Ciprofloxacin or Metronidazole for the Treatment of Perianal Fistulas in Patients with Crohn's Disease: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

Kelvin T. Thia, MBBS, Uma Mahadevan, MD,† Brian G. Feagan, MD,‡ Cindy Wong, MSc,‡ Alan Cockeram, MD,§ Alain Bitton, MD, | Charles N. Bernstein, MD,¶ and William J. Sandborn, MD**

Background: Although metronidazole and ciprofloxacin are used to treat perianal Crohn's disease (CD), no placebo-controlled trials have been performed.

Methods: We performed a placebo-controlled pilot trial to evaluate the efficacy and safety of metronidazole and ciprofloxacin in patients with perianal CD. Twenty-five patients with CD and actively draining perianal fistulas were randomized to receive ciprofloxacin 500 mg, metronidazole 500 mg, or placebo twice daily for 10 weeks. Remission and response of perianal fistulas were defined as closure of all fistulas and closure of at least 50% of fistulas that were draining at baseline, respectively. The primary endpoint was remission at 10 weeks.

Results: Ten patients were randomized to ciprofloxacin, 7 to metronidazole, and 8 to placebo. Remission at week 10 occurred in 3 patients (30%) treated with ciprofloxacin, no patients (0%) treated with metronidazole, and 1 patient (12.5%) treated with placebo ($P = 0.41$). Response at week 10 occurred in 4 patients (40%) treated with ciprofloxacin, 1 patient (14.3%) treated with metronidazole, and 1 patient (12.5%) treated with placebo ($P = 0.43$). Termination of the trial prior to week 10 occurred in 1 patient (10%) treated with ciprofloxacin, 5 patients (71.4%) treated with metronidazole, and 1 patient (12.5%) treated with placebo ($P < 0.02$). No serious adverse events occurred.

Conclusion: Remission and response occurred more frequently in patients treated with ciprofloxacin but the differences were not significant in this pilot study. Ciprofloxacin was well tolerated.

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Key Words: antibiotics, perianal fistula, Crohn's disease, inflammatory bowel disease

Perianal complications are common in Crohn's disease (CD) and generally denote a more aggressive phenotype.[1–3] The cumulative frequency of perianal fistulas in patients evaluated at referral centers has been reported to range from 14% to 38%.[4–9] From population-based studies, the burden of perianal fistulizing disease in the community is also significant, with a reported frequency range of 10%–26%.[10–12] Complex fistulas rarely heal spontaneously and medical and/or surgical therapy are often necessary.[13] Medical therapies reported to be of clinical benefit in uncontrolled trials include metronidazole,[14,15] ciprofloxacin,[16,17] 6-mercaptopurine,[18] methotrexate,[19] and cyclosporine.[20–22] Few controlled trials of therapy for perianal fistulas have been performed; however, effectiveness has been demonstrated for both induction and maintenance of fistula healing with infliximab therapy[23,24] and fistula clinical improvement with tacrolimus.[25] A pilot placebo-controlled trial of ciprofloxacin as adjunctive therapy to infliximab in patients with perianal CD has suggested a possible benefit of combination therapy.[26]

Despite an absence of controlled trial data demonstrating the efficacy of ciprofloxacin or metronidazole in the treatment of perianal fistulas, antibiotics have become widely accepted as first-line medical therapy based on uncontrolled small studies reporting short-term benefit.[13–17,27–30] We performed a 10-week placebo-controlled trial of ciprofloxacin or metronidazole 1000 mg per day in patients with perianal CD.

MATERIALS AND METHODS

Selection of Patients

This study was a multicenter, randomized, double-blind, placebo-controlled study that was conducted between April 2002 and May 2004. Eligible patients were at least 16

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From the *Miles & Shirley Fiterman Center for Digestive Diseases, Mayo Clinic, Rochester, Minnesota, †Division of Gastroenterology, University of California San Francisco, San Francisco, California, ‡Robarts Research Institute, University of Western Ontario, London, Ontario Canada, §Saint John Regional Hospital and Dalhousie University, New Brunswick, Canada, | Division of Gastroenterology, McGill University, Montreal, Quebec, Canada, ¶Section of Gastroenterology and University of Manitoba IBD Clinical Research Centre, Winnipeg, Manitoba, Canada.

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Reprints: William J. Sandborn, MD, Miles & Shirley Fiterman Center for Digestive Diseases, Mayo Clinic, 200 First St. SW, Rochester, MN 55905 (e-mail: Sandborn.William@mayo.edu).

