Arthralgia is a common extraintestinal manifestation of inflammatory bowel disease (IBD). Alterations of the immunologic regulation in the gut may contribute to the pathogenesis of arthralgia. Probiotics (VSL#3) have proven effective in the treatment of pouchitis in patients with ileal pouch anal anastomosis after panproctocolectomy for ulcerative colitis both in maintaining remission and in preventing a flare-up without side effects. The aim of this study was to determine the safety and efficacy of VSL#3 in patients with quiescent IBD who suffered from arthralgia for more than two weeks. An open-label trial was conducted using VSL#3. Pre- and post-treatment joint pain intensity were measured on the Ritchie Articular Index and visual analog scale. Disease activity of the bowel was assessed by the Truelove-Witts and the Harvey-Bradshaw scores. Sixteen of 29 patients completed the trial; in 10 of the 16 patients a statistically significant improvement was documented by the Ritchie Articular Index. No one of the patients had a relapse of intestinal disease while on probiotics. These preliminary results suggest that the probiotic mixture VSL#3 may be an alternative treatment for arthralgia in patients with IBD without inducing exacerba-
tion of the disease. Because probiotics may be effective in the treatment of IBD as well, our results suggest that patients with active disease and arthralgia may also derive benefit from this treatment. Proper randomized controlled studies are indicated.

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Introduction
Spondyloarthropathies (SpA) of the peripheral and the axial joints, including arthritis and arthralgia, are common extraintestinal manifestations in inflammatory bowel disease (IBD). These disorders are reported to occur in 10–35% of patients from various studies (1, 2). They are part of the seronegative, nonerosive and nondeforming arthropathies (3). Thomas et al. found that pouchitis and symptoms of the joints occurred more frequently in ulcerative colitis patients than in patients with familial polyposis (4).

The etiology of arthralgia in IBD is still unclear. In many patients arthralgia is not related to disease activity. A link with Gram-negative enterobacteria in association with IBD was confirmed in several studies (5, 6). The involvement of Yersinia and Salmonella in reactive arthritis (7, 8), as well as that of Shigella and Campylobacter spp. has been reported. The clinical presentation of IBD-related SpA resembles reactive arthritis resulting from acute bacterial infection with these species. Klebsiella species have been associated with ankylosing spondylitis, based on increased serum antibody titers (9, 10).

Increased intestinal permeability is often observed in patients with IBD and in SpA (11). The resulting increased intestinal mucosal leakage may lead to an increased bacterial translocation, which in turn leads to bacterial mimicry depending on an increased absorption of antigens such as in Klebsiella infections with activation of the immune system (12–14). Transport of these and other antigens from gut to joint has been hypothesized based on their activation of lymphocytes whose lymphoid-tissue trafficking and recruitment are regulated by adhesins and homing molecules. The role of activated intestinal T lymphocytes as precursor of this disorder has been reported in several studies (15–17). Treatment of IBD-associated SpA may be difficult; nonsteroidal anti-inflammatory drugs (NSAIDs) are often effective, but they can induce a flare-up of intestinal inflammation (18), whereas COX-2–specific inhibitors may be contraindicated due to procoagulative potential (19, 20).

Because the effects of probiotics in the treatment of ulcerative colitis and Crohn’s disease is being studied at present, we wanted to restrict this preliminary study to patients with arthralgia who are in IBD remission for the reasons described above.

Methods
An open-label pilot study was carried out at an Amsterdam referral university hospital gastroenterology outpatient department. According to local law and regulations, probiotics are considered to be a nutritional supplement for which pharmaceutical ethical evaluation is not warranted. The assessment of effects of this supplement as described in this paper together with the patient information form with consent procedure were discussed with and approved by the president of the institutional medical ethical committee.

