Thalidomide as rescue therapy for acute severe ulcerative colitis

A. DIAMANTI, D. KNAFELZ, F. PANETTA, P. DE ANGELIS[1], M. CANDUSSO, F. BRACCI, B. PAPADATOU, P. FRANCALANCI[2], L. MONTI[3], G. TORRE

Gastroenterology and Nutrition Unit, "Bambino Gesù" Children Hospital, Rome, Italy
[1]Digestive Surgery and Endoscopy, "Bambino Gesù" Children Hospital, Rome, Italy
[2]Units of Pathology Molecular Medicine and Neurosciences Hepatic Surgery, "Bambino Gesù" Children's Hospital, Rome, Italy
[3]Department of Radiology, "Bambino Gesù" Children's Hospital, Rome, Italy

Abstract. – INTRODUCTION: Acute severe exacerbations of Ulcerative Colitis (UC) represent a medical emergency in children and adults. Intravenous steroids remain the first line therapy for this condition, although the steroid refractoriness is common. Second-line therapy, based on the infliximab or thiopurines should be started if no response to corticosteroids is noted. The use of infliximab in children with acute severe UC, nevertheless, does not avoid the colectomy in all cases.

METHODS: We present a case of severe acute UC in a paediatric patient successfully treated with thalidomide following the failed treatment with infliximab and a review of the literature.

CONCLUSIONS: This is the first case of a patient presenting with acute severe UC who was treated with thalidomide, with favorable evolution. In our case the use of this drug was able to avoid the colectomy that represent the conventional but very invasive recommended therapeutic option of this condition. Therefore, thalidomide may be considered as rescue therapy in selected and carefully monitored cases of acute severe CU.

Key Words:
Severe acute ulcerative colitis, Thalidomide, Infliximab, Basiliximab, Cyclosporine, Children.

Introduction

Acute severe exacerbations of Ulcerative Colitis (UC) represent a medical emergency in children and adults[1]. Intravenous steroids remain the first line therapy for this condition[1]. Nevertheless, steroid refractoriness is common, making early recognition of acute severe exacerbation important, so that appropriate medical and, if necessary, surgical treatment can be provided in a timely kind to minimize morbidity[1]. Second-line therapy, based on the infliximab or thiopurines should be started if no response to corticosteroids is noted[1]. The use of infliximab in children with acute severe UC, nevertheless, does not avoid the colectomy in all cases. We report a case in which thalidomide was used as rescue medical third therapy in a patient who failed infliximab therapy for acute severe UC.

Case Report

A 12.5-year-old adolescent female presented with a seven-day history of more than ten large volume bloody diarrhea per day. She experiences also colicky abdominal pain, vomiting, worsening fatigue and weight loss (about 2.5 kg since the symptoms onset). She was, therefore, admitted for a suspected onset of an inflammatory bowel disease (IBD). Her initial bloodwork showed reduced level of hemoglobin, raised inflammatory markers (CRP, ESR and platelets) and fecal calprotectin and positive pANCA. Stool cultures and stool test for Clostridium difficile toxins A and B were all negative. Abdominal radiography excluded colonic dilatation and silent perforation.

Transabdominal ultrasound showed an increased bowel wall thickness (small bowel and colon) with associated lymphatic hyperplasia.

For the suspected IBD the patient underwent upper and lower GI endoscopy. Endoscopic findings revealed ulcers and erythema in the stomach, erythema in the duodenum, pseudopolyps in the colon and stenosis in the ileo-cecal valve, that impeded the intubation of the terminal ileum. Histological features were according to an acute colonic inflammation and to a chronic gastritis, without abnormalities suggesting Crohn's Disease (CD) or UC. The ultrasound findings, the

