

# Management of refractory fistulizing *pouchitis* with infliximab

A. VISCIDO, A. KOHN\*, C. PAPI\*\*, R. CAPRILLI

GI Unit, Department of Clinical Sciences, University "La Sapienza" – Rome (Italy)

\*GI Unit, San Camillo-Forlanini Hospital – Rome (Italy)

\*\*GI Unit, Department of Gastroenterology, San Filippo Neri Hospital – Rome (Italy)

**Abstract.** – This study provides the long-term follow-up data on the efficacy of infliximab in the treatment of chronic refractory pouchitis complicated by fistulae following ileo-pouch anal anastomosis (IPAA) for ulcerative colitis (UC).

**Methods:** Seven patients (4 F, 3 M) with chronic refractory pouchitis complicated by fistulae were included in an open study. Pouchitis was diagnosed by clinical plus endoscopic and histological criteria. Fistulae were: pouch-bladder in 1, vaginal in 3, perianal in 2, both vaginal and perianal in 1 patient. Extraintestinal manifestations were present in 4 patients. All the patients were refractory to antibiotics (3 patients also to steroids). Crohn's disease was carefully excluded in all patients after re-evaluation of the history, re-examination of the original proctocolectomy specimen, examination of the proximal small bowel. Patients received Infliximab 5 mg/kg at 0, 2 and 6 weeks. Azathioprine (2.5 mg/kg) was also started for all patients as bridge therapy. Clinical response was classified as complete, partial, and no response. Fistulae closure was classified as complete, partial, and no closure. The pouchitis disease activity index (PDAI) and quality of life (QoL) were also used as outcome measures.

**Results:** Clinically, all patients improved. At 10-week follow-up, 6 out of 7 patients had a complete clinical response, and 5 out of 7 patients had complete fistulae closure. At 10-week follow-up, median PDAI dropped from 12 (baseline) (range, 10-15) to 5 (range, 3-8); median QoL decreased from 37 (range, 33-40) to 14 points (range, 9-18), respectively. Extraintestinal manifestations (erythema nodosum and arthralgiae) completely remitted soon after the first infusion of infliximab. Clinical response and fistulae closure were maintained in the long-term follow-up.

**Conclusions:** These results seem indicate that infliximab plus azathioprine may be recommended for the treatment of refractory pouchitis complicated by fistulae following IPAA for UC.

## Key Words:

Ileo-pouch anal anastomosis (IPAA), Ulcerative colitis (UC), Pouchitis, Fistulae, Infliximab.

## Introduction

Ileal-pouch-anal anastomosis (IPAA) represents the surgical procedure of choice for patients with ulcerative colitis (UC) undergoing elective restorative proctocolectomy<sup>1</sup>. The most frequent long-term complication following IPAA is non-specific and idiopathic inflammation of the ileal mucosa of the pouch, commonly known as pouchitis<sup>2</sup>. Pouchitis is considered to be a recurrent UC in the small bowel mucosa, or a novel form of recurrent inflammatory bowel disease (IBD)<sup>2,3</sup>. The etiology is unclear, but it is generally accepted that bacterial overgrowth plays an important role, and that lesions and symptoms are associated with over-production of pro-inflammatory cytokines<sup>2-7</sup>.

Diagnosis is commonly obtained by means of clinical, endoscopic and histological criteria using the Pouchitis Disease Activity Index (PDAI), which also allows a severity score of pouchitis<sup>8,9</sup>.

The course of pouchitis is variable and is commonly classified as acute, relapsing, and continuously chronic<sup>7</sup>.

Therapy is based on the use of probiotics, antibiotics, mesalazine, corticosteroids, and immunosuppressants<sup>2,3,11,12</sup>. However, resistance to medical therapy is reported in 5-20% of the cases<sup>2,12</sup>.

Pouchitis lead, in about 10% of the cases, to the development of complications such as fistulae and perianal disease that require further surgery<sup>1,13,15-17</sup>.

Some authors consider the development of fistulae in patients with pouchitis a sufficient reason for changing diagnosis from UC to Crohn's disease (CD)<sup>18,19</sup>. We agree that appearance of perianal fistulae, especially if com-

plex and not originating from the dentate line area, should raise suspicion about the possibility of CD, and that in these conditions diagnosis has to be reconsidered<sup>1,2,13,20</sup>. However the diagnosis of CD needs the presence of positive criteria such as epithelioid granulomas, discontinuous crypt distortion, and discontinuous inflammation<sup>20-22</sup>. Absence of positive criteria for diagnosis of CD after re-examination of the original proctocolectomy specimen and investigation of the proximal small bowel indicates the diagnosis of pouchitis<sup>20,21</sup>.

