possible hypothesis is transmural inflammations leading to mucosal ulcers erode to blood vessels. On endoscopic examinations, all of our patients had diffuse deep ulcers and majority of them (86%) had active oozing. Since severe hemorrhage usually develops from ulcers eroding into blood vessels, any treatment that can rapidly heal the mucosa is an ideal therapeutic tool to control and prevent recurrent hemorrhage. Anti-TNF-α (infliximab) has been shown to induce rapid mucosal healing[19,20]. Therefore, infliximab has a possible role in treating severe hemorrhagic CD. Moreover, the identification for precise bleeding site is not required since infliximab can systematically heal multiple small bowel ulcers.

To date, eleven CDs related GIB treated with infliximab from the seven series has been reported (Table

3)[7,21-26]. Severe hematochezia was presented in eight flare-up CD patients and the other three presented with hematochezia as their initial CD manifestation. Four patients previously had undergone for surgical treatment including ileocolectomy and total colectomy[7,23,25,26]. Colon and ileocolon were the most common locations of GIB. Ileocolonoscopy showed multiple discrete deep ulcers in all. Majority of patients had more than one potential site of bleeding[7,21-26]. The high risk bleeding stigmata was found in only one patient that presented with diffuse spontaneous mucosal bleeding[21]. One patient underwent a total colectomy and small bowel resection, but the bleeding recurred[23]. No patient underwent angiographic therapy. Infliximab was administered as a last resource for uncontrolled bleeding. Most of patients responded to the first dose of infliximab. Only one patient required the second dose of infliximab on day fourteenth to control recurrent bleeding[26]. Six patients received three doses of infliximab and another five received only a single dose of infliximab. Maintenance with infliximab was considered only in one patient[23]. Surgery was not pursued in any[4,15-20].

To our knowledge, we report the largest cases series of severe GIB in CD in which infliximab had been used. Infliximab was able to control hemostasis as a result of rapid ulcer healing. Definite hemostasis was achieved after the first or second dose of infliximab. Nevertheless, more further prospective studies are required to confirm the utilization of infliximab for severe GIB in CD.

In conclusion, infliximab may be a good alternative treatment to control severe bleeding related to small bowel and colonic ulcers in active CD especially in patients with high risk for surgery and/or high risk to develop a short bowel syndrome.

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