Study population
Participants were recruited from February 2003 through February 2004. Inclusion criteria required patients with quiescent IBD, aged 18–70 years, providing informed consent. IBD was classified according to the criteria of Lennard-Jones (21). Quiescent disease was defined as quiescent or mild disease according to the Truelove-Witts score for ulcerative colitis (22) in combination with a normal C-reactive protein level, and a Harvey-Bradshaw score for Crohn’s disease lower than 5 (23). Furthermore, two patients had an ileostomy for which an adjusted Harvey-Bradshaw score was used. Complaints of arthralgia must have been present for more than 2 weeks with stable medical therapy. Regarding the exclusion criteria, the following medications were not permitted to be changed in the indicated period: mesalazine (<2 weeks), steroids (<last 4 weeks), azathioprine (<12 weeks), methotrexate (<8 weeks), initiation of first infliximab course during the last 12 weeks. Patients with arthritis were excluded on the presence of redness, synovial thickening, joint edema or joint dysfunction during physical examination, and the presence of signs of inflammation in the laboratory investigations. We also excluded patients using NSAIDs, pregnant patients and those with expected noncompliance. All patients were examined by the same investigator. A total of 16 of the 29 patients with quiescent IBD and stable medical therapy who met the inclusion criteria completed the trial. The patients received two VSL#3 sachets per day, each
containing 450 billion viable lyophilized bacteria of four strains of Lactobacillus, three strains of Bifidobacterium, and one strain of Streptococcus salivarius subsp. Thermophilus. This probiotic mixture was produced by VSL Pharmaceuticals Inc., Fort Lauderdale, FL, USA, and distributed by Sigma Tau Ethipharma, Assen, the Netherlands.

Arthralgia scores and outcome measures
The assessment of pain is known to be subjective. In order to make a quantitative objective assessment of pain, we chose the Ritchie Articular Index (RAI) as a primary outcome measure and used intensity and changes in tenderness to quantify pain. All 53 joints were assessed separately (24). However, the proximal interphalangeal and metacarpophalangeal joints of each hand, the metatarsophalangeal joints of each foot, the temporomandibular joints, the sternoclavicular joints and the acromioclavicular joints were calculated as a single unit. The highest score for a single joint gave the score for the group. The joints were graded for tenderness on a 0–3 scale, with 3 being maximal tenderness: 0 = patient had no tenderness; 1 = patient complained of pain on pressure; 2 = patient complained of pain and winced; 3 = patient complained of pain, winced and withdrew.

The visual analog scale (VAS) score indicated the intensity of the patients’ subjective joint pain. The highest VAS score meant no arthralgia. Decreasing scores accompanied increasing joint pain intensity.

Study design
All subjects followed the treatment protocol for 3 months. Treatment with VSL#3 b.i.d. was initiated following the assessment of severity of both IBD and arthralgia. Arthralgia was assessed by both RAI and VAS scores, which were measured at baseline. VAS was applied the week before assessment (VAS I) and on the day of the assessment (VAS II). Prior treatment for IBD, as initiated by the clinician according to each patient’s clinical condition, remained unchanged. At week 6, assessments of complaints were conducted by telephone interview and the patients were asked to complete VAS I and VAS II as described above. At week 12, arthralgia was reassessed by RAI and VAS scores, as was the disease activity according to the Harvey-Bradshaw or Truelove-Witts score in the outpatient department. Treatment compliance was checked by counting the remaining dosage of VSL#3. Laboratory parameters (erythrocyte sedimentation rate, C-reactive protein, hemoglobin, hematocrite, mean corpuscular volume, platelet count, leukocyte count, sodium, potassium, creatinine, γ-GT, alkaline phosphatase and alanine transaminase) were evaluated at baseline and at week 12.

Safety was reviewed by analyzing the incidence of adverse events, including clinically significant laboratory abnormalities defined by the Modified World Health Organization (WHO) Common Toxicity Grading Scale. Adverse events were defined as any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physical observations occurring in a patient during the period of treatment with VSL#3, and 30 days afterward. Adverse events were classified according to the Modified WHO Common Toxicity Grading Scale.

Statistical analysis
Statistical analysis was performed using Instat 3 software. The baseline and follow-up data were compared by Wilcoxon matched-pair U-signed-ranks test and paired Student’s t-test when applicable. The significance of RAI and VAS scores was determined by the p value of the results. The level of statistical significance was set at p <0.05.