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years of age with a confirmed diagnosis of CD for at least 1 month, stable concomitant medications (see below), and 1 or more open actively draining perianal fistulas. Female patients of child-bearing potential were required to have a negative pregnancy test and agreed to a medically accepted method of birth control. The following patients were not eligible: those who had received any antibiotics (including metronidazole and ciprofloxacin) within 2 weeks; those in need of urgent surgical intervention for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intraabdominal abscess requiring surgical drainage; those with local or systemic infection (including septic lesions in the perianal region); those with open draining rectovaginal fistulas, or open communicating or draining enterovesical, or abdominal wall fistulas; patients with planned inpatient hospitalization and those with a history of alcohol or other drug abuse, or any conditions associated with poor compliance within 6 months. In addition, patients with a history of an irreversible serum creatinine level >2.0 mg/dL; those with suspected or known intolerance or allergy to metronidazole or ciprofloxacin, and female patients who were pregnant or breast-feeding were also ineligible. The decision of whether surgical consultation, examination under anesthesia, and imaging of the perineum before study entry was left to the clinical discretion of individual investigators. The Institutional Review Board at each center approved the study and all participants gave their written consent.

Concomitant Therapy

Concomitant therapy with azathioprine, 6-mercaptopurine, methotrexate, mycophenolate mofetil, or oral steroids (conventional corticosteroids or budesonide) was permitted if the patient had been treated for at least 8 weeks in the case of azathioprine, 6-mercaptopurine, methotrexate, or mycophenolate mofetil and if the patient had been treated for at least 4 weeks with a stable dose for at least 2 weeks in the case of oral steroids. Patients could also receive oral mesalamine, sulfasalazine, olsalazine, or balsalazide, and/or topical rectal therapy with mesalamine or steroids if the dose had been stable for at least 2 weeks. Nutritional therapy (parenteral nutrition or enteral nutrition with elemental or semi-elemental diets) was discontinued at baseline. Patients receiving thalidomide, tacrolimus, cyclosporine, infliximab, or investigational therapies within 4 weeks were excluded. Patients receiving warfarin or theophylline within 2 weeks were also excluded. Any setons present were removed at the screening visit.

Study Medication

Metronidazole was supplied in 250 mg tablets and ciprofloxacin was supplied in 500 mg tablets. Eligible patients were randomly assigned to receive either metronidazole 500 mg orally twice daily plus 1 placebo tablet with a similar appearance to ciprofloxacin twice daily, or ciprofloxacin 500 mg orally twice daily plus 2 placebo tablets with similar appearance to metronidazole twice daily, or 3 placebo tablets twice daily (1 tablet with similar appearance to ciprofloxacin and 2 tablets with similar appearance to metronidazole).

Study Design

The 10-week study was a randomized, double-blind, double-dummy, placebo-controlled trial performed by the Clinical Alliance of the Crohn's and Colitis Foundation of America (CCFA) and the Clinical Consortium of the Crohn's and Colitis Foundation of Canada (CCFC). Twelve centers (10 in Canada, 2 in United States) participated in this study (Appendix). After a 1-week screening period, eligible patients were assigned to treatment groups (oral metronidazole, oral ciprofloxacin, or placebo) in a 1:1:1 ratio, based on a computer-generated randomization schedule prepared by Robarts Research Institute, University of Western Ontario, London, Ontario, Canada. The randomization was balanced by permuted blocks and stratified by center and patients were assigned to a treatment group according to a schedule maintained by the Investigational Pharmacist Service of the Mayo Clinic Pharmacy.

At entry (screening visit), each patient's demographics, characteristics, medical history, and current medications were recorded. Disease activity was assessed at the screening visit, baseline (week 0, randomization) visit, and after 2, 6, and 10 weeks. Patients recorded on diary cards the frequency of stools, the extent of their abdominal pain, and their well-being during the 7 days before each visit. At each visit a physical examination, fistula evaluation, quality of life assessment, and laboratory tests were conducted and patients were evaluated for adverse events.

