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Ciprofloxacin for prevention of postoperative recurrence in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study

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Abstract

Background—The commensal bacterial flora plays a critical role in postoperative recurrence of Crohn's disease (CD). We conducted a randomized, double-blind, placebo-controlled 6 months pilot trial of ciprofloxacin for the prevention of endoscopic recurrence in patients with CD who underwent surgery.

Methods—Thirty-three patients with CD, who had undergone surgery with ileo-colonic anastomosis within the previous 2 weeks, were randomized to treatment with ciprofloxacin (500 mg twice daily) or placebo tablets for 6 months. Endpoints were endoscopic recurrence at 6 months and safety and tolerability of long-term ciprofloxacin therapy.

Results—Thirty-three patients were randomized; 14 patients discontinued the study early. Significant endoscopic recurrence was observed in 3 of 9 patients (33%) in the ciprofloxacin

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group and 5 of 10 patients (50%) in the placebo group at 6 months after surgery (p<0.578). The intention-to-treat analysis demonstrated endoscopic recurrence in 11/17 patients (65%) in the ciprofloxacin group and 11/16 patients (69%) in the placebo group at month 6 (p<0.805). Thirty-six adverse events (AE's) occurred in 19/33 patients (58%). Possible drug associated AE's occurred significantly more often in the ciprofloxacin group (p<0.043), leading to study drug discontinuation in 24% (4/17) and 6% (1/16) patients in the ciprofloxacin group and placebo group, respectively (p<0.166).

Conclusion—In this pilot study, ciprofloxacin was not more effective than placebo for the prevention of postoperative recurrence in patients with CD. Long-term ciprofloxacin therapy is limited by drug-associated side effects. Future studies in postoperative prevention of CD should evaluate antibiotic approaches with a more favorable safety profile.

Keywords

Crohn's disease/surgery; ciprofloxacin; quinolone; Anti-Infective Agents/adverse effects; inflammatory bowel diseases

Introduction

Several factors are thought to contribute to the chronic relapsing nature of the intestinal inflammatory process in patients with CD. These factors include as-yet unidentified environmental exposures, a genetic disposition and an unbalanced immune reaction to the commensal microbiota of the intestine [1]. Despite advances in the use of immunosuppressive and biologic agents such as thiopurines and monoclonal antibodies to tumor necrosis factor (TNF), surgical resection is eventually required in more than one half of patients with CD [2]. Recurrence of active disease occurs in the majority of patients after resection and is a serious limitation of surgical management. Clinical recurrence depends on several factors including, the age at operation, the anatomic location and the presence of fistulizing disease and environmental factors such as cigarette smoking [3-7]. Clinical (symptomatic) relapses occur cumulatively in 34% of patients 3 years after surgery and in approximately 40%-65% of patients 5-15 years after surgery [3, 6, 8, 9]. Reoperation rates are also high ranging from 30-70% after 10 years [6, 10-12]. Therefore more effective strategies to prevent the recurrence of CD after surgery are needed.

The intestinal microbiota plays a critical role in the reoccurrence of inflammation at the resection site. This has been elegantly proven by the infusion of intestinal contents in the excluded ileum after protective loop ileostomy in patients with CD, which induced mucosal inflammation in the neoterminal ileum comparable to lesions seen endoscopically in postoperative relapse [13]. Prophylactic therapy with imidazole antibiotics (metronidazole or ornidazole) following surgical resection demonstrated reduced rates of both postoperative recurrence of endoscopically visible lesions after 3 and 12 months and clinical recurrence [14, 15]. However, in these trials a high rate of drug-associated side effects was observed leading to the withdrawal of up to 32% of treated patients, thus limiting the clinical utility of both drugs.