Corresponding Author: Antonella Diamanti, MD; e-mail: diamanti@opbg.net

blood and stool examinations and the involvement of the upper gastrointestinal tract led us to conclude that she was affected by a subtype of IBD suggesting the CD and, therefore, she started mesalazine (50 mg/kg), oral prednisolone (2 mg/kg) and azathioprine (2 mg/kg) that determined some beneficial effects (increased weight, reduced volume and blood in the stool). The patient was discharged although nocturnal diarrhea and hematochezia persisted. Two weeks later, at the first follow up after the discharge, she presented with patent bloody diarrhea. Then the patient was ever readmitted two days later due to the severe re-exacerbation of the symptoms, with bowel movement frequency >12/day, bloody diarrhea, colicky abdominal pain, vomiting and weight loss. Intravenous prednisolone and metronidazole were started without beneficial effects on the symptoms. The abdominal radiograph showed a paucity of bowel gas in all the colon. Upper and lower endoscopy were repeated. Upper endoscopy revealed only a mild gastric erythema. The colonscopy showed diffuse and continuous mucosal inflammation involving the rectum, without terminal ileum involvement. Mucosa was easy bleeding when touched by endoscope and it showed loss of vascular pattern and diffuse small superficial ulcers (Figure 1A). Histology of the colon specimen confirmed acute UC with inflammation of the mucosa and crypt abscesses throughout. Magnetic resonance imaging and capsule endoscopy were also performed, but did not show features suggesting for CD. As a result of all the above findings, we started infliximab therapy at 5 mg/kg, after we had suspended azathioprine. The PUCAI index was 65. Since the first infusion, although the bowel movement frequency decreased, she was still having six to seven bowel movements per day with more than 50% of stools that were bloody. The PUCAI index dropped at 50. Based on this partial response, we scheduled the further infliximab infusions at higher dose (10 mg/kg), one and two weeks later. The patient experienced at the third infliximab infusion an anaphylactic reaction, that required the infusion's suspension.

Meanwhile her symptoms deteriorated and she was passing liquid blood-stained stools ten times per day. On examination, she was distressed, apyrexial and appeared anemic. Parenteral nutrition by a central venous catheter was started; within a few days, her hemoglobin dropped and she required transfusion. The PUCAI index increased at 65.

After a frank discussion with the parents and the patient about the available options, represented by the colectomy and by the unconventional medical therapy by thalidomide or basiliximab, both used in previous cases of UC refractory to conventional therapy, they decided to try medical therapy once more before deciding for the colectomy. The previous treatment by infliximab, led us to choice the thalidomide in this patients. Therefore, patient and family were fully informed about the potential side effects of this therapy (teratogenicity, peripheral neuropathy, drowsiness and rash). A written consent to the treatment was obtained from the parents. Thus, the patient was enrolled in the program of the Italian Ministry for Health for the control of the use of the thalidomide. A detailed neurologic examination including responses to vibration and pin-prick tendon reflexes and nerve conduction studies (electromyography) were performed before starting thalidomide. A baseline complete evaluation of the coagulation assessment was also performed. Thalidomide was started at 50mg/day and continued at 50 and 100 mg every other day. The patient's symptoms resolved at this dosage, with initial improvement of abdominal pain and diarrhea between 1 and 2 weeks and complete remission of the symptom at 1 months of the therapy. The last colonscopy (Figure 1B) reveales maintained vascular pattern without mucosal inflammation and scar tissue in ascending colon and cecum. Histological findings resulted according to a quiescent UC. The PUCAI when she was submitted to the second colonscopy was 5. Therefore, we decreased the dosage of thalidomide at 50 mg/day. At the current time, nine months after starting thalidomide, the patient is asymptomatic, has 2-3 regular bowel movements/day, without blood or mucus. He denies abdominal pain, nausea, and vomiting and complaint of neuropathy. Her weight increased by 9 kg. Laboratory test shows normal inflammatory activity (CRP, ESR, calprotectin, platelet and hemoglobin within the normal range). The patient was continuously monitored since the discharge by clinical and biochemical evaluations performed every week during the first three months and every month up to the last follow up.

