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Antimycobacterial Therapy in Crohn's Disease: The End of a Long Controversy?

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It has been almost a century since Dalziel, who first described what is at the present time known as Crohn's disease (CD), commented on its similarity to Johne's disease, which occurs in dairy herds and is caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP) (1). Interest in a possible infectious origin for CD was renewed in 1989 when Chiodini, et al cultured apparently identical MAP from three patients with CD (2). The controversy has even increased following alarming reports on the detection of MAP in water supplies and milk (3, 4), although this was not confirmed in a recent case-control study (5). Detection of the specific DNA insertion sequence *IS900* of MAP in a significant number of patients with CD, but not in controls (6,7), and the finding of MAP in the bloodstream of these patients (8) has also contributed to enhancing the controversy.

Both advocates and detractors of this theory almost invariably conclude their demonstration by saying that the most irrefutable evidence that MAP causes CD would lie in long-term remission of clinical manifestations and altered natural history of the disease following clearance of the infection with antibiotics. Fourteen studies assessing the efficacy of antimycobacterial therapy in CD, and which enrolled a total of 508 patients, have been published, with differing results (Table 1) (9–23). In 2000, a meta-analysis suggested that antimycobacterial treatment may be effective in maintaining remission achieved by corticosteroids (24). However, because of the heterogeneity of the trials, which used a wide range of antibiotic combinations administered for variable periods to a small number of patients, no definitive conclusion could be drawn. Those studies were also criticized because they used earlier tuberculosis drugs, such as ethambutol and isoniazid, which are not effective against *M. avium* complex infection, and fewer than three antibiotics (a number considered critical for preventing development of drug resistance). Clarithromycin and azithromycin, macrolide compounds which are considered to be the most effective drugs for treatment of MAP, were then used in four subsequent studies with encouraging results (11,13,14,16,21). However, the only placebo-controlled randomized trial was of three-month duration, and the antibiotic regimen associated only two drugs, clarithromycin and ethambutol (13). The general conclusion of most experts in the field was that the proof of efficacy of combination antibiotic therapy in CD remained elusive due to the absence of a properly conducted large placebo-controlled randomized trial.

Recently, in a large placebo-controlled, double-blind, randomized trial which enrolled a total of 213 patients with active CD (CDAI ≥ 200), Selby, et al evaluated the efficacy of two-year combination ther-

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Table 1.
Efficacy of antimycobacterial therapy in CD in open-label and randomized controlled (RCT) trials.

Author (year)	*Patients Included (n)*	*Trial*	*Antibiotic Combination Therapy*	*Concomitant Steroid Therapy*	*Treatment Period (months)*
Elliott (1982)[12]	51	RCT	Sulfadoxine, pyrimethamine	No	12
Schaffer (1984)[20]	27	RCT	Ethambutol, rifampin	No	12
Basilisco (1989)[10]	24	RCT	Rifabutin	No	6
Hampson (1989)[15]	20	Open-label	Ethambutol, rifampin, isoniazid, clofazimine (or pyrazinamide)	Yes	9
Prantera (1989)[17]	5	Open-label	Dapsone	No	1
Afdhal (1991)[9]	49	RCT	Clofazimine	Yes	12
Rutgeerts (1992)[19]	16	Open-label	Rifabutin, ethambutol	No	6–12
Prantera (1994)[18]	40	RCT	Clofazimine, rifampin	Yes	9
Swift (1994)[22], Thomas (1998)[23]	126	RCT	Ethambutol, rifampin, isoniazid	No	24
Gui (1997)[14]	46	Open-label	Rifabutin, clarithromycin (or azithromycin)	Yes	19
Leiper (2000)[16]	25	Open-label	Clarithromycin	Yes	1–15
Goodgame (2001)[13]	31	RCT	Clarithromycin, ethambutol	Yes	3
Shafran (2002)[21]	36	Open-label	Clarithromyci, rifabutin	No*	4–17
Borody (2002)[11]	12	Open-label	Clarithromycin, rifabutin, clofazimine	Yes	24

*A probiotic supplement was given to counterbalance antibiotic-induced degradation of the intestinal flora.

apy with clarithromycin (750 mg/d), rifabutin (450 mg/d) and clofazimine (50 mg/d) in maintaining clinical remission following corticosteroid withdrawal (25). During an induction period of 16 weeks, patients were randomized to receive a tapering regimen of corticosteroids in association with these three antibiotics or placebo. At week 16, 122 patients who achieved remission entered the maintenance phase in which they continued trial medications for two years. After two years of treatment, trial medications were ceased, and patients in remission were followed up one more year. The primary endpoints were the proportion of subjects experiencing at least one relapse of CD at one, two and three years. At the end of the 16-week induction period, there was a significantly greater percentage of subjects in remission in the antibiotic arm (66%) than in the placebo arm (50%, $p = 0.02$). The proportion of patients who relapsed at one, two and three years was not significantly different in the two arms: 39% in the antibiotic group relapsed between week 16 and week

