REVIEW

Antibacterial and antimycobacterial treatment for inflammatory bowel disease

TOSHIKUMI OHKUSA AND NOBUHIRO SATO

Department of Gastroenterology, Juntendo University School of Medicine, Tokyo, Japan

Abstract  A variety of medicines have been used for the treatment of inflammatory bowel disease. Antibacterial therapy has demonstrated promise by both improving symptoms and causing disease remission. The mechanism is unknown, but may be related to either eliminating a key pathogen, decreasing the number of bacterial secretory products or defective particles, a direct immunomodulating effect, or reducing secondary bacterial invasion. Historically, a large number of bacterial species have been suspected as being major contributors to the etiology of inflammatory bowel disease, including ulcerative colitis and Crohn’s disease. Many trials of antibacterial agents have been carried out in inflammatory bowel disease. Recently, treatments have focused on Gram-negative anaerobes and mycobacteria. The present paper briefly reviews antimicrobial and antimycobacterial treatments in inflammatory bowel disease.

INTRODUCTION

It has been postulated that inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease (CD), may be caused by an overly aggressive cell-mediated immune response to endogenous intestinal bacterial constituents in genetically susceptible hosts.1 Recently, it has become clear that bacteria play an important role in the pathogenesis of mucosal inflammation. The evidence for a pathophysiological role of certain luminal bacteria strains comes from a number of animal models.2–5 Normal luminal bacteria are involved in spontaneous colitis, which does not develop in germ-free, knockout mice.6–9 Recent advances in studies of innate immunity, such as toll-like receptors (TLR) and NOD isoforms, suggest that there is a genetic weakness to bacterial infection in IBD patients and the bacterial infection may cause the intestinal inflammation.10,11 Previously, a large number of bacterial species have been suspected as being major contributors to the etiology of IBD. Many trials of antibacterial or antimycobacterial agents have been carried out in IBD. This brief review focused on the recent trials on antimicrobial and antimycobacterial treatments in inflammatory bowel disease.
<table>
<thead>
<tr>
<th>Reference (study type)</th>
<th>Year</th>
<th>$n$</th>
<th>Classification</th>
<th>Length of study</th>
<th>Treatment/day/duration</th>
<th>Adjunctive therapy</th>
<th>Remission (%) (treatment vs control)</th>
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</thead>
<tbody>
<tr>
<td>Truelove and Jewell^{12} (open, no placebo)</td>
<td>1974</td>
<td>49</td>
<td>Severe</td>
<td>5 years</td>
<td>Predonisolone 60 mg i.v./5 days Tetracycline 250 mg q.i.d. i.v.</td>
<td>Predonisolone 10–15 mg q.i.d. SASP 500 mg q.i.d. Hydrocortisone 100 mg enema b.i.d.</td>
