Oral beclomethasone dipropionate in chronic refractory pouchitis

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Abstract

Background: Pouchitis is the major long-term complication after ileal-pouch anal-anastomosis for ulcerative colitis. Ten to 15% of patients develop chronic pouchitis, either treatment responsive or treatment refractory.

Aim: To evaluate the efficacy of oral beclomethasone dipropionate in inducing remission and improving quality of life in patients with chronic refractory pouchitis.

Methods: Ten consecutive patients with active pouchitis, not responding to 1-month antibiotic treatment, were treated with beclomethasone dipropionate 10 mg/day for 8 weeks. Clinical, endoscopic and histological evaluations were undertaken before and after treatment, according to the Pouchitis Disease Activity Index (PDAI). Remission was defined as a combination of PDAI clinical score of ≤2, endoscopic score of ≤1 and a total PDAI score of ≤4. The quality of life was assessed with the Inflammatory Bowel Disease Questionnaire (IBDQ).

Results: Eight of 10 patients (80%) achieved remission. The median total PDAI scores before and after therapy were, respectively, 12 (range 8–14) and 3 (range 2–9) (P < 0.001). The median IBDQ score also significantly improved from 120 (range 77–175) to 175 (range 85–220) (p < 0.001).

Conclusion: Eight-week treatment with oral beclomethasone dipropionate appears effective in inducing remission in patients with active pouchitis refractory to antibiotic treatment.

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1. Introduction

Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) has emerged over the past 15 years as the surgical procedure of choice for the management of ulcerative colitis (UC). Pouchitis, a non-specific, idiopathic inflammation of the ileal reservoir, has become the most frequent long-term complication following pouch surgery for UC. The reported incidence of pouchitis is largely variable, due to the different follow-up duration and nature and, particularly, because of the several diagnostic criteria used to define this syndrome. Most patients develop acute pouchitis within

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the first year after surgery, but some may suffer their first attack some years later. 4

This syndrome is clinically characterized by variable symptoms, including increased stool frequency and fluidity, rectal bleeding, abdominal cramping, urgency and tenesmus, incontinence, fever and extraintestinal manifestations. 8–10 The clinical diagnosis should be always confirmed by endoscopy and histology. 10 The endoscopic features of pouchitis are mucosal erythema, oedema, friability, petechia, granularity, loss of vascular pattern, erosions and superficial ulceration. 10

Histological examination shows acute inflammatory infiltrate, with crypt abscesses and ulceration, next to a chronic inflammation, including villous atrophy, crypt hyperplasia, which probably represents an adaptive response of the pouch mucosa to faecal stasis. 9,10 The absence of clear and universally accepted criteria for the diagnosis, classification and definition of activity of pouchitis has determined a great variability in the results of the studies on the incidence of pouchitis, and in the assessment of the therapy. To overcome this problem, Sandborn et al. developed the Pouchitis Disease Activity Index (PDAI). 11 It is an 18-point index based on clinical symptoms and endoscopic appearance, as well as acute histological findings, and represents an objective and reproducible scoring system for pouchitis. Active pouchitis is defined as a score of ≥7 and remission is defined as a score of <7.

Treatment of pouchitis is largely empiric and only few small placebo-controlled trials have been conducted. 12 Antibiotics are the mainstay of the treatment, with metronidazole and ciprofloxacin as the most common initial approaches. 13–16

Ten to 15% of patients with pouchitis experience chronic pouchitis, either ‘treatment responsive’ or ‘treatment refractory’. Patients with treatment-responsive chronic pouchitis respond to the therapy, and experience a pouchitis relapse when the therapy is stopped. Patients with treatment-refractory pouchitis do not respond to conventional available therapies, and continue to suffer symptoms. 10,17

In a recent open study, we demonstrated that oral administration of budesonide was effective in the treatment of active refractory pouchitis, with complete remission in 75% of patients previously unresponsive to 4-week antibiotic treatment. 18

Beclomethasone dipropionate (BDP) is a topically acting corticosteroid characterized by prompt and potent anti-inflammatory activity and low systemic bioavailability, which is mainly achieved through an extensive first-pass liver metabolism. Compared with systemically active corticosteroids, BDP has the potential advantage of reducing the occurrence of adverse side effects, by minimizing the suppression of the hypothalamic–pituitary–adrenal axis. 19

Rectal administration of BDP, in the management of active distal UC, has been extensively studied and there is consistent evidence of efficacy. 20 A gastro-resistant methacrylate film coating and a modified release core of hydroxypropyl methylcellulose that dissolves at pH values below 6.0, constitute the oral formulation of BDP. This formulation allows the drug to be firstly released in the distal small bowel and then through the whole colon. 21

In clinical trials, oral BDP has been shown to be effective in mild to moderate UC 22–25, and also in Crohn's disease (CD). 26 Considering this background, we hypothesized that oral BDP could be a rational therapeutic option for patients with refractory pouchitis.

