Cystic fibrosis and Crohn’s disease: Successful treatment and long term remission with infliximab

Francesca Vincenzi, Barbara Bizzarri, Alessia Ghiselli, Nicola de’ Angelis, Fabiola Fornaroli, Gian Luigi de’ Angelis

INTRODUCTION

The association of cystic fibrosis (CF) and Crohn’s disease (CD) is well known, but, to date, there are very few cases in the literature of patients suffering from mucoviscidosis who have required treatment with infliximab. We report the case of a 23-year-old patient suffering from cystic fibrosis and severe CD treated successfully with infliximab without any infective complications or worsening of the pulmonary disease and with a long term (2 years) complete remission.

© 2010 Baishideng. All rights reserved.

Key words: Cystic fibrosis; Crohn’s disease; Infliximab

Peer reviewers: Dr. Marco Scarpa, PhD, Department of Surgical & Gastroenterological Sciences (Gastroenterology section), University of Padova, via Giustiniani 2, Padova 35128, Italy; Stefan Riss, MD, Department of General Surgery, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

Vincenzi F, Bizzarri B, Ghiselli A, de’ Angelis N, Fornaroli F, de’ Angelis GL. Cystic fibrosis and Crohn’s disease: Successful treatment and long term remission with infliximab. World J Gastroenterol 2010; 16(15): 1924-1927 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i15/1924.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i15.1924
data is the fear that the immunosuppressive properties of such a biological treatment would be contraindicated by the characteristic infections in CF; especially of the lung.

We report the case of a 23-year-old patient suffering from CF and severe CD who was treated successfully with infliximab and who is in long term remission.

CASE REPORT

This is a report of the case of a 23-year-old female suffering from CF who, from the age of 16 years, started having recurrent abdominal pain associated with weight loss. She was regularly followed up by a centre for CF.

At the age of 14 years, she underwent explorative laparotomy with appendicectomy for suspected acute abdomen. The operation was complicated by the appearance of a cutaneous fistula at the site of the surgical wound. Because of persistence of symptoms associated with severe deterioration of nutritional condition, she was sent to our centre. A low digestive endoscopy carried out at our unit showed a condition of acute pancolitis compatible with chronic inflammatory bowel disease. The histological examination of the multiple biopsies taken confirmed the suspected diagnosis of CD.

An induction treatment cycle with prednisone, full dose for 4 wk, with mesalazine and metronidazole was initiated. Having obtained clinical and endoscopic histological remission, we reduced the prednisone dose, stopped metronidazole and continued maintenance treatment with mesalazine. The patient continued treatment with mesalazine alone with good clinical progress for about four years during which she did not come to us for check-ups but preferred to go to the hospital in her city of residence.

In 2003, she underwent emergency laparotomy at another centre following the appearance of acute abdomen. Surgery showed a pericolic abscess collection in the cecum and ascending colon; she was then subjected to ileocecal resection and ileotransverse colonic anastomosis. The working of the lungs was kept stable during exacerbation), but she developed chronic exacerbation of her disease. The CD activity index (CDAI) was 390. Index values of 150 and below are associated with quiescent or non-active disease (i.e. “remission”); values over 150 are indicative of active disease, and over 450, extremely severe disease[5]. Total parenteral nutrition was therefore started with complete suspension of fractionated feeding by oral administration and medical treatment was resumed (cortisone, metronidazole as antibiotic and mesalazine as anti-inflammatory).

Due to the steroid therapy, fasting blood glucose pathologically increased (320 mg/dL) and therefore subcutaneous insulin therapy was started with an improvement of glucose intolerance.

Endoscopic histological examination performed after a short time (4 wk), showed only modest improvement of the lesions found earlier during the endoscopic examination, despite improvement of the general condition.

