

Indications and Challenges of Probiotics, Prebiotics, and Synbiotics in the Management of Arthralgias and Spondyloarthropathies in Inflammatory Bowel Disease

Ouafae Karimi, MSc and Amado Salvador Peña, MD, PhD, FRCP, AGAF

Abstract: Arthralgia and spondyloarthropathy of the peripheral and the axial joints are common in patients with inflammatory bowel diseases. Evidence for this association has been provided by clinical, epidemiologic, and immunologic studies confirming the presence of shared inflammatory pathways in gut and joint. Bacterial gut infections such as *Salmonella typhimurium*, *Yersinia enterocolitica*, *Shigella*, *Campylobacter jejuni* may induce reactive peripheral arthritis and 20% of these patients may develop chronic spondyloarthropathy. It is not certain that arthralgias in inflammatory bowel diseases are more frequent than in the general population but clinical articular manifestations compatible with spondyloarthropathy are present in 10% to 40% of patients with inflammatory bowel diseases. These enteropathic peripheral arthropathies without axial involvement are subdivided into a pauciarticular of large joints and a bilateral symmetrical polyarthropathy. The rationale and the challenges of using prebiotics, probiotics, and synbiotics in the management of patients with inflammatory bowel diseases with arthralgias and spondyloarthropathy are briefly reviewed. The rationale is based on the modulation of the ubiquitous intestinal flora by bacteria and their products that have been proven to be safe. The challenge is to find the “window of opportunity” to treat the evolutionary stage of joint inflammation. It seems to us that the major aim is not to treat patients who have a self-limited inflammatory joint disorder, but those patients with persistent arthralgias in an early phase of the disease. Seronegative and seropositive patients with early arthritis, before damage may occur, could be managed by this approach to improve the quality of life and to positively influence the natural course of the disease.

Key Words: probiotics, prebiotics, synbiotics, arthralgias, Spondyloarthropathy

(*J Clin Gastroenterol* 2008;00:000–000)

Received for publication December 18, 2007; accepted December 19, 2007.

From the Department of Pathology, VU University Medical Centre, Amsterdam, The Netherlands.

The authors declare no conflict of interest.

The authors confirm that there is no financial arrangement with anyone.

Reprints: Amado Salvador Peña, MD, PhD, FRCP, AGAF, Department of Pathology, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands (e-mail: as.pena@vumc.nl; pena.as@gmail.com).

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Since a few decades, the concept of spondyloarthropathy (SpA) has evolved into a distinct clinical entity, including axial involvement and peripheral inflammatory arthritis.¹ Typical axial symptoms are low back pain and morning stiffness, alternating buttock pain, decreased mobility of the spine, and impaired thoracic expansion; characteristic radiographic lesions are sacroiliitis and spondylitis. These are the most salient features of ankylosing spondylitis (AS).

The peripheral arthritis affects predominantly the large and small joints of the lower limbs in an asymmetric pauciarticular pattern and is frequently associated with an enthesiopathy or inflammation of the insertion of the tendon to the bone.

Enteropathic peripheral arthropathy without axial involvement has been subdivided into a pauciarticular large joint arthropathy and a bilateral symmetrical polyarthropathy. Both subgroups can be distinguished by the different distribution of the joint involvement and the natural history of the disease. Patients with recorded joint swelling or effusion were classified as type 1 (pauciarticular) when < 5 joints were involved and classified as type 2 (polyarticular) when 5 or more joints were swollen. Patients with joint pain but without evidence of swelling in the joints were classified as suffering from arthralgia.²

Another classification on the basis of serologic markers distinguishes 2 groups of SpA. Seronegative spondyloarthritides enclose a group of SpA characterized by the consistent absence of the rheumatoid factor, the involvement of the sacroiliac joints, and by the involvement of peripheral inflammatory arthritis. These SpA are also known as nonerosive and nondeforming arthropathies.³

The concept is further characterized by a frequent association with the human leukocyte antigen (HLA)-B27 phenotype and a positive family history of SpA. Several clinical entities belong to this concept: AS, reactive arthritis in patients with a recent history of urogenital or intestinal infection, some forms of psoriasis or psoriatic arthritis or juvenile chronic arthritis, and the extraintestinal articular manifestations of inflammatory bowel disease (IBD). Patients with SpA without being classifiable in one of the clinical entities are defined as undifferentiated SpA.