The aim of this study was to evaluate the efficacy of oral BDP for the treatment of chronic refractory pouchitis, and to evaluate its impact on the quality of life of these patients.

2. Materials and methods

This open-label, non-randomised study was conducted at the IBZ centre of Bologna University. Eligible patients were adults up to 18 years of age with current active refractory pouchitis, defined as a PDAI score of ≥7 and no response to at least a 4 weeks standard antibiotic treatment (ciprofloxacin 1 g once a day or metronidazole 1 g once a day). Histological and endoscopic acute inflammation further to clinical symptoms had to be present for patients to be diagnosed with active pouchitis.

Patients were excluded from entry if they had any of the following: (a) use of steroids or immunosuppressants, within 2 weeks from the screening baseline; (b) use of non-steroidal anti-inflammatory drugs within 2 weeks from the baseline; (c) evidence of perianal disease (including abscess, fissure, stricture with delayed emptying, or anal sphincter weakness); (d) evidence of Crohn's disease or cufitis. Patients were also excluded for the following: presence of severe cardiovascular, respiratory, hepatic (including primary sclerosing cholangitis) or renal diseases; verified pregnancy or ongoing breast-feeding.

Concurrent use of anti-diarrhoeal, topical mesalazine or topical steroid agents or narcotic drugs was not allowed.

2.1. Study medication

Patients received two capsules of BDP 5 mg once daily for 8 weeks. The dose was then tapered by 5 mg every 2 weeks until suspension. Compliance was assessed by questioning the patients.

2.2. Evaluation and scheduling

Demographics and pouchitis risk factors (recent tobacco cessation, sclerosing cholangitis, extraintestinal manifestation, and pan-colitis) have been assessed at baseline.

The PDAI was determined at the baseline and at week 8 and it included: symptom assessment (stool frequency, rectal bleeding, faecal urgency, abdominal cramps, and fever), endoscopic examination of the ileal pouch and of the first centimetres of the ileum, with mucosal biopsies, and histological assessment.

General laboratory tests (complete blood cell counts, blood chemistry measurements, C-reactive protein and erythrocyte sedimentation rate) and serum cytomegalovirus (CMV) DNA antigenemia pp65 (a buffy-coat preparation) on the peripheral leukocytes were performed at baseline and at week 8. Stool Clostridium difficile toxins A and B were identified by enzyme immunoassay (C. difficile TOX A/B Test; TechLab Inc., Blacksburg, VA, USA). Crohn’s disease was excluded through a careful re-examination of the colonic surgical and histological specimens.

Active pouchitis was defined as a total PDAI score of ≥7. Remission was defined as a clinical score of ≤2 (total possible range 0–6), endoscopic PDAI score of ≤1 (total
possible range 0–6) and total PDAI of ≤4. Clinical partial response was defined as an improvement in the above pouch-associated symptoms (Table 1).

Health related quality of life was also assessed at the baseline and at week 8, by using the Inflammatory Bowel Disease Questionnaire (IBDQ), which considers bowel, systemic and emotional symptoms as well as social functions. The IBDQ ranges from 32 (worst quality of life) to 224 (best quality of life).

2.3. Safety assessment

All unfavourable, unexpected symptoms were recorded in the diary kept by patients during the study. Laboratory studies, including a complete blood count and blood chemistry measurements (including blood glucose), were performed at baseline and at the end of the treatment.

2.4. Statistical analysis

Statistical analysis was performed with Prism Version 2.0 (GraphPad Inc., San Diego, CA, USA). For the description of data, the medians and ranges were calculated.

The Wilcoxon signed rank test (paired, two-tailed) was used to compare pre-treatment and post-treatment bowel frequency, and the PDAI scores. The primary measure of efficacy was the comparison between the pre-treatment and post-treatment PDAI scores.

3. Results

3.1. Patient characteristics

From January 2010 to May 2012, ten consecutive patients with chronic, refractory pouchitis were included in this trial. All patients had a J shape constructed pouch; a 3-stage IPAA was performed in 8 patients and a two-stage IPAA in 2 patients. The demographic and clinical characteristics are shown in Table 2.

Six patients failed to respond to ciprofloxacin alone, and 4 to metronidazole alone. No patients withdrew from the trial. No CMV or C. difficile infections were detected.

3.2. Clinical results

Eight (80%) of the 10 treated patients achieved remission, while 2 had only a mild improvement. The median bowel frequency decreased significantly from 10 (range 7–15) to 6 (range 3–11) after BDP treatment (P < 0.001), as the median PDAI total score did [12 (range 8–14) vs 3 (range 2–9) (P < 0.001)]. The changes in the total PDAI scores and sub score are illustrated in Fig. 1. Table 3 shows the median total PDAI scores and the median score of each component of the PDAI at baseline, and at weeks 8.

The clinical, endoscopic and histological characteristics of the patients who did not respond to oral BDP were similar to those of the patients who responded.

