Combination ciprofloxacin and metronidazole in severe perianal Crohn's disease

MJ SOLOMON, MB, BCH, BAO (HONS), FRACS, RS McLEOD, MD, FRCSC, FACS, BI O'CONNOR, BScN, AH STEINHART, MD, FRCPC, GR GREENBERG, MD, FRCPC, Z COHEN, MD, FRCSC, FACS

MJ SOLOMON, RS McLEOD, BI O'CONNOR, AH STEINHART, GR GREENBERG, Z COHEN. Combination ciprofloxacin and metronidazole in severe perianal Crohn's disease. *Can J Gastroenterol* 1993;7(7):571-573. Severe perianal involvement in Crohn's disease often is refractory to both medical and surgical treatment. The object of this study was to review retrospectively the response of patients with severe perianal Crohn's disease to a combination of ciprofloxacin and metronidazole. Fourteen patients (seven males, seven females, mean age 34.8 years) were treated consecutively with a combination of ciprofloxacin (1000 to 1500 mg/day) and metronidazole (500 to 1500 mg/day). All had quiescent bowel disease. Perianal disease had been present for a mean of 28.4 months. Six patients were on metronidazole at presentation and seven had had previous perianal surgery (mean of three operations per patient). All patients were symptomatic. Nine patients had complex fistula, six had anal canal ulceration, one had a rectovaginal fistula and five had discharging abscesses. Seven patients had multiple perianal lesions. Physician assessment at a mean of 12 weeks after commencing therapy revealed three patients healed, nine improved, one unchanged and one worsened, requiring a defunctioning stoma. Thus, 12 of 14 (85%) showed benefit from combination therapy. Patients have been followed a mean of 6.4 months since commencing therapy. Five patients had therapy stopped at 12 weeks and have not required further treatment, six patients required continuous low dose therapy (ciprofloxacin 500 to 1000 mg/day plus metronidazole 500 to 750 mg/day), three patients stopped therapy at 12 weeks but subsequently restarted therapy because of relapse. Thus, nine of 14 patients (64%) required continuous or repeat therapy. At present, seven patients have quiescent, six have mild, and one has moderate perianal disease. These results suggest that ciprofloxacin plus metronidazole may be effective in severe perianal Crohn's disease. (*Pour résumé, voir page 572*)

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Inflammatory Bowel Disease Unit and Department of Surgery and Medicine, University of Toronto and Mount Sinai Hospital, Toronto, Ontario

Correspondence and reprints: Dr RS McLeod, Suite 451, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5

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PERIANAL DISEASE OCCURS IN 43 TO 94% of patients with Crohn's disease (1,2). Clinical features are variable and include skin tags, ulceration, perianal abscess and fistulas, anal canal ulcers, fissures, induration and stenosis. Perianal abscess and fistula often occur simultaneously and are usually symptomatic.

Many patients have mild symptoms or are asymptomatic and require no intervention. Others have symptoms ranging from pain and discharge to gross fecal incontinence with restriction of lifestyle and sexual activity.

Treatment includes surgical and nonsurgical modalities. Surgery usually is limited to simple, low fistula (anal canal to skin) and drainage of perianal abscesses. More aggressive surgery may result in damage to the anal sphincter and incontinence. Severe disease may require defunctioning stomas or abdominoperineal excision. Thus, medical therapies have been the mainstay of treatment and include corticosteroids, azathioprine, 6-mercaptopurine as well as antibiotics. Only 6-mercaptopurine, metronidazole and ciprofloxacin have shown any effectiveness in small uncontrolled trials (3-8). The concerns of significant side effects using 6-mercaptopurine, such as bone marrow suppression, leukemia and pancreatitis, have limited the general use of this drug.