Next to HLA-B27, other genetic and environmental factors explain the often observed familial aggregation of SpA and IBD.⁴⁻⁶ Different HLA associations may define phenotypical distinct subgroups.

In this review, we focus on the extraintestinal articular manifestations of IBD, Crohn's disease (CD) and ulcerative colitis (UC), and AS.

The relation between SpA and gut inflammation has been confirmed by several studies.⁷⁻⁹ Two types of inflammation were distinguished: acute inflammation, resembling infectious enterocolitis; and chronic inflammation, more suggestive of early CD.¹⁰ There is increasing genetic and immunologic evidence supporting the clinical and histologic overlap between gut inflammation in SpA and CD. Subclinical gut inflammation was described in several SpA patients.^{11,12} Gastrointestinal infections associated with SpA usually involve the terminal ileum and sometimes also the colon, in most cases without joint symptoms.^{13,14}

Involvement of the gastrointestinal tract as feature of SpA¹⁵ was found in 25% to 75% of SpA patients.¹⁶ UC and CD are the most frequently encountered types of idiopathic IBD that are associated with SpA.

Subclinical inflammatory lesions of the gut can evolve to clinically overt CD. Clinical articular manifestations compatible with SpA are present in up to 39% of patients with IBD.⁶ Immunopathologic studies, such as increased E-cadherin/catenin complex expression, have been observed in clinically overt IBD and in subclinically inflamed bowel mucosa from SpA patients.^{17,18}

MECHANISM OF ACTION OF PREBIOTICS, PROBIOTICS, AND SYNBIOTICS IN ARTHRALGIA AND SPA IN IBD

Recently, focus has been placed on prebiotic, probiotic, and synbiotic therapies, which aim to restore balance to the gastrointestinal microbiota and reduce intestinal inflammation. However, a greater understanding of the mechanisms behind their action on the gastrointestinal microbiota is required to determine which prebiotic, probiotic, or synbiotic is the most beneficial.¹⁹

Probiotics are live microbial feed supplements, which benefit the host by improving its intestinal microbial balance and probably complement the normal nutrition.²⁰ Although the full mechanisms of action are still unclear, proven beneficial activities are (1) inhibition of pathogenic bacterial growth or epithelial attachment preventing invasion, (2) improvement of the epithelial barrier function, (3) promoting homeostatic immunoregulation by the induction of interleukin (IL)-10, transforming growth factor (TGF)- β and by the inhibition of tumor necrosis factor (TNF)- α and IL-12 synthesis,²¹ and (4) inhibition of the p38 mitogen-activated protein kinase (MAPK) pathway.²² The "p38 MAPK" is a mediator of endotoxin-induced production of cyclooxygenase-2 (COX2) in enterocytes.²³

Inhibition of Pathogenic Bacterial Growth or Epithelial Attachment Preventing Invasion

Several studies have suggested a link between gram-negative enterobacteria and IBD.^{24,25} The involvement of *Yersinia* and *Salmonella* in reactive arthritis, as well as *Shigella* and *Campylobacter* spp. and *Klebsiella* was reported.^{25,26} The observations of Orchard and Jewell²⁷ 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 with a group of CD patients without ileocecal resection. Patients who underwent an ileocecal resection, presented fewer arthritic complications.²⁷

IMPROVEMENT OF THE EPITHELIAL BARRIER FUNCTION

An important feature of CD is the impairment of the integrity of the epithelial barrier. Evidence shows an increased exposure to foreign antigens suggesting a possible link between increase in intestinal permeability and antigenic penetration. This is based on the observation that proinflammatory cytokines, such as TNF- α and IL-13, induce epithelial apoptosis in T_H2 immune responses and thereby upregulate the apoptotic rate and single apoptotic conductivity both in UC and CD.²⁸

Patients with seronegative SpA, even in the absence of gastrointestinal symptoms, showed evidence of gut inflammation, probably inducing an increased gut permeability with transgression of the oral tolerance and absorption of provocative antigens into the circulation.⁷ In IBD and SpA, there is a polygenic predisposition and a high prevalence of increased intestinal permeability.²⁹⁻³²