The patients were assessed at each visit for the presence of open and actively draining perianal fistulas (defined as open fistulas with either spontaneous drainage or the ability to express drainage with gentle compression).[23] At baseline, a fistula diagram was completed for each patient and each particular perianal fistula that was open and draining was numbered. At each subsequent visit each of these numbered fistulas were evaluated and classified as open or closed. Closure of a fistula was defined as the absence of drainage, both spontaneous and on gentle compression. The disease-specific instrument used for measuring the activity of perianal fistula was the Perianal Disease Activity Index (PDAI).[31] The PDAI evaluates 5 categories affected by fistulas: discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration. Each category was graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4), with a higher score indicating more severe disease. Clinical disease activity was assessed with the Crohn's Disease Activity Index (CDAI); scores

<150 points indicates clinical remission, score of 150–219 indicates mildly active disease, scores of 220–450 indicates moderately active disease, and scores >450 indicate severely active disease.[32,33] We also measured disease-specific health-related quality of life using the Inflammatory Bowel Disease Questionnaire (IBDQ); scores <170 points indicate clinically active disease and scores ≥170 points indicate clinically inactive disease.[34] The patient and physician global assessment of fistula activity were measured; the patient was asked from the questionnaire "How much of a problem is (are) your fistula(s) causing you at this time?" and the physician was asked from the questionnaire "How much of a problem is (are) your patient's fistula(s) causing him or her at this time?" The patient and physician global responses to the respective questionnaires were scored as: 0 = no problems, 1 = a slight problem, 2 = a moderate problem, 3 = a serious problem, and 4 = a severe problem. The patient and physician global assessment of fistula activity, fistula closure assessment, PDAI, and IBDQ scores were determined at screening, baseline, 2, 6, and 10 weeks and the CDAI score was determined at baseline, 2, 6, and 10 weeks.

Outcomes and Statistical Analysis

The primary outcome measure was remission of perianal fistula (defined as closure of all open actively draining fistulas at baseline) and the primary endpoint, as specified in the study protocol, was remission at week 10. This primary outcome measure was a modification of the definition of fistula closure assessment used previously in an infliximab trial for fistula,[23] which defined remission or response as closure or reduction in draining fistula which was sustained over 2 consecutive visits (i.e., at least 21 days apart). The secondary outcome measures that were specified in the study protocol were: 1) remission at weeks 2 and 6; 2) improvement (defined as at least a 50% reduction from baseline in the number of open actively draining fistulas) at weeks 2, 6, and 10; 3) short-term durability of fistula closure (defined as maintaining remission for at least 2 visits, including week 10, i.e., at least 4 weeks); 4) patient and physician global assessment measured at weeks 2, 6, and 10; 5) PDAI at weeks 2, 6, and 10; 6) IBDQ at weeks 2, 6, and 10; and 7) CDAI at weeks 2, 6, and 10. The intention-to-treat population included all patients treated with study medication and had postrandomization outcome data. For group comparisons of the proportion of patients with fistula remission and improvement, Fisher's exact test was used. Analysis of variance was used for comparisons of physician and patient global assessment, PDAI, CDAI, and IBDQ scores. Safety analysis included all patients who had received at least 1 dose of the study medication. All tests were 2 sided. *P*-values <0.05 were considered statistically significant.