Association de ciprofloxacine et métronidazole dans la maladie de Crohn périanale sévère

RÉSUMÉ: L'atteinte périanale sévère dans la maladie de Crohn est souvent réfractaire au traitement médical et chirurgical. Le sujet de ces études était de passer en revue rétrospectivement la réponse de patients atteints de maladie de Crohn périanale sévère à une association de ciprofloxacine et de métronidazole. Quatorze patients (sept hommes, sept femmes; moyenne d'âge 34,8 ans) ont été traités consécutivement avec une association de ciprofloxacine (1000 à 1500 mg/jour) et de métronidazole (500 à 1500 mg/jour). Ils présentaient tous une maladie intestinale quiescente. La maladie périanale était présente depuis en moyenne 28,4 mois. Six patients étaient sous métronidazole au moment de la présentation et sept avaient déjà subi une chirurgie périanale (moyenne de trois interventions par patient). Tous les patients étaient symptomatiques. Neuf patients présentaient une fistule complexe, six avaient une ulcération du conduit anal, une présentait une fistule rectovaginale et cinq des abcès avec écoulement. Sept patients présentaient des lésions périanales multiples. L'évaluation médicale, en moyenne 12 semaines après l'amorce du traitement, a révélé que trois patients avaient cicatrisé, neuf s'étaient améliorés, un était resté inchangé et un s'était aggravé, nécessitant une stomie. Ainsi, 12 des 14 (85 %) ont bénéficié du traitement d'association. Les patients ont été suivis sur une moyenne de 6,4 mois après l'amorce du traitement. Cinq patients ont interrompu leur traitement à 12 semaines et n'ont pas nécessité d'autre traitement, six patients ont nécessité un traitement continu à faible dose (ciprofloxacine 500 à 1000 mg/jour plus métronidazole 500 à 750 mg/jour), trois patients ont interrompu le traitement après 12 semaines mais l'ont repris par la suite à cause d'une rechute. Ainsi, neuf des quatorze patients (64 %) ont nécessité un traitement continu ou répété. À l'heure actuelle, sept patients sont quiescents, six présentent une maladie légère et un une atteinte périanale modérée. Ces résultats suggèrent que la ciprofloxacine plus métronidazole pourrait être efficace dans la maladie de Crohn périanale sévère.

Symptomatic severe perianal Crohn's disease invariably involves some degree of sepsis and may explain the tendency for perianal disease and colitis to respond more successfully than small bowel disease to antibiotic therapy. The mechanism of action of antibiotic therapy in Crohn's disease has not been fully elucidated. However, there are data from uncontrolled trials that indicate that metronidazole or ciprofloxacin alone may be beneficial in chronic active perianal Crohn's disease (3-7). However, no randomized trials have validated these conclusions.

In clinical practice many patients do not respond to metronidazole alone, and ciprofloxacin has recently become an alternative (either alone or in combination with metronidazole). After initial encouraging results in patients refractory to metronidazole, we have attempted to determine the response of patients with severe perianal disease to a combination of ciprofloxacin and metronidazole in a small case series of 14 patients.

PATIENTS AND METHODS

The medical records of all patients with severe, symptomatic perianal Crohn's disease treated consecutively with a combination of ciprofloxacin and metronidazole over the previous 14 months at the inflammatory bowel disease unit at Mount Sinai Hospital were retrospectively reviewed. Charts were reviewed by one research assistant onto a data sheet created for this purpose. Response to therapy was determined from the physician's global assessments at two to four months after commencing therapy and graded as healed, improved, unchanged or worsened. The need for continuation or recommencing of therapy, further perianal surgery and current status of perianal disease (quiescent, mild, moderate or severe) was determined from the last clinical evaluation. Five patients had not been reviewed in the previous two months and were contacted by telephone to ensure no clinical change since the last clinical evaluation. The duration of fol-

low-up, however, was measured from the most recent clinical evaluation.

RESULTS

Fourteen patients (seven males and seven females, mean age 34.8 ± 12.5 years, range 23 to 66) were treated over a 14-month period.

Perianal disease had been present for a mean of 28.4 ± 37 months (range one to 120). Four patients had previous pelvic pouch procedures performed a mean of 22.5 ± 18.4 months (range nine to 48) before developing perianal disease and the diagnosis changed from ulcerative colitis to Crohn's disease. Nine patients (64%) had had previous large bowel inflammatory disease documented, with disease in five patients limited to the small bowel. Three patients had previous small bowel resections. Seven patients had no previous perianal surgery and seven patients had a mean of three operations (range one to six) for perianal disease before this presentation.

All patients had clinically quiescent bowel disease at presentation. Six patients had already been taking metronidazole for a mean of 18.7 months (range one to 48) at referral. Four patients were on no therapy, three on systemic steroids, three on aminosalicylic acid and one on azathioprine. The presenting symptoms were pain in five patients, discharge in five, and both pain and discharge in four. Nine patients had complex fistula, six had anal canal ulceration, one had a rectovaginal fistula and five had abscesses. Seven patients had multiple perianal lesions.