Since infliximab has been successfully used for refractory patients with CD of the ileoanal pouch<sup>18,19</sup>, and since high tumor necrosis factor-alpha (TNF- $\alpha$ ) expression occurs in ileal mucosa during pouchitis<sup>4</sup>, the use of infliximab also in refractory pouchitis following IPAA for UC appears to be reasonable.

We recently reported the efficacy and safety of infliximab in the treatment of patients with chronic refractory pouchitis complicated by fistulae following IPAA for UC. In our series of 7 patients, the development of fistulae complicating pouchitis raised suspicion about the possibility of CD but this diagnosis was unequivocally excluded in all the patients. In fact, before surgery, all the 7 patients had clinical, radiographic, endoscopic and pathologic features typical of UC; the blind review of original proctocolectomy specimen confirmed the diagnosis of UC in all the patients; radio-

logical and endoscopic examination of the gastrointestinal tract distant from the pouch resulted to be normal; finally, endoscopic biopsies of pouch and pre-pouch mucosa did not contain positive features for CD<sup>23</sup>.

We report here the long-term follow-up results of the previously published study in which infliximab was used in patients with chronic refractory pouchitis, complicated by fistulae, following IPAA for UC.

## Materials and Methods

### Patients

Seven patients with chronic refractory pouchitis and fistulae were included in the study. Refractory pouchitis was defined as persistent active pouchitis unresponsive to continuous intake of antibiotics. Table I shows the demographic and clinical characteristics of the patients at the time of infliximab therapy. The median age of the patients was 30 years (range, 19-51 years). Four out of 7 patients were female. The median duration from UC diagnosis to IPAA was 4 years (range, 1-14 years). The indication for proctocolectomy was "refractory disease" in all cases. The constructed pouch had a J shape in 6, and a W shape in 1. The median time between IPAA and the diagnosis of pouchitis was 12 months (range, 6-36 months). The median time from

Table I. Characteristics of the patients at baseline, before treatment with infliximab.

Pts	Age (years)	Sex	Years from UC diagnosis to IPAA	Months from IPAA to pouchitis	Months from IPAA to fistulae	Previous treatments	PDAI	Fistulae	Extra intestinal manifestations
1	27	M	1	14	70	Antibiotics	10	Perianal	-
2	51	M	5	12	20	Antibiotics	12	Pouch-bladder	Arthralgiae
3	32	F	14	6	10	Antibiotics Steroids	10	Vaginal	Erythema nodosum
4	19	F	4	6	12	Antibiotics Azathioprine	10	Perianal Vaginal	-
5	25	M	2	8	37	Antibiotics	12	Perianal	-
6	30	F	2	13	20	Antibiotics Steroids	14	Vaginal	Arthralgiae Erythema nodosum
7	39	F	5	36	42	Antibiotics Steroids	15	Vaginal	Arthralgiae Erythema nodosum

IPAA and the development of fistulae was 20 months (range, 10-70 months).

The median PDAI was 12 (range, 10-15). The median QoL was 37 (range, 33-40).

All patients had actively draining fistulae for at least 3 months: 1 patient had a simple pouch-bladder fistula, 2 patients had a perianal complex fistula, 3 patients had a complex ano-vaginal fistula, 1 patient had both perianal and vaginal fistulae. Four patients had also extraintestinal manifestations: 1 male had arthralgiae, 1 female had erythema nodosum, and 2 females had both arthralgiae and erythema nodosum.

Serum perinuclear antineutrophil cytoplasmic antibodies (pANCA) were positive in 6 out of the 7 patients.

### **Diagnosis**

Development of fistulae led us to suspect underlying CD. In order to exclude CD, diagnosis in all patients was reconsidered according to standard criteria<sup>2,20-22</sup>. UC history, post-surgical course, and colectomy specimen were reviewed. In addition all patients underwent investigation of the remaining small bowel by means of endoscopy, histology and radiology. All patients were submitted to defecography.

As far as history concerns, all patients had clinical, radiological, endoscopical, and histopathological features diagnostic of UC. None out of the 7 patients had never smoked, and no patient had undergone appendectomy before colectomy. Blind pathological review of the colectomy specimens confirmed diagnosis of UC. Endoscopic and histologic examinations above the pouch excluded lesions high up in all patients. Small bowel follow-through resulted normal in all patients.