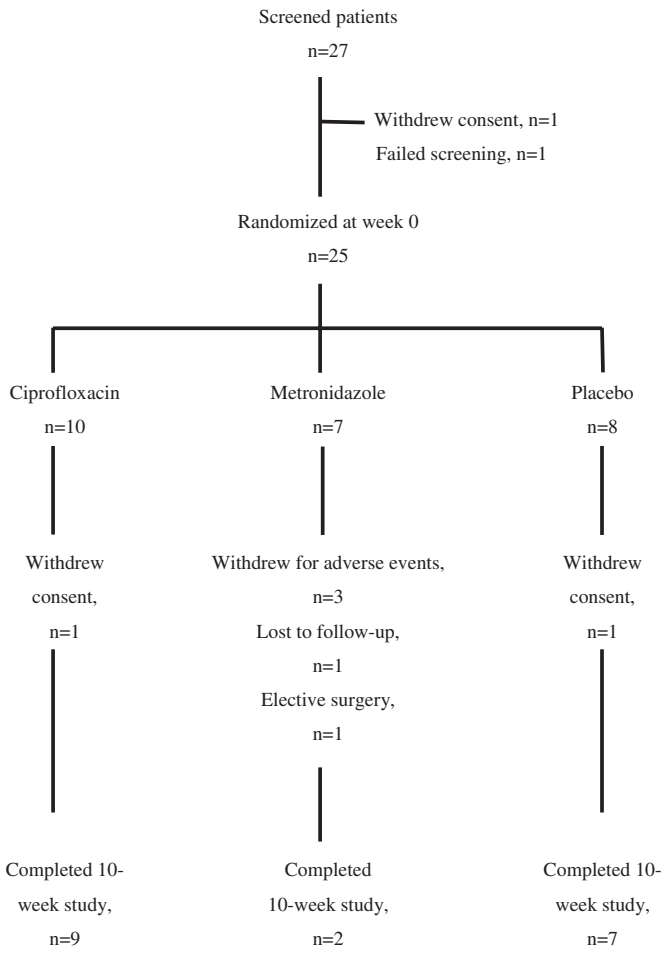

FIGURE 1. Enrollment and treatment of patients.

Sample Size

We estimated that 56 patients per treatment group were needed in order to have 80% power to detect a true difference in the proportion of patients who achieved remission at week 10, assuming that the proportion in the ciprofloxacin and metronidazole groups was 40%, that the proportion in the placebo group was 15%, and that 15% of patients would be lost to follow-up. We planned to recruit 168 patients.

RESULTS

A total of 27 patients at 12 centers were screened and 25 patients were enrolled in the study; 10 patients were randomized to treatment with ciprofloxacin, 7 to metronidazole, and 8 to placebo. All 25 patients met the inclusion and exclusion criteria and comprised the intention-to-treat population. A total of 7 subjects had early termination from the study. The proportion of patients with early termination were significantly greater in the metronidazole group (71.4%, $n = 5$) than in the ciprofloxacin group (10%, $n = 1$) and the placebo group (12.5%, $n = 1$) ($P < 0.02$). The reasons for

TABLE 1. Baseline Characteristics of the Patients

Variable	Ciprofloxacin $n=10$	Metronidazole $n=7$	Placebo $n=8$	*P*-value
Male sex	6 (60)	3 (42.9)	6 (75)	0.45
White race	9 (90.0%)	6 (85.7)	8 (100)	0.73
Mean (SD) age at entry, in years	36.7 (12.6)	49.3 (16.5)	33.1 (11.8)	0.08
Mean (SD) years since diagnosis	8.8 (9.1)	10.3 (9.7)	8.9 (7.4)	0.93
Current smoker	0 (0)	3 (42.9)	1 (12.5)	0.05
Previous surgery for Crohn's disease	7 (70)	2 (28.6)	5 (62.5)	0.27
Small intestinal resection	1 (10)	0 (0)	1 (12.5)	1.00
Ileocolic resection	3 (30)	1 (14.3)	1 (12.5)	0.69
Perianal surgery (abscess drainage, fistulotomy)	7 (70)	1 (14.3)	5 (62.5)	0.08
Number of open draining fistulas at baseline				
1	4 (40)	3 (42.9)	2 (25)	
2	5 (50)	3 (42.9)	5 (62.5)	0.94
≥3	1 (10)	1 (14.3)	1 (12.5)	
Patient Global Assessment,[a] mean (SD)	1.7 (0.7)	2.3 (0.5)	2.1 (0.6)	0.15
Physician Global Assessment,[a] mean (SD)	1.7 (0.5)	1.9 (0.7)	1.9 (0.4)	0.73
PDAI score,[b] mean (SD)	8.6 (2.7)	9.3 (2.8)	7.1 (1.8)	0.24
CDAI score,[c] mean (SD)	132.5 (109.2)	131.1 (63.7)	149.3 (91.5)	0.91
IBDQ score,[d] mean (SD)	180.1 (24.2)	151.0 (29.4)	181.2 (29.6)	0.07
Concomitant medications				
Azathioprine or 6 mercaptopurine	2 (20)	1 (14.3)	2 (25)	1.00
5-aminosalicylates (mesalamine or sulphasalazine)	4 (40)	3 (42.9)	4 (50)	1.00
Prior treatment with infliximab at any time	2 (20)	1 (14.3)	1 (12.5)	1.00

Data are expressed as number (percent) unless otherwise indicated.
[a]Scores ranging from 0-4, with higher scores indicating more severe disease.
[b]Scores ranging from 0-20, with higher scores indicating more severe disease.
[c]Scores <150 points indicates clinical remission, scores of 150-219 indicate mildly active disease, scores of 220-450 indicate moderately active disease, and scores >450 indicate severely active disease.
[d]Scores <170 points indicate clinically active disease, and scores ≥170 points indicate clinically inactive disease.

early termination included lost to follow-up ($n = 1$), withdrawal of consent ($n = 2$), adverse events ($n = 3$), and other reasons ($n = 1$). A summary of the patient disposition is provided in Figure 1. Enrollment in the study was open for ≈2.5 years and was terminated in July 2004 due to very slow recruitment before the target enrollment of 168 randomized patients was reached. The baseline characteristics of the 3 groups are as shown in Table 1.

