Spondyloarthritis (SpA) is associated with significant disability and adversely affects quality of life. It affects individuals during their most economically productive years. Until recently, with the advent of biologic therapies, effective treatment of spinal disease in SpA was limited to non-steroidal antiinflammatory drugs (NSAID) and physical therapy. The efficacy of disease-modifying drugs with proven benefits in rheumatoid arthritis (RA) such as methotrexate (MTX) and sulfasalazine have been disappointing in SpA. While effective in SpA, the high cost of biologic therapy, together with an associated risk of serious infection such as tuberculosis, means that investigation of cheaper and safer alternative therapies is still important.

Probiotics have been suggested as one such potential therapy. Probiotics are defined by the World Health Organization as “Livemicroorganisms, which when administered in adequate amounts, confer a health benefit on the host”. They are widely available without prescription. It is estimated that each year over 20 billion doses of probiotics are sold. Proposed beneficial effects include modulation of intestinal microbiota, strengthening of the epithelial barrier, and immunomodulation. Probiotics have been shown both in vitro and in vivo to reduce mucosal inflammation via modulation of cytokine levels and other inflammatory mediators. In interleukin 10 (IL-10) knockout mice and inflammatory bowel disease (IBD) patients with pouchitis, administration
of probiotics has resulted in stimulation of antiinflammatory cytokines (IL-10, transforming growth factor β) and suppression of proinflammatory cytokines (tumor necrosis factor-α, TNF-α)\textsuperscript{10,11}. Evidence of a clinical benefit in patients with IBD has come from studies of probiotics in the prevention of pouchitis and maintenance of remission in ulcerative colitis\textsuperscript{12,13}. Improvement in abnormal intestinal permeability in patients with IBD has also been demonstrated following probiotic therapy\textsuperscript{14}. There is evidence that multistrain and multispecies probiotic preparations are superior to preparations containing a single probiotic strain, particularly if the strains used are synergistic\textsuperscript{15}. It should also be noted that evidence for potential harm from the use of probiotics has come from studies in patients with pancreatitis and immunosuppression\textsuperscript{16,17}.

A rationale for probiotics as a potential treatment in SpA lies both in the presence of ileocolitis in SpA\textsuperscript{18} and demonstration of a potential role for the enteric microflora in the development of SpA\textsuperscript{19}. Evidence of intestinal inflammation in patients with SpA comes from ileocolonoscopy showing both macroscopic and histologic changes resembling IBD\textsuperscript{18}. In addition, fecal calprotectin, a noninvasive measure of intestinal inflammation, is elevated in patients with SpA and their relatives\textsuperscript{20}. While ileocolitis in patients with SpA has been described as asymptomatic, we have shown that patients with active SpA have bowel symptoms similar in severity to patients with Crohn’s disease\textsuperscript{21}. Although the intestinal bacterial profile in patients with SpA is similar to that of controls\textsuperscript{22}, individuals with SpA exhibit a loss of tolerance to their autochthonous microbiota. For example, patients with ankylosing spondylitis (AS) produced significantly less IL-10 than controls on exposure to autologous bacteroides species\textsuperscript{23}. Increased intestinal permeability has also been demonstrated in patients with SpA compared to healthy controls\textsuperscript{24}. A suggested link between gut inflammation and the pathogenesis of SpA involves an increase in intestinal permeability allowing luminal antigens or bacteria to interact with the host immune system more readily\textsuperscript{25}. A dysfunctional immune response to these antigens may result in development and chronicity of SpA\textsuperscript{23}.

We hypothesized that administration of an oral probiotic may reduce intestinal inflammation in individuals with SpA with a consequent clinical improvement in disease activity, well-being, and intestinal symptoms. The objective of our study was to investigate the efficacy and safety of an orally administered probiotic in patients with active SpA over a period of 12 weeks.

**MATERIALS AND METHODS**

**Patients.** Patients meeting the European Spondyloarthropathy Study Group (ESSG) criteria for SpA were recruited from a database in the Department of Rheumatology, Dunedin Hospital, New Zealand\textsuperscript{26}. Only patients with active disease as defined by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 3, Bath Ankylosing Spondylitis Functional Index (BASFI) ≥ 3, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) ≥ 2, or peripheral joint count ≥ 2 were included in the trial\textsuperscript{27,28,29}. Patients were excluded if they were pregnant, under 18 years of age, had a diagnosis of IBD, severe immunosuppression, or current gastrointestinal infection. Participants received their usual medication, including treatment with NSAID, oral or intraarticular steroids, and disease-modifying antirheumatic drugs (DMARD). Details of treatment with these therapies were recorded. Participants were advised not to take yogurt or any probiotic-containing preparation for the duration of the trial.

