Original article

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Octreotide for the treatment of diarrhoea in patients with ileal pouch anal anastomosis: a placebo-controlled crossover study

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Abstract

Aim Diarrhoea with urgency is a debilitating long-term complication of ileal pouch anal anastomosis (IPAA) after a proctocolectomy. Somatostatin analogues are used to control diarrhoea and high-output ostomies. Hence, we designed a prospective, double-blind, crossover trial to explore the efficacy and tolerability of octreotide to reduce diarrhoea in adult patients with IPAA.

Method Patients were randomized to octreotide subcutaneously (SC), 500 μg three times daily (t.i.d.), or matching placebo SC for 7 days. Responders (a reduction in stool frequency of three or more stools per 24-h period and with a reduction in stool frequency of at least 30% after 7 days of treatment compared with baseline; the primary end-point) remained in the same group and nonresponders could cross over to the alternative treatment for 7 days. Open-label octeotide LAR 30 mg was offered to all responders on day 14. Flexible pouchoscopy with biopsies was performed at baseline in all patients and was repeated on days 7 and 14 in patients with pouchitis.

Results Fifteen patients (11 men, median age 52 years), all with ulcerative colitis, were randomized. Three patients were withdrawn for side effects during the blinded phase. Response was achieved by two of 12 and two of 11 patients treated with octreotide or placebo, respectively (including crossover, $P = 0.9$). The median stool frequency remained stable in both groups [Δoctreotide: 0 (IQR, −4 to 0), Δplacebo: −1 (IQR, −1 to 1), $P = 0.45$]. Octreotide had no effect on the modified pouch disease activity index (mPDAI), and pouchitis persisted in five of six subjects with pouchitis at onset. One subject received open-label octreotide LAR.

Conclusion Octreotide has no clear beneficial effect on the stool pattern or on pouchitis severity in patients with high stool frequency after IPAA.

Keywords Ileal pouch anal anastomosis, octreotide, medical therapy, diarrhoea, ulcerative colitis, somatostatin

What is new in this paper?

Octreotide subcutaneously has no clear benefit in the treatment of diarrhoea in patients with ileal pouch anal anastomosis.

Introduction

Total proctocolectomy with ileal pouch anal anastomosis (IPAA) is the preferred surgical treatment for treatment-refractory disease or for colonic dysplasia or cancer in patients with ulcerative colitis (UC) [1]. Also, patients with familial adenomatous polyposis, who have a high colorectal cancer risk, are eligible for this surgical procedure. Although IPAA offers a good quality of life to most patients, increased stool frequency can be debilitating. The ileal pouch does not have the same absorptive and reservoir capacity as the native colon and rectum. Furthermore, post-IPAA syndromes, such as the high-output pouch, can cause debilitating diarrhoea [2,3]. Pouchitis, an idiopathic inflammation of the ileal pouch, occurs in almost half of colectomized UC patients after 10 years of follow up [3], and mimics the symptoms of UC with frequent stools and tenesmus. The disease is exceedingly rare in patients treated with surgery for familial adenomatous polyposis. Moreover, the irritable pouch syndrome, which is a chronic condition without signs of mucosal inflammation, is associated with

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diarrhoea and abdominal cramps. In these conditions the pathophysiology of the diarrhoea is probably caused by a combination of increased secretion and disturbed small-bowel motility [4]. Acute pouchitis is treated with antibiotics usually to resolution. However, 5–19% of patients develop chronic or relapsing pouchitis [3,5]. For chronic pouchitis, long-term probiotics or antibiotics, and in more severe cases immunosuppressives, are used [1]. Treatment options for irritable pouch or functional diarrhoea in IPAA patients are limited to anti-diarrhoeal drugs. The proportion of patients with debilitating diarrhoea and urgency after IPAA varies among different published cohorts, but 10 years after surgery anti-diarrhoeals are used by a third of patients [6].

Octreotide (Sandostatin® and Sandostatin® LAR®; Novartis, Basel, Switzerland) has been shown to be beneficial for secretory and functional diarrhoea associated with a variety of diseases, such as chemotherapy-induced mucositis, high-output jejunostomies and graft *vs* host disease [7–10]. The treatment is generally well tolerated, and treatment-related side effects are rare. However, not all data supporting the use of octreotide to treat diarrhoea is based on properly controlled clinical trials.

Given the reported efficacy of octreotide to treat chronic diarrhoea, we designed a prospective placebo-controlled trial to explore the efficacy and safety of subcutaneous octreoteide (Sandostatin®) and intramuscular slow-release octreotide (Sandostatin® LAR®) in the treatment of diarrhoea in patients with IPAA.