Ciprofloxacin has not been evaluated for prevention of postoperative recurrence of CD as demonstrated by endoscopy or clinical symptoms. Ciprofloxacin is a quinolone that is primarily effective against Enterobacteriaceae including *E. coli* and aerobic Gram positive and negative cocci [16]. Adherent or invasive *E. coli* have been reported to occur with increased frequency in the neoterminal ileum of patients with CD who experience postoperative endoscopic recurrence of inflammation, thereby providing a rationale to evaluate ciprofloxacin for prevention of postoperative endoscopic recurrence in patients with CD following surgical resection [17, 18]. Several controlled and uncontrolled trials have reported possible efficacy of ciprofloxacin in the therapy of fistulizing CD and inflammatory luminal disease [19]. However, no preliminary data exist regarding the efficacy and tolerability of long–term ciprofloxacin therapy in patients with CD following surgical resection.

We conducted a pilot randomized, double-blind, placebo-controlled 6 months trial of ciprofloxacin for the prevention of endoscopic recurrence in patients with CD who underwent surgery with ileo-colonic anastomosis.

Methods

Study design and patients

This study was a pilot multicenter, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of ciprofloxacin for the prevention of postoperative recurrence in patients with CD. The study was conducted at 6 centers between January 2008 and March 2011. The institutional review boards of each participating center approved the study and all patients provided written informed consent.

Patients who had undergone ileal or ileocolonic resection with ileocolonic anastomosis for CD within the previous 2 weeks were eligible for the trial. Patients were excluded if there was gross evidence of CD at the operative margins or in the proximal or distal segments of the intestine. Other exclusion criteria were the presence of a stoma, serum creatinine concentration > 1.5 mg/dl, the desire to become pregnant during the study, known malignancies, intolerance to quinolones or previous long-term therapy with ciprofloxacin of > 4 weeks prior to surgery. Perianal disease was not an exclusion criterion. No other treatments for CD or therapies involving more than 10 days of broad-spectrum antibiotics were permitted.

The study was registered with ClinicalTrials.gov (NCT00609973).

Treatment

Patients were randomized in a 1:1 ratio to oral treatment with ciprofloxacin 500 mg or identical appearing placebo twice daily for 6 months. Generic ciprofloxacin 500 mg tablets and placebo tablets were provided by Apotex (Toronto,Canada) from 2008-2010 and by Mylan (Cannonsburg, USA) from 2010-2011. Randomization took place at the trial central pharmacy at the University of North Carolina. Randomization was performed by permuted-block randomization with a block size of 4 per site.

Study endpoints

This pilot study had the following efficacy endpoints: a) evaluation of the percentage of patients with an endoscopic recurrence in the neoterminal ileum and at the ileocolonic anastomosis 6 months after enrollment and clinical recurrence during the study; b) assessment of safety and tolerability of a 6-month therapy of ciprofloxacin (500 mg bid). For the assessment of endoscopic recurrence ileocolonoscopy was performed 6 months after inclusion in the study. To assess the recurrence in the neoterminal ileum, the Rutgeerts score was used [9]. The definitions were as follows: i0 - no lesions; i1 - ≤ 5 aphthous lesions; i2 - ≥ 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis (i.e., < 1 cm in length); i3 - diffuse aphthous ileitis with diffusely inflamed mucosa; i4 - diffuse inflammation with already larger ulcers, nodules, and/or narrowing. The previously developed Marteau score was used for endoscopic recurrence in the colon. The scores were as follows: c0 - no macroscopic lesions; c1 – less than 5 aphthous or superficial ulcerations per segment or frank erythema or edema without ulceration; c2 – more than 5 aphthous or superficial ulcerations on at least one colonic segment; c3 - Deep ulceration affecting less than 10% of the surface of the entire colon and less than 5 deep ulcerations in each colonic segment; c4 - Deep ulcerations affecting more than 10% of the surface of the colon, or more than 5 deep ulcerations in a colonic segment, or presence of strictures [20]. Endoscopic recurrence was defined as a Rutgeerts score ≥ i2 or a Marteau score ≥ c2. Also photo-documentation of the anastomosis and neoterminal ileum of each patient was reviewed in a blinded fashion by two of the investigators (H.H., K.I.). All scores of this second evaluation were in agreement with the initial evaluation. Clinical recurrence was assessed using the Harvey-Bradshaw Index for CD activity [21]. A score of ≥ 5 at any postoperative visit or an interval increase of 3 points over the previous visit score defined clinical recurrence.