The median IBDQ score, at the end of the study, was significantly improved compared to the baseline [175 (range 85–220) vs 120 (range 77–175) respectively (p < 0.001)].

Table 2 Pouchitis disease activity index.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency</td>
<td></td>
</tr>
<tr>
<td>Usual postoperative stool frequency</td>
<td>0</td>
</tr>
<tr>
<td>1–2 stool/day &gt; postoperative usual</td>
<td>1</td>
</tr>
<tr>
<td>3 or more stool/day &gt; postoperative usual</td>
<td>2</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
</tr>
<tr>
<td>None or rare</td>
<td>0</td>
</tr>
<tr>
<td>Present daily</td>
<td>1</td>
</tr>
<tr>
<td>Faecal urgency or abdominal cramps</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Occasional</td>
<td>1</td>
</tr>
<tr>
<td>Usual</td>
<td>2</td>
</tr>
<tr>
<td>Fever (temperature &gt; 37.8 °C)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Endoscopic inflammation</td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>1</td>
</tr>
<tr>
<td>Granularity</td>
<td>1</td>
</tr>
<tr>
<td>Friability</td>
<td>1</td>
</tr>
<tr>
<td>Loss of vascular pattern</td>
<td>1</td>
</tr>
<tr>
<td>Mucous exudates</td>
<td>1</td>
</tr>
<tr>
<td>Ulceration</td>
<td>1</td>
</tr>
<tr>
<td>Acute histological inflammation</td>
<td></td>
</tr>
<tr>
<td>Polymorphonuclear leucocyte infiltration</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>Moderate – cript abscess</td>
<td>2</td>
</tr>
<tr>
<td>Severe + cript abscess</td>
<td>3</td>
</tr>
<tr>
<td>Ulceration per low-power field (mean)</td>
<td></td>
</tr>
<tr>
<td>&lt;25%</td>
<td>1</td>
</tr>
<tr>
<td>25–50%</td>
<td>2</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>3</td>
</tr>
</tbody>
</table>
3.3. Follow-up

The 2 patients with only mild clinical improvement after 8 weeks of therapy were retreated with BDP 10 mg/day for another 8 week period. At week 16, the 2 patients achieved remission. One year after the end of treatment, 7 patients were still experiencing remission, while 3 patients had a mild relapse.

3.4. Safety

No serious or significant adverse drug-related effects were reported during the study.

4. Discussion

In this open study, oral administration of BDP was effective in the treatment of active refractory pouchitis. Treatment with BDP determined a significant improvement of the clinical, endoscopic and histological items of PDAI, with complete remission in 80% of patients and prolonged remission in 70% of patients, previously unresponsive to a 4-week antibiotic treatment. Moreover, the two patients who had only minor improvement, achieved remission after 8-week retreatment with oral BDP. Treatment with BDP was also effective in improving significantly the IBDQ score and was very well tolerated.

Refractory pouchitis is a rare but frustrating condition due to the lack of an effective therapy and may cause pouch failure. Prolonged combined antibiotic was shown to be effective in three open studies in patients with refractory pouchitis, however side effects, and also antibiotic resistance may limit this therapeutic approach and may be an issue. Anti-TNF drugs have also been shown to determine a prolonged response in 27–56% of patients in open studies. These drugs however are very expensive and are not devoid of side effects. Therefore we believe that the results obtained with oral BDP are of particular value because of the prolonged remission obtained in the majority of patients, and the very good safety profile of the drug. Similar results were also obtained with oral budesonide CIR that induced remission in the 75% of patients.

Due to its pharmacokinetic and pharmacodynamics properties, oral BDP has been tested successfully both in active UC and CD at doses of 5–10 mg/day.

We decided to use 10 mg/day dose because our patients were very refractory (persistence of mean PDAI of 12 after antibiotic treatment), and because this dose was shown to be effective both in refractory UC and in CD. Moreover BDP 5 mg/day had similar efficacy as 2.4 g/day of mesalazine in UC. The main limitation of the current study is that it is an open study carried-out on a small group of subjects. It is worth noting that chronic refractory pouchitis is not a very common situation, and that the available controlled trials on this topic are scarce and included very few patients. For these reasons we believe that the information coming from this study may be helpful in clinical practice management of this disappointing condition.

In conclusion, treatment with oral BDP over an 8-week period appears to be effective in the treatment of patients with chronic, refractory pouchitis and may represent a valid alternative to combined antibiotic prolonged therapy and oral budesonide, before using immunosuppressive or biological drugs.

Author contributions

Dr Paolo Gionchetti, Calabrese C and Dr Fernando Rizzello, initiated the study, coordinated the conduct of the whole study, performed the endoscopies. Dr Praticò C, Calafiore A and Capozzi N prepared the draft of the manuscript. Dr. Silvio Laureti and Prof. Gilberto Poggioli G, performed the surgical procedures, Gionchetti P and Campieri M reviewed the manuscript. All authors approved the final version of the manuscript.

References