Microbial manipulation as primary therapy for Crohn’s disease

Randy S Longman, Arun Swaminath

Abstract

While antimicrobials are clinically effective in preventing post-operative recurrence, the role for antibiotics in primary therapy for Crohn’s disease (CD) remains unclear. The recent multicenter phase 2 trial by Prantera et al received wide attention because it demonstrated an increase in the week 12 remission rate in patients with moderately active CD treated with rifaximin and renewed interest in microbial manipulation as primary therapy for CD. In this commentary, we discuss aspects of durability, immune cell polarization, and safety of microbial manipulation as primary therapy for CD.

© 2013 Baishideng. All rights reserved.

Key words: Inflammatory bowel disease; Rifaximin; Microbiome
in patients with IBD by 16S ribosomal RNA sequence (instead of conventional culture methods)\cite{6} led to the characterization of an IBD microbiome, reflecting a general reduction in bacterial diversity, a decrease in the clostridial family Lachnospiraceae, and an expansion of proteobacteria. More specific characterization of clinical phenotype [ileal Crohn’s disease (ICD), colonic CD, ulcerative colitis] in a cohort of Swedish twins revealed the particular prevalence of Escherichia coli (E. coli) species in ICD with a unique contribution of Ruminococcus gnavus\cite{7}. One interesting finding by Scarpignato et al\cite{1} is that clinical remission was maintained in 63% of the patients in the treatment group up to 12 wk after finishing rifaximin therapy. Prior studies have shown return of pretreatment levels of microbiota within 1-2 wk after discontinuing rifaximin, so it remains unclear whether the durability of this treatment is secondary to a permanent change in the intestinal microbiota or a suppression of a specific pathogenic species. While this analysis is beyond the scope of the study offered by Prantera et al\cite{8}, future studies will need to incorporate microbial analysis as well as metatranscriptomic analysis (e.g., what the bacteria are doing) in order to recognize the full diagnostic and therapeutic potential of antimicrobial therapy.

Given rifaximin’s broad spectrum of activity against anaerobic and aerobic gram-negative and gram-positive organisms, it is possible that rifaximin treatment eliminates a particular pathogenic or group of pathogenic bacteria that was unaffected by the antibiotics used in previous investigations. If so, does this explain the lack of a dose response in the study? In contrast to previous studies, Prantera et al\cite{9} show no benefit to colonic location of disease [odds ratio (OR) 0.5, \(P = 0.004\)]. Does this mean that clinical remission may be a reasonable conclusion. Given the distri-

Table 1 Randomized controlled trials of antibiotic therapy in inflammatory bowel disease

| Ref.          | Antibiotic therapy | Patients (n) | Primary outcome | Results                                      |
|---------------|--------------------|--------------|----------------|----------------------------------------------|
| Afshari et al\cite{10} | Clomaznide        | 49           | DAS < 5        | 64% (vs 50% placebo, NS)                     |
| Sutherland et al\cite{11} | Metronidazole     | 105          | ↓CDAI (16 wk)  | 81% (vs -1 placebo, \(P = 0.001\))          |
| Prantera et al\cite{12} | Ethambutol, rifabutin, clofazimine, dapson | 45          | Relapse (9 mo) | Likelihood ratio: 4.6                       |
| Steinhardt et al\cite{13} | Ciprofloxacin, metronidazole | 130        | Remission (8 wk) | 33% (vs 38% placebo, NS)                     |
| Arnold et al\cite{14} | Ciprofloxacin     | 47           | ↓CDAI (6 mo)   | 75% (vs 25 placebo, \(P < 0.001\))          |
| Prantera et al\cite{15} | Rifaximin         | 83           | ↓CDAI < 150 (12 wk) | 52% (vs 33% placebo, NS)                     |
| Selby et al\cite{16} | Clarithromycin, rifabutin, clofazimine | 213         | Relapse (2 yr) | 66% (vs 50% placebo, \(P = 0.02\))          |
| Leiper et al\cite{17} | Clarithromycin    | 41           | ↓CDAI < 150 (3 mo) | 26% (vs 27% placebo, NS)                     |

DAS: Disease Activity Score; CDAI: Crohn’s disease activity index; NS: Not significant.

Rifaximin’s broad spectrum of activity against anaerobic and aerobic gram-negative and gram-positive organisms, it is possible that rifaximin treatment eliminates a particular pathogenic or group of pathogenic bacteria that was unaffected by the antibiotics used in previous investigations. If so, does this explain the lack of a dose response in the study? In contrast to previous studies, Prantera et al\cite{18} show no benefit to colonic location of disease [odds ratio (OR) 0.5, \(P = 0.004\)]. Does this mean that a suspected pathogen isn’t restricted to the colon or that colonic localization is not required? Given the distribution of CD throughout the gastrointestinal tract, this may be a reasonable conclusion.