Schedule of study evaluations

Study visits including laboratory evaluations (complete blood count, liver function tests (AST, ALT), serum electrolytes (sodium and potassium, creatinine, urea, C-reactive protein), physical exam and evaluation of disease activity using the Harvey Bradshaw Index were performed at weeks 4, 12 and 24 after the start of medication. Each patient was interviewed for possible side effects during the study visits at week 4, 12 and 24 and additionally by phone at weeks 8, 18 and 28. The investigator classified each patient-reported AE according to relationship/causality (unrelated, unlikely related, possibly related, probably related and definitely related) criteria and also reported the final outcome of each AE. Total ileocolonoscopy was performed at week 24 (6 months) after surgery.

Statistical analysis

The main goals of this pilot study were to investigate the safety and tolerability of long-term therapy with ciprofloxacin and the endoscopic recurrence of CD 6 months after surgery. However, the study was not designed to definitively determine the effectiveness of ciprofloxacin, but rather to generate feasibility data. It was planned to randomize 40 patients in this pilot trial in order to design a larger definitive trial.

The analyses utilized descriptive statistics to define the characteristics of the study cohort in this exploratory trial. For statistical comparisons between the two arms of the study the Wilcoxon rank sum test was employed for continuous variables and the chi-square or Fisher's exact for categorical variables. Intention to treat (ITT), a modified ITT (mITT) and per-protocol (PP) analysis were performed. For the ITT analysis patients without ileo-colonoscopy and clinical evaluation at the 6-months visit were considered to have endoscopic and clinical recurrence of CD. The mITT included all patients undergoing ileocolonoscopy and clinical evaluation at the 6 months visit, but stopped the study drug before the 6 months ileocolonoscopy (n=3). Patients completing all study visits including the final ileocolonoscopy and remained on study drug throughout the study were included in the PP analysis. SAS System version 8.1 was used to conduct all statistical analyses.

Results

Thirty-three patients (17 in the ciprofloxacin and 16 in the placebo group) were recruited into the study. The baseline characteristics were similar in the 2 patient groups (Table 1). The flow of patients through the trial is shown in Figure 1. Altogether 14 patients discontinued the study for the following reasons: AE (n=2), serious AE (n=1, anastomotic leak requiring re-operation), prohibited medication use (n=2; development of a new enterocutaneous fistula requiring broad-spectrum antibiotics, kidney infection requiring long-term broad-spectrum antibiotics), protocol non-compliance (n=5), lost to follow-up (n=3) and withdrawal of consent (n=1). Additionally, 3 patients discontinued the study drug due to an AE but remained in the study for safety follow-up and underwent ileocolonoscopy at 6 months and were included in the mITT analyses. The study was terminated prematurely in March 2011 due to slow recruitment, the large number of study discontinuations, and expiration of funding.

Clinical effectiveness of ciprofloxacin

Endoscopic recurrence—Nine patients in the ciprofloxacin group and 10 patients in the placebo group underwent endoscopy at 6 months after inclusion in the trial and were included in the mITT analysis. Endoscopic recurrence ≥ Rutgeerts score i2 was observed in 3/9 patients (33%) in the ciprofloxacin group and 5/10 patients (50%) in the placebo (Figure 2) ($p< 0.578$). There were no significant differences in the distribution of the Rutgeerts scores across both groups (Figure 3). One patient in the ciprofloxacin group was found to have mild colonic inflammation (Marteau score 1). All the remaining patients had a colonic Marteau score of 0. According to the ITT analysis 11/17 patients (65%) in the ciprofloxacin group and 11/16 patients (69%) in the placebo group were classified as having recurred endoscopically at 6 months ($p<0.805$). Seven patients in the ciprofloxacin group and 9 in the placebo group completed the study per-protocol. In the per-protocol analysis there was no significant difference between the groups with respect to Rutgeerts scores ≥ i2 (42% (3/7) in the ciprofloxacin group vs 55% (5/9) in the placebo group) ($p<0.614$).