Results
Of the 29 patients included in our study, 13 (10 women and 3 men, aged 30–59 years) failed to complete the protocol. There were nine cases of Crohn’s disease and four cases of ulcerative colitis, with a period of intestinal disease varying from 5–37 years. Six patients had a surgical history. Seven patients withdrew informed consent due to personal reasons (three patients), spontaneous improvement (two patients) and rhinitis, which had been present before initiation of probiotic treatment (one patient). One of two patients with an ileostomy bag had handling problems with the ileostomy and discontinued the probiotics after three days. The other six patients withdrew due to distaste (two patients), nausea (one patient), mild to moderate abdominal bloating (one patient), non-IBD-related deterioration of general well-being (one patient) and nonspecific gastrointestinal symptoms (one patient).

Sixteen patients (13 women and 3 men, aged 29–63 years) completed the 3-month protocol (Table I). There were nine cases of Crohn’s disease and seven cases of ulcerative colitis, with a period of intestinal disease varying from 1–29...
Probiotics (VSL#3) in arthralgia in patients with ulcerative colitis and Crohn’s disease

Table I. Baseline characteristics of study participants (n = 16).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>46.7 (8.3)</td>
</tr>
<tr>
<td>Men</td>
<td>3</td>
</tr>
<tr>
<td>Women</td>
<td>13</td>
</tr>
<tr>
<td>Duration of IBD, mean (SD), years</td>
<td>11 (8.6)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>7</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>9</td>
</tr>
<tr>
<td>Peripheral arthralgia</td>
<td>15</td>
</tr>
<tr>
<td>Axial arthralgia</td>
<td>1</td>
</tr>
</tbody>
</table>

*Age and duration of IBD are presented as mean (SD).

years. Two patients had a surgical history. According to the WHO Common Toxicity Grading Scale, none of the adverse events exceeded Grade 1.

In this group, a significant decrease of the RAI was observed, from a median of 11 (0–28) to 5.5 (0–18) (p = 0.02) (Table II). VAS I score indicated the patients’ subjective pain intensity score in the week before assessment. The average VAS I score was 57 (SD 22) at the start of the study, 72 (SD 24) at week 6 and 58 (SD 29) at the end of the study. VAS II score indicated the patients’ subjective pain intensity score at the moment of assessment. The average VAS II score was 66 (SD 24) at the start of the study, 76 (SD 27) at week 6 and 73 (SD 28) at the end of the study. Results of both the VAS I and VAS II scores were not significant (Table III).

Five patients reported improvement of gastrointestinal symptoms, with concomitant increase of general well-being. Two patients reported nausea at the beginning, but completed the trial. Decrease in gastrointestinal symptoms leading to improvement in general well-being was reported as an unexpected positive effect by three patients.

The results showed a difference for axial and peripheral arthralgia. Patients with peripheral arthralgia reported improvement of their joint complaints as well as improvement in their general well-being. However, patients with axial arthralgia reported no improvement of arthralgia.

Treatment compliance was checked by counting the remaining dosage of VSL#3, and was high for those patients participating for 3 months. All patients completed the dosage of VSL#3. We found no changes in laboratory results between baseline and week 12. According to the WHO Common Toxicity Grading Scale, none of the reported adverse events exceeded Grade 1.

Discussion

This pilot study showed a significant improvement in arthralgia in patients with quiescent IBD who used the probiotic mixture VSL#3. The improvement was objectively assessed by RAI scores. VAS scores did not change significantly and remained unchanged in this group of patients, who were in remission of IBD and had only arthralgia as a complaint. It is interesting that only 16 patients of the 29 who met the inclusion criteria completed the trial successfully. This withdrawal rate has not been observed in previous VSL#3 trials under other conditions, for example in patients with pouchitis (25). No one of the total group of patients who completed the 3-month trial had a relapse of the intestinal disease, and three patients reported better stool consistency.

To our knowledge, the exploration of the response of peripheral joint involvement in IBD within our open-label study has not been previously reported. It allows an estimation to be made of the therapeutic potential of probiotics for this indication. Therefore, a randomized placebo-controlled study would be warranted.
trial is necessary to further confirm the efficacy of VSL#3 or other probiotics in the management of arthralgia in IBD. With the experience reported here we believe that probiotics also should be tried in patients with reactive arthritis or arthralgia.