<td>16/49 (33%) vs no control 12 first attack 4 relapse</td>
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<tr>
<td>Dickinson^{13} (double blind placebo)</td>
<td>1985</td>
<td>33</td>
<td>Moderate to severe</td>
<td>Discharge &gt;1 year</td>
<td>Vancomycin 500 mg q.i.d./7 days</td>
<td>Predonisolone 40 mg/day p.o. Remission: 5 mg decrements per 3 days</td>
<td>Short term 16/18 (89%) vs 8/15 (53%) Long term, &gt;1 year 7/18 (39%) vs 5/15 (33%) 14/19 (74%) vs 14/20 (70%)</td>
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<tr>
<td>Chapman^{14} (double blind placebo)</td>
<td>1986</td>
<td>39</td>
<td>Severe</td>
<td>5 days</td>
<td>Metronidazole 500 mg i.v. t.i.d./5 days</td>
<td>Methyl predonisolone 16 mg i.v. q.i.d. Hydrocortisone 100 mg enema b.i.d.</td>
<td>14/19 (74%) vs 14/20 (70%)</td>
</tr>
<tr>
<td>Burke^{15} (double blind placebo)</td>
<td>1990</td>
<td>84</td>
<td>Mild to severe</td>
<td>21–28 days</td>
<td>Tobramycin 120 mg t.i.d./7 days</td>
<td>Predonisolone 60 mg/day p.o. Predonisolone 30 mg/day p.o. Hydrocortisone 100 mg enema b.i.d.</td>
<td>31/42 (74%) vs 18/42 (43%)</td>
</tr>
<tr>
<td>Lobo and Burke^{16} (double blind placebo)</td>
<td>1993</td>
<td>81</td>
<td>Mild to severe</td>
<td>2 years</td>
<td>Tobramycin 120 mg t.i.d./7 days</td>
<td>Predonisolone 60 mg/day p.o. Predonisolone 30 mg/day p.o. Hydrocortisone 100 mg enema b.i.d.</td>
<td>6months: 22/40 (55%) vs 12/41(29%); $P&lt;0.05$ 1 year: 40% vs 24% 2 years: 24% vs 12%</td>
</tr>
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<tr>
<td>Mantzaris(^{17}) (double blind placebo)</td>
<td>1994</td>
<td>39</td>
<td>Severe Four first attack Three first attack</td>
<td>10 days</td>
<td>Metronidazole 500 mg i.v. t.i.d./10 days Tobramycin 4 mg/kg i.v. t.i.d./10 days</td>
<td>Hydrocortisone 100 mg q.i.d.</td>
<td>12/19 (63%) vs 13/20 (65%)</td>
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<tr>
<td>Mantzaris(^{18}) (randomized placebo control)</td>
<td>1997</td>
<td>70</td>
<td>Mild to moderate Eight first attack Six first attack</td>
<td>7–9 weeks</td>
<td>Ciprofloxacin 250 mg b.i.d./14 days</td>
<td>Olsalazine 500 mg b.i.d. Betamethason enema 2 g per night Predonisolone 20–40 mg/day p.o.</td>
<td>24/34 (70.5%) vs 26/36 (72%)</td>
</tr>
<tr>
<td>Turunen(^{19}) (double blind placebo)</td>
<td>1998</td>
<td>83</td>
<td>NA</td>
<td>12 months</td>
<td>Ciprofloxacin 500–750 mg b.i.d./6 months</td>
<td>Predonisolone 37.5–12.5 mg/50 kg/day p.o.</td>
<td>Treatment failure 6 months: 8 (21%) vs 20 (44%); P = 0.02 12 months: 17 (45%) vs 27 (60%); P = 0.07</td>
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<tr>
<td>Gionchetti(^{20}) (double blind placebo)</td>
<td>1999</td>
<td>26</td>
<td>Moderate to severe Refractory to steroid</td>
<td>6 months</td>
<td>Rifaximin 400 mg b.i.d./10 days</td>
<td>Steroid treatment</td>
<td>9/14 (64%) vs 5/12 (42%); NS</td>
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</table>