The careful investigation of the entire small bowel failed to show the presence of positive criteria for the diagnosis of CD. Diagnosis in all patients was therefore of UC pouchitis.

### **Previous Treatment**

All patients had been continuously treated with antibiotics (metronidazole and ciprofloxacin) for a median time of 4 months (range, 3-5). The 3 patients with erythema nodosum were also given steroids. Response to therapy was unsatisfactory in all patients.

### **Infliximab Treatment**

After giving informed consent and after being screened for tuberculosis, patients were

treated with infliximab (Remicade, Schering-Plough, Milan, Italy) administered in a dose of 5 mg/kg as a 2-hour intravenous infusion, at time 0, and thereafter at weeks 2 and 6. After the third infusion, patients were submitted to a retreatment schedule with infliximab reinfusion "on demand". Therefore, patients received a different number of infusions depending on the clinical response.

Adverse effects were regularly monitored during and after the infusions. From baseline, patients were clinically evaluated after 2, 6, 10 weeks and every 2 months since then. Patients underwent endoscopic and histologic examinations both at baseline and 10 weeks later.

### **Concurrent Treatment**

Azathioprine (2.5 mg/kg/day) was started for all patients at the time of the first infliximab infusion as bridge therapy.

### **Outcome Measures**

Response to therapy was assessed evaluating clinical response, pouchitis disease activity index (PDAI), fistulae closure, and health related quality of life (QoL).

Clinical response was classified into three categories: complete response, partial response, and no response. Complete response was defined to be as gained well-being and cessation of diarrhoea, urgency/incontinence, stool blood, abdominal pain. A partial response was defined as an improvement or reduction – not cessation though – of the symptoms as below. All other outcomes were defined as no response.

PDAI, based on clinical, endoscopical, and histological criteria was evaluated according to Sandborn criteria<sup>8</sup>. The PDAI score ranges from 0 to 18, the higher level indicating the worst inflammation. Based on Sandborn criteria, a total PDAI  $\geq 7$  score was considered the cut-off value to diagnose active pouchitis. Patients with a total PDAI score  $< 7$  were classified as not having pouchitis<sup>8,9</sup>.

Fistulae closure was classified into three categories: complete closure, partial closure, and no closure. Complete closure was defined as cessation of fistulae drainage and total closure of all fistulae. A partial closure was defined as a reduction in the number, size, drainage, or discomfort associated with the fistulae. No regression or worsening was defined as no closure.

QoL has been assessed using an Italian questionnaire derived from IBDQ for Italian

population<sup>24</sup>. The QoL score ranges from 0 to 87, the higher score indicating the worst function. Descriptive statistics included median values and range.

### Results

All patients experienced clinical improvement after treatment with infliximab. Improvement was gained after the first infusion considering both clinical response and fistulae closure.

#### Ten-Week Outcome

Among the 7 patients with pouchitis who received infliximab, 6 had a complete clinical response, and 1 patient had partial clinical response 10 weeks after the first infusion (Figure 1). Five out of 7 patients had complete fistulae closure, and 2 out of 7 patients had partial fistulae closure 10 weeks after infliximab (Figure 2).

The patient with the pouch-bladder fistula fully responded with complete fistula closure after the first infusion of infliximab, but he had an early recurrence of pneumaturia that was, however, greatly reduced in frequency at week 10 (partial closure). Also a female patient with perianal and vaginal complex fistula had partial fistulae closure since, despite the 2 perianal fistulae closure, the vaginal fistula was still draining.

Figure 3 shows the changes in PDAI score in all patients. Ten weeks after infliximab treatment, the median PDAI score improved from

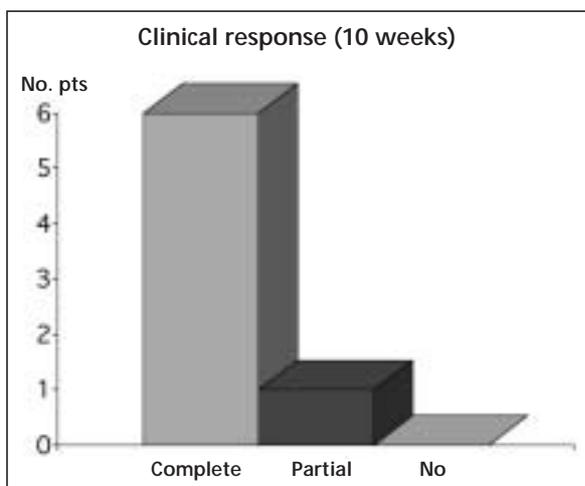


Figure 1. Clinical response at 10-week follow-up.