Clinical recurrence—Four patients experienced a clinical recurrence at week 24 as determined by a Harvey Bradshaw index ≥5 (mITT: ciprofloxacin 18% (2/11) and placebo

18% (2/11); p<1.000; PP: ciprofloxacin 22% (2/9) and placebo 20% (2/10); p<0.924). All patients with a clinical recurrence had at least an endoscopic Rutgeerts score of i2.

Assuming clinical activity of CD in all discontinued patients without follow-up (n=8 ciprofloxacin and n=6 placebo), clinical recurrence of active disease occurred in 10/17 patients 59% in the ciprofloxacin group and 8/16 patients (50%) in the placebo group (p<0.611).

Safety and Tolerability of ciprofloxacin—Overall 36 AE's occurred in 19/33 (58%) of randomized patients (10 patients in the ciprofloxacin group and 9 patients in the placebo group) (Tables 2 and 3). Of the AE's, 28% (10/36) were thought to be possibly or probably related to the study drug. All side effects resolved without sequelae during the study or after the study drug was stopped. After unblinding of the randomization, 10 AE's, which were judged to be possibly or probably related to the study drug, occurred more frequently in the ciprofloxacin group relative to the placebo group (9 AE's in 6 patients in the ciprofloxacin group vs. 1 AE in 1 patient in the placebo group, p<0.043) (Table 3). Of the drug-related AE's, 44% occurred within the first 10 days, 33% between day 10-20 and 33% more than 30 days after the start of the study drug. Five patients stopped the study drug due to the possible drug-related AE (4 patients in the ciprofloxacin group (24%) vs 1 patient in the placebo group (6%); p<0.166). The relative risk for experiencing a drug-related side effect in the ciprofloxacin compared to the placebo group was 5.6 (95% confidence intervals (CI) 0.8-42). No laboratory abnormalities attributable to the study drug and no cases of *Clostridium difficile* infection were observed during the study period.

Discussion

Targeted suppression or regulation of the intestinal bacterial flora with antibiotics is a compelling concept to prevent postoperative recurrence of CD. However, this pilot trial did not demonstrate any trends towards efficacy of ciprofloxacin for prevention of endoscopic postoperative recurrence in patients with CD. Fifty eight percent of the patients experienced at least one AE during the 6 months trial period. Although the overall numbers of AE's or the number of patients who experience AE's were not significantly different between the ciprofloxacin and placebo-treated patients, there were significantly more AE's that were judged as possibly drug related in the ciprofloxacin group and these AE's also led to a higher patient withdrawal rate. All drug related AE's found in this study are known to be associated with quinolone antibiotics [22, 23]. Moreover, there were some additional AE's in the ciprofloxacin group as listed in Table 2 that were not judged to be related to the study drug, but are known to be a side effect of quinolone therapy. Due to the small sample size and the resulting large 95% confidence interval, the observed increased relative risk for experiencing a ciprofloxacin-related side effect did not reach statistical significance. Nevertheless, one could reasonably assume that such differences might well become significant in a larger trial thus limiting postoperative therapy with ciprofloxacin.

The high percentage of AE's observed in this trial need to be put into context with the results of 3 previous trials using similar doses of ciprofloxacin over time periods up to 6 months in patients with CD and ulcerative colitis. Two of the trials did not report

significantly higher rate of drug-related side effects in the ciprofloxacin group compared to the placebo controls [24, 25]. However in both trials the participating patients had active disease and were also on a concomitant steroid taper. The steroid use and the disease activity could have influenced the occurrence of some of the AE's. Additionally, the desire to become healthier might have resulted in underreporting of mild AE's by the patients. One trial performed in 1997 included 89 patients with CD and randomized them to either ciprofloxacin (500-750 mg bid) or placebo for 6 months. This trial is mentioned only in an analysis of a pharmaceutical database [22]. Ciprofloxacin-associated side effects were reported in 20% of the patients with a discontinuation rate of 18%, which is in the same range as observed in our trial (28% and 24%, respectively).