Microbial analysis suggests several candidate bacteria may be involved in the pathophysiology of CD. Notably, adherent-invasive E. coli (AIEC) have been described to be attached to the ileal mucosa of patients with ICD\cite{9}. These invasive bacteria may sustain inflammation in genetically susceptible individuals and generate systemic immune responses (reflected by serologies) (Figure 1). While E. coli are sensitive to rifaximin in vitro, the effect
of rifaximin on AIEC populations \emph{in vivo} has not been clearly defined, but could be studied in this cohort. In addition to AIEC, analysis of a post-operative ICD cohort revealed the correlation of the clostridial species, \emph{Faecalibacterium prausnitzii} (\emph{F. prausnitzii}), with a decreased incidence of post-operative recurrence\cite{9}. \emph{Clostridium} species IV and XIv (which include \emph{F. prausnitzii}) have been shown in mouse models to induce the accumulation of regulatory T cells in the colon\cite{11} (Figure 1). Further microbial analysis of primary antimicrobial therapy for CD may offer deeper insight into the mechanism of rifaximin therapy.

If the efficacy of rifaximin depends on microbial mediated disease, perhaps there are clinical or diagnostic parameters that may highlight patients that will derive maximal benefit from antimicrobial therapy? Subgroup analysis by Prantera \emph{et al}\cite{10} revealed maximal benefit in patients with “early disease”, defined as < 3 years at time of entry into the study (OR 1.7, \(P = 0.02\)). Recent data in mice showed that the timing of introduction of microbiota into “germ-free” animals regulates the influx of immune cells into intestinal tissue by modulating the expression of genes involved in recruiting these cells\cite{11}. Perhaps “early disease” maintains immunologic plasticity whereas longstanding disease has already been programmed to support inflammation. Further characterization may reveal distinct microbial components of their cohort. Finally, it would be interesting to know if disease susceptibility alleles correlate with antimicrobial response. A recent study of microbiota in patients with IBD revealed that genetic susceptibility alleles for nucleotide-binding oligomerization domain-containing protein 2 and autophagy-related protein 16-1 correlate with alterations in the microbiome\cite{11}. These clinical and genotypic parameters may improve the targeted use of antibiotic therapy for CD.

The safety of widespread and long-term antibiotics also remains an issue of concern. Rifaximin has minimal systemic absorption. As such, rifaximin does not have notable systemic side effects or interactions associated with imidazole or fluoroquinolone antibiotics. \emph{C. difficile} remains a major problem in the clinical management of IBD with rising rates of CDI associated with morbidity, mortality and need for colectomy\cite{10}. Although rifaximin may help treat \emph{C. difficile}, one case of \emph{C. difficile} was seen in the 800 mg ER bid group. Further studies will be needed to determine the strength of this association. Rifaximin resistance has evolved in AIEC and should be evaluated before widespread use is adopted\cite{11}.

In summary, this study by Prantera \emph{et al}\cite{10} offers important results and safety data for the use of rifaximin and supports the role for this anti-microbial in improving remission rates in mild to moderate CD. Hard endpoints including mucosal healing and measurements of systemic inflammation will enable crucial evaluation of the efficacy of rifaximin in phase 3 trials. Further analysis of the microbial alterations during rifaximin therapy are important in not only understanding the biology of the microbiome in IBD, but also in designing rational therapeutic strategies for microbial manipulation. Disease location, systemic inflammatory markers, host genotype, and intestinal microbial signatures will ultimately guide a personalized medical approach to the clinical use of directed antimicrobial and/or bacteriotherapy. Although many questions of mechanism and durability remain, Prantera \emph{et al}\cite{10} offer an important step forward in the role for microbial manipulation in the clinical management of IBD.

REFERENCES

1. Prantera C, Loche H, Grimoldi M, Danese S, Scrivano ML, Gionchetti P. Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn’s disease. \emph{Gastroenterology} 2012; \textbf{142}: 473-481.e4 [PMID: 22155172 DOI: 10.1053/j.gastro.2011.11.032]

2. Frank DN, St Amand AL, Feldman RA, Boedecker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. \emph{Proc Natl Acad Sci USA} 2007; \textbf{104}: 13780-13785 [PMID: 17699621]

3. Willing BP, Dickved J, Halfvarson J, Andersson AF, Lucio M, Zheng Z, Järnerot G, Tysk C, Jansson JK, Engstrand L. A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. \emph{Gastroenterology} 2010; \textbf{139}: 1844-1854.e1 [PMID: 20816635 DOI: 10.1053/j.gastro.2010.08.049]

4. Scarpignato C, Pelosini I. Experimental and clinical pharmacology of rifaximin, a gastrointestinal selective antibiotic. \emph{Digestion} 2006; \textbf{73} Suppl 1: 1-27 [PMID: 16498249]