Efficacy

At week 10, complete closure of all fistula (remission) was achieved in 30% of patients (3 of 10) in the ciprofloxacin group, no patients (0 of 7) in the metronidazole group, and 12.5% of patients (1 of 8) in the placebo group ($P = 0.41$). The improvement of fistulas at week 10 was seen in 40% of patients (4 of 10) in the ciprofloxacin group, 14.3% of patients (1 of 7) in the metronidazole group, and 12.5% of patients (1 of 8) in the placebo group ($P = 0.43$). The proportions of patients with remission, remission maintenance, and improvement at weeks 2, 6, and 10 in all 3 groups are shown in Table 2. The other secondary efficacy parameters measured (patient and physician global assessment, PDAI, CDAI, and IBDQ scores) at weeks 0, 6, and 10 are shown in Table 3.

Adverse Events

The frequency of adverse events is summarized in Table 4. Nineteen (76.0%) of the 25 patients reported adverse events, 7 patients (70.0%) in the ciprofloxacin group, 7 (100.0%) in the metronidazole group, and 5 (62.5%) in the placebo group ($P = 0.25$). The most frequently reported adverse events were unpleasant taste or sore mouth, cold symptoms or upper respiratory tract infections, and abscesses or open fistulas. Eight (32.0%) of the 25 patients reported adverse events that were considered possibly, probably, or definitely related to study medications: 2 (20%) in the ciprofloxacin group, 4 (57.1%) in the metronidazole group, and 2 (25.0%) in the placebo group ($P = 0.27$). Significantly more

TABLE 2. Proportions of Remission, Remission Maintenance, and Improvement in the 3 Treatment Groups

	Ciprofloxacin (n=10)	Metronidazole (n=7)	Placebo (n=8)	P-value
Remission				
Week 2	2 (20)	0 (0)	2 (25)	0.51
Week 6	1 (10)	1 (14.3)	3 (37.5)	0.46
Week 10	3 (30)	0 (0)	1 (12.5)	0.41
Remission maintenance				
Week 6	1 (10)	0 (0)	2 (25.0)	0.46
Week 10	1 (10)	0 (0)	1 (12.5)	0.99
Clinical improvement				
Week 2	5 (50)	1 (14.3)	2 (25.0)	0.32
Week 6	4 (40)	2 (28.6)	4 (50.0)	0.87
Week 10	4 (40)	1 (14.3)	1 (12.5)	0.43

Data expressed as number (percent).

patients in the metronidazole group (42.9%, n = 3) discontinued the study due to adverse events as compared with no patients (0%) in the ciprofloxacin and placebo groups (P = 0.02). However, there appeared to be little relationship with metronidazole (1 patient reported a mild rash and the other 2 patients had adverse events that were considered as remote or no relationship).

DISCUSSION

The results of this randomized, double-blind, placebo-controlled pilot study of ciprofloxacin or metronidazole for the treatment of CD perianal fistula failed to demonstrate that either antibiotic was more effective than placebo in the induction of remission for open actively draining perianal fistulas. However, the rates of fistula remission and improvement of 30% and 40%, respectively, in the ciprofloxacin treatment group were higher than in the metronidazole and placebo treatment groups. There were no differences seen in the scores of PDAI, CDAI, IBDQ, and patient and physician global assessment at any timepoint during the study.