Methods

Adult patients at least 18 years of age with IPAA and a functioning pouch without an ileostomy for at least 6 months, and who reported pouch dysfunction based on an increased stool frequency, were eligible for inclusion. Inclusion criteria were: a minimal stool frequency of seven or more loose stools in 24 h for at least seven consecutive days prior to study entry; subjects taking loperamide or antibiotics were required to be on a stable dose for at least 7 days prior to inclusion; and patients previously treated with somatostatin or an analogue were eligible provided that this treatment had been discontinued for at least 5 days if treated with a short-acting somatostatin analogue and for at least 12 weeks if treated with a long-acting somatostatin analogue. Exclusion criteria were: ongoing or recent (within 14 days) enteritis or a positive stool culture for enteric pathogens or *Clostridium difficile* toxin positivity; short bowel syndrome; pouch-related fistula or stenosis of the pouch outlet; known allergy to Sandostatin® or one of its compounds; symptomatic cholelithiasis; and poorly controlled diabetes mellitus (Hba1c > 10%). Written informed consent was obtained from all patients included in this trial, and the protocol was approved by the University of Leuven Ethics Committee for Clinical Trials.

Study set up and end-points

This was a placebo-controlled double-blind 14-day crossover trial comparing subcutaneously (SC) administered octreotide (Sandostatin®) with placebo followed by an open-label extension with intramuscular (IM) slow-release octreotide (Sandostatin® LAR® 30 mg). Patients received octreotide 500 μg or matching placebo SC three times daily (t.i.d.) for 7 days. The syringes for injection were prepared by removal, by a nurse not involved with the study team, of 500 μl of fluid from blinded vials containing a clear fluid. On the first day a reduced dose of 250 μg was given to confirm tolerance. The primary end-point of this trial was the proportion of patients achieving a clinical response after 7 days of treatment with octreotide or placebo. Clinical response was defined as a reduction in stool frequency of three or more stools per 24-h period and with a reduction in stool frequency of at least 30% after 7 days of treatment compared with baseline. After 7 days nonresponders were eligible to cross over to the alternative treatment arm (octreotide or placebo) for 7 days (Fig. 1). Responders continued in the same stratum for 7 days. Patients responding after the 14 days of the blinded period were eligible to enter an open-label extension study of treatment with long-acting octreotide (Sandostatin LAR 30 mg) every month for 6 months. All patients were observed for safety for

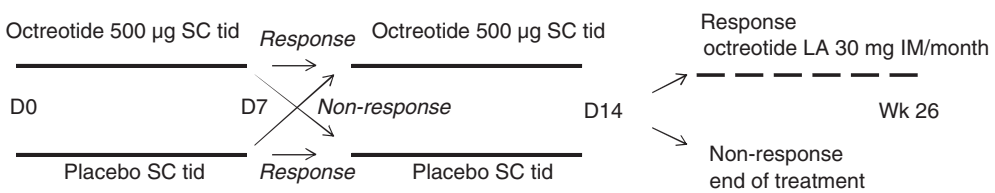

Figure 1 Design of the crossover study. After 1 week, nonresponder patients in both groups were allowed to cross over to the other group. Responding patients remained in the original group. D, day; IM, intramuscularly; SC, subcutaneously; t.i.d., three times daily.

6 months after the induction study. Other prespecified end-points included: the proportion of patients with clinical response after 14 days in the induction phase and after 3 and 6 months in the maintenance phase; and the proportion of patients with a durable response over 3 and 6 months. Endoscopy was performed in all patients at the entry visit and on days 7 and 14 in patients with active pouchitis at baseline. Stool frequency, abdominal pain, general state, times of injections and adverse events were recorded in patient diaries throughout the study. Laboratory analyses (for haemoglobin, white blood cell count, serum creatinine and blood urea nitrogen, fasting blood glucose, electrolytes, liver tests and C-reactive protein) were performed at baseline, and at days 7 and 14 and after 3 and 6 months in the observational maintenance period. The Modified Pouchitis Disease Activity Index (mPDAI) was used in patients with active pouchitis at baseline. The mPDAI is a pouchitis severity score that measures symptoms, and endoscopic and histological lesions [11]. The intensity of the abdominal pain was measured on a 5-point Likert scale, with 0 being no pain and 5 being very intense pain.

Statistical considerations

The proportion of patients responding in both groups (the primary end-point) was analyzed using a 2×2 contingency table (Fisher's exact test). Continuous variables, such as stool frequency, were analyzed using the Mann–Whitney *U*-test for nonparametric data. At the design of the trial it was estimated that 30 patients would be required in each study group to detect a 30% difference between active treatment and placebo with a power of 80% (α error 5%). Hence, a 30% difference in the response rate was judged to be clinically relevant.