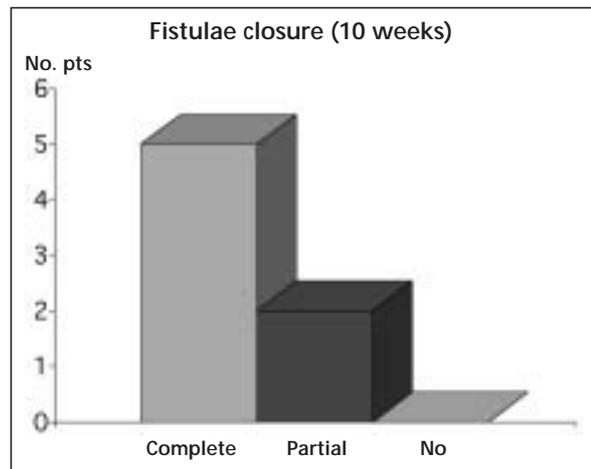


Figure 2. Fistulae closure at 10-week follow-up.

12 (range, 10-15) at baseline to 5 (range, 3-8). In 5 out of 7 patients, PDAI scores resulted under the value of 7, the cut-off value to diagnose pouchitis. In these patients, healing of endoscopic lesions and significant improvement of histologic signs of pouchitis was observed.

Figure 4 shows the healing of fistulae (A: complete; B: partial) visualized by defecography.

Figure 5 shows the changes in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Ten weeks after infliximab treatment, the median ESR value improved from 25 mm/h (range, 18-52) at baseline to 10 mm/h (range, 5-15). The median CRP value improved from 2.3 mg/dL (range, 1.0-7.2) at baseline to 0.4 mg/dL (range, 0.2-1.9), respectively. In 5 out of 7 patients, CRP levels resulted under the value of 0.8 mg/dL, the upper limit of normal values.

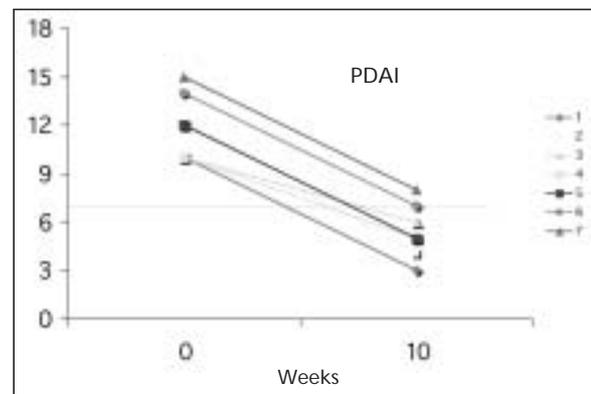
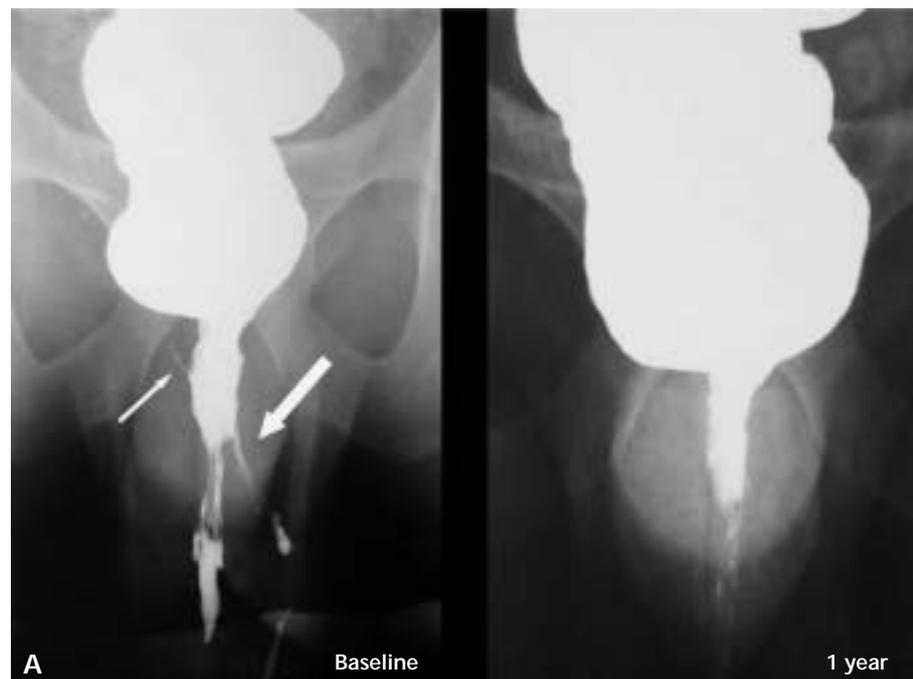
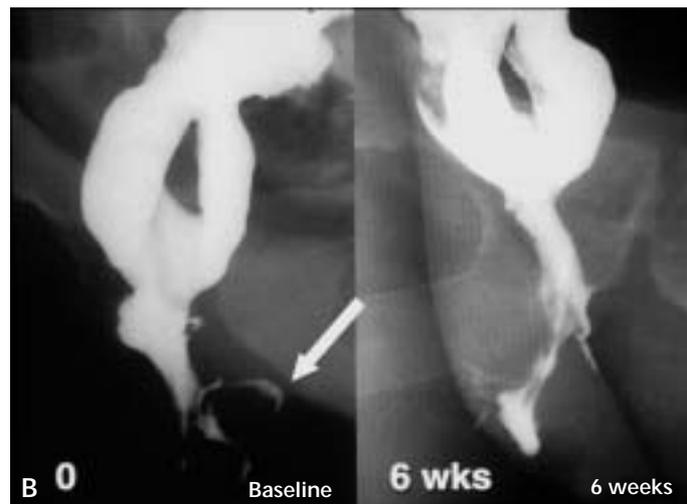