NA, not available.
Averaged more than 3 years. However, the study was uncontrolled and the patients were treated with prednisolone and SASP after the 5-day treatment. Therefore, drugs other than tetracycline might influence the follow-up study.

Vancomycin, a non-absorbable antibiotic agent against Gram-positive bacteria, was administered orally to patients with UC. Dickinson et al.\textsuperscript{13} reported that 16 of 18 vancomycin treated patients (89%), compared to 8 of 15 placebo controls (53%), were stabilized and discharged from hospital, while non-discharged patients required colectomy for moderate to severe UC. However, there was no significant difference in long-term outcome (>1 year) between the groups (vancomycin 39%, placebo 33%).

Metronidazole, an agent effective against anaerobic bacteria, was given intravenously in severe UC as an adjunct to the intensive intravenous regimen. In a double-blind placebo controlled trial, Chapman et al.\textsuperscript{14} reported that no benefit was observed in the group receiving metronidazole. However, there is no study of whether this drug is also ineffective when given orally.

Tobramycin, a non-absorbable antibiotic directed against Gram-negative bacteria, was given orally patient with UC. Burke et al.\textsuperscript{15} reported that 84 patients with an acute relapse and a first attack of UC were randomized to receive either oral tobramycin or placebo for 7 days as an adjunct to steroid therapy. At the endpoint of 18–21 days after treatment, 31 of 42 patients (74%) in the tobramycin group and 18 of 42 patients (43%) in the placebo group achieved clinical remission (\(P = 0.008\)). However, in the same study, Lobo and Burke et al.\textsuperscript{16} reported that this difference remained significant at 6 months after the trial, but by 1 year the difference between the groups had disappeared. Furthermore, Mantzaris et al.\textsuperscript{17} reported that a combination of tobramycin and metronidazole administered intravenously, together with steroid therapy, in acute, severe UC did not provide a beneficial outcome.

Ciprofloxacin, an antibacterial agent against a broad spectrum of Gram-positive and negative microbes, has also been explored. Mantzaris et al.\textsuperscript{18} reported that a short course of ciprofloxacin did not increase the proportion of patients with active UC achieving remission. In contrast, in a double-blind placebo-controlled study, Turunen et al.\textsuperscript{19} reported that the addition of a 6-month ciprofloxacin treatment to conventional therapy with steroids, mesalazine or sulfasalazine was significantly superior to placebo during the first 6-month period of administration. There were no significant differences between the ciprofloxacin and placebo groups for endoscopic, histological, or clinical findings after the follow-up period at 12 months.

Recently, rifaximin, a non-absorbable broad-spectrum antibiotic, has been given orally in severe attacks that were refractory to steroid treatment. Gionchetti et al.\textsuperscript{20} showed in a small, double-blind, placebo controlled trial an improvement in 9 of 14 patients (64%) in comparison with 5 of 12 patients (42%) treated with placebo after 10 days of therapy. However, the response rate in the rifaximin group was not significantly higher than the placebo group and the results of long-term follow-up were not described.

In conclusion, antimicrobial therapies for UC tend to be beneficial for short-term, but not for long-term follow up. Recent studies have elucidated some intestinal bacteria are related to UC.\textsuperscript{21–23} The most critical point is that in the present clinical practice antimicrobial agents are selected at random from broad-spectrum antibiotics. For effective treatment of UC, an antibiotic agent appropriately chosen to target the specific bacteria must be applied. Further investigations to establish a reliable, evidence-based consensus that can provide sufficient information about which antimicrobial agent should be applied to target which bacterium are needed.

**ANTIBACTERIAL THERAPY IN CROHN’S DISEASE**

Clinical studies using antibacterial drugs are summarized in Table 2. Metronidazole is a prodrug and a member of the nitroimidazole group. After bacterial enzymes activate the drug, its primary target is bacterial DNA, which is fragmented by the drug. Metronidazole has intracellular activity and is commonly used for the treatment of infections with anaerobic bacteria, *Helicobacter pylori* or parasites. Ursing and Kamme\textsuperscript{24} first reported the use of metronidazole in CD in 1975. They described five patients with active disease who had not responded to sulfasalazine and/or prednisolone, and who had been placed on 400–600 mg/day for 1–7 months. All improved and were followed for up to 7 months. Two patients stopped the drug and remained in remission over a 3–7-month period. In 1976, Holdstock\textsuperscript{25} gave 400 mg t.i.d. to six patients with CD. Over a 6-month period, three had considerable and two had moderate improvement.