Results

Patient demographics

Fifteen patients (11 men, median age 52 year), all with UC and with a median time of 117 (IQR, 7.5–149) months since a functioning IPAA had been formed, were randomized. The median daily stool frequency was 9 (IQR, 8–12), 6 of 15 patients had pouchitis and 11 of 15 patients were on a stable dose of loperamide (Table 1). The median dose of loperamide was 6 mg (range 3–8 mg). None of the 15 patients had previously received octreotide.

An interim analysis was performed after 15 patients had concluded the blinded induction phase of this trial. Owing to the absence of a trend for efficacy and because of octreotide-related possible adverse events, further recruitment in the study was terminated and intention-to-treat analysis was performed on this population.

Table 1 Patient demographics.

Gender	11/15 males
Median age	52 (range 37–68)
Ulcerative colitis before IPAA	15/15
Pouchitis previously	7/15
Median number of stools at baseline	9 (IQR 8–12)
Pouchitisat baseline	6/15
Concomitant loperamide	11/15
Concomitant antibiotics	2/15

IPAA, ileal pouch anal anastomosis; IQR, interquartile range.

Efficacy

Nine patients were randomized initially to octreotide and six were randomized to placebo (Fig. 2). On day 7, three patients crossed over from placebo to octreotide and five patients crossed over from octreotide to placebo. At the end of the blinded period (7 days of treatment, including the cross over), response (primary end-point) was reached by two (17%) of 12 patients treated with octreotide and by two (18%) of 11 patients treated with placebo for at least 1 week (including the cross over, $P = 0.9$, 95% CI of variation around the difference in proportions: −30% to 27%). The median stool frequency at day 7 showed no significant change compared with the baseline value in either octreotide- or placebo-treated patients [Δoctreo-

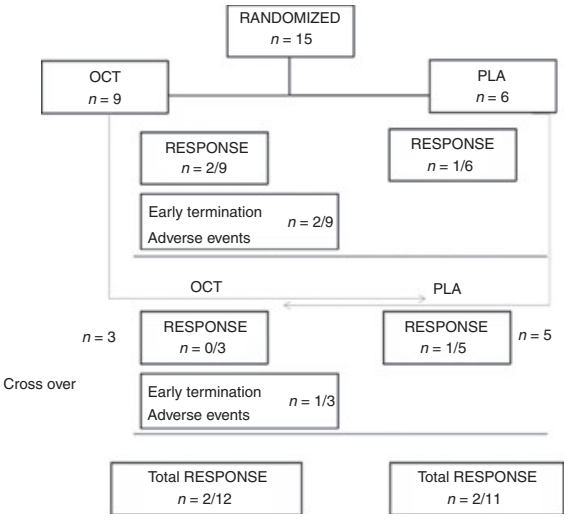

Figure 2 Distribution of patients in the trial. Of the 15 patients originally randomized, three and five crossed over to the octreotide and placebo groups, respectively, while still blinded. Total response summarizes the outcomes in the initially randomized and the crossover groups. OCT, octreotide; PLA, placebo.

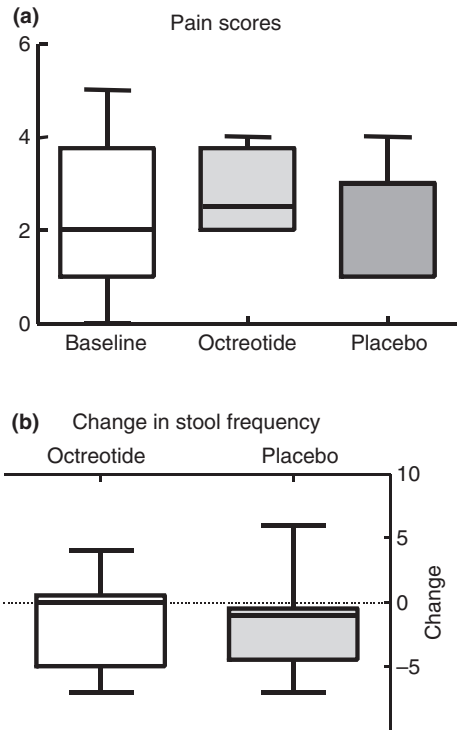

Figure 3 Influence of treatment on pain scores and change in stool pattern. (a) Median pain scores at baseline, after 1 week of sandostatin or placebo. (b) Change in pain scores in the two treatment arms. Box plots represent medians and interquartile ranges.

tide: 0 (IQR, −4 to 0), Δplacebo: −1 (IQR, −1 to −1), $P = 0.45$] (Fig. 3). Abdominal pain scores were also similar in both groups on day 7 ($P = 0.72$, Fig. 3). The median change in mPDAI was similar, although there was a trend towards a greater degree of improvement in placebo-treated patients [octreotide: 0 (IQR, −1 to 1.5), placebo: −2 (IQR, −1.75 to −3), $P = 0.08$].