Figure 3. PDAI scores at baseline and at 10-week follow-up.



**Figure 4.** Examples of defecography changes in the pouch fistulae after infliximab therapy. Defecography. **A**, Patient 5. Antero-posterior view: Two fistulae, the first (small arrow) arising from the lower part of the pouch upward to the right. The second (big arrow) arising from the middle part of the anal canal downward to the left near the anal verge, after splitting in two branches. On the right, complete fistulae healing demonstrated 1 year after therapy. **B**, Patient 6. Lateral view: Fistula (arrow) arising from the anterior-lower part of the pouch. On the right, partial fistula healing demonstrated 6 weeks after therapy.



After 10 weeks, median QoL had greatly changed improving from 37 (range, 33-40) at baseline to 14 (range, 9-18).

In patients with extraintestinal manifestations, arthralgiae and erythema nodosum promptly and completely disappeared after the first infusion. Steroids were completely withdrawn.

#### **Updated Follow-up**

Table II summarizes the outcomes at the last follow-up visit. Median follow-up is 35 months (range: 31-57 months). Median number of infusions was 4 (range, 3-7).

All 7 patients, with the exception of one, had a lasting complete clinical response at their last follow-up visit. The patient who lost clinical response had relapse of fistula and developed anal stenosis at 31-months follow-up. The patient who had partial remission at 10-week follow-up, gained complete clinical response after retreatment.

At the last follow-up visit, out of 7 patients, 5 had complete fistulae closure, 1 had partial closure, 1 patient had relapse of fistula and was considered as failure.

Extraintestinal manifestations did not recur. Steroids were not needed. All patients