Previous studies investigating long-term antibiotic therapy for postoperative prevention of CD also reported a high frequency of adverse events. In studies comparing metronidazole for 3 months or ornidazole for 12 months with placebo controls, AE's were observed in 38% and 47% of all patients, respectively [14, 15]. In both trials patients on antibiotic therapy experienced significantly more drug related AE's compared to the placebo group. Interestingly, a recent postoperative trial using approximately 10 mg/kg bodyweight metronidazole (3x250 mg/day) described fewer drug-associated AE's compared to a similar trial using 20 mg/kg bodyweight metronidazole [15, 26] suggesting that lowering the dosage of an antibiotic may decrease the extent of drug-associated AE's in the postoperative setting.

The aim of this trial was not to evaluate the efficacy of ciprofloxacin in the prevention of postoperative endoscopic recurrence, but rather to evaluate the feasibility of such a trial in the USA and to determine a crude estimate of the frequency of endoscopic recurrence after 6 months in order to plan a larger definitive trial. Therefore no definitive conclusion with regard to clinical efficacy of ciprofloxacin can be drawn from this study.

In our trial the endoscopic relapse rate was 50% in the placebo group. Most postoperative studies, which employed the Rutgeerts scoring system, assessed postoperative endoscopic recurrence in patients 3 months after the surgery [14, 15, 26-32]. These studies, with the exception of a Canadian trial [27], were all performed in Europe and demonstrate heterogeneity of the endoscopic recurrence with 35%-75% of the Rutgeerts scores being reported ≥ i2. Five clinical trials evaluated the endoscopic relapse at the anastomosis after 12 months and lesions with a Rutgeerts score of ≥ i2 occurred in 58%-85% [14, 26, 30, 31, 33]. We chose an endoscopic evaluation after 6 months, because we anticipated that recurrence rates would be rather low in a 3-months trial. A 12-months study was judged to be not feasible due to concerns of safety and tolerability of the antibiotic therapy. Before now, the only other study with a 6-month postoperative endoscopic evaluation reported an endoscopic recurrence rate of 38% with a Rutgeerts score ≥ i2 [20].

We encountered significant problems in both recruiting and retaining patients after randomization. Generally, the reasons for recruitment-related problems encountered by investigator-initiated trials are multifactorial including competition from industry-sponsored trials, legal contract issues with individual sites, limited monetary reimbursement for study efforts, patient preferences and engagement of the investigators [34, 35]. The retention problems in the study can partially be explained by the fact that the study was recruited in

tertiary centers for inflammatory bowel diseases. Many patients are referred to these centers for surgery but often receive their basic gastroenterological care a long distance away in their home community. Most of the non-compliant study patients were recruited postoperatively on the surgical ward but had not been previously treated at the site. Moreover, the awareness of the study participants that the study drug was a well-established antibiotic therapy, to which most of the participants had been exposed probably at least once during the previous disease course, might have influenced the compliance in the study. Newer drugs with uncertain long-term effects might increase adherence to a study protocol.

In conclusion, in this pilot study ciprofloxacin was not more effective than placebo for the prevention of postoperative recurrence in patients with Crohn's disease. Ciprofloxacin was poorly tolerated and led to treatment discontinuation in a high proportion of patients. Any future studies of antibiotics in this patient population should evaluate antibiotics with a more favorable safety profile.

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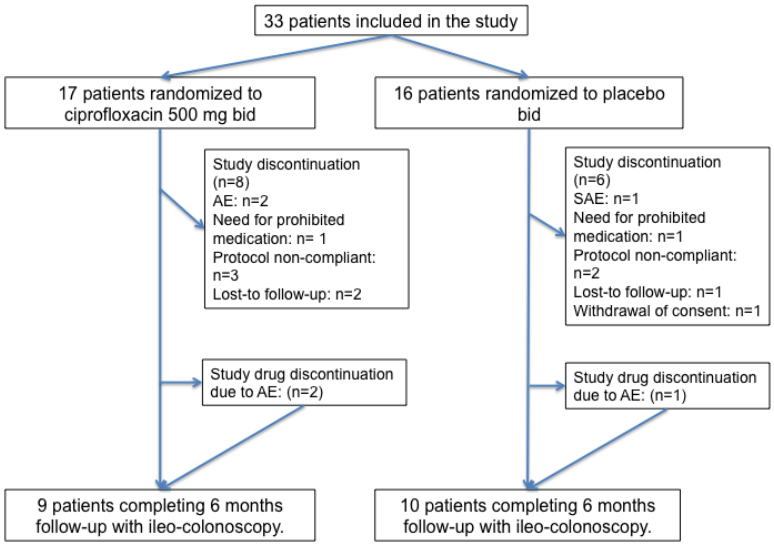

Figure 1.

