A Probiotic for Ulcerative Colitis: The Culture Wars Continue

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Of the phenotypes of inflammatory bowel diseases (IBD), mild–moderate ulcerative colitis (UC) is the most amenable to single-agent nonsteroidal, non-biologic, non-immunosuppressant therapy for both the induction and maintenance of remission, typically as a formulation of mesalamine [1, 2]. Encouraged by this apparent susceptibility to minimalist pharmacological approaches, this very same population is also considered the most amenable to alternative and adjunctive, non-pharmacological interventions [3, 4].

Given the well-founded assumption that microbiota–host interactions are fundamental to the pathogenesis of IBD [5–7] and the demonstration of alterations in the gut microbiota among those with active IBD [8], interventions that seek to modulate the composition of gastrointestinal bacterial communities have proven especially attractive [5–9]. Although approaches ranging from dietary changes through prebiotics and onto fecal microbiota transplantation have been studied [5–9], the supplementation of the diet with probiotics has proven to be the most popular approach in practice [10]. Though results have been mixed, some success has been reported in achieving and/or maintaining remission in mild–moderate UC [10–14]. These studies and even meta-analyses based on their results have been criticized on the basis of numerous methodological shortcomings; suffice it to say that high-quality studies are infrequent [15]. The assumption is that the administration of a probiotic (or probiotics) restores “balance” to the microbiota and, in so doing, eliminates the pro-inflammatory environment that an “unbalanced” microbiota has generated. It is undoubted that this concept is a gross simplification, not only of interactions between luminal bacteria and the host immune system, but also of those between individual bacteria in the gut. Whether

any of these goals (“normalizing” bacterial populations and reducing inflammatory drive) is actually achieved by probiotics in UC has scarcely been addressed in humans.

The study reported in this month’s *Digestive Diseases and Sciences* by Matsuoka et al. [16] set out to address many of the shortcomings of prior studies. They hypothesized that the probiotic *Bifidobacterium breve* strain Yakult (BFM) given as a fermented milk product once a day could prevent relapse of UC among those in remission. In the study, UC patients with left-sided or pancolitis (but not disease limited to the rectum) in 7 different centers in Japan were randomized to receive this strain in milk form (BFM) or a non-fermented energy drink as placebo. To qualify for inclusion, patients had to be in remission for at least 4 weeks prior to enrollment—defined on the basis of the Sutherland disease activity index scale with a rectal bleeding score of 0 and an endoscopic score of 0 or 1. After stratification based on age, gender, duration of disease, study site, and compliance with 5-aminosalicylate therapy, they evaluated, over 48 weeks, a clearly defined primary endpoint: relapse-free survival of UC defined as a lack of rectal bleeding and/or need for induction therapy for active disease. Their secondary endpoints included time to worsening or relapse of UC and change in clinical activity scores. One center also investigated the impact of the intervention on the microbiota of 43 UC patients using 16S or 23S rRNA-targeted reverse transcriptase (RT)-quantitative polymerase chain reaction (PCR)-based assays.

This study has several positive aspects: It was carefully and appropriately designed, treatment groups were comparable, dropout rate was extremely low, and compliance with treatment was very high. There are some limitations, however. These revolve around their understandable failure to recruit sufficient patients to fulfill the required sample size. Interpretation is also complicated by the investigator’s decision to subsequently enroll a smaller number of subjects and perform an interim analysis; this lower target was also not achieved. Following the interim analysis, the study was discontinued due to the lack of difference in primary or secondary endpoints between the two groups. These

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methodological differences notwithstanding, it is hard to escape from the conclusion that the probiotic preparation had no effect.

Why did this laudable effort—targeted at the outcome and the patient population most likely to benefit from a probiotic, fail to show a positive outcome? Was the study, the population, or the probiotic at fault? It is certainly possible that the relatively small (in relation to expectations) study population could have rendered the study susceptible to a type II error and missed a small benefit from the active intervention. With regard to the study population, relapse rates were low; overall, approximately 80% of patients remained in remission regardless of therapy, leaving the investigators with a very limited number of subjects on which to measure the effect of the intervention. Was it the probiotic? This particular *Bifidobacterium* has been well studied, and its probiotic properties [17] adequately demonstrated [18, 19]. Evidence for biologically relevant effects in IBD (promotion of an anti-inflammatory cytokine response and engagement with the intestinal mucosa) is available from preclinical studies [20, 21] but, in comparison with other species and strains, is limited [10]. Clinical experience with this probiotic preparation in IBD is also limited—while a prior study did show benefit in a relatively small study among patients with mild-to-moderate UC, this involved the additional administration of a prebiotic in the form of a galacto-oligosaccharide [22]. Were, as the authors, suggest, bacterial numbers in the probiotic product simply too few? The absence of any impact on the microbiota suggests that this may be the case; however, this question remains unanswered given that dose-ranging studies of probiotics in any indication are notable for their paucity.

Matsuoka and colleagues set out to perform a well-designed study of a probiotic in a well-defined and potentially responsive IBD population and, despite their problems in implementing a well thought out protocol, seem to show no effect, for this strain of *Bifidobacterium* at least.

What does the future hold? Matsuoka and colleagues have shown how studies of this question might be done and, in their valiant effort, exposed the challenges that lie ahead for those who are brave enough to take up the gauntlet that they have thrown down. Is there room for improvement? Strain selection, optimization of formulation, and its delivery are obvious priorities. With regard to the former, a portfolio of in vitro and animal studies indicating appropriate effects is certainly a start but is, by no means, a guarantee of clinical success [9]. Perhaps more attention should be paid to the demonstration of anti-inflammatory effects in humans before embarking on large-scale studies. Strain selection may also be aided in the future by careful attention to the emerging literature on fecal microbiota transplantation in UC [23]—what are the essential components of a successful transplant? Most studies of the gut microbiota in IBD

(and indeed, in most clinical disorders) have shown, at best, associations [24], and we are still some way from the direct incrimination of a single bacterium or collection of bacteria in IBD pathogenesis—we simply do not know what we need to replace.

All the evidence points to a fundamental contribution of the microbiota to UC pathogenesis; the hope is that the ever-increasing knowledge of microbiota–host interactions can be translated into an effective therapeutic intervention that could ultimately replace the many pharmacological options now available.

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