Several studies have been performed to compare the efficacy of metronidazole with placebo or drugs such as sulfasalazine that are used in the treatment of CD. Blichfeldt et al.\textsuperscript{26} gave placebo or metronidazole, 250 mg q.i.d. to 22 patients with active CD for 2 months. After 1–4 weeks of rest they were crossed over to the other drug for an additional 2 months. There was no significant improvement in the metronidazole group in comparison with the placebo, apart from six patients with only colon involvement. In these six patients, significant improvement was observed. Ursing et al.\textsuperscript{27} compared metronidazole and sulfasalazine in 78 patients with active CD. The patients were divided into two groups, each group was treated for 4 months with one drug and then switched over to the other drug for another 4 months. Both treatments were comparable in the first treatment period, metronidazole being slightly more efficient. Patients who initially were treated with sulfasalazine and then switched over to metronidazole showed a significant improvement, whereas initial treatment with metronidazole, followed by sulfasalazine, gave no changes. Ambrose et al. compared the use of metronidazole alone, cotrimoxazole alone, metronidazole and cotrimoxazole, and double placebo in 72 patients with active CD over a 1-month period. Cotrimoxazole is a sulfonamide derivative that is active against aerobes and exerts a profound inhibitory effect on intestinal microflora. However, none of the regimens
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<tbody>
<tr>
<td>Ursing(^{24}) (case study)</td>
<td>1975</td>
<td>5</td>
<td>S:2, S + C:3</td>
<td>4 months–12 years</td>
<td>Metronidazole 400–600 mg t.i.d./1–7 months</td>
<td>4/5 (80%), 3/4 steroid and SASP withdrawn</td>
</tr>
<tr>
<td>Holdstock(^{25}) (case study)</td>
<td>1975</td>
<td>6</td>
<td>NA</td>
<td>6 months</td>
<td>Metronidazole 400 mg t.i.d./6 months</td>
<td>5/6 (83%) improved</td>
</tr>
<tr>
<td>Blichfeldt(^{26}) (double-blind crossover, placebo)</td>
<td>1978</td>
<td>22</td>
<td>S:3, S + C:13, C:6</td>
<td>2 months</td>
<td>Metronidazole 250 mg q.i.d./2 months</td>
<td>Significant improvement in six patients with colon disease</td>
</tr>
<tr>
<td>Ursing(^{27}) (double-blind, crossover)</td>
<td>1982</td>
<td>78</td>
<td>S:26, S + C:39, C:13</td>
<td>4 months</td>
<td>Metronidazole 400 mg b.i.d. vs sulfasalazine 1500 mg b.i.d./4 months</td>
<td>Metronidazole slightly more effective than sulfasalazine</td>
</tr>
<tr>
<td>Brandt(^{21}) (open, no placebo)</td>
<td>1982</td>
<td>26</td>
<td>S:1, S + C:11, C:13, P:1</td>
<td>&gt;3–18 months</td>
<td>Metronidazole 20 mg/kg/ &gt;3–18 months</td>
<td>10 patients complete healing, 16 advanced healing of the perineal disease (100%)</td>
</tr>
<tr>
<td>Jakobovitis(^{32}) (open, no placebo)</td>
<td>1984</td>
<td>8</td>
<td>S + C:8</td>
<td>6–34 months</td>
<td>Metronidazole 1000–1500 mg/day/ 1–34 months</td>
<td>All patients showed improvement from the perineal disease, 4/8 (50%) patients went into remission</td>
</tr>
<tr>
<td>Ambrose(^{28}) (randomized, placebo)</td>
<td>1985</td>
<td>72</td>
<td>S:22, S + C:25, C:25</td>
<td>4 weeks</td>
<td>Metronidazole 400 mg b.i.d. and/or cortrimoxazole 960 mg b.i.d./4 weeks</td>
<td>Metronidazole 44%, cortrimoxazole 62%, M+C 57%, placebo 41%</td>
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\( ^\d \) Refers to the site of disease: C, colon; S, small bowel; S + C, small bowel and colon; P, perineum; NA, not available; NS, not significant.
Table 2  Continued