At the end of the blinded treatment, five of six subjects had active pouchitis (one patient treated with placebo was in mPDAI remission with no endoscopic lesions). Abdominal pain scores recorded by the patient were similar before and after treatment in both groups (day 0, placebo: 2 (IQR, 2–2.75), octreotide: 1.5 (IQR, 1–2.75); and day 7, placebo: 2 (IQR, 2–2.75), octreotide: 2.5 (IQR, 2–3.25); $P = 0.72$ at day 7).

One patient (an octreotide responder) was enrolled in the open-label extension phase with octreotide LAR. After 2 months his stool frequency had returned to baseline and he was considered to have lost response.

Adverse events

During the blinded phase, 12 (100%) of 12 octreotide-treated patients and 6 (67%) of 11 placebo-treated patients experienced an adverse event. The individual side effects reported during the blinded phase and their proportional occurrences are listed in Table 2. The patient in the open-label extension had an injection-site reaction to Sandostatin LAR.

Table 2 Adverse events in the blinded crossover phase of the trial.

	Octreotide ($n = 12$)	Placebo ($n = 11$)
Proportion of patients with at least one adverse event	100% (12/12)	67% (6/11)
Specific adverse events (no. of patients with the event)		
Fatigue	1	0
Worsening abdominal pain	2	0
Flu-like syndrome	1	0
Nausea	3	1
Urticaria	0	1
Injection site reaction	0	1
Urgency and anal pain	3	0
Constipation	2	0
Hoarseness	0	1

Adverse events that were classified as at least possibly related, are represented.

Three patients were withdrawn early from the study. One serious adverse event occurred in one patient who had a recurrence of an oesophageal adenocarcinoma that was discovered at a scheduled gastroscopy after entering the study. This event was classified as unrelated. The two other patients were withdrawn from the study because of increased urgency, tenesmus and anal pain within the first week of the blinded induction phase. Both patients were receiving octreotide.

Of note, no hyperglycaemia or change in serum potassium or creatinine was detected, and none of the patients had intestinal obstruction.

Discussion

In contrast to previous observations in multiple disease states characterized by increased stool frequency and rectal urgency, in our blinded placebo-controlled study we did not observe a clear effect of octreotide on stool frequency in patients with an ileoanal pouch. Also, no improvement in the severity of pouchitis was observed. In addition, two patients reported an increase in urgency with painful tenesmus, which led to the discontinuation of octreotide treatment.

The somatostatin analogues octreotide and lantreotide are used to control chemotherapy and radiotherapy-induced diarrhoea, but beneficial effects on diarrhoea associated with graft-*vs*-host disease and on fluid and electrolyte losses in patients with short bowel syndrome and high-output jejunostomies have also been reported. Octreotide is a long-acting synthetic analogue of endogenous somatostatin, with a high affinity for the somatostatin (SST)2 receptor. It also binds SST5 and SST3 receptor subtypes, albeit with lower affinity [12]. The rationale for the use of these analogues can be inferred from their proven inhibitory effect on intestinal motility, on pancreatic exocrine excretion, on the release of stimulatory gastrointestinal peptide hormones, and from stimulatory effects on water and electrolyte absorption [13].

As urgency and a high stool frequency is one of the most debilitating long-term complications of IPAA, we opted to explore the efficacy of octreotide in this setting. The minimal number of stools required for entry in this trial was seven. We realize that patients with IPAA may have more than seven stools daily and still report a very good quality of life. However, the stool frequency was disabling for all patients who entered our study. In contrast to mostly uncontrolled observations in patients with short bowel syndrome or graft *vs* host disease, in our study we did not observe a decrease in stool frequency or in urgency in patients treated with octreotide, which was the primary end-point. On the contrary, two patients had to interrupt octreotide treatment because of debilitating urgency and painful tenesmus. With this information we decided to halt further recruitment in the trial after interim analysis. The primary end-point before and after cross over was set at day 7. The pharmacokinetic properties and potential mechanism of action of SC octreotide make it highly unlikely that we would have missed any late effects.