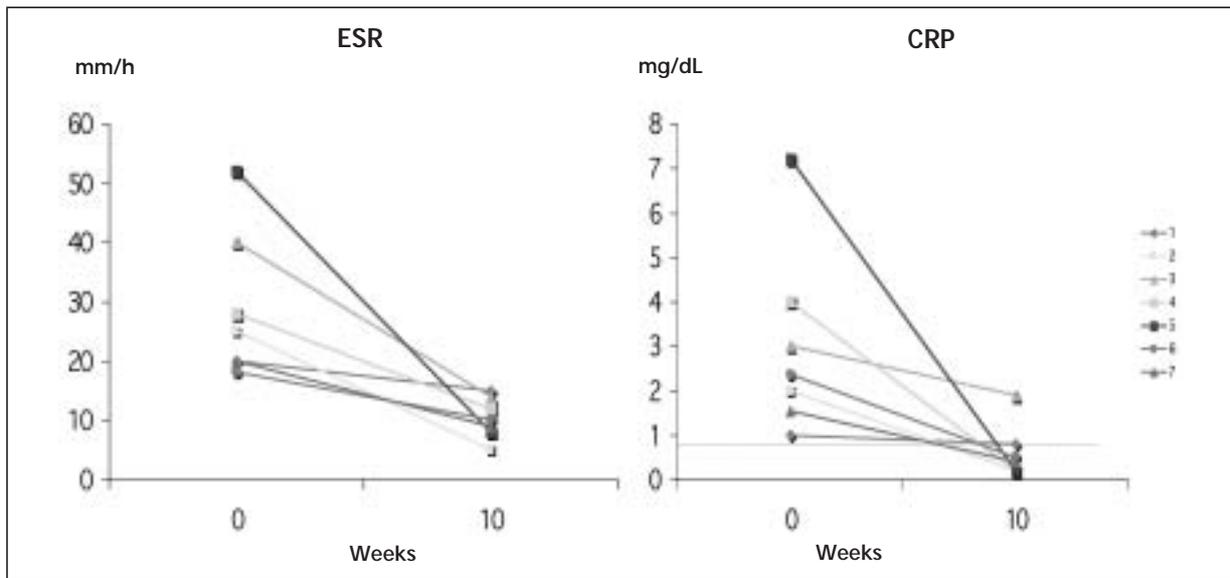


Figure 5. ESR and CRP values at baseline and at 10-week follow-up.

were in treatment with azathioprine. Three patients were also given antibiotics.

**Adverse Events**

Infusions of infliximab were well tolerated. At 6-month follow-up, 1 patient developed a thoracic herpes simplex virus infection, which required treatment with Aciclovir (4 g/day for 10 days), without withdrawn of immunosuppressive treatment.

**Discussion**

This open study shows the long-term efficacy of infliximab plus azathioprine in the treatment of refractory chronic pouchitis with fistulae after IPAA for UC. Clinical improvement

occurred in all patients. PDAI score dropped to a value < 7 in 5 patients indicating absence of active pouchitis according to Sandborn criteria<sup>8</sup>. All these 5 patients showed healing of endoscopic lesions and significant improvement of histologic signs of pouchitis. Remarkably, all fistulae responded to treatment, and complete closure was observed in 5 patients. At long term follow-up all patients, with the exception of one, showed complete clinical response and closure of fistulae.

Development of fistulae complicating pouchitis raised suspicion about the possibility of CD. Diagnosis was therefore reconsidered in all the patients. It should be stressed that, pre-operatively, all 7 patients had clinical, radiographic, endoscopic and pathologic features of UC. The blind review of original procto-

Table II. Response to treatment and characteristics at the last follow-up evaluation.

Pts	Follow-up (months)	No. of infliximab infusions	Clinical response	PDAI	Fistulae closure	Extraintestinal manifestations	Concurrent treatments	Adverse events
1	57	4	Complete	3	Partial	-	Azathioprine	-
2	53	6	Complete	4	Complete	Healed	Azathioprine	H. Zoster
3	36	3	Complete	6	Complete	Healed	Azathioprine	-
4	35	7	Complete	5	Complete	-	Azathioprine	-
5	32	3	Complete	5	Complete	-	Azathioprine	-
6	32	4	Complete	7	Complete	Healed	Azathioprine	-
7	31	3	Failure	8	Failure	Healed	Azathioprine	-

colectomy specimen confirmed the diagnosis of UC in all the patients. Examination, by means of radiologic and endoscopic studies of the gastrointestinal tract distant from the pouch, resulted to be normal. Endoscopic biopsies of pouch and pre-pouch mucosa did not contain CD features. The diagnosis of UC was therefore unquestionable in all patients.

Some authors consider the development of fistulae complicating pouchitis a sufficient reason for changing diagnosis from UC to CD<sup>18,19</sup>. However, it has been reported that diagnosis of CD is often excluded after systematic review of the diagnosis in patients with pouchitis presenting with certain features resembling CD, such as serpiginous pouch ulcerations or fistulae<sup>14,20,21,25</sup>. Epithelioid granulomas, discontinuous crypt distortion, and discontinuous inflammation are considered essential features to make diagnosis of CD<sup>21,22</sup>. Several authors have suggested that a diagnosis of CD in an ileal pouch should be made only when reexamination of the original proctocolectomy specimen or investigation of the proximal small bowel is diagnostic of CD<sup>2,20-22</sup>. All patients included in this study were evaluated according to these criteria.

It has been suggested that in patients with pouchitis, the development of fistulae is most likely related to chronic course of inflammation and does not necessarily imply an incorrect original diagnosis of UC<sup>13</sup>. This suggestion seems to be validated by the observation of an association between a particular TNF gene haplotype and the development of pouch-specific complications, including fistulae, in patients with UC after IPAA<sup>26</sup>.

