POINTS OF VIEW

Probiotics in arthralgia and spondyloarthropathies in patients with inflammatory bowel disease. Prospective randomized trials are necessary

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ABSTRACT

Arthralgias and spondyloarthropathies of the peripheral and axial joints are common in inflammatory bowel disease. Evidence for a strong association between these clinical manifestations and diseases of the joints has been provided by several clinical and epidemiological studies. Immunological studies have shown the presence of shared inflammatory cells both in the gut and the synovium in spondyloarthropathies. Genetic factors play a crucial role in the pathogenesis of spondyloarthropathies and inflammatory bowel disease. The role of the ubiquitous bacterial flora and pathogenic microorganisms present in the intestinal lumen may induce these joint diseases in patients with inflammatory bowel disease. In this review we will focus on the pathogenesis of spondyloarthropathies and arthralgia in patients suffering from inflammatory bowel disease. Based on preliminary clinical observations in patients with arthralgia and IBD, we put forward the hypothesis that probiotics may be helpful in the management of common extraintestinal manifestations such as arthralgia in patients with ulcerative colitis and Crohn's disease.

Key words: Arthralgias. Spondyloarthropathies. Inflammatory bowel disease. Crohn's disease.

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INTRODUCTION

Seronegative spondyloarthritides, a subgroup of spondyloarthropathies (SpA), enclose a group of arthropathies characterized by the consistent absence of the rheumatoid factor, the involvement of sacro-iliac joints and the involvement of peripheral inflammatory arthritis. These SpA are also known as non-erosive, non-deforming arthropathies (1). This group is clinically distinguishable from the group of patients with seropositive rheumatoid arthritis. The prevalence of SpA was shown to be higher in Crohn's disease (CD) than in ulcerative colitis (UC) (2). Immunopathological studies, such as increased E-cadherin/catenin complex expression has been observed in clinically overt IBD and in the subclinically inflamed bowel mucosa from spondyloarthropathy (SpA) patients (3,4).

SpA is associated with the histocompatibility antigen HLA-B27. This marker and other yet unknown genetic and environmental factors explain the often observed familial aggregation of SpA and IBD (5-7). Involvement of the gastrointestinal tract is a feature of SpA (8). Subclinical inflammatory lesions of the gut can evolve to clinically overt CD. These lesions are found in 25-75% of SpA patients (9). Clinical articular manifestations compatible with SpA are shown by 39% of patients with IBD (7). A research group in Oxford showed that enteropathic peripheral arthropathy without axial involvement can be subdivided into a pauciarticular large joint arthropathy and a bilateral symmetrical polyarthropathy. Both subgroups can be distinguished by the different distribution of joint involvement and the natural history of the disease. Patients with recorded joint swelling or effusion were classified as type 1 (pauciarticular) when less than five joints were involved, and classified as type 2 (polyarticular) when five or more joints were swollen. Patients with joint pain but no evidence of swelling in the joints were classified as suffering from arthralgia (10).

THE GUT AND THE JOINT

Gastrointestinal infections associated with SpA usually involve the terminal ileum and sometimes also the colon, in most cases without joint symptoms (11,12). Generally two types of inflammation exist; an acute inflammation resembling enterocolitis and a chronic inflammation resembling CD.

The involvement of the genetic marker HLA-B27 may explain the pathogenesis of joint inflammation. The HLA-B27 marker is an HLA class-I molecule that binds microbial antigenic peptides known as arthritogenic peptides. HLA-B27 presents these peptides to $CD8^+$ cytotoxic T-cells in the synovium, thus inducing inflammation. Bacteria that are present in the intestinal lumen of IBD patients may share epitopes with HLA-B27 antigens. Recently, IBD-specific autoantibodies were found in patients with HLA-B27-associated SpA (13). According to Orchard et al. pauciarticular arthropathy (type 1) is clinically and immunogenetically similar to the manifestations of SpA. According to these authors, different HLA associations may define phenotypically distinct subgroups. In type 1: HLA-DRB1*0103 in 33% (relative risk (RR) = 12.1), B*35 in 30% (RR = 2.2), and B*27 in 26% (RR = 4.0). In type 2, i.e., polyarticular arthropathy: HLA-B*44 in 62% (RR, 2.1)(14). In IBD and SpA there is a polygenic predisposition and a high prevalence of increased intestinal permeability (15-18). This may suggest a common etiopathogenesis for arthralgia and SpA in IBD. Endoscopy and the histology of ileal biopsy specimens have shown a high prevalence of asymptomatic intestinal inflammation in patients with assumed idiopathic ankylosing spondylitis (chronic SpA) with or without the HLA-B27 marker (19-21).