Several explanations for the difference between our results and those reported previously in patients with high-output jejunostomies, short bowel and chemotherapy-induced diarrhoea come to mind. First of all, this was a blinded, placebo-controlled trial. Recently, placebo-controlled trials with octreotide or Sandostatin® LAR to prevent radiotherapy- and chemoradiotherapy-induced diarrhoea failed to show a benefit of the octreotide formulations [14,15]. Also in human immunodeficiency virus/acquired immune-deficiency syndrome (HIV/AIDS)-associated diarrhoea, a double-blind placebo-controlled trial failed to show efficacy to control diarrhoea with SC octreotide induction therapy, whereas the long-acting Sandostatin® LAR was beneficial in an open-label extension study [16]. All other evidence in noncancer-related diarrhoea or fluid loss related to, for instance, short bowel syndrome or high-output enterostomies, is based on open-label trials. In patients with a pouch after pelvic surgery, long-acting octreotide appeared to provide complete relief of diarrhoea in five of seven patients, but again this was an open-label trial [17]. In contrast, a double-blind placebo-controlled cross-over study in patients with dumping syndrome showed efficacy of octreotide to control diarrhoea [18]. The diarrhoea associated with dumping syndrome is related to imbalances in the secretion of gastrointestinal hormones and this is directly affected by somatostatin analogues.

The mechanisms underlying diarrhoea and urgency in patients with IPAA may be different from other forms of secretory or dysmotility-related diarrhoea.

Therefore, we also allowed patients with active pouchitis to enter the trial. In an exploratory analysis there was no signal that octreotide reduced stool frequency more in the group with or without pouchitis. Of note, all patients were recruited based on disabling stool frequency, and pouchitis was only found at screening endoscopy. We have no reason to believe that the inflammatory reaction in patients would be specifically targeted by octreotide.

We acknowledge that the interpretation of our results is limited by the small sample size and the premature discontinuation of recruitment. Therefore, we may have missed less pronounced effects of octreotide. However, it should be noted that only two (17%) of 12 patients reported a 30% reduction of stool frequency with SC octreotide and two (18%) of 11 patients reported a 30% reduction of stool frequency with placebo. For that reason, only one patient agreed to enrol in the open-label trial with Sandostatin® LAR. This precludes any conclusion on the tolerance and efficacy of long-term IM octreotide in patients with IPAA. A case series of seven patients reported by Gullichsen [17] suggested improvement of diarrhoea in patients with IPAA, but these data were uncontrolled and no short-acting octreotide was used initially. An earlier open-label study published as an abstract only describes no effect of of octreotide in the same setting [19].

Adverse events were frequent in both octreotide and placebo-treated patients. We did not identify a patient with hyperglycemia, and no patient developed intestinal obstruction. The latter potential adverse event has been an issue in patients with previous abdominal surgery, such as short bowel or dumping syndrome. Two patients reported 'constipation' while on octeotide, despite four stools or more daily. In one patient this complaint coincided with the tenesmus and he retired early from the study. The other patient was a responder and reported a decreased daily frequency of stools, from seven to four. The suboptimal tolerability of octreotide in patients with IPAA is in stark contrast to observations in patients with

dumping syndrome and chemotherapy-induced diarrhoea. We have no clear explanation for the increased tenesmus and urgency in two patients, other than an altered reservoir function and disrupted neuronal pathways after re-anastomosis of an ileal pouch to the anal canal. However, this hypothesis needs to be explored further. Of interest, in a recently reported placebo-controlled trial with lanreotide (another somatostatin analogue) in polycystic liver disease, a significantly increased rate of diarrhoea was observed in actively treated patients [20]. The serious adverse event of a recurrent oesophageal adenocarcinoma in a placebo-treated patient with previous subtotal oesophagectomy was classified as unrelated because it was discovered at a previously scheduled gastroscopy.

In conclusion, in this double-blind controlled proof-of-concept trial, we did not observe a signal of efficacy of SC octreotide to treat diarrhoea associated with IPAA. To verify if the lack of benefit and possible reduced tolerance is specific to patients with an ileoanal pouch, larger controlled trials should be carried out in a well-defined population of patients with pouch dysfunction.

Conflict of interests

GVA: consultancy for Novartis Pharma. Other authors: no conflicts. MF holds a postdoctoral position and GVA and SV are senior clinician-scientists of the Fonds voor Wetenschappelijk Onderzoek Vlaanderen.

Authors' contribution

GVA and AD: protocol development, patient follow-up, manuscript preparation, patient recruitment. SV, MN, MF, AW, FP, PR: patient recruitment, patient follow-up, safety assessments, manuscript review. KR, LV: study coordination, adverse event reporting, CRF completion.

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