Because of the severity of the lesions, particularly of the anus, and after informing the patient and the pneumologists, we decided to start a biological treatment cycle with infliximab in addition to treatment with azathioprine (AZA) (2.5 mg/kg per day) in a single administration in the morning, associated with antibiotic treatment with 3rd generation cephalosporin and glycopeptide. The infusions of infliximab can be superimposed with this treatment regime, which is used in our centre, with an initial treatment at 0, 2, and 6 wk, followed by a maintenance phase with infusions every 8 wk.

At the discontinuation of steroids, insulin therapy was no longer necessary.

After the first three intravenous infusions of infliximab, endoscopic examination showed complete regression of anal lesions and distinct improvement of the lesions of the sigmoid rectum, with healing appearance of the mucosa and no continuous lesions up to the ileocolic anastomosis.

The appearance of the ileum, explored to about 40 cm, was within acceptable limits. Nine months after beginning the treatment and after 7 infusions of infliximab, the patient showed distinct improvement in her general condition and body weight increased by 13 kg.

Twelve months after commencement of the treatment, condition continues to be optimal and there has been no complication involving infection in the lung or septic episodes. The working of the lungs was kept stable during...
the course of treatment with infliximab (forced expiratory volume in 1 s (FEV1) 85% in April 2006 and FEV1 80% in July 2007), without any pulmonary exacerbations.

Suspension of the biological treatment was therefore programmed after the 10th infusion, while treatment with AZA and mesalazine as maintenance continued. Since the last infliximab infusion two years have passed and a complete remission of CD has been maintained both clinically and endoscopically (Figure 2).

DISCUSSION

This report deals with the case of a patient suffering from CF who, at the age of 16 years, was diagnosed as suffering from CD. The literature reports frequent cases of CD during the course of CF. The prevalence is about 17 times greater than that of controls[8]; this shows that there is a pathogenic relationship between the two diseases. The etiopathogenesis has not yet been identified but a number of mechanisms have been proposed, the most probable of which is an altered immune response to a chronic infection[4]. Furthermore, patients who are carriers of the AF 508 mutation seem to have increased risk of developing gastrointestinal problems[9].

The literature contains case reports of diagnosis of CD in patients suffering from CF who complain of long periods of abdominal pain and most of all, loss of weight, in spite of appropriate nutritional and therapeutic support[8]. As in the case of our patient, protracted gastrointestinal symptoms and lack of response to basic treatment make it necessary to conduct instrumental examinations, in particular endoscopic examinations such as gastrocopy and colonoscopy, associated with perendoscopic biopsies, which allow a differential diagnosis between CD and fibrosing colonopathy[7,8]. This has led, in the last few years, to an increase in the diagnosis of CD during the course of CF[7], which was not suspected in the past. The aim of treatment during the course of CD is to induce and maintain remission of the disease. Corticosteroids have demonstrated a high efficiency in inducing clinical remission in patients with moderate to severe forms of disease[8,9]. In order to maintain the remission and to reduce the risk of dependence on corticosteroids, there is general agreement regarding the early introduction of immunosuppressants such as AZA, MTX, 6 mercaptopurine (MP) and also infliximab[11-13]. In the case of our patient, given the modest clinical and endoscopic response after one month of treatment with steroids, this therapeutic opportunity was also discussed with the pneumologists. Biological treatment with infliximab associated with AZA was therefore started, because of the presence of significant anal lesions, although the literature currently contains few case reports of patients suffering from CF treated with infliximab. However, numerous studies have shown the efficacy of infliximab in inducing or maintaining remission of disease in adults suffering from CD who have moderate-severe forms, with perianal localization or with fistulizing forms[18,19]. In patients with CF the presence of bronchiectasis and colonization with Pseudomonas, as in our patient, would normally represent a relative contraindication to the administration of infliximab, but numerous studies of bronchoalveolar lavage fluid from patients with CF have shown a high concentration of inflammatory mediators such as tumor necrosis factor α (TNFα)[18]. Indeed, drugs such as azithromycin ameliorate lung function in cystic fibrosis patients while also reducing the levels of TNFα[19].