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<tr>
<td>Sutherland(^29) (double-blind, placebo)</td>
<td>1991</td>
<td>99</td>
<td>S:40, S + C:47, C:12</td>
<td>16 weeks</td>
<td>Metronidazole 10, 20 mg/kg/2–16 weeks</td>
<td>36% in 10 mg/kg group and 27% in 20 mg/kg group vs 25% in placebo group (NS)</td>
</tr>
<tr>
<td>Peppercorn(^36) (case study)</td>
<td>1993</td>
<td>4</td>
<td>S:3, S + C:1</td>
<td>12 weeks</td>
<td>Ciprofloxacin 500 mg b.i.d./12 weeks</td>
<td>4/4 (100%) remission</td>
</tr>
<tr>
<td>Prantera(^37) (open, no placebo)</td>
<td>1994</td>
<td>31</td>
<td>S:5, S + C:8, C:18</td>
<td>3 months</td>
<td>Metronidazole 250 mg q.i.d. and ciprofloxacin 500 mg b.i.d./3 months</td>
<td>22/31 (71%) went into complete or partial remission, CDAI decreased in 22 patients who completed the trial</td>
</tr>
<tr>
<td>Rutgeerts(^30) (double-blind, placebo)</td>
<td>1995</td>
<td>60</td>
<td>S:60, after ileal resection</td>
<td>3 months–3 years</td>
<td>Metronidazole 20 mg/kg/3 months</td>
<td>Recurrence rate: metronidazole vs placebo, 1 year: 4% vs 25%, 2 year: 26% vs 43%, 3 year: 30% vs 50%</td>
</tr>
<tr>
<td>Prantera(^38) (randomized, steroid control)</td>
<td>1996</td>
<td>41</td>
<td>S:15, S + C:16, C:10</td>
<td>12 weeks</td>
<td>Metronidazole 250 mg q.i.d. and ciprofloxacin 500 mg b.i.d./3 months vs methylpredonisolone 0.7–1 mg/kg/day/12 weeks</td>
<td>10/22 antibiotics patients (46%) vs 12/19 steroid patients (63%)</td>
</tr>
<tr>
<td>Greenbloom(^39) (open, no placebo)</td>
<td>1998</td>
<td>72</td>
<td>S:27, S + C:22, C:23</td>
<td>9 months</td>
<td>Metronidazole 250 mg t.i.d. and ciprofloxacin 500 mg b.i.d./10 weeks</td>
<td>49/72 (68%) went into remission</td>
</tr>
<tr>
<td>Colombel(^40) (randomized, mesalamine control)</td>
<td>1999</td>
<td>40</td>
<td>S:14, S + C:16, C:10</td>
<td>6 weeks</td>
<td>Ciprofloxacin 500 mg b.i.d. vs mesalamine 2000 mg b.i.d./6 weeks</td>
<td>Ciprofloxacin 13/18 (72%) vs mesalamine 13/22 (59%)</td>
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\(^1\)Refers to the site of disease: C, colon; S, small bowel; S + C, small bowel and colon; P, perineum; NA, not available; NS, not significant.
led to more improvement than in the placebo-treated group. Sutherland et al. performed a double-blind placebo-controlled study to compare the efficacy of two doses of metronidazole with the placebo. Only 56 of the 105 patients completed the 16 weeks of treatment. Results indicated significant improvement, as measured by both CD activity index (CDAI) and serum orosomucoid. Their results suggest a better response to treatment for patients with either colon disease or disease in both the small and large bowel, as compared with patients with only small bowel disease.

Metronidazole has also been used to try to prevent or decrease the rate of recurrence of CD after ileal resection and ileocolonic anastomosis for Crohn’s ileitis. Within a 12-week period, in a double-blind controlled trial of 60 patients, the placebo group had new lesions more frequently in the neoterminal ileum than did the metronidazole group. Moreover, the incidence of severe endoscopic recurrence was reduced for 1 year by metronidazole compared with placebo. However, there were no significant reductions at 2 and 3 years.

Metronidazole has been used in the treatment of patients with perineal involvement and has resulted in the healing of perineal lesions. Metronidazole use was associated with complete healing of chronic unretaining perineal CD in 10 of 26 patients who were maintained on therapy. Metronidazole could be successfully discontinued only in a small number of patients because dosage reduction resulted in exacerbation of disease activity. Sixteen of the patients were treated for 12 or more months. Treatment was discontinued in 13 patients after 3–18 months. Jakobovits and Schuster treated eight patients with CD-associated fistulae with metronidazole in an open study. All patients had reduced numbers of fistulae, relief of fistula-associated pain, and overall CD symptoms and four of the patients (50%) experienced complete resolution of symptoms. After a mean time of 6.6 weeks (range 2–12 weeks) improvement was noted for general CD symptoms, and after a mean of 10.2 weeks (1–6 months) maximum benefit for fistulae was reached. Patients were followed for 6 months after treatment and showed continued improvement. All patients experienced metronidazole side-effects, which were resolved after completion of treatment.