Primary Endpoints	*Efficacy (main result): Treatment/placebo (%)*
Changes in CDAI scores	Clinical remission: 38/50
Changes in CDAI scores (or any clinical indicator of disease activity)	Clinical remission: 36/64
Changes in the Harvey-Bradshaw index	Clinical remission: 29/38
Clinical remission defined as CDAI <150	Clinical remission: 50
Changes in CDAI scores and mucosal healing	Clinical remission: 40
Clinical remission (use of modified CDAI scores)	Clinical remission: 64/50
Endoscopic healing in the noeterminal ileum	Mucosal healing: 0
Clinical remission and mucosal healing	Clinical remission: 84/35
Changes in the Harvey-Bradshaw index and CDAI scores, steroid sparing, need for surgery, radiological change	Clinical remission: 35/38
Changes in the Harvey-Bradshaw index and serum C-reactive protein, steroid sparing, need for surgery	Induction of clinical remission: 93.5
Changes in the Harvey-Bradshaw index and serum C-reactive protein	Clinical remission: 32–48
Changes in the lactulose-mannitol test and the Harvey-Bradshaw index	Changes in the Harvey-Bradshaw index in the active arm: P = 0.08 versus placebo
Response defined as marked improvement in CDAI scores	Clinical response:58.3
Changes in the Harvey-Bradshaw index	Clinical remission: 25

52 versus 56% in the placebo group (p = 0.054); 26% versus 43% relapsed at 2 years (p = 0.14); and 59% versus 50% at three years (p = 0.54). The number of subjects remaining in the study fell progressively from 16 weeks, and only 32 patients completed the study. The study thus did not meet its primary endpoints (25). The authors conclude that these results do not support a role for MAP in CD, and that the use of antibiotics with a broad spectrum of activity against luminal organisms may explain the early efficacy of antibiotic combination added to corticosteroids as induction therapy.

Results of this first long-term, large-scale randomized placebo-controlled trial appear to be particularly convincing for several reasons. The authors used a combination of three antibiotics active intracellularly, with good tissular diffusion and effective against MAP, thus minimizing the risk of drug resistance. Antibiotics were given for up to two years. Corticosteroids, which are active against MAP [that resembles *M. leprae* more

than *M. tuberculosis* in its response to corticosteroids (26)], were given in association during the induction period in order to optimize antibiotic efficacy, as previously shown (24). The negative message from this study was reinforced by the lack of improvement observed in important secondary parameters such as C-reactive protein and mucosal healing in a subset of patients. The low number (n = 32) of patients remaining at three years could raise the possibility of a type II error, but most withdrawals were due to progression of disease, even when repeat courses of prednisolone were used. This finding, together with high observance rates (69%–74% for weeks 53–104), are in favor of true failure of trial medication rather than a statistical bias.

Do these results definitely refute any therapeutic role of antimycobacterial therapy in CD? Because the Australian trial may have several limitations, this question remains open.

First, Selby, et al did not assess *IS900* DNA in biopsies by PCR and serological response to MAP before and after therapy. There is thus no evidence that MAP, if present, was cleared by treatment.

Secondly, subtherapeutic doses of rifabutin (450 mg), clarithromycin (750 mg) and clofazimine (50 mg) per day (25) were used, while the optimal dose of rifabutin, clarithromycin, and clofazimine for treatment of *M. avium* complex infections is 600 mg/d, 1000–2000 mg/d, and 100 mg/d, respectively (27,28). Despite being used in combination, low-dose antibiotics may fail in the long run due to the development of drug resistance. Interestingly, a retrospective study, also from Australia, recently demonstrated mucosal healing in 22/39 (56.4%) patients treated with higher doses of rifabutin (up to 600 mg/d), clofazimine (up to 100 mg/d) and clarithromycin (up to 1 g/d) for six months to nine years (29). Whether such antibiotic regimen may be more more effective than that used in the study by Selbi, et al remains to be determined in prospective studies.

Thirdly, in Selby, et al's trial, concomitant use of immunomodulatory therapy was the only parameter that was associated with a significantly greater response in the antibiotic group. Since it has recently been shown that 6-mercaptopurine and methotrexate inhibit MAP growth in vitro (30), clinical improvement in IBD patients treated with immunomodulators could be due to treatment of a MAP infection (30).

Finally, as stated by the authors, the aim of this trial was not to definitively prove or disprove the hypothesis that MAP plays a role in the etiology of CD (25).

In conclusion, the results of this landmark study do not support the use of antimycobacterial therapy in CD. It should help to refute arguments favoring MAP as an etiologic agent, even if it will not definitively eradicate that hypothesis. Nor does it dismiss the connection between the bacteria and the disease. Indeed, despite its broad-spectrum activity, the antimycobacterial antibiotic regimen used in the Australian study is not particularly effective against Gram-negative bacteria. New therapeutic trials should target members of the intestinal flora, such as adhesive *Escherichia coli*, that have now been associated with CD by different groups throughout the world (31). ■

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(continued on page 17)

(continued from page 14)

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