In our experience with this patient, we observed a significant clinical improvement even after the first dose. This improvement was endorsed by the resolving of endoscopic and histological lesions, as is also reported in the literature[20,21]. The association of infliximab with AZA was justified by the fact that concurrent treatment with AZA, 6 MP or MTX may be helpful in maintaining the clinical response to infliximab, reducing the amount of circulating antibodies directed towards the latter; which are thought to be responsible for some cases of non-response[22,23].

As shown in the literature[18,19], as well as in the case of our patient, the moment a treatment focused for CD was introduced, although not free of risks, a distinct improvement of the general condition was observed with weight increase of about 13 kg. After over 12 mo of treatment with infliximab and AZA, no pulmonary complication which would have compelled suspension of treatment was observed. In addition, the literature shows that no severe adverse events have occurred and that there was no reported increase in the prevalence of respiratory tract infections during infliximab administration in patients with chronic obstructive pulmonary disease[20].

The main questions arising from treatment with infliximab in this patient were, firstly, the possibility that the biological treatment could increase susceptibility to infections by opportunistic pathogens given the concurrent basic lung disease, since patients with cystic fibrosis already spontaneously suffer from such infections. Moreover, the infections most frequently reported during infliximab infusions are respiratory tract infections and urinary tract infections (35% infliximab-treated patients vs 25% placebo recipients)[27].

Secondly, given the excellent clinical, endoscopic, and histological progress of the patient, there was doubt regarding the best moment for suspension of the drug.
especially taking into consideration the possibility of causing allergies or reduced efficacy in case of re-treatment because of the possible presence of antibodies against infliximab.\cite{1,2,22,23,26,29}

As regards the first challenge, the constant cover with antibiotic treatment was found to be effective in keeping the lung disease under control, as it did not worsen but rather remained stable as is shown by the spirometry tests taken during the course of immunosuppressive treatment.

As regards suspension of treatment, in the absence of precise bibliographic guidance, we believed that it was appropriate to suspend treatment in accordance with previously reported data after a period of not less than one year.\cite{1}