Overall, it appears that metronidazole, when used alone, has activity in the treatment of CD but, with the exception of perineal disease, the effect is not great and the frequency of side-effects is high. Duffy et al. reported that peripheral neuropathy occurred in 11 (85%) of 13 pediatric patients with CD after 4–11 months of metronidazole therapy (10–33 mg/kg/day). However, because peripheral neuropathy is an uncommon side-effect of metronidazole when used in low doses or for a short duration, low-dose metronidazole therapy (<10 mg/kg/day) for CD should be studied in future. Given the results of animal studies, there has been concern about the potential carcinogenic and mutagenic effects of metronidazole. At present, these serious reactions have not been shown to occur in humans.

Ciprofloxacin is a quinolone that is mainly effective against aerobic Gram-positive bacteria. The drug inhibits its DNA synthesis by affecting the DNA gyrase. In 1993, four patients with Crohn’s ileitis who wished to avoid steroids received ciprofloxacin treatment for 6 weeks. Dosages were then tapered down over the following 4–6 weeks and finally stopped. All patients showed dramatic clinical responses with no symptoms after only 1 week of treatment. Three remained asymptomatic 3–6 months after treatment. One of the patients returned after 6 months with recurrent symptoms and again responded to ciprofloxacin upon retreatment. A control group was not used. Pranter et al. used a combination of metronidazole and ciprofloxacin for 3 months in 31 patients with active and refractory CD. Clinical remission (CDAI < 150) or partial clinical remission (CDAI < 170) was obtained in all 22 patients who completed the 3 months of treatment. At the end of 3 months, the CDAI for the 22 patients decreased. After the open study, the same researchers undertook a prospective, partially masked and randomized study with a control group that received methylprednisolone. Improvement in symptoms was achieved by 3 weeks and comparable clinical remission was achieved in patients with active disease in both groups. They concluded that the combination therapy of metronidazole and ciprofloxacin could be an alternative to the steroid therapy for active CD. Greenbloom et al. also used a combination of metronidazole and ciprofloxacin in 72 patients with active CD. When treatment was continued for a mean of 10 weeks, 49 (68%) patients were in remission and 55 (76%) patients showed a clinical response. After a mean follow-up time of 9 months, 38 patients, 12 of whom were still on antibiotic treatment, were still in remission. Recently, Colombel et al. investigated the efficacy of ciprofloxacin compared with mesalazine in a randomized controlled study for treating active CD. Complete or partial remission was observed in 13 patients (72%) treated with ciprofloxacin and 13 patients (59%) treated with mesalazine. They concluded that ciprofloxacin is as effective as mesalazine in treating active CD.

**ANTIMYCOBACTERIAL THERAPY IN CROHN’S DISEASE**

The gross and histological similarities between CD and tuberculosis have been noted since the original description of the disease by Dalziel, and the possibility that CD is a mycobacterial disease has never been dismissed. In 1978, Burnham et al. isolated *Mycobacterium kansasi* from the lymph node of a patient with CD and pleomorphic material, indicative of cell wall-deficient organisms, from 80% of CD patients and 54% of UC patients. However, the hypothesis that *M. kansasi* plays an etiologic role in both CD and UC was short-lived. This organism is an opportunistic pathogen that exacerbates existing chronic diseases and is not a primary pathogen in healthy individuals. Subsequent studies have revived the interest in the role of mycobacteria in CD. In a series of studies, Chiiodini et al. reported the isolation of two strains of a *Mycobacterium paratuberculosis*-like organisms from 11 patients with CD, but not...
from those diagnosed with UC or other bowel diseases. These isolates were pathogenic for mice via intravenous or intraperitoneal routes and produced hepatic and splenic granulomas containing acid-fast mycobacteria. Oral inoculation of one of the strains into a newborn goat produced a granulomatous ileocolitis after 5 months. The authors concluded that the isolates were strains of *M. paratuberculosis* or a biovariant that plays an etiological role in some cases of CD. Interestingly, *M. paratuberculosis* causes Johne disease, an intestinal disorder in ruminants such as cattle, horses and goats, which resembles CD both clinically and histologically.