5. Baumgart M, Dogan B, Rishniw M, Weitgman G, Bosworth B, Yantiss R, Orsi RH, Wiedmann M, McDonough P, Kim SG, Berg D, Schukken Y, Scherl E, Simpson KW. Culture independent analysis of ileal mucosa reveals a selective increase in invasive Escherichia coli of novel phylogeny relative to depletion of Clostridiales in Crohn’s disease involving the ileum. \emph{ISME J} 2007; \textbf{1}: 403-418 [PMID: 18043660]

6. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Oyarzábal X and Willing BP. Role of microbiota in intestinal inflammation. \emph{World J Gastroenterol} 2009; \textbf{15}: 22442383 DOI: 10.1126/science.1198469

7. Atarashi K, Tanoue T, Shima T, Takeda K, Hori S, Ivanov II, Umesaki Y, Itoh K, Honda K. Induction of colonic regulatory T cells by indigenous \emph{C. difficile}. \emph{Science} 2011; \textbf{331}: 337-341 [PMID: 21025640 DOI: 10.1126/science.1198469]

8. Olszak T, An D, Zeissig S, Vera MP, Richter J, Franke A, Glickman JN, Siebert R, Baron RM, Kasper DL, Blumberg RS. Microbial exposure during early life has persistent effects on natural killer T cell function. \emph{Science} 2012; \textbf{336}: 489-493 [PMID: 22442833 DOI: 10.1126/science.1219328]

9. Frank DN, Robertson CE, Hamm CM, Kapadeh Z, Zhang T, Chen H, Zhu W, Sartor RB, Boedecker EC, Harpaz N, Pace NR, Li E. Disease phenotype and genotype are associated with shifts in intestinal-associated microbiota in inflammatory bowel diseases. \emph{Inflamm Bowel Dis} 2011; \textbf{17}: 179-184 [PMID: 20839241 DOI: 10.1002/ibd.21339]

10. Ananthakrishnan AN, Binion DG. Impact of Clostridium difficile on inflammatory bowel disease. \emph{Expert Rev Gastroenterol Hepatol} 2010; \textbf{4}: 589-600 [PMID: 20932144 DOI: 10.1586/ egh.10.55]

11. Dogan B, Scherl E, Bosworth B, Yantiss R, Altier C, McDonough PL, Jiang ZD, Dupont HL, Garneau P, Harel J, Rishniw
Longman RS et al. Microbial manipulation for CD

M, Simpson KW. Multidrug Resistance Is Common in Escherichia coli Associated with Ileal Crohn’s Disease. *Inflamm Bowel Dis* 2013; 19: 141-150 [PMID: 22508665]

12 Afdhal NH, Long A, Lennon J, Crowe J, O’Donoghue DP. Controlled trial of antimycobacterial therapy in Crohn’s disease. Clofazimine versus placebo. *Dig Dis Sci* 1991; 36: 449-453 [PMID: 2007362]

13 Sutherland L, Singleton J, Hanauer S, Kravitt E, Rankin G, Summers R, Mekhjian H, Greenberger N, Kelly M. Double blind, placebo controlled trial of metronidazole in Crohn’s disease. *Gut* 1991; 32: 1071-1075 [PMID: 1916494]

14 Prantera C, Kohn A, Mangiarotti R, Andreoli A, Luzi C. Antimycobacterial therapy in Crohn’s disease: results of a controlled, double-blind trial with a multiple antibiotic regimen. *Am J Gastroenterol* 1994; 89: 513-518 [PMID: 8147352]

15 Steinhart AH, Feagan BG, Wong CJ, Vandervoot M, Mikolannis S, Croitoru K, Seidman E, Leddin DJ, Bitton A, Drouin E, Cohen A, Greenberg GR. Combined budesonide and antibiotic therapy for active Crohn’s disease: a randomized controlled trial. *Gastroenterology* 2002; 123: 33-40 [PMID: 12105831]

16 Arnold GL, Beaves MR, Pryjduen VO, Mook WJ. Preliminary study of ciprofloxacin in active Crohn’s disease. *Inflamm Bowel Dis* 2002; 8: 10-15 [PMID: 11837933]

17 Prantera C, Lochi H, Campieri M, Scribano ML, Sturniolo GC, Castiglione F, Cottone M. Antibiotic treatment of Crohn’s disease: results of a multicentre, double blind, randomized, placebo-controlled trial with rifaximin. *Aliment Pharmacol Ther* 2006; 23: 1117-1125 [PMID: 16611272]

18 Selby W, Pavli P, Crotty B, Florin T, Radford-Smith G, Gibson P, Mitchell B, Connell W, Read R, Merrett M, Ee H, Hetzel D. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn’s disease. *Gastroenterology* 2007; 132: 2313-2319 [PMID: 17570206]

19 Leiper K, Martin K, Ellis A, Watson AJ, Morris AI, Rhodes JM. Clinical trial: randomized study of clarithromycin versus placebo in active Crohn’s disease. *Aliment Pharmacol Ther* 2008; 27: 1233-1239 [PMID: 18315579]