REFERENCES

1 Chaudry G, Navarro OM, Levine DS, Oudhjane K. Abdominal manifestations of cystic fibrosis in children. Pediatr Radiol 2006; 36: 233-240
2 Fields TM, Michel SJ, Butler CL, Kriess VM, Albers SL. Abdominal manifestations of cystic fibrosis in older children and adults. AJR Am J Roentgenol 2006; 187: 1199-1203
3 Dobbin CJ, Moriarty C, Bye PT. Granulomatous diseases in a patient with cystic fibrosis. J Cyst Fibros 2003; 2: 35-37
4 Lerner A, Gal N, Mares AJ, Maor E, Iancu TC. Pitfall in diagnosis of Crohn's disease in a cystic fibrosis patient. J Pediatr Gastroenterol Nutr 1991; 12: 369-371
5 Lloyd-Still JD. Crohn's disease and cystic fibrosis. Dig Dis Sci 1994; 39: 880-885
6 Baxter PS, Dickson JA, Variend S, Taylor CJ. Intestinal disease in cystic fibrosis. Arch Dis Child 1988; 63: 1496-1498
7 Modolelli I, Alvarez A, Guarner L, De Gracia J, Malagelada JR. Gastrointestinal, liver, and pancreatic involvement in adult patients with cystic fibrosis. Pneumon 2001; 22: 395-399
8 Lowe ME, Ameen N, Freedman S, Mulberg AE, Warner SL. Research agenda for pediatric gastroenterology, hepatology and nutrition: cystic fibrosis and pancreatic diseases. Report of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition for the Children's Digestive Health and Nutrition Foundation. J Pediatr Gastroenterol Nutr 2002; 35 Suppl 3: S258-S262
9 Hyams JS, Markowitz JF. Can we alter the natural history of Crohn disease in children? J Pediatr Gastroenterol Nutr 2005; 40: 262-272
10 Travis SP, Stange EF, Lémann M, Oreslund T, Chowers Y, Forbes A, D'Aëns G, Kitis G, Cortot A, Prantera C, Marteau M, Mortensen NJ. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. Gut 2006; 55 Suppl 1: i66-i135
11 Markowitz J, Grainger K, Kohn N, Daum F. Immunomodulatory therapy for pediatric inflammatory bowel disease: changing patterns of use, 1990-2000. Am J Gastroenterol 2002; 97: 928-932
12 Jacobstein DA, Mamula P, Markowitz JE, Leonard M, Baldassano RN. Predictors of immunomodulator use as early therapy in pediatric Crohn's disease. J Clin Gastroenterol 2006; 40: 145-148
13 Jaspers GJ, Venkade HJ, Escher JC, de Riedler L, Taminius JA, Rings E. Azathioprine maintains first remission in newly diagnosed pediatric Crohn's disease. Inflamm Bowel Dis 2006; 12: 831-836
14 Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braunak T, DeWoody KL, Schaible TF, Rutgeerts P, A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease CA2 Study Group. N Engl J Med 1997; 337: 1029-1035
15 Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Koznik JE, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350: 876-885
16 Hyams JS, Markowitz J, Wyllie R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. J Pediatr 2000; 137: 192-196
17 Baldassano RN, Braegger CP, Escher JC, DeWoody K, Hendricks DF, Keenan GF, Winter HS. Infliximab (REMCACE) therapy in the treatment of pediatric Crohn's disease. Am J Gastroenterol 2003; 98: 833-838
18 Casserly B, Donat W. Stabilization of lung function and clinical symptoms in a patient with cystic fibrosis (CF) after institution of infliximab: a monoclonal antibody that blocks tumor necrosis factor alpha. Lung 2009; 187: 149-152
19 Cigana A, Assael BM, Melotti P. Azithromycin selectively reduces tumor necrosis factor alpha levels in cystic fibrosis airway epithelial cells. Antimicrob Agents Chemother 2007; 51: 975-981
20 Borrelli O, Bascietto C, Viola F, Bueno de Mesquita M, Barba M, Mancini V, Bosco S, Cucchiara S. Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. Dig Liver Dis 2004; 36: 342-347
21 D’Haens G, Van Deventer S, Van Hogezaed R, Chalmers D, Kothe C, Baert F, Braunak T, Schaible T, Geboes K, Rutgeerts P. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology 1999; 116: 1029-1034
22 Baert F, Noman M, Vermeire S, Van Assche G, D’Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003; 348: 601-608
23 Miele E, Markowitz JE, Mamula P, Baldassano RN. Human antichimeric antibody in children and young adults with inflammatory bowel disease receiving infliximab. J Pediatr Gastroenterol Nutr 2004; 38: 502-508
24 Lémann M, Mary JY, Duclos B, Veyrac M, Dupas JL, Delchier JC, Laharie D, Moreau J, Cadiot G, Picon L, Bourrellé A, Sobhani I, Colombel JF. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. Gastroenterology 2006; 130: 1049-1061
25 Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. Am J Gastroenterol 2001; 96: 722-729
26 van der Vaart H, Koeiter GH, Postma DS, Kauffman HF, ten Hacken NH. First study of infliximab treatment in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005; 172: 465-469
27 Bionski W, Lichtenstein GR. Safety of biologic therapy. Inflamm Bowel Dis 2007; 13: 769-796
28 Rodrigo L, Pérez-Panflete JM, Fuentes D, Cadahia V, Garcia-Carbonero A, Niño P, de Francisco R, Tojo R, Moreno M, González-Ballina E. Retreatment and maintenance therapy with infliximab in fistulizing Crohn's disease. Rev Esp Enferm Dig 2004; 96: 548-554; 554-558
29 Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, Olson A, Bao W, Rutgeerts P. Incidence and importance of antibody responses to infliximab after maintenace or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2004; 2: 542-553
30 Behm BW, Dickson JA. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008; CD006893

S-Editor Wang JL, L-Editor Logan S, E-Editor Lin YP