Clinical assessments were undertaken in the outpatient clinic at Weeks 0, 4, 8, 12, and 16 by a single assessor. Both patients and assessor were blinded to the treatment received. The following baseline data were recorded: age, sex, ethnicity, diagnosis, disease duration, comorbidities, and history of uveitis or psoriasis. Medications and doses were recorded at each visit. The ASessments in Ankylosing Spondylitis International Working Group (ASAS) endorsed core set of domains and appropriate measurement tools for their assessment were employed\textsuperscript{30}. Function was measured using the BASFI consisting of 10 questions relating to daily activities, such as putting on socks and climbing stairs. Each activity is rated on a 100-mm visual analog scale (VAS) and a total score divided by 10 (giving a range 0–10)\textsuperscript{28}. The BASDAI was used as a measure of disease activity, with 6 questions about fatigue, spinal pain, peripheral arthritis, enthesitis, and morning stiffness (range 0–10)\textsuperscript{27}. Patient global and pain assessments were recorded on a 10-cm VAS. For the global assessment, patients were asked, “Considering all the ways in which illness and health conditions may affect you, please mark on the line below to show how well you are doing,” with the anchors being “very well” and “very poorly.” The statement for the pain assessment “please mark the line at the point which best represents your level of pain today” was accompanied by the anchors “no pain” and “pain as bad as it could be.” For both scales a higher score (range 0–10) indicates poorer well-being and higher level of pain, respectively.

In addition, intensity of fatigue was measured using the Multidimensional Assessment of Fatigue (MAF) scale, expressed as the total Global Fatigue Index (GFI). The MAF-GFI scale contains 16 items measuring 4 dimensions of fatigue: severity, distress, degree of interference with activities of daily living, and timing. MAF-GFI scores range from 0 (no fatigue) to 50 (severe fatigue)\textsuperscript{31}. This scale has been demonstrated to have a strong correlation with both disease activity and functional impairment in patients with AS\textsuperscript{32}. Convergent validity has been reported with correlation coefficients of 0.692 (p < 0.001) and 0.712 (p < 0.001) for the BASDAI and BASFI, respectively\textsuperscript{32}. The Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), measuring self-perceived severity of disease, current flare of symptoms, and general health was also administered\textsuperscript{33}. The ASQoL contains 18 items concerning the influence of disease from the patient’s perspective. For each statement the patient responds “yes” or “no.” The total score ranges from 0 (good QoL) to 18 (poor QoL). The ASQoL has demonstrated both reproducibility and construct validity and correlates highly with both the BASFI and BASDAI in AS patients. Bowel symptoms were assessed using the Dudley Inflammatory Bowel Symptom Questionnaire (DISQ). Developed to assess bowel symptoms in patients with IBD, it has shown validity in quantifying bowel symptoms in patients with AS\textsuperscript{31}. Physician’s global assessment on a 100-mm VAS was also recorded.

Physical examination included peripheral joint count and MASES index\textsuperscript{29}. Peripheral joint inflammation was assessed according to the 66/68 joint count. For this measure, swelling or tenderness of individual joints is assessed and recorded to give a total score out of 66 (swollen) or 68 (tender joints). The hip joints are excluded from the swollen joint count. The MASES involves palpation of 13 entheseal regions: first and seventh costochondral joints, posterior and anterior superior iliac spines, iliac crests, fifth lumbar spinous process, and proximal insertion of the Achilles tendons. The regions are scored as tender or nontender with a final score ranging from 0 to 13.

Spinal and hip mobility was assessed using the Bath Ankylosing Spondylitis Metrology Index\textsuperscript{34}, which includes measures of cervical spine rotation, tragus to wall distance, lumbar side flexion, lumbar flexion (modified Schober), and intermalleolar distance. Scores range from 0 to 10, a
higher score indicating greater limitation of movement. Skin and nails were
examined for evidence of psoriasis, and presence or absence of sacroiliac
joint tenderness on direct palpation was noted. Chest expansion was meas-
ured at the level of the fourth intercostal space in centimeters. Body mass
index was recorded. Radiographs of the sacroiliac joints were reviewed by
a radiologist for the presence of sacroiliitis.

