

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

## Probiotics in the Management of Ulcerative Colitis

Richard N. Fedorak, MD, FRCPC  
Associate Vice President of Research  
University of Alberta  
Edmonton, Alberta

### G&H How do probiotics affect intestinal mucosa?

**RF** Probiotics work by several different mechanisms. First, they act as a barrier; they line the intestinal tract close to the brush border and, through competitive inhibition, prevent other luminal bacteria from reaching the lamina propria and stimulating the mucosal immune system. Second, probiotics enhance mucus production so that patients will have a thicker mucus layer, which protects against invasive bacteria, and probiotics can alter the consistency of the mucus, thereby changing bacterial adherence patterns. Third, probiotics cause the mucosal immune system in the patient's intestinal tract to secrete protective immunoglobulins (Ig) such as secretory IgA and a host of protective defensins and bacteriocins into the lumen. Finally, probiotics alter the function of the mucosal immune system to make it more anti-inflammatory and less pro-inflammatory; specifically, probiotics can stimulate dendritic cells to make them slightly less responsive and slightly less reactive to bacteria within the lumen. This latter mechanism appears to be particularly important in ulcerative colitis (UC). Working via these mechanisms, probiotics can downregulate the effects of luminal bacteria in initiating and sustaining an intestinal inflammatory response.

### G&H What is the rationale for using probiotics to treat UC?

**RF** This rationale is 2-fold. First, UC is believed to be a disorder that requires an underlying genetic mutation; this mutation in some way permits "aggressive" luminal

bacteria to initiate a mucosal inflammatory response that is never terminated. In this regard, the rationale for probiotic treatment is that changing existing luminal bacteria so that the colony is less aggressive and more anti-inflammatory could in some way abrogate mucosal inflammation. The second consideration is that UC is a mucosal disease, so a therapy that works at the level of the mucosa should be beneficial. Together, this thinking led researchers to test probiotics in a number of clinical trials to see whether they would prove effective for the treatment of UC.

### G&H What data are available to support the use of probiotics for the induction and maintenance of remission in UC?

**RF** Both small anecdotal trials and larger randomized controlled clinical trials have shown efficacy with 2 specific probiotics. One probiotic, *Escherichia coli* Nissle (Mutaflor, Ardeypharm), is a nonpathogenic strain of *E. coli* that has been shown to be effective for both inducing remission in patients who have UC and maintaining remission for at least 1 year. Researchers have compared *E. coli* Nissle to mesalamine, which is the standard treatment for UC, and in a number of large clinical trials, *E. coli* Nissle was found to be just as effective as mesalamine for both inducing and maintaining remission over a 1-year period. More recently, trials were published that tested a probiotic product called VSL#3 (VSL Pharmaceuticals, Inc.), which is a combination of 8 probiotics: *Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, *L. bulgaricus*, and *Streptococcus thermophilus*. Like the trials of *E. coli* Nissle, trials of VSL#3 have demonstrated efficacy for inducing remission in UC. Although there has not yet been a long-term maintenance trial with VSL#3, available studies have demonstrated that VSL#3 induced remission and maintained a benefit over 24 weeks.

### G&H Is there enough information to say which probiotics are most promising for the management of UC?

**RF** It is very important to note that not all probiotics are the same. Indeed, there are studies in which probiotic preparations (ie, *Lactobacillus* species) have not shown efficacy in treating UC. Based on the clinical trial evidence available to date, only *E. coli* Nissle and VSL#3 appear to be effective in the management of UC. Both patients and physicians therefore need to review the literature carefully and find trials that have demonstrated efficacy in order to identify probiotics that work for the treatment of UC. Patients cannot simply go to a pharmacy or a health food store, buy a probiotic, and assume that it will treat UC.

### G&H What are the practical considerations when probiotics are included in the treatment regimen for UC?

**RF** The first consideration is that physicians and patients must choose the correct probiotic. Remember, not all probiotics are the same. The second consideration is that the selected formulation must be able to colonize the intestine in order to be effective; if patients take a probiotic by mouth, it has to get past stomach acid and bile and reach the large intestine in sufficient numbers to colonize and grow properly. Unfortunately, one of the functions of stomach acid is to kill bacteria, so patients must take enough of the probiotic for a sufficient period of time to overcome this obstacle. Patients probably need to take millions and millions of these bacteria—perhaps billions of them—before the bacteria can overcome stomach acid and reach the intestine, and patients need to continue taking the probiotic for at least 7–10 days to colonize the intestine. Even after the probiotic has colonized the intestine, patients must continue taking the probiotic to maintain its benefits; if the probiotic is discontinued, then the patient's own gastrointestinal organisms will take over and the probiotic will be lost. Thus, if a probiotic is used to treat UC, the correct formulation must be chosen and taken continuously to have a long-term therapeutic benefit.

