Review: Antimycobacterial therapy does not increase the rate of maintenance of remission in Crohn disease

Borgaonkar MR, MacIntosh DG, Fardy JM. **A meta-analysis of antimycobacterial therapy for Crohn's disease.** Am J Gastroenterol. 2000 Mar;95:725-9.

QUESTION

In patients with Crohn disease, is antimycobacterial therapy effective in inducing or maintaining remission?

DATA SOURCES

Randomized controlled trials were identified by searching MEDLINE and *Index Medicus* (1966 to 1998); conference abstracts from *Gut*, *Gastroenterology*, and *American Journal of Gastroenterology* (1990 to 1998); and bibliographies of review articles and included studies.

STUDY SELECTION

Studies were selected if antimycobacterial therapy was compared with placebo in patients with Crohn disease. The exclusion criterion was comparison of antimycobacterial therapy with alternative therapies.

DATA EXTRACTION

Data were extracted in duplicate on study quality, therapeutic regimen, sample size, patient characteristics, and outcomes measured (number of patients who achieved or maintained remission).

MAIN RESULTS

29 studies were evaluated, and 8 met the inclusion criteria. 6 of these were full studies (317 patients), and 2 were abstracts (35 patients). Treatment regimens ranged from 1 to 4 drugs given for 6 to 24 months. Drugs studied were rifampin (4 studies), clofazimine (2 studies), ethambutol (2 studies), dapsone (1 study), isoniazid (1 study), sulfadozine (1 study), and pyrimethamine (1 study). Adjunctive therapy was different in all studies, was not uniform across patients within studies, and was not included in the analysis. Heterogeneity existed among the studies. For the published studies, antimycobacterial therapy was not associated with maintenance of remission (pooled odds ratio [OR] 1.10, 95% CI 0.69 to 1.74). Subgroup analyses showed that antimycobacterial therapy was associated with maintenance of remission in the 2 trials that used corticosteroids to induce remission (OR 3.37, CI 1.38 to 8.24) but was not associated with maintenance of remission in the 4 studies that did not use corticosteroids to induce remission (OR 0.69, CI 0.39 to 1.21).

CONCLUSION

Antimycobacterial therapy is not associated with maintenance of remission in Crohn disease, although subgroup analyses indicated that initial use of corticosteroids for induction of remission may increase the rate of maintenance with antimycobacterial therapy.

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COMMENTARY

The potential role of mycobacteria in the pathogenesis of Crohn disease is controversial. The concept that a microbe causes Crohn disease is attractive given the parallels with Johne disease, a granulomatous enteritis of ruminants caused by *Mycobacterium paratuberculosis,* and the identification of other bacteria as the cause of such diseases of the gut as duodenal ulcer and Whipple disease.

Antimetabolites—methotrexate and azathioprine—are the only drugs that have proved effective for remission maintenance (1, 2). Thus, other therapeutic approaches are desirable. Borgaonkar and colleagues have done a methodologically rigorous meta-analysis of 8 randomized controlled trials that evaluated antimycobacterial therapy for maintenance therapy. Their conclusion is that antimyocobacterial therapy is ineffective.

However, they also speculate that 2 trials in which glucocorticoid therapy was combined with antimycobacterial therapy had sufficient heterogeneity that they should be analyzed separately. This analysis yielded an OR of 3.37 (CI 1.38 to 8.24) in favor of antimycobacterial therapy. This subgroup analysis was derived from post-hoc inspection of the data and therefore should only be considered as hypothesis generating. Moreover, confirming this finding in an independent trial would only provide indirect support for a causal role for mycobacteria because antimycobacterial therapy also has activity against bacteria other than mycobacteria. Animal models have consistently shown the importance of conventional bacterial flora in perpetuating intestinal inflammation, and limited data suggest metronidazole is somewhat effective as a treatment for active Crohn disease.

Randomized controlled trials are currently being done that will ultimately define the role of broad-spectrum antibiotic therapy. In the interim, clinicians should remain skeptical about both the causal role of mycobacteria in Crohn disease and the benefits of broad-spectrum antibiotic therapy.

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References

1. **Feagan BG, Fedorak RN, Irvine EJ, et al.** A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. N Engl J Med. 2000;342:1627-32.
2. **Pearson DC, May GR, Fick GH, Sutherland LR.** Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. Ann Intern Med. 1995; 123:132-42.