The role of increased intestinal permeability was confirmed by abdominal scintigraphy with technetium-99m hexamethylpropylene amine oxime in SpA patients (22). Colonoscopy showed a statistically significant concordance with abdominal scintigraphy (23).

Immunohistochemical studies in mucosal biopsy specimens of SpA patients showed an increase in immunoglobulin-containing cells, similar to CD and UC (24). Among immune alterations, an increased number of the macrophage scavenger receptor CD163 was found in the synovium and colonic mucosa of SpA patients (25-27). Several studies have suggested a link between Gram-negative enterobacteria and IBD (21,28). The involvement of Yersinia and *Salmonella* in reactive arthritis, as well as *Shigella, Campylobacter spp.* and *Klebsiela*, was reported (28,29). The observations by Orchard and Jewell are consistent with the hypothesis that luminal bacteria in this region are important in the pathogenesis of reactive arthritis. They compared a group of CD patients with ileocecal resection to a group of CD patients without ileocecal resection. Patients who underwent ileocecal resection had less arthritic complications (30).

NOT ALL PROBIOTICS ARE ALIKE; COMPARATIVE STUDIES ARE NECESSARY

In order to understand the mechanisms of action of probiotics, two different concepts have been approached –one based on the effects of one single strain used as a food supplement (e.g., *Lactobacillus* GG and *L. casei* Shirota), the other derived from observations made using a mixture of *Lactobacilli*, bifidobacteria, and *streptococcus* (VSL#3) in patients with IBD and arthralgia (31). With the exception of a recently published study (32), no comparative studies of different strains or mixtures are available to date. The choice for one particular strain is empiric, and a careful recording of their effects is necessary. In the only comparative study that has been published, two different strains (*Lactobacillus salivarius* and *Bifidobacterium infantis*) were compared in patients with irritable bowel syndrome. *Bifidobacterium infantis* was found to normalize the antiinflammatory-to-proinflammatory cytokines ratio, whereas no changes in the cytokine profiles were induced by *L. salivarius* and placebo. More comparative studies are needed to find the superiority of each specific strain for a specific symptom (32,33).

PROBIOTICS IN POUCHITIS AND IBD

Probiotics are live microbial feed supplements that benefit the host by improving intestinal microbial balance, and that probably induce benefits in health that normal nutrition is not able to achieve (34). The lumen of the intestine contains bacteria, bacterial products, and dietary antigens capable of initiating and sustaining inflammation. Although the mechanisms of action of probiotics are still unclear, their beneficial effects on the improvement of intestinal microbial balance have already been described for decades (35).

Evidence for a therapeutic role of probiotics in the remission and prevention of patients with pouchitis, a nonspecific ileal inflammation occurring in the ileal reservoir after proctocolectomy for UC, was provided by Gionchetti et al. (36).

PROBIOTICS IN THE MANAGEMENT OF ARTHRALGIA IN PATIENTS WITH IBD

To study the safety and efficacy of probiotics in patients with quiescent IBD who suffered from arthralgia for more than two weeks, Karimi et al. administered oral probiotics (VSL#3) to these patients. Preliminary results suggested that this probiotic mixture may be an alternative treatment for arthralgia in some patients with IBD, without inducing exacerbation of inflammatory bowel

disease as NSAIDs do (37,38).

OBSERVATIONS AND RATIONALE SUPPORTING AN INDICATION FOR PROBIOTICS IN ARTHRALGIA AND SpA IN PATIENTS WITH IBD

The beneficial effects of *Lactobacillus GG* both in the prevention and treatment of T-cell-dependent experimental arthritis were also demonstrated in two animal models suggesting a beneficial effect of the use of probiotics in experimental arthropathy (39).

BASIC MECHANISMS

The modulation of COX2 expression is an important mechanism of the anti-inflammatory and anticarcinogenic property of some probiotics (40). The probiotic *Lactobacillus rhamnosus* GG was found to induce COX2 expression in human T84 colon epithelial cells (41). The importance of COX2-dependent arachidonic acid metabolites as immunoregulatory molecules in the intestinal mucosa is emphasized by the observation that NSAIDs, often efficacious in the treatment of arthropathy, may induce a flare-up of IBD (42-44). COX2-dependent arachidonic acid metabolites are essential in the development and maintenance of intestinal immune homeostasis (45).