An important limitation to our study is the small number of patients evaluated, with only 25 (14.9%) patients enrolled out of the 168 planned, and with only 18 (72.0%) of the enrolled patients completing the week 10 assessment. Therefore, differences in remission of fistula may not have been detected due to a type 2 statistical error. The study was initiated in November 2001 and was anticipated to complete enrollment by November 2004. However, a decision was made to terminate the study in July 2004 due to the very slow rate of patient recruitment. Some of the reasons for the inadequate rate of recruitment included a high prevalence of antibiotic usage in routine clinical practice and the increasing use of azathioprine, 6-mercaptopurine, and especially infliximab in patients with perianal fistulas.[13,35] For these reasons we believe that it is not feasible to conduct a placebo-controlled trial of antibiotics for the treatment of draining perianal fistulas. Alternative study designs that might be feasible include: 1) a placebo-controlled antibiotic withdrawal trial in patients who received antibiotic therapy for draining perianal fistulas, experienced fistula healing, and are receiving maintenance antibiotic therapy; and 2) a placebo-controlled trial of antibiotics as adjunctive therapy to treatment with an antitumor necrosis factor agent (see below). Notwithstanding these concerns regarding feasibility, we believe that it is vital to determine whether antibiotic therapy is effective because of the potential consequences of inappropriate use of these drugs. The important rising public health problem of *Clostridium difficile* colitis associated with the use of broad-spectrum antibiotics (including ciprofloxacin), and in particular the recent emergence of a virulent fluoroquinolone-resistant strain associated with increased mortality[36–38] underscore this point of view.

Another possible reason for failure to demonstrate a beneficial effect of ciprofloxacin and metronidazole may be due to a relatively weak treatment effect of both of these antibiotics for the induction of fistula remission. In an open-label study of 21 patients with perianal CD treated with metronidazole at 20 mg/kg/day, 56% were reported to have complete healing of their fistula, with clinical improvement typically occurring after 6–8 weeks of therapy.[14] A follow-up study of 17 of these patients, along with 9 additional patients, showed exacerbation of disease with dosage reduction.[15] These response rate should be interpreted with caution given these were open-label studies.

At the time our study was initiated there were no reported controlled trials on antibiotic treatment of perianal fistulas. More recently, a controlled study by West et al[26] reported on the use of ciprofloxacin as an adjunctive therapy

TABLE 3. Other Secondary Efficacy Parameters in the 3 Treatment Groups

	Ciprofloxacin (n=10)	Metronidazole (n=7)	Placebo (n=8)	P-value
Patient Global Assessment,[a] mean (SD)				
Week 0	1.7 (0.7)	2.3 (0.5)	2.1 (0.6)	0.15
Week 2	1.5 (0.7)	1.4 (1.1)	1.8 (0.9)	0.66
Week 6	1.3 (0.8)	1.7 (1.0)	1.1 (0.6)	0.51
Week 10	1.3 (1.0)	1.0 (0.0)	1.1 (0.7)	0.83
Physician Global Assessment,[a] mean (SD)				
Week 0	1.7 (0.5)	1.9 (0.7)	1.9 (0.4)	0.73
Week 2	1.5 (0.7)	1.3 (1.0)	1.5 (0.8)	0.78
Week 6	1.2 (0.9)	1.7 (0.8)	0.9 (0.6)	0.71
Week 10	1.2 (1.1)	1.5 (0.7)	1.4 (0.8)	0.96
PDAI, mean (SD)[b]				
Week 0	8.6 (2.7)	9.3 (2.8)	7.1 (1.8)	0.24
Week 2	7.2 (3.0)	6.7 (3.6)	5.9 (1.5)	0.72
Week 6	6.4 (3.5)	8.0 (3.8)	4.8 (1.8)	0.34
Week 10	6.1 (4.4)	4.5 (2.1)	5.6 (2.1)	0.73
CDAI, mean (SD)[c]				
Week 0	132.5 (109.2)	131.1 (63.7)	149.3 (91.5)	0.91
Week 2	127.6 (99.1)	157.4 (80.4)	171.4 (102.6)	0.28
Week 6	127.8 (102.1)	123.0 (85.0)	143.0 (102.4)	0.93
Week 10	125.1 (116.6)	101.0 (100.4)	161.0 (112.5)	0.22
IBDQ, mean (SD)[d]				
Week 0	180.1 (24.2)	151.0 (29.4)	181.2 (29.6)	0.07
Week 2	186.5 (13.9)	155.6 (32.5)	185.3 (28.7)	0.53
Week 6	187.2 (15.8)	160.0 (32.2)	188.6 (33.1)	0.71
Week 10	188.9 (16.7)	166.0 (50.9)	191.1 (30.6)	0.21

Data are expressed as number (percent) unless otherwise indicated.
P-values are derived from analysis of covariance with adjustment for the baseline score.
[a]Scores ranging from 0-4, with higher scores indicating more severe disease.
[b]Scores ranging from 0-20, with higher scores indicating more severe disease.
[c]Scores <150 points indicates clinical remission, scores of 150-219 indicate mildly active disease, scores of 220-450 indicate moderately active disease, and scores >450 indicate severely active disease.
[d]Scores <170 points indicate clinically active disease, and scores ≥170 points indicate clinically inactive disease.