Many studies have examined the effect of antimycobacterial therapy in CD, and there have been several studies that were randomized, placebo-controlled trials as summarized in Table 3. Six were fully published and three were abstracts. In 1982, Elliott et al. reported a treatment study over 12 months duration with sulfadoxine and pyrimethamine for 51 patients with CD. Sulfadoxine is a long-acting sulfonamide that has been used in the treatment of *Mycobacterium leprae*. Pyrimethamine, closely related to trimethoprim but longer-acting, acts in sequential blockade with sulfonamides in folic acid metabolism. Six patients were withdrawn from analysis. Nine of 25 patients (36%) on sulfadoxine and pyrimethamine treatment decreased their CDAI score over the 12-month period by >50, compared with 10 of 20 patients (50%) in the placebo group. This double-blind controlled trial has shown no benefit from the use of sulfadoxine and pyrimethamine over a 12-month period in active CD. Kelleher et al. studied the effect of clofazimine on 20 patients with CD. Clofazimine, a rimino phenazine derivative, is a broad-spectrum antimycobacterial agent with concomitant anti-inflammatory and phagocyte-stimulating properties. Twenty patients with CD were randomized to receive either clofazimine or placebo. Preexisting medications were withdrawn within the first 4 weeks of treatment. In the course of a 6-month study, three relapses occurred in the placebo treated group (30%), whereas there were none in the clofazimine treated group (0%). They concluded that the preliminary findings indicated a potential role for clofazimine in the treatment of CD. Afdhal et al. also tried a monotherapy of clofazimine for CD patients. Forty-nine patients with active CD were randomized to either prednisolone or placebo. Sixteen of 25 patients (64%) went into disease remission in the rifampicin/ethambutol period and 8 of 14 patients (57%) went into remission in the placebo period. They found no significant benefit of the combination therapy for CD. Prantera et al. reported a 9-month trial of 40 patients with refractory,
steroid-dependent CD that used ethambutol, clofazimine, dapsone, and rifampicin.\textsuperscript{49} Sixteen of 19 patients (84\%) on active drugs and 6 of 17 patients (35\%) on placebo entered remission. Remission maintenance was significantly more effective in the four antibiotic combination therapy group. A 2-year study with 130 patients treated with a combination of rifampicin, isoniazid and ethambutol or placebo was performed by Swift \textit{et al.}\textsuperscript{50} Results were assessed by radiology, prednisolone doses needed, body weight, CDAI, and blood analyses. No significant differences were observed between the drug and the placebo group.

\textit{M. paratuberculosis}, like \textit{M. avium}, is generally resistant to standard antituberculous drugs and in vivo infections are known to be difficult to eradicate. In 1992, Rastogi \textit{et al.} reported that the newly developed macrolide antibiotic, clarithromycin, is the most effective known antibiotic for killing \textit{M. paratuberculosis}.\textsuperscript{54} Graham \textit{et al.} conducted a 12-month placebo-controlled trial with clarithromycin for 15 patients with CD.\textsuperscript{52} Five of the seven patients (71\%) who received clarithromycin achieved remission by the end of the initial 3 months of therapy, as compared to only one of eight patients (13\%) in the placebo. Approximately 1 year after completion of the study, the successfully treated patients remained in remission. They concluded that a short course of clarithromycin therapy was effective for achieving prolonged remission of CD. The same group reported a 3-month regimen of clarithromycin and ethambutol for 31 patients with CD.\textsuperscript{53} The study was also randomized, blinded and placebo-controlled. Patients were chosen based on lactulose-mannitol permeability test results. Efficacy of treatment was measured by the Harvey-Bradshaw activity index and the lactulose-mannitol permeability test for a follow-up period of 12 months. No significant improvement was observed in either group. Rifabutin is a derivative of rifampicin and is seemingly more effective than its predecessor against \textit{M. paratuberculosis}. Basilisco \textit{et al.} studied the effect of rifabutin on 24 patients with active CD for 6 months.\textsuperscript{47} Five patients in the rifabutin group dropped out because of side-effects, and four patients in the placebo group dropped out who were lost to follow-up or did not follow the treatment schedule. Therefore, seven patients treated with rifabutin and eight patients treated with placebo completed the 6 months trial. Clinical evaluation of induction of remission and improvement of the disease activity index were similar in both groups.