Recently, a mitogen-activated protein kinase (MAPK) called p38 has been reported as a mediator of endotoxin-induced production of COX2 in enterocytes (46). The inhibition of the p38 MAPK pathway may inhibit COX2 expression. This is relevant because previous studies have shown that probiotic bacteria inhibit the p38 MAPK pathway (47). We therefore hypothesize that the link between p38 and COX2 may explain the beneficial effect of probiotics in the treatment of arthralgia since probiotic bacteria inhibit this pathway and have a role in preventing intestinal cancer.

INFLIXIMAB (ANTI-TNF-α), NF-κB AND PROBIOTICS IN PATIENTS WITH ANKYLOSING SPONDYLITIS, IBD, AND SpA, AND IN EXPERIMENTAL ANIMAL MODELS OF COLITIS

The efficacy and safety of infliximab in patients with ankylosing spondylitis has been tested in a randomized, placebo-controlled trial showing that infliximab was well tolerated and effective in a large cohort of patients with ankylosing spondylitis during a 24-week study period (48). Patients with Crohn's disease and SpA have also been effectively treated with infliximab, a tumor necrosis factor alpha (TNF-α) blockade (49,50). In an experimental study, the administration of VSL#3 to IL-10 deficient mice showed a reduction of microscopic infection together with a reduction in the mucosal secretion of TNF-α and IFN-γ (51). These studies may suggest that probiotics may facilitate an anti-inflammatory effect of TNF-α blockade. Probiotic VSL#3 appears to reduce the inflammation of the gut mucosa by blocking NF-κB activity and to increase cytoprotection through heat shock protein induction, mediated by inhibition of the proteasome (52).

INTESTINAL PERMEABILITY, IL-10 AND PROBIOTICS IN PATIENTS WITH IBD AND IN EXPERIMENTAL ANIMAL MODELS OF COLITIS

Treatment with the probiotic VSL#3 has demonstrated a reduction of colonic permeability in both IL-10 gene-deficient mice and control mice. This may suggest that the type and quantity of bacterial species in the colon modulate intestinal permeability (53-55). Furthermore, Ulisse et al. have shown that VSL#3 probiotics induce a significant increase in the expression of the anti-inflammatory cytokine IL-10 in the mucosal reservoir of patients with pouchitis compared to similar patients treated with antibiotics (56). The administration of VSL#3 probiotic has been studied in a Th1 T-cell colitis, which was induced by trinitrobenzene sulfonic acid treatment in SJL/J mice. Daily administration of VSL#3 to these mice for a period of 3 weeks, during a remission period between a first and second course of trinitrobenzene sulfonic acid, resulted in a milder form of recurrent colitis than observed in mice administered PBS during this same period. This outcome was due to the induction of an immunoregulatory response involving TGF-β-bearing regulatory cells since anti-IL-10R or anti-TGF-β abolished the beneficial effects of the probiotic mixture (57).

Although the safety of probiotics containing *lactobacilli* and *bifidobacteria* has been evaluated critically, and probiotics were considered to be at least as safe as appropriate traditional reference food (58), one has to take into consideration that not all probiotic bacteria have similar therapeutic effects as stated earlier.

The terminal ileum, and in particular the increased permeability of the terminal ileum, play a key role in the link between intestinal inflammation and SpA. It seems that the most important effect of probiotics in ameliorating arthralgia in patients with IBD and SpA is the enhancement of the intestinal barrier. This hypothesis is supported by experimental observations in mice described by Madsen et al. (59). Isolauri et al. (55) described that prolonged cow milk challenge in suckling rats increases gut permeability to intact proteins, whereas *Lactobacillus GG* counteracts this permeability disorder.

CONCLUSION

Based on the results of experimental animal models,

the concepts described in this review and our preliminary clinical observations, we believe that the use of probiotics may be effective in the management of patients with IBD suffering from arthralgia and/or SpA. Controlled randomized clinical trials to investigate the unresolved issues related to efficacy, dose, and duration of use, single or multi-strain formulation, are necessary to prove the beneficial effect of probiotics in patients with IBD, arthralgia and/or SpA.

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