EFFECTS ON ADHESION MOLECULES

E-cadherin, an adhesion molecule, seems to play an important role in the barrier integrity by mediating homotypic, homophilic intercellular adhesion in epithelial cells. As was shown by Demetter et al¹⁸ in clinical IBD, it seems to be upregulated in active inflammation. Because structural or functional perturbation in any of the molecules of the E-cadherin-catenin complex results in loss of intercellular adhesion, the preexistent epithelium may benefit from upregulation to try to maintain its normal architecture under inflammatory conditions. In acute and chronic active bowel inflammation of SpA patients, upregulation of the E-cadherin/catenin glycoprotein complex was observed. Chronic lesions in a quiescent state did not show such an upregulation, whereas chronic inflammation was associated with an increase in E-cadherin mRNA. As some of the SpA patients with subclinical gut inflammation develop IBD, upregulation of the E-cadherin/catenin complex in inflamed bowel mucosa from SpA patients may point to early cellular changes in the development of IBD and, thereby mimicking the situation in CD.¹⁷

PROMOTION OF HOMEOSTATIC IMMUNOREGULATION BY THE INDUCTION OF IL-10, TGF- β , AND BY THE INHIBITION OF TNF- α AND IL-12 SYNTHESIS

E-cadherin is also a ligand for the α E β 7 integrin on intraepithelial T cells. Therefore, changes may also play a role in the homing of specific T-lymphocyte populations in SpA gut mucosa. Phenotypic characterization of IL-2 expanded T-cell lines (CD3 and CD8) from mucosal biopsies showed upregulated α E β 7 expression in CD.^{33,34} A similar upregulation of α E β 7 in AS demonstrated that similar T-cell populations may be present in the bowel in both diseases.³⁵ Interestingly, a differential expression of the integrins α E β 7 and α 4 β 7 on synovium-derived T-cell lines in SpA was seen, whereas one of the ligands of α 4 β 7, VCAM-1, is highly expressed in SpA synovium.^{33,36} An impaired T_H1 cytokine profile is observed in gut mucosal lymphocytes from patients with SpA. The mucosal T-cell populations in CD and AS were functionally characterized with regard to the T_H1/T_H2 cytokine profile. Analyzing the percentage of cytokine-producing cells, there was a global predominance of interferon- γ and IL-2 compared with IL-4 and IL-10 in both conditions. However, in colon lamina propria lymphocytes in both SpA and CD, a proportional decrease of IFN- γ and IL-2 producing CD3⁺ and CD3⁺CD8⁻ lymphocytes was observed compared with the control situation, suggesting a relative impairment of T_H1 cytokine production.^{37,38}

EFFECTS ON DENDRITIC CELLS AND MACROPHAGES

Macrophages expressing CD163 were found to be increased in colonic mucosa in SpA and in CD, stressing the relationship between these entities. The increased number of CD163⁺ macrophages in colon mucosa of patients with SpA suggests that this is another argument for a role of macrophage scavenger receptors in this group of diseases. Based on these observations, the hypothesis is that the mucosal immune system may be abnormally exposed to bacterial antigens in AS, leading to specific T-cell reactivity. Therefore, the immune cells involved in antigen handling and presentation in gut mucosa from patients with SpA and CD were further investigated using a similar immunohistochemical approach.³⁹

Patients with SpA and CD were associated with large numbers of CD68⁺ macrophages, whereas there were no prominent alterations in dendritic cell populations. The colons of SpA patients and CD patients, but not UC patients, showed increased numbers of macrophages expressing the scavenger receptor CD163. Among the immune alterations, an increased number of the macrophage scavenger receptor CD163 was found in the synovium and colonic mucosa of SpA patients.⁴⁰⁻⁴² These findings highlight the presence of early immune alterations in the SpA gut mucosa that are reminiscent of CD, and suggest that macrophage populations and, more generally, the innate immune system, rather than acquired

immunity, may be involved in the inflammatory process in AS.

Inhibition of the p38 MAPK Pathway

Inflammatory molecules such as COX2 are important.²³ The modulation of COX2 expression is an important mechanism of the anti-inflammatory and anticarcinogenic property of some probiotics.⁴³ The probiotic *Lactobacillus rhamnosus* GG was found to induce COX2 expression in human T84 colon epithelial cells.⁴⁴ Recently, a MAPK called p38 has been reported to act as a mediator in the endotoxin-induced production of COX2 in enterocytes.²³ The inhibition of the p38 MAPK pathway may inhibit the COX2 expression. This is relevant because previous studies have shown that probiotic bacteria inhibit the p38 MAPK pathway.²² We, therefore, hypothesize that the link p38 and COX2 may explain the beneficial effect of probiotics in the treatment of arthralgia, because probiotic bacteria inhibit this pathway and have a role in preventing intestinal cancer.

