Inflammatory bowel disease

Probiotics, prebiotics, synbiotics: ecological treatment for inflammatory bowel disease?

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Ecological treatment may be beneficial in patients with ulcerative colitis

A clinical study published previously in *Gut* suggests for the first time that an ecological treatment combining a prebiotic mixture of fructo-oligosaccharides (FOS) of different chain length with a *Bifidobacterium longum* (a synbiotic) could have therapeutic benefits in the distal colon of patients with acute ulcerative colitis.[1]

In this randomised double-blind pilot trial, a marked decrease in endoscopic lesions in the distal colon was observed in the ecological treatment group but not in the placebo group. The biological markers of inflammation in the mucosa, tumour necrosis factor α, interleukin (IL) 1-α and the human β-defensins 2, 3 and 4, decreased (ie, were ameliorated) in the group receiving the ecological treatment. This study will probably not convince most clinicians because of the low number of subjects, the use of concomittent treatments and the lack of histological inflammation score. However, pilot studies such as this one will hopefully bridge the expanding animal data and still limited human clinical research and help select products for powered randomised controlled trials. Many ecological treatments have now been shown to be effective in the treatment of experimental inflammatory bowel disease (IBD) in rodents.[2] The term probiotic defines ''live microorganisms which when administered in adequate amounts confer a health benefit on the host''. Efficient probiotic strains have been found in different bacterial genera including bifidobacteria, lactobacilli, streptococci and also *Escherichia coli* or clostridia.[2–5] Yeast may also be effective.[2 3] However, this is not a general property of any ingested microorganism and there are differences in efficacy even between strains within a single species. The mechanisms of action involve modulation of the immune system as reviewed by Ghosh *et al*[4] in a previous issue of the journal. Wehkamp *et al*[6] have recently reported that some probiotics may induce defensins in epithelial cells. They observed that several probiotic bacteria including the probiotic strain *E coli* Nissle 1917 strongly induced the expression of the human β-defensin 2 in Caco2 cells in contrast with (or much more than) a large series of non-probiotic bacteria. Defensins are natural antimicrobial peptides secreted in the intestine and this study shows for the first time that some of them may be induced not only by pathogens and inflammation but also by some ecological treatments.

Prebiotics have been defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon, which have the potential to improve the hosts health. Prebiotics such as inulin, FOS, lactulose or resistant starch have also been shown to beneficially influence experimental IBD.[2 7–9] This ''non-living ecological treatment'' may act via modulation of the endogenous flora or some of their fermentation products. Among those, butyrate receives special attention, as it exhibits potent trophic, differentiating and pro-apoptotic properties in the colon.[10] Fermentation is usually a rapid process occurring in the proximal colon so that the luminal concentration of butyrate is lower in the distal colon and faeces than in the proximal colon.[11] This may explain the higher risk of adenocarcinoma in the distal colon versus proximal colon and the localisation of ulcerative colitis. This also underscores the interest for substrates with a slow fermentation profile, potentially leading to increased concentrations of butyrate in the distal colon.

Selection of ecological treatment for clinical trials is presently a challenge. In their pilot trial targeting the distal colon, Furrie *et al* chose the prebiotic Synergy I, which contains a mixture of long-chain FOS (which are expected to be fermented distally) and short-chain FOS. They selected the probiotic strain from 19 strains of bifidobacteria on the basis of its aerotolerance, acid tolerance, bile resistance, adhesion to epithelial cells and ability to use FOS as an energy source. Ingested bifidobacteria often have a high survival rate in the human gastrointestinal tract.[11] Probiotics act as vectors that deliver active constituents to various places in the gastrointestinal tract (target sites) and protect them from digestion, inhibition or absorption upstream.[12] Candidates should therefore be selected on their active constituents and on their pharmacokinetic characteristics. Searching for microorganisms with potentially interesting intrinsic properties is a good way to progress. A recent trial has shown that a probiotic strain of *Lactobacillus farciminis* able to produce nitric oxide improved trinitrobenzene sulphonic acid-induced colitis in rats via nitric oxide delivery.[13] Another possibility is to select candidate microorganisms on their pharmacokinetics and engineer them to make them produce therapeutic molecules in vivo. Most studies on genetically modified probiotics used lactococci (especially *Lactobacillus lactis* MG1363) as vectors for the transgene,[14–17] as these bacteria are easy to manipulate. However, lactococci (including *L lactis* MG1363) have a low survival capacity in the human gastrointestinal tract[18] and may not be the best vector for colonic diseases in humans. Steidler *et al*[19] pioneered the studies when they reported that lactococci, which had been genetically manipulated to produce IL-10 had a therapeutic effect in murine models of colitis. To contain the genetically modified organism and prevent its survival in the external environment, they replaced the *Lactococcus* gene for thymidilate synthase by the IL-10 transgene so that the microorganism becomes dependent on the presence of thyminine or thymidine in the environment. Clinical studies are now under way using this ''biologically contained *L lactis*-secreting IL-10'' in patients with Crohn's disease. In a recent trial, Vandenbroucke *et al*[17] used the same principle for in situ delivery of trefoil factors. These molecules have important roles in the protection and healing of the intestinal epithelium. They have a considerable therapeutic efficacy on histological lesions of dextran sulphate-induced colitis when given rectally, but not when given orally, because they stick to the mucus of the small bowel and are removed from the lumen at the caecum.[17] In a series of experiments, gastric administration of this ''trefoil factor-secreting ecological treatment'' led to active delivery of trefoil factors in the colon and to prevention and healing of dextran sulphate-induced colitis in mice, whereas the

vector without the transgene and the trefoil peptides alone were ineffective.

These studies offer a large field of potential applications for preclinical and clinical research and hopefully will lead to new treatments. The development of complex ecological treatment associating several strains of probiotics with several prebiotics is appealing to companies and to marketing. However, it complicates the situation for researchers who wish to establish modes of action. Whatever the product, the clinician should keep in mind that his decision should be taken on facts (results of trials) rather than on concepts; at present, the evidence is still scarce to make any recommendation in the field of IBD except for VSL#3 in pouchitis and *E coli* Nissle 1917 to prevent the recurrence of ulcerative colitis.[20 21]

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