C-reactive protein (CRP; mg/l) was measured at Weeks 0, 4, 12, and 16.
A subgroup of 31 patients provided fecal samples at Weeks 0, 12, and 16.
Calprotectin measurements as a marker of intestinal inflammation were
performed on all fecal samples by ELISA. Calprotectin, a calcium-binding
protein, is present in all body fluids in proportion to the degree of inflam-
mation present. It has proven to be a useful biomarker of intestinal
inflammation and can be easily quantified in a single fecal sample using
ELISA measurements are given in mg/kg. Among control populations,
median values for fecal calprotectin range from 10 to 35 mg/kg. Elevated
values in excess of 50–150 mg/kg have been suggested as identi-
fying patients with potential IBD.

Random block number generation by BLIS Technologies (Dunedin, New
Zealand) was used for randomization and sequentially numbered containers
assured allocation concealment. This external treatment allocation enabled
patient randomization with blinding of both patients and assessors. Patients
and assessors remained unaware of allocation throughout the trial. The study
drug was identified by the assessors as a random number sequence, to allow
documentation of treatment. The allocation code was broken only at comple-
tion of the data entry process to enable statistical analysis.

Study treatment. The probiotic preparation contained 3 strains of bacteria,
which contributed 5.5% of the weight of the powder composition. The
remains of the formulation consisted of the excipient ingredients, identi-
cal to placebo. The strains used in the active treatment were Streptococcus
tabilis K12 (1 x 10^9 cfu/g), Bifidobacterium lactis LAFTI B94 (4 x 10^9
CFU/g), and Lactobacillus acidophilus LAFTI L10 (4 x 10^9 cfu/g). The
placebo consisted of glucide 36.7%, trehalose 56.9%, and vanilla flavor
0.43% and was identical in appearance, taste, and texture to the active pro-
biotic treatment. Both probiotic and placebo were formulated by BLIS
Technologies. BLIS Technologies had no involvement in study funding,
study design, patient assessment, or statistical analysis. Participants were
provided with a small plastic spoon and instructed to take one level spoon-
ful (approximately 0.8 g) by mouth twice daily for 12 weeks. They were
advised to keep the study drug in a cool dark place, but not necessarily
to refrigerate. At baseline, Week 4, and Week 8 patients were given a fresh
supply of probiotic or placebo and any remaining study drug from the pre-
ceding 4 weeks was collected to monitor compliance.

Outcome measures. The primary outcome measure was an improvement
from baseline in physical function as measured by BASFI. Additional out-
come measures included improvement from baseline of individual
domains: disease activity according to BASDAI, pain VAS, patient global
VAS, fatigue according to MAF, bowel symptoms measured by DISQ,
metatarsophalangeal joints. 18/63 (28.6%) were prescribed
DMARD, 8/32 (25.0%) in the probiotic and 10/31 (31.3%)
in the placebo group (Table 2). Thirty-one patients pro-
vided fecal samples at baseline. Fecal calprotectin concen-
tration was increased at baseline, with a median concentra-
tion of 96 mg/kg (range 29–1194 mg/kg). There was no sig-
nificant difference between probiotic (174 mg/kg) and
placebo groups (190 mg/kg) at baseline (p = 0.79). Measures of disease activity and function were similar
between active and placebo groups at baseline (Table 3).

Compliance. Participants returned all study drug containers
at Weeks 4, 8, and 12. Containers were weighed to doc-
ument compliance. Over the 12-week trial participants
were instructed to take a total of 134 g of the treatment powder. In
the probiotic group the mean amount taken was 124 g and
in the placebo group 122 g, indicating excellent compliance.