In acute and chronic active bowel inflammation of SpA patients, E-cadherin mRNA is upregulated.¹⁷ Because E-cadherin is also a ligand for the α E β 7 integrin on intraepithelial T cells, it may play a role in the homing of specific T-lymphocyte populations to the gut mucosa. As some of the SpA patients with subclinical gut inflammation develop IBD, upregulation of the E-cadherin/catenin complex in inflamed bowel mucosa from SpA patients may point to early cellular changes in the development of IBD and thereby mimicking the situation in CD.¹⁷

EFFECT ON THE INNATE IMMUNE SYSTEM

Other immune alterations found in the synovium and colonic mucosa of SpA patients are an increased number of the macrophage scavenger receptor CD163.⁴⁰ These findings demonstrate that the innate immune system rather than the acquired immunity may be involved in the inflammatory process of early arthritis. Prebiotics have several proposed mechanisms of action, including the enhancement of luminal concentrations of endogenous *Lactobacilli* spp. and *Bifidobacterium* spp. Prebiotics, probiotics, and synbiotics stimulate the production of short chain fatty acids, particularly butyrate enhancing the water-holding capacity of the stool.²¹

INFLUENCE OF GENETIC FACTORS AND EXPRESSION

According to Orchard et al⁴⁵ 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 IBD and SpA, there is a polygenic predisposition and a high prevalence of increased intestinal permeability.²⁹⁻³² Endoscopy and histology of ileal biopsy specimens have shown a high prevalence of asymptomatic intestinal inflammation in patients with

assumed idiopathic AS (chronic SpA) with or without the HLA-B27 marker.^{8,10,24}

SpA patients with subclinical chronic gut inflammation were found to cluster with CD patients by means of expression of 95 genes.⁴⁶ Among these genes 2 genes were already described in the context of CD: acyl-coenzyme A oxidase, whose activity was strongly reduced in patients with CD; and glutathione peroxidase 2, exclusively expressed in the intestine and over expressed in the normal colonic tissue of CD patients and SpA patients with chronic gut inflammation.^{47,48} This suggests that some of these genes can act as an early genetic marker for evolution to CD in SpA patients.⁴⁶

COMMON IMMUNOLOGIC MECHANISMS

Immunohistochemical studies in mucosal biopsy specimens of SpA patients also showed an increase of immunoglobulin-containing cells, similar to CD and UC.⁴⁹

This suggests that gut inflammation is linked to peripheral joint disease in AS and SpA, raising the question of common immunologic and inflammatory pathways in these 2 distinct organ manifestations.

The gut-joint recirculation of lymphocytes was supported by the identification of identical T-cell expansions in both the colon mucosa and the synovium of a patient with enterogenic SpA.⁵⁰ Gut-derived lymphocytes from IBD patients were shown to bind to synovial vessels using multiple homing receptors and their corresponding endothelial ligands, including vascular adhesion protein-1.⁵¹ Moreover, analysis of synovial fluid T cells and synovial membrane specimens in SpA and rheumatoid arthritis confirmed that the decreased T_H1 (IFN- γ)/ T_H2 (IL-4) ratio also extended to the joints of SpA patients.^{52,53} This confirms the concept that a defective T_H1 response at the mucosal site may impair the immune defense against intracellular bacteria and thereby contribute to a decreased immune tolerance against bacterial antigens.

Paralleling the observations in the gut, low secretion of IFN- γ , IL-2, and/or TNF- α and an increase in IL-10 production by T cells were also reported in the peripheral blood of patients with several types of SpA.⁵⁴⁻⁵⁶

Similar expression of T lymphocyte adhesion molecules and their ligands and a similar functional behavior (impaired T_H1 / T_H2 profile) further underscore the immunologic link between joints and the gut in AS and SpA.