### G&H Does the effect of a probiotic differ if it is administered rectally?

**RF** When doctors administer a probiotic rectally, it does not have to overcome stomach acid and bile, so it should be possible to give less of the probiotic and still achieve a beneficial effect. The mechanism of action would be the same, however; the probiotic would still need to be administered over 7–10 days to grow and colonize the

entire intestine. Overall, doctors could achieve the same effect by giving a probiotic rectally, but patients often find it more convenient and preferable to take a pill rather than a rectal enema or solution.

### G&H Is viability a concern with the available probiotic formulations?

**RF** Because the US Food and Drug Administration (FDA) does not strictly regulate probiotics, manufacturers do not always use viable bacteria, and there are few rules and regulations regarding the claims that might be made on probiotics' bottles. When patients purchase a bottle of probiotics from a health food store, therefore, it may not contain the probiotics they think it will contain. Even if the formulation does contain the right probiotic, it may be nonviable and less effective, or even ineffective. As a result, there is a need for better FDA-directed rules and regulations regarding both the manufacturing of probiotics and the claims that companies make about their probiotics.

### G&H Does the current lack of regulation for probiotics hinder their clinical utility?

**RF** Yes. From a regulatory standpoint, probiotics are currently identified as a food (or sometimes as a nutraceutical) and are thus subject to food regulations, which are much less stringent than the regulations for medications. Unlike the pharmaceutical industry, companies selling probiotics are not required to conduct clinical trials to prove that their probiotics are effective for treating a specific disease such as UC. Companies can also make claims about the efficacy of probiotics that would not be acceptable for drugs. This situation confuses not only patients but also physicians. Because of this confusion, patients may take the wrong probiotic, or they may receive an ineffective formulation, and when it does not work, they assume that all probiotics do not work.

### G&H How does the efficacy of probiotics compare to that of conventional treatments for UC?

**RF** The probiotic *E. coli* Nissle was compared to mesalamine in several large head-to-head trials, and both treatments were found to be equally effective. VSL#3 has not been directly compared to mesalamine, but studies of VSL#3 achieved rates for induction of remission that were similar to those associated with mesalamine. Given these results, the data suggest that if patients are taking the right numbers of these probiotics in the right way, then the efficacy of both *E. coli* Nissle and VSL#3 is probably similar to that of mesalamine.

### G&H How do the data on probiotics for the management of UC compare with the data regarding the use of probiotics in Crohn's disease?

**RF** UC is a mucosal disease in which probiotics seem to be quite effective, at least in clinical trials that have looked at *E. coli* Nissle and VSL#3. In contrast, studies of probiotics in Crohn's disease have not been as successful. It may be that researchers have not found the right probiotic for Crohn's disease, or the pilot studies that have been performed for Crohn's disease may have been too small to show results. While studies have shown some efficacy with *E. coli* Nissle, VSL#3, and *Saccharomyces boulardii* (Florastor, Biocodex USA) in Crohn's disease, these studies have been difficult to interpret, as they were all small, open-label studies. Gastroenterologists are therefore unlikely to use probiotics in Crohn's disease because the evidence of benefit in these patients is weak, whereas probiotics are used in UC because the evidence there is much stronger.

### G&H What further research is needed to support the use of probiotics for the management of UC?

**RF** Gastroenterologists need to know that scientists are working to gain a better understanding of the mechanisms of action of probiotics. So far, research has shown that probiotics work through some well-defined anti-inflammatory, immune-modulating mechanisms, but each probiotic needs to be studied in randomized controlled trials before researchers can say which work for a

particular condition. Also, patients need to avoid buying probiotics on the Internet, and both doctors and patients should remain skeptical about online testimonials and claims, as they tend to highly overestimate the benefits of the probiotic being sold.

Finally, doctors need to engage in a dialogue with the FDA regarding the regulation of probiotics because physicians and patients are no longer treating probiotics as food, but rather using them as a medication to treat specific diseases, such as UC. The FDA needs to be aware of this shift in thinking so that probiotics can be regulated in a manner appropriate to their current use. With tighter regulations, doctors would know that patients are receiving the prescribed dose from a probiotic, that these formulations contain viable organisms, and that they have been manufactured to the same standards as drugs.

### Suggested Reading

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