Pouchitis is the most frequent long-term complication following IPAA for UC and is considered to be a non-specific and idiopathic recurrent inflammation of the ileal mucosa of the pouch<sup>2,3</sup>. A series of evidence suggest that pouchitis could result from a reactivation of immunologic mechanisms that lead to UC. It has been observed that ileal pouch mucosa of patients with pouchitis synthesizes a variety of pro-inflammatory molecules, including TNF- $\alpha$ , with an imbalance between pro-inflammatory and anti-inflammatory cytokines<sup>4-7</sup>. Furthermore, patients who develop pouchitis show highly increased levels of STAT1 (signal transducer and activator of transcription-1) activation in the pouch mucosa<sup>27</sup>. STAT1 is a pro-inflammatory transcription factor similar to nuclear factor  $\kappa$ B, which activates genes in-

involved in inflammatory and immunological responses<sup>27</sup>. Considering that STAT1 activation correlates to clinical disease activity<sup>27</sup>, it can be hypothesized that patients with continuously active chronic pouchitis have a continuous STAT1 activation with unrestricted over-production of pro-inflammatory molecules in their pouch mucosa. These molecules can flow into the systemic circulation and therefore can act both locally and systemically<sup>7,13</sup>.

In our series of patients with chronic refractory pouchitis and fistulae, 4 patients had systemic complications such as erythema nodosum or arthralgiae.

The variability in the severity of the course of pouchitis, including the development of complications, may reflect the heterogeneity in the host ability to react to the excessive luminal antigenic (i.e., bacterial) load after creation of an IPAA. It has been suggested that particular genetic factors may predispose patients with IPAA to resistance to medical therapy or to development of complications<sup>26</sup>. It has been observed that a particular TNF microsatellite haplotype may define a subgroup of medically unresponsive patients with UC with severe clinical course. This specific TNF haplotype is present in more than one-third of patients with UC with medically refractory disease requiring colectomy compared with about 10% of patients with UC responsive to medical therapy. Out of the patients with IPAA, 55% of the patients with the specific TNF haplotype have pouch-specific complications compared with 33% who do not have the haplotype<sup>26,28</sup>. This observation intriguingly suggests a genetic basis for aggressive course and development of complications after IPAA.

Therapy of pouchitis is mainly aimed to interfere with luminal bacteria (antibiotics, probiotics)<sup>2,11,12</sup>. Considering, however, that pouchitis seems to result from deregulated immune activation<sup>27</sup>, the use of immunosuppressants may be rational. The observation of increased TNF- $\alpha$  expression in ileal mucosa during pouchitis<sup>4</sup> and that specific TNF haplotypes may define particular subgroups of UC patients prone to develop pouch-specific complications<sup>26</sup> seems to support the use of infliximab.

These results suggest that infliximab is safe and efficacious in the treatment of patients with chronic refractory pouchitis after IPAA for UC, complicated by fistulae. It may be speculated that this agent can work also in uncomplicated pouchitis.