Discussion

Thalidomide has re-emerged as an anti-inflammatory and immunosuppressive drug. The effects
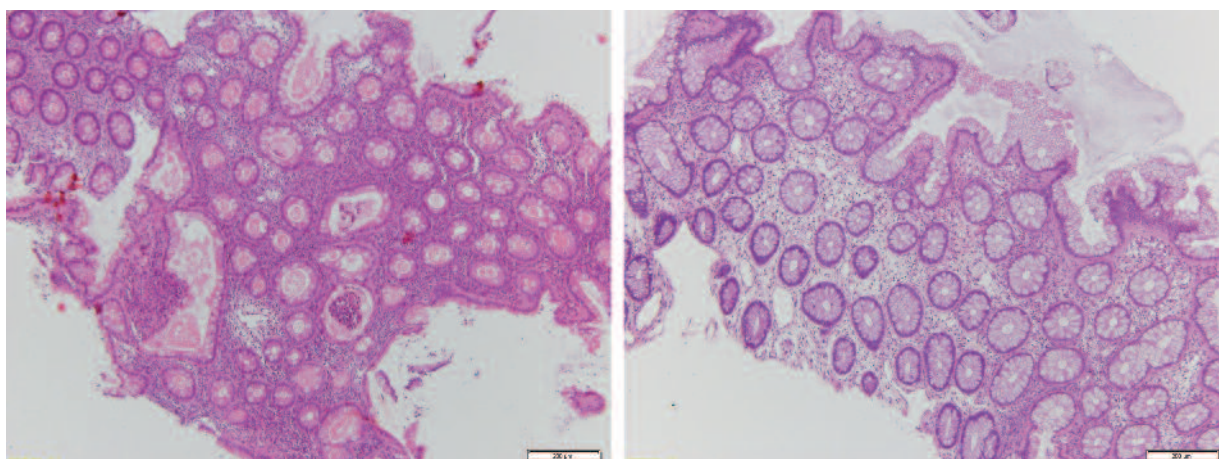
Figure 1. A, Active ulcerative colitis. There is active chronic on inflammation with crypt abscesses and early crypt rupture. Crypt epithelium is attenuated with goblet cell depletion. HE, 10x. **B,** Resolved ulcerative colitis with no evidence of previous damage. The goblet cell population is recovering. Mild oedema of the lamina propria. HE, 10x.

of thalidomide relate, in part, to the down-regulation of TNF-α, and the inhibition of angiogenesis[2]. It also inhibits NFκB activity, and suppresses IL-12[3,4]. This drug has been used mainly in CD[5]. Only a previous Italian survey[6] reported the use of this drug in UC patients. In this study Lazzerini et al found that 5 out of the 9 UC patients enrolled, affected by mild-moderate activity and not responder to steroids, thyopurine and infliximab, achieved the remission by thalidomide. In this survey, nevertheless, patients with severe fulminant disease in imminent need of surgery were excluded.

Therefore, this is the first reported case of using thalidomide as rescue medical therapy from the surgery due to the failure of infliximab therapy. The patient responded with rapid clinical improvement over 4 weeks and she did not relapse after 6 months since the thalidomide starting. Acute severe UC may represent a relevant medical emergency at pediatric age, and intravenous corticosteroids represent the first line therapy for it[1]. The steroid refractoriness rate in acute severe UC is 34%[7,8]. For pediatric patients failing intravenous corticosteroids a second line therapy should be approached before indicate the surgery. In this cases, indeed, the use of either calcineurin inhibitors or infliximab (if an adequate previous trial of thiopurine failed) is recommended, as second line therapy[1]. However, the failed response to infliximab therapy, as seen in our case, is not rare in children and adolescents: although the colectomy, indeed, declined since the use of infliximab, the short-term and 1-year colectomy rates after infliximab

therapy seem to be 9% and 19% respectively[9]. Patients positive to pANCA, as in our case, seem to be at risk of a suboptimal response to infliximab, according to that reported in adults[10]. If the second line therapy fails, sequential therapy (calcineurin inhibitor following infliximab or *viceversa)* is not recommended. Therefore, in our patient we had two options: the conventional surgery or the attempt of unconventional medical therapy, as strongly required by parents and patient, who refused the colectomy. In literature basiliximab and thalidomide have been reported in the cases of severe UC refractory to other conventional therapies. The successful use of basiliximab has been reported in 4 children poorly responsive to combined therapy with intravenous steroids and calcineurin inhibitors, but not previously treated with infliximab[11]. Thus, we decided to begin the thalidomide according to the previously reported Italian survey, in which the use of thalidomide followed that of infliximab, with continuous clinical and biochemical monitoring over the time. The patient did not show any side effects of thalidomide until now and she is continuing at 50 mg/day. We have scheduled a further colonscopy at one year and the suspension of the thalidomide at 18-24 months since the beginning of this treatment, in absence of clinical and histological relapse of the disease, that will require the surgery. The maintenance therapy will be modulated on the results of the further endoscopic and histologic examinations and it may be based on mesalazine alone or mesalazine associated with azathioprine.