to infliximab in patients with perianal CD. Twenty-four patients with draining perianal fistulas were randomized to receive ciprofloxacin 500 mg twice daily or placebo for 12 weeks. In addition, all the patients in both treatment groups received infliximab 5 mg/kg at weeks 6, 8, and 12. After 6 weeks of ciprofloxacin or placebo treatment (before infliximab), only 1 (9%) patient in the ciprofloxacin group and 2 (15%) in the placebo group ($P = 1.0$) had a clinical response (defined as a least a 50% reduction in baseline draining perianal fistulas), which were lower compared to the clinical response of 40% in the ciprofloxacin and 50% in the placebo group for our study at the same point in time. A possible reason for the lower clinical response in the study by West et al could be due to a more severe population of patients in their study, as evidenced by a higher frequency (54.2%) of concomitant azathioprine treatment. At 18 weeks, more patients assigned to ciprofloxacin had responded (73%) than those who had received placebo (39%); however, this difference was not significant ($P = 0.12$). In addition, there were also fewer cases of perianal abscess development in the ciprofloxacin group (1 case) compared with placebo (3 cases) after the infliximab therapy. This study was also limited by the small number of patients evaluated. Accordingly, further studies are needed to evaluate the efficacy of adjunctive therapy with antibiotics in patients treated with infliximab for perianal CD.

Early termination from the study occurred only among patients treated with metronidazole, but we could not establish a clear relationship of these adverse events to the known side effects of metronidazole.[39] Furthermore, given that only

TABLE 4. Adverse Events in the 3 Treatment Groups

	Ciprofloxacin (n=10)	Metronidazole (n=7)	Placebo (n=8)	P-value
Any adverse events	7 (70)	7 (100)	5 (62.5)	0.25
Any adverse event possibly, probably, or definitely related to study drug	2 (20)	4 (57.1)	2 (25)	0.27
Frequent adverse events				
Unpleasant taste/sore mouth	1 (10)	2 (28.6)	1 (12.5)	0.65
Cold symptoms/upper respiratory tract infection	4 (40)	1 (14.3)	1 (12.5)	0.43
Abscess/open fistula	2 (20)	3 (42.9)	0 (0)	0.14

Data are expressed as number (percent) unless otherwise indicated.

2 patients had completed 10 weeks of metronidazole, the tolerability of this drug among CD patients treated for perianal fistula cannot be adequately evaluated in this study. Our results are similar to those reported in uncontrolled trials of metronidazole for the treatment of perianal CD in which adverse events occurred commonly at a frequency of 50%–100%.[14,29] In our study the frequency of adverse events considered possibly, probably, or definitely related to ciprofloxacin treatment was 20%, which was similar to the placebo group. The adverse events observed in patients treated with ciprofloxacin were mild and did not require discontinuation of the medication. Our finding that ciprofloxacin was generally well-tolerated is similar to the experience from the other recent controlled trial of ciprofloxacin therapy in patients with perianal CD fistula.[26,40]

In conclusion, in this small double-blind placebo-controlled pilot study, remission (complete fistula closure) and response occurred more frequently in patients treated with ciprofloxacin than metronidazole or placebo, but the differences did not reach statistical significance.

APPENDIX

CCFA Member Institutions and Affiliates Institutions and CCFC Participating Centers

Brian Feagan, MD, University Campus, Department of Medicine, London, Ontario; Pierre Paré, MD, CHA-Hospital St-Sacrement, Quebec; Desmond Leddin, MD, Queen Elizabeth II, Health Sciences Center, Halifax, Nova Scotia; Eugene Greenberg, MD, Carle Clinic, Urbana, Illinois; Charles Bernstein, MD, Section of Gastroenterology, University of Manitoba, Winnipeg, Manitoba; Alain Bitton, MD, Royal Victoria Hospital Montreal, Quebec; Chrystian Dallaire, MD, Ctr Hosp U Quebec-St. Francois, Quebec City, Quebec; Alaa Rostom, MD, The Ottawa Hospital, Ottawa, Ontario; Remo Panaccione, MD, Calgary, Alberta; Alan Cockeram, MD, Saint John Regional Hospital, New Brunswick; Douglas Wolf, MD, Atlanta Gastroenterology Associates, LLC, Atlanta, Georgia.

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