## References

- 1) DOZOIS RR, KELLY KA. The surgical management of ulcerative colitis. In: Kirsner JB, ed. *Inflammatory Bowel Disease*. 5th ed. Philadelphia: WB Saunders company, 2000: 626-657.
- 2) Sandborn WJ. Pouchitis in the Kock continent ileostomy and the ileoanal Pouch. In: Kirsner JB, ed. *Inflammatory Bowel Disease*. 5th ed. Philadelphia: WB Saunders company, 2000: 736-747.
- 3) SANDBORN WJ. Pouchitis following ileal pouch-anal anastomosis: definition, pathogenesis and treatment. *Gastroenterology* 1994; 107: 1856-1860.
- 4) PATEL RT, BAIN I, YOUNGS D, KEIGHLEY MRB. Cytokine production in pouchitis is similar to that in ulcerative colitis. *Dis Colon Rectum* 1995; 38: 831.
- 5) BULOIS P, TREMAINE WJ, MAUNOURY V, et al. Pouchitis is associated with mucosal imbalance between interleukin-8 and interleukin-10. *Inflamm Bowel Dis* 2000; 6: 157-164.
- 6) EVGENIKOS N, BARTOLO DCC, HAMER-HODGES DW, GOSH S. Assessment of ileoanal pouch inflammation by interleukin 1 $\beta$  and interleukin 8 concentrations in the gut lumen. *Dis Colon Rectum* 2002; 45: 249-255.
- 7) PATEL RT, PALL AA, ADU D, KEIGHLEY MR. Circulating adhesion molecules in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1995; 7: 1037-1041.
- 8) SANDBORN WJ, TREMAINE WJ, BATTIS KP, PEMBERTON JH, PHILLIPS S. Pouchitis after ileal pouch-anal anastomosis: a pouchitis disease activity index. *Mayo Clin Proc* 1994; 69: 409-415.
- 9) SHEN B, ACHKAR JP, LASHNER BA, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. *Gastroenterology* 2001; 121: 261-267.
- 10) SANDBORN WJ. Pouchitis: definition, risk factors, frequency, natural history, classification, and public health perspective. In: McLeod RS, Martin F, Sutherland LR, et al. eds. *Trends in inflammatory bowel disease 1996*. Lancaster, UK, Kluwer Academic Publishers, 1997: 51-63.
- 11) MIMURA T, RIZZELLO F, HELWIG U, et al. Four-week open-label trial of metronidazole and ciprofloxacin for the treatment of recurrent or refractory pouchitis. *Aliment Pharmacol Ther* 2002; 16: 909-917.
- 12) GIONCHETTI P, RIZZELLO F, VENTURI A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119: 305-309.
- 13) GOLDSTEIN NS, SANFORD WW, BODZIN JH. Crohn's-like complications in patients with ulcerative colitis after total proctocolectomy and ileal pouch-anal anastomosis. *Am J Surg Pathol* 1998; 22: 1040-1041.
- 14) DAYTON MT, LARSEN KR, CHRISTIANSEN DD. Similar functional results and complications after ileal pouch-anal anastomosis in patients with indeterminate vs ulcerative colitis. *Arch Surg* 2002; 137: 690-695.
- 15) MACLEAN AR, O'CONNOR B, PARKES R, COHEN Z, MCLEOD RS. Reconstructive surgery for failed ileal pouch-anal anastomosis: a viable surgical option with acceptable results. *Dis Colon Rectum* 2002; 45: 880-886.
- 16) MACRAE HM, MCLEOD RS, COHEN Z, O'CONNOR BI, TON EN. Risk factors for pelvic failure. *Dis Colon Rectum* 1997; 40: 257-262.
- 17) GECIM IE, WOLFF BG, PEMBERTON JH, DEVINE RM, DOZOIS RR. Does technique of anastomosis play any role in developing late perianal abscess or fistula? *Dis Colon Rectum* 2000; 43: 1241-1245.
- 18) RICART E, PANACCIONE R, LOFTUS EV, TREMAINE WJ, SANDBORN WJ. Successful Management of Crohn's disease of the ileoanal pouch with Infliximab. *Gastroenterology* 1999; 117: 429-432.
- 19) COLOMBEL JF, RICART E, LOFTUS EV, et al. Management of Crohn's disease of the ileoanal pouch with Infliximab. *Am J Gastroenterol* 2003; 98: 2239-2244.
- 20) SHEPHERD NA, HULTEN L, TYTGAT GNI, et al. Workshop: Pouchitis. *Int J Colorect Dis* 1989; 4: 205-229.
- 21) WARREN BF, SHEPHERD NA. The role of pathology in pelvic ileal reservoir surgery. *Int J Colorect Dis* 1992; 7: 68-75.
- 22) JENKINS D, BALSITIS M, GALLIVAN S, et al. Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. *J Clin Pathol* 1997; 50: 93-105.
- 23) VISCIDO A, HABIB FI, KOHN A, et al. Infliximab in refractory pouchitis complicated by fistulae following ileo-anal pouch for ulcerative colitis. *Aliment Pharmacol Ther* 2003; 17: 1263-1271.
- 24) MARTIN A, LEONE L, FRIES W, NACCARATO R. Quality of life in inflammatory bowel disease. *Ital J Gastroenterol* 1995; 27: 450-454.
- 25) SUBRAMANI K, HARPAZ N, BILOTTA J, et al. Refractory pouchitis: does it reflect underlying Crohn's disease? *Gut* 1993; 34: 1539-1542.
- 26) FACKLIS K, PLEVY SE, VASILIAUSKAS EA, et al. Crohn's disease-associated genetic marker is seen in medically unresponsive ulcerative colitis patients and may be associated with pouch-specific complications. *Dis Colon Rectum* 1999; 42: 601-605.
- 27) KUHBACHER T, GIONCHETTI P, HAMPE J, et al. Activation of signal-transducer and activator of transcription 1 (STAT1) in pouchitis. *Clin Exp Immunol* 2001; 123: 395-401.
- 28) ACHKAR JP, LASHNER BA. TNF haplotype and pouch complications: Invited editorial. *Dis Colon Rectum* 1999; 42: 605-606.