1692

Conclusions

To our knowledge, this is the first case report of a patient presenting with acute and severe UC who was treated with thalidomide, with favorable evolution. In our patient the use of this drug was able to avoid the colectomy that represents the conventional but very invasive recommended[1] therapeutic option of this condition. Therefore, thalidomide may be considered as rescue therapy in selected and carefully monitored cases of severe acute UC.

_____

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) TURNER D, TRAVIS SP, GRIFFITHS AM , RUEMMELE FM, LEVINE A, BENCHIMOL EI, DUBINSKY M, ALEX G, BALDASSANO RN, LANGER JC, SHAMBERGER R, HYAMS JS, CUCCHIARA S, BOUSVAROS A, ESCHER JC, MARKOWITZ J, WILSON DC, VAN ASSCHE G, RUSSELL RK; EUROPEAN CROHN'S AND COLITIS ORGANIZATION; PORTO IBD WORKING GROUP, EUROPEAN SOCIETY OF PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. Am J Gastroenterol 2011; 106: 574-588.

2) GINSBURG PM, DASSOPOULOS T, EHRENPREIS ED. Thalidomide treatment for refractory Crohn's disease: a review of the history, pharmacological mechanisms and clinical literature. Ann Med 2001; 33: 516-525.

3) BAUDITZ J, WEDEL S, LOCHS H. Thalidomide reduces tumour necrosis factor alpha and interleukin 12 production in patients with chronic active Crohn's disease. Gut 2002; 50: 196-200.

4) KEIFER JA, GUTTRIDGE DC, ASHBURNER BP, BALDWIN AS JR. Inhibition of NF-kappa B activity by thalidomide through suppression of IkappaB kinase activity. J Biol Chem 2001; 276: 22382-22387.

5) FELIPEZ LM, GOKHALE R, TIERNEY MP, KIRSCHNER BS. Thalidomide use and outcomes in pediatric patients with Crohn disease refractory to infliximab and adalimumab. J Pediatr Gastroenterol Nutr 2012; 54: 28-33.

6) LAZZERINI M, MARTELOSSI S, MARCHETTI F, SCABAR A, BRADASCHIA F, RONFANI L, VENTURA A. Efficacy and safety of thalidomide in children and young adults with intractable inflammatory bowel disease: long-term results. Aliment Pharmacol Ther 2007; 25: 419-427.

7) TURNER D, WALSH CM, STEINHART AH, GRIFFITHS AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a metaregression. Clin Gastroenterol Hepatol 2007; 5: 103-110.

8) TURNER D, GRIFFITHS AM. Acute severe ulcerative colitis in children: a systematic review. Inflamm Bowel Dis 2010; 17: 440-449.

9) TURNER D, MACK DR, LELEIKO N, WALTERS TD, UUSOUE K, LEACH ST, DAY AS, CRANDALL W, SILVERBERG MS, MARKOWITZ J, OTLEY AR, KELJO D, MAMULA P, KUGATHASAN S, HYAMS J, GRIFFITHS AM. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. Gastroenterology 2010; 138: 2282-2291.

10) FERRANTE M , VERMEIRE S , KATSANOS KH, NOMAN M, VAN ASSCHE G, SCHNITZLER F, ARIJS I, DE HERTOGH G, HOFFMAN I, GEBOES JK, RUTGEERTS P. Predictors of early response to infliximab in patients with ulcerative colitis. Inflamm Bowel Dis 2007; 13: 123-128.

11) NG SC, CHAN FK, SUNG JJ. Review article: the role of non-biological drugs in refractory inflammatory bowel disease. Aliment Pharmacol Ther 2011; 33: 417-427.