Antimycobacterial therapy for Crohn's disease: a reanalysis

Selby and colleagues[1] have recently published their findings from a 2-year study of triple antibiotic treatment (clarithromycin, rifabutin, and clofazamine) in Crohn's disease. By analysis at early and late timepoints, they asked whether there was a demonstrated benefit in terms of induction of remission (at 16 weeks) and maintenance of remission (at 52, 104, and 156 weeks). Their analysis suggested that the answers to these questions were yes and no respectively. However, a close inspection of the numerators and denominators points to a different inference about the benefit of this treatment.

All patients in the trial were treated with steroids at the outset, and randomised to the addition of antibiotics or placebo.[1] Those in remission at 16 weeks served as the numerator for the first question (induction of remission), and then became the denominators for the second question (maintenance of remission). Based on this approach, a 16% absolute benefit was observed at 16 weeks, but differences at later timepoints were not significant. However, this form of analysis has two limitations. First, it does not ask whether effects observed at 16 weeks were maintained, but rather whether any incremental benefit accrued beyond this time. Second, this analysis assumes that the two groups were equally distributed in other unmeasured variables at the 16-week point, which is unlikely since the two groups had already experienced large and differential losses of patients in the first 16 weeks. Since randomisation occurred at week 0, an intention-to-treat analysis is indicated, using as denominators all patients recruited to the two study groups (figure). With this approach, one instead observes that the absolute benefit seen at 16 weeks persists at 52 and 104 weeks, with significant differences at these timepoints (p=0·003 and p=0·005, respectively).

Importantly, the benefit observed was not as high as predicted by open-label trials,[2] which could indicate that only a subset of patients derived benefit from the treatment, or rather that the cocktail selected only provides partial benefit. Nonetheless, a clinically significant effect was seen that is in the same order as other treatments for Crohn's,[3] and of longer duration. In view of recent genomic findings that implicate altered innate immune responses to intracellular bacteria in the aetiopathogenesis of Crohn's disease,[4] the effect seen in this trial may be telling, and suggests the value of further studies, both fundamental and clinical, on the role of mycobacteria in Crohn's disease.

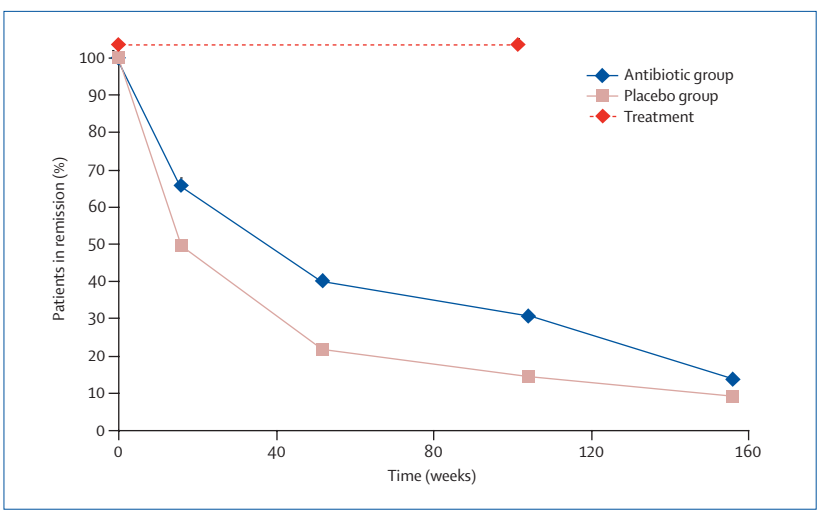

***Figure*: Therapeutic effect of clarithromycin, rifabutin, and clofazamine treatment over time for patients with Crohn's disease**
Data from reference 1.

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We declare that we have no conflicts of interest.

1 Selby W, Pavli P, Crotty B, et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology* 2007; **132:** 2313–19.
2 Gui GP, Thomas PR, Tizard ML, Lake J, Sanderson JD, Hermon-Taylor J. Two-year-outcomes analysis of Crohn's disease treated with rifabutin and macrolide antibiotics. *J Antimicrob Chemother* 1997; **39:** 393–400.
3 Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357:** 228–38.
4 Parkes M, Barrett JC, Prescott NJ, et al. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. *Nat Genet* 2007; **39:** 830–32.