In contrast to a few years ago, different preparations of probiotics are now available. Based on several recent studies it is clear that not all probiotics have the same therapeutic effects for diseases. The differences in therapeutic effects between single strains or mixtures of probiotics need to be addressed. The lumen of the intestine contains bacteria, bacterial products, and dietary antigens capable of initiating and sustaining inflammation. The healthy intestinal epithelium provides a relatively impermeable barrier to these luminal constituents (26).

The beneficial effects on human health of such probiotics as lactic acid bacteria, based on improving the intestinal microbial balance, have already been described for decades, though the mechanisms by which they exert these beneficial effects remain to be elucidated (27).

Cross-talk between bacteria and between bacteria and antigen-presenting cells of the intestine seem to play an important role in controlling overgrowth of potentially pathogenic microorganisms with a bacterial, viral or fungal origin. Adhesion and colonization lead to immune modulation, which in turn helps to enhance leukocyte phagocytic activity against enterobacteria. Survival during intestinal transit also appears to be important for modifying the host's immune reactivity by regulation of the balance between pro-inflammatory and anti-inflammatory cytokines (26). Furthermore, there is evidence for increasing intestinal permeability in experimental models with ulcerative colitis and Crohn's disease, in which probiotics have been shown to enhance the intestinal barrier function (28).

VSL#3 treatment was demonstrated to reduce colonic permeability in both IL-10 gene-deficient mice and control mice, suggesting that the type and quantity of bacterial species in the colon modulate intestinal permeability (29, 30). Furthermore, VSL#3 was able to induce a significant increase in the expression of the anti-inflammatory cytokine IL-10 in the mucosal pouch compared to inflamed and antibiotic-treated patients (31). Probiotic VSL#3 appears to reduce gut mucosa inflammation by blocking NF-κB activity and increasing cytoprotection through heat-shock-protein induction, mediated by inhibition of proteasome (32).

More recently, the probiotic Lactobacillus rhamnosus GG (LGG) was found to induce COX-2 expression in human T 84 colon epithelial cells (33). The importance of COX-2-dependent arachidonic acid metabolites as immunoregulatory factors in the intestinal mucosa is supported by the observation that NSAIDs exacerbate clinical activity in human IBD (34, 35). COX-2-dependent arachidonic acid metabolites are essential in the development and maintenance of intestinal immune homeostasis (36). LGG has been used in patients with rheumatoid arthritis for 12 months. The mean number of tender and swollen joints decreased from 8.3 to 4.6 in the Lactobacillus group and from 5.5 to 4.8 in the placebo group. Although there were no statistically significant differences in rheumatoid arthritis activity, more subjects in the LGG group reported subjective well-being (37).

Interestingly, the beneficial effects of LGG both in prevention and treatment of T-cell-dependent experimental arthritis were demonstrated in two animal models, thus providing experimental evidence of probiotic use in arthropathies (38). In another experimental model, subcutaneous administration of L. salivarius 118 significantly attenuated colitis in the IL-10 knockout model and suppressed collagen-induced arthritis. This study suggested that the oral route may not be essential for probiotic anti-inflammatory effects (39). However, care should be taken in extrapolating results obtained in animal models to patients with IBD.

Although the safety of probiotics containing lactobacilli and bifidobacteria has been evaluated critically, and although they were considered to be at least as safe as appropriate traditional reference food products without evidence suggesting risk of infection (40), one has to take into consideration that not all probiotic bacteria have similar therapeutic effects.

Moreover, the many documented effects of probiotics on inflammatory processes notwithstanding, the specific therapeutic mechanism of VSL#3 that may induce beneficial effects in IBD-associated arthralgia is yet unclear. As recently stated by Fedorak and Madsen (41), "Rigorously designed, controlled clinical trials are vital to investigate the unresolved issues related to efficacy, dose, duration of use, single- or multistrain formulation, and the concomitant use of probiotics, synbiotics or antibiotics."
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