When used alone, even the most effective bactericidal antimycobacterial drug will usually lead to the emergence of resistant variants in the bacterial population before a therapeutic endpoint is reached. The use of two or three drugs greatly reduces the frequency of this outcome.\textsuperscript{35} In 1994, Mor \textit{et al.} showed that the most effective drug regimen known for the treatment of \textit{M. avium} infection is a combination of macrolide antibiotics and rifabutin.\textsuperscript{56} In 1997, Gui \textit{et al.} described the results of treatment of CD patients with a combination of macrolide antibiotics, clarithromycin or azithromycin, and rifabutin.\textsuperscript{57} They called their treatment RMAT (rifabutin and macrolide antibiotic treatment; as summarized in Table 4). Of 52 patients treated with RMAT for 6–
35 months, six were unable to tolerate RMAT. Of the remaining 46 patients who were able to tolerate RMAT, 43 (94%) went into clinical remission. A reduction in CDAI occurred and an improvement in inflammatory parameters was observed. In addition, only 2 of 19 patients who were steroid-dependent at the beginning of the study continued to require steroids. However, controls were not used in the study. In 1999, Douglass et al. reported a 6-month open pilot study of 20 patients with rifabutin, clarithromycin and clofazamine.58 Twelve (60%) of the 20 patients who were steroid dependent, refractory or needed surgery, achieved remission by 6 months. Recently, Shafran et al. reported an open trial of RMAT with a probiotic for 36 patients with active CD.59 Seven patients withdrew from the study because they were unable to tolerate medications. Twenty-one of the remaining 29 patients (58%) reached a sustained state of improvement, defined as a decrease of 70 points in CDAI scores, together with the absence of a need for all other medications (e.g. steroids and immunosuppressants). Borody et al. were successful in their study of 12 patients who were treated for 6–54 months with rifabutin, clarithromycin and clofazamine.60 Six of the 12 patients (50%) achieved complete clinical, colonoscopic and histological remission. Four of six patients were able to cease treatment after 24–46 months, three of whom remained in total remission without treatment for up to 26 months. One patient relapsed after being off treatment for 6 months. A partial response was seen in two patients showing complete clinical remission with mild histological inflammation. The four studies summarized show that between 2/3 and 3/4 of patients with active CD who can tolerate the RMAT long-term will go into remission with healing of the intestine when treated with these agents. However, there has been no randomized, placebo-controlled trial for the RMAT. A large multicenter clinical trial is needed to further explore the efficacy of the RMAT. Conversely, the use of RMAT has been limited because of side-effects. New agents with a low occurrence of side-effects during long-term administration are needed.

CONCLUSION

At present, most agree that UC and CD are best considered as syndromes with possible different etiological factors, but similarities in presentation. Therefore, one conclusion that can be drawn, based on the available data regarding antibiotic therapy for UC or CD management, may be that antibiotic therapy does have a role in some cases. The present review shows that antimicrobial and anticybacterial therapy is often successful in the induction and maintenance of remission of IBD. Especially in perineal disease and fistulas of CD, the evidence indicates that anaerobes play an important role, and therefore metronidazole should be effective in the majority of patients. Conventional therapies directed at suppressing the immune system are indeed effective for IBD, however, drug free status is not usually obtained. It is noteworthy that drug free status in several cases has been obtained after antibiotics therapy. We believe that in future, the likely UC and CD treatment will be a combination of antibacterial drugs.

REFERENCES


52 Graham DY, Al-Assi MT, Robinson M. Prolonged remission in Crohn’s disease following therapy for Mycobacte-