A combination of ciprofloxacin (1000 to 1500 mg/day) plus metronidazole (500 to 1500 mg/day) was commenced in all patients with physician assessments performed at a mean of 12.2 ± 4.7 weeks (range four to 20); this revealed that three patients healed, nine improved, one was unchanged and one worsened (requiring a defunctioning stoma). Thus, 12 patients (85%) showed improvement with ciprofloxacin and metronidazole. Of the six patients already taking metronidazole, two healed, three improved and one remained unchanged.

After a mean follow-up of 6.4 ± 3.9

months (range two to 12), five patients have had therapy successfully stopped and not required any further therapy. Six patients have required continuous lower dose therapy, and three patients who were successfully stopped at 12 weeks have subsequently relapsed and restarted ciprofloxacin and metronidazole. Thus, nine patients (64%) have required continuous or repeat therapy. At present, the perianal disease is quiescent in seven patients, mild in six and moderate in one. None has severe perianal disease.

DISCUSSION

Therapy in perianal Crohn's disease has largely been decided by small uncontrolled trials, smaller case series and the opinions of respected authorities based on anecdotal clinical experience. Only 6-mercaptopurine, metronidazole and ciprofloxacin have shown any effectiveness in these small uncontrolled trials. 6-Mercaptopurine demonstrated a 56% improvement in a small number of patients with perianal fistulas (8).

Metronidazole has been widely used for acute exacerbations of perianal Crohn's disease since the first uncontrolled trial reported some improvement in active Crohn's disease in 1975 (9). No randomized controlled trials have been performed with metronidazole in perianal Crohn's despite encouraging results in uncontrolled trials.

There are two uncontrolled trials of metronidazole in perianal Crohn's disease. Bernstein et al (3) reported an uncontrolled trial of 21 consecutive pa-

tients with chronic unremitting perianal Crohn's disease with symptoms present for more than five years (3) – it was less likely that symptoms in these patients would spontaneously resolve. All patients received metronidazole (20 mg/kg/day). Objective criteria (photography to document the number of fistulas) were used to determine outcome. Symptomatic improvement occurred within two weeks in 90%, with the remaining 10% noted by six to eight weeks. Objective assessment was performed at eight and 12 weeks, with 83% of chronic perianal lesions healed or showing objective signs of healing (appeared to be clinically significant).

Brandt et al (4) followed this same group of patients (from Bernstein's study) with nine more patients to determine their outcome when metronidazole was discontinued; the investigators noted a 78% recurrence within four months of cessation of therapy. Jakobovits and Schuster (5) reported an uncontrolled trial that included eight consecutive patients with intractable chronic perianal fistulas, and reported that 50% of fistulas closed on metronidazole.

Ciprofloxacin is a fluoroquinolone antibiotic with a broad spectrum of bacterial coverage, including Gram-negative aerobic organisms. No randomized controlled trials have been reported involving ciprofloxacin in Crohn's disease. Two small uncontrolled trials have shown some benefit with ciprofloxacin in severe perianal Crohn's disease. Turunen et al (6) re-

ported eight patients with continuously active perianal Crohn's disease previously treated with metronidazole and various surgical procedures. All eight patients treated with ciprofloxacin (1000 to 1500 mg) for three to 12 months showed improvement in physician and patient global assessments, and in six patients the results were considered to be very good.

Wolf (7) reported disappearance of perianal pain in four of five acute perianal Crohn's disease patients after four days to five weeks of ciprofloxacin treatment; in these patients, fissures healed in three patients, the perianal fistula became asymptomatic and a rectovaginal fistula partially closed.

Our small retrospective case series demonstrates marked improvement in results with a combination of both antibiotics. Within this series, 43% of patients previously had no improvement with metronidazole alone. A randomized controlled trial is needed to confirm the efficacy of combination metronidazole and ciprofloxacin in acute severe perianal Crohn's disease and to determine the role of continuous therapy. Assessment of severity of illness and the response to treatment is difficult to quantitate objectively. More objective outcomes, such as the perianal disease activity index and quality of life assessments, should be incorporated into trials (10). Transanal ultrasonography may become an important tool in the detection of fistulous tracts and abscess cavities, and as a determinant of disease activity (11,12).

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