Study flow diagram. Two study subjects in the ciprofloxacin group and 1 study subject in the placebo group, who dropped out due to AE and stopped taking the drug underwent colonoscopy and were analyzed according to ITT.

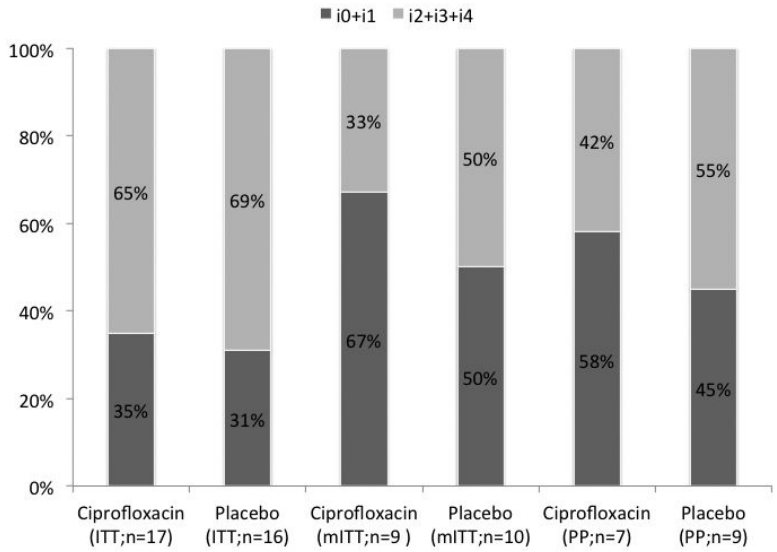

Figure 2.

Proportion of patients in endoscopic remission (endoscopic grade score of i0 or i1) vs recurrence (endoscopic grade score of i2, i3, or i4) of CD at 6 months after random assignment to ciprofloxacin or placebo. ITT; intention to treat analysis; mITT; modified intention to treat analysis; PP; per protocol analysis.