Efficacy. The following outcome measures showed
improvement over the 12-week trial in both groups, with no
statistically significant difference between probiotic and
placebo (Table 3). The mean BASFI fell from 3.5 (SD 2.0)
to 2.9 (SD 1.9) in the probiotic group and from 3.6 (SD 1.9)
to 3.1 (SD 2.2) in the placebo group (p = 0.839). The mean
BASDAI dropped from 4.2 (SD 2.2) to 3.2 (SD 2.1) in the
probiotic group and 4.5 (SD 2.0) to 3.9 (SD 2.2) in the
placebo group (p = 0.182). Bowel symptoms as measured by
the DISQ improved in both groups over the 12-week trial,
with mean scores falling from 8.2 (SD 4.7) to 6.6 (SD 5.1)
in the probiotic group and 10.1 (SD 6.7) to 8.8 (SD 8.0) in
the placebo group (p = 0.442). The following indicators
showed improvement in both groups during the study: pain
VAS, patient global VAS, MAF, ASQoL, and physician

Ethical approval for the study was obtained from the Lower South
Regional Ethics Committee. All subjects were over 18 years of age and
gave written informed consent, in accord with the Declaration of Helsinki.

RESULTS

Participants. In total, 63 patients were randomized to treat-
ment with probiotic (n = 32) or placebo (n = 31) (Figure 1). All
63 patients completed the 12-week trial. Table 1 shows baseline
characteristics of the 2 groups. There were no dif-
ferences between the groups at baseline. The mean age of
participants was 43.3 years (range 19–76) and the majority
of patients were male (63%). Mean disease duration was 8.9
years (range 1–53), with 57/63 patients (90.5%) positive for
HLA-B27. The majority of patients (81.0%) had a diagnosis
of AS, the remainder having undifferentiated SpA (17.5%) and
psoriatic SpA (1.6%). A history of current or previous
anterior uveitis was present in 19 (30.2%) and a history of
psoriasis in 5 (7.9%). At baseline 48/63 (76.2%) patients
were receiving concomitant treatment with NSAID and 2/63
were taking oral glucocorticoids. 3/63 patients had at least
one intraarticular steroid injection within the 3 months prior
to the trial, 1 in the placebo group and 2 in the probiotic
joint. Joints injected included ankle, knee, elbow, and
metatarsophalangeal joints. 18/63 (28.6%) were prescribed
DMARD, 8/32 (25.0%) in the probiotic and 10/31 (31.3%)
in the placebo group (Table 2). Thirty-one patients pro-
vided fecal samples at baseline. Fecal calprotectin concen-
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the placebo group (p = 0.442). The following indicators
showed improvement in both groups during the study: pain
VAS, patient global VAS, MAF, ASQoL, and physician
global assessment, but none of these changes were statistically significant.

Applying the ASAS20 criteria, a response was observed in the minority of participants with no statistically significant difference between active and placebo groups. At Week 4 an ASAS20 was achieved by 1/32 in the probiotic group and 1/31 in the placebo group (p = 0.982). At Week 12, 6/32 (18.8%) in the probiotic and 9/31 (25.8%) in the placebo group met ASAS criteria for a 20% improvement (p = 0.338).

At Week 12 the median calprotectin concentrations were essentially unchanged (probiotic group 173 mg/kg, placebo 177 mg/kg) with no significant probiotic effect.

**Adverse events.** A total of 26 patients reported adverse events, 14/32 (43.8%) in the probiotic group and 12/31 (38.7%) of those taking placebo (Table 4). There were no

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**Table 1.** Baseline characteristics of participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Probiotic, n = 32</th>
<th>Placebo, n = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>19 (59)</td>
<td>21 (68)</td>
</tr>
<tr>
<td>Mean (SD) age, yrs</td>
<td>45.5 (15)</td>
<td>41.1 (10)</td>
</tr>
<tr>
<td>Mean (SD) disease duration, yrs</td>
<td>9.8 (13)</td>
<td>7.9 (7)</td>
</tr>
<tr>
<td>HLA-B27-positive (%)</td>
<td>30 (94)</td>
<td>27 (87)</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>27 (84)</td>
<td>24 (77)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Undifferentiated spondyloarthitis</td>
<td>4 (13)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>History of anterior uveitis (%)</td>
<td>9 (28)</td>
<td>10 (32)</td>
</tr>
<tr>
<td>History of psoriasis (%)</td>
<td>4 (13)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

**Table 2.** Concomitant treatment at baseline.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Probiotic, n = 32</th>
<th>Placebo, n = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID (%)</td>
<td>24 (75)</