Bacterial persistence could lead to tissue inflammation by direct stimulation of inflammatory cells such as monocytes, macrophages, and neutrophils, but also intestinal epithelial cells. In general, innate immune cells such as macrophages recognize microbial pathogen-associated molecular patterns through their toll-like receptors (TLRs) and initiate a rapid and quite non-specific innate immune response upon TLR triggering. After binding of bacterial lipoproteins (TLR2), endotoxins (TLR4), flagellin (TLR5), bacterial CpG dinucleotides (TLR9) or bacterial heat shock proteins, the TLRs in

association with the adapter molecule MyD88 initiate a signaling cascade resulting in the activation of NF- κ B and the induction of oxidative stress, the production of inflammatory cytokines, and apoptosis. In IBD and SpA, there is evidence of an abnormal expression of TLRs on gastrointestinal epithelial cells in IBD.⁵⁷

TLR2 and TLR4, showing an increased expression on the CD163-positive macrophages, are also significantly increased in SpA synovium compared with rheumatoid arthritis synovium.⁵⁸

Treatment in vivo with TNF- α blockers leads to a significant reduction of the abnormal TLR expression on these cells, which was functionally paralleled by a decreased production of proinflammatory cytokines upon lipopolysaccharide triggering but not upon TLR-independent stimulation.

Together with the role for nucleotide-binding oligomerization domain containing 2/ caspase recruitment domain family, member 15 in SpA, the concept that the combination of microbial triggering and an abnormal inflammatory response of the innate immune system in genetically susceptible hosts can lead to a breakdown of the normal immunologic tolerance and to a pathogenic cellular immune response to specific bacterial species and/or cross-reacting self-molecules is supported. As indicated, this may lead to a disturbed balance between proinflammatory cytokines such as TNF- α and anti-inflammatory cytokines such as IL-10, which may ultimately result in inflammation in the gut and the joint.

THE ROLE OF PRE PROBIOTICS IN SPA

Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of medical therapy in AS and are recommended as first-line therapy in all AS patients.⁵⁹ However, NSAID therapy in AS patients with concomitant IBD may have deleterious effects on IBD. There are numerous reports on patients without AS suggesting that NSAIDs exacerbate IBD or reactivate preexisting IBD.⁶⁰⁻⁶³

Prebiotics are dietary substances, mostly nondigested carbohydrates, which promote the growth and metabolic activity of beneficial enteric bacteria. Prebiotics have been studied less extensively; however, they may become an ideal treatment or cotreatment option because of their capacity to increase endogenous lactobacillus and bifidobacteria. Combined probiotics and prebiotics (synbiotics) can restore a predominance of beneficial *Lactobacillus* and *Bifidobacterium* spp.; however, as far as we know no studies have been performed in IBD patients with arthralgia.

We have undertaken a proof-of-concept study to determine the safety and efficacy of probiotics in patients with quiescent IBD who suffered from arthralgia for more than 2 weeks. The results suggest that VSL no. 3 may be an alternative treatment for arthralgia in patients with IBD.^{64,65}

Probiotics differ in the modulation of the intestinal inflammatory response. 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,⁶⁶ one has to take into consideration that not all probiotic bacteria have similar therapeutic effects as stated earlier.

Prebiotics have several proposed mechanisms of action, including the enhancement of luminal concentrations of endogenous *Bifidobacterium* spp., stimulating production of short chain fatty acids, particularly butyrate, and enhancing water-holding capacity of the stool.²¹

THE FUTURE

Future research in this field needs to focus on determining which probiotics are the most efficacious in patients with arthritis, SpA, and IBD. How the genetic and bacterial profiles of the patient will influence treatment responsiveness. In this direction an interesting study has been published. A glass-based microarray, based on the identification of 2625 expressed sequence tags that are differentially expressed in the colon of patients with CD or SpA was used to analyze colon biopsy specimens from 15 patients with SpA, 11 patients with CD, and 10 controls. The genes expressed from patients with SpA with subclinical chronic gut inflammation, cluster together and are more related to those with CD than the controls. This result suggests that some of these genes can act as an early genetic marker for evolution to CD in SpA patients.⁴⁶

CONCLUSIONS

On the basis of the results of the 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 as yet unresolved issues with regard to efficacy, dose, and duration of use and/or single or multistrain formulation are necessary to prove this beneficial effect. A major challenge at present is to find markers to be able to identify those patients in the early phase of the disease.

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