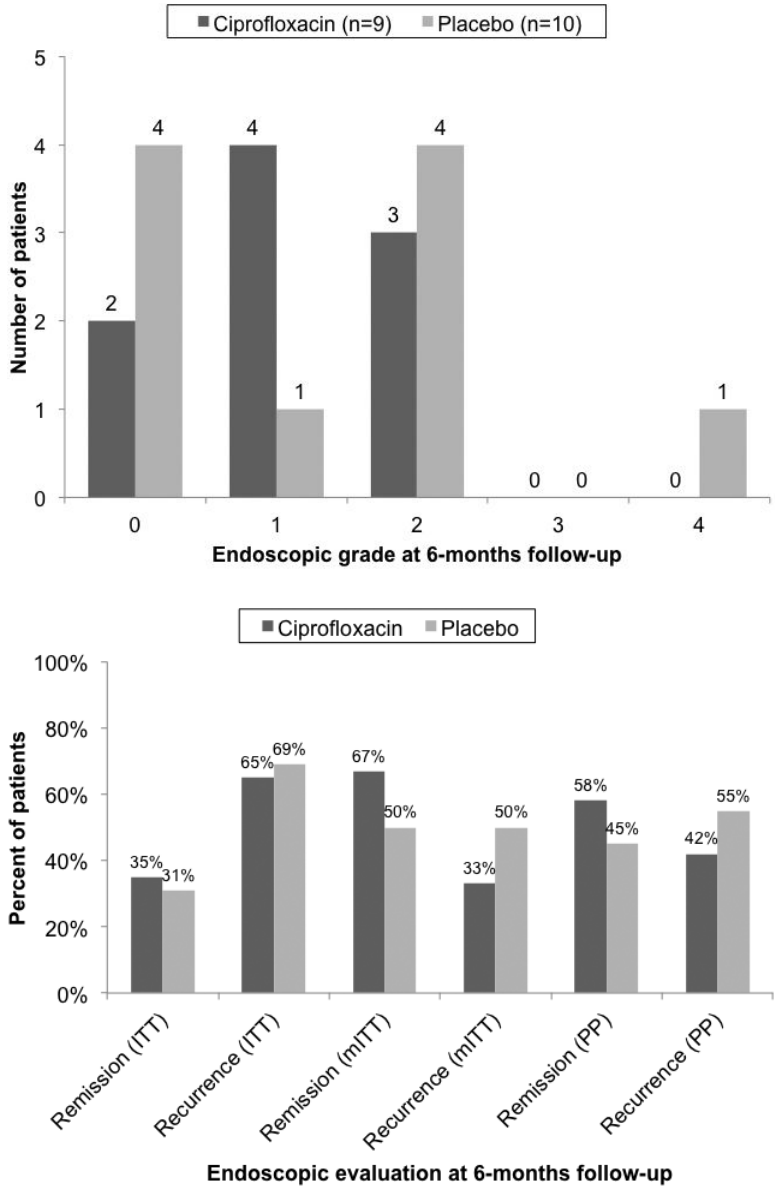

Figure 3.

Distribution of patients across Rutgeerts endoscopic grades of CD recurrence 6-months after assignment to ciprofloxacin or placebo.

Table 1

Baseline characteristics in the Ciprofloxacin compared with the Placebo Group (none of the values were statistically significant)

	Ciprofloxacin	Placebo	p-value
Sex, n (M/F)	10/7	8/8	<0.731
Median age at resection (years) (Range)	33 (19-70)	27 (18-61)	<0.179
Median duration of disease (years) (Range)	10 (0 -51)	6 (0-25)	<0.035
Smoker, n	4	0	<0.161
Number of resections, n			<0.957
1	14	13	
2	2	2	
3		1	
>3	1		
Disease Behavior, n (%)			<0.721
Non-stricturing, non-penetrating	4 (24%)	2 (13%)	
Stricturing	8 (47%)	10 (63%)	
Penetrating	5 (29%)	4 (25%)	
IBD drug therapy before surgery, n (%)			
Mesalamine	4 (24%)	5 (31%)	<0.708
Immunosuppression*	3 (18%)	5 (31%)	<0.438
Steroids**	7 (41%)	4 (25%)	<0.464

*Azathioprine/6-MP or anti-TNF agent

**Systemic steroids or budesonide (Entocort®)

Table 2

List of adverse events, which were classified as not or unlikely related to the study drug.

	Both groups	Ciprofloxacin	Placebo
Adverse event			
Abdominal pain	3	2	1
Joint pain	3	1	2
Headache	2	2	0
Minor wound healing problems	2	1	1
Urinary tract infection	2	0	2
Bloating	2	0	2
Sleeplessness	1	1	0
Constipation	1	1	0
Low back pain	1	0	1
Sinus infection	1	0	1
Rectal bleeding	1	1	0
Dehydration	1	1	0
Acne upper chest	1	1	0
Dry Eyes	1	1	0
Skin lesion	1	1	0
Fatigue	1	1	0
Nausea	1	1	0
Tinnitus	1	1	0
All	**26**	**16**	**10**

Table 3

List of adverse events, which were classified as probably or possibly related to the study drug.

	Both groups	Ciprofloxacin	Placebo
Adverse event			
Increase of diarrhea	2	2	
Headache	1	1	
Increased abdominal gas			1
Sun sensitivity	1	1	
Yeast infection	1	1	
Oral candidiasis	1	1	
Difficulty breathing	1	1	
Pharyngeal paresthesia (tickling)	1	1	
Tendonitis	1	1	
Total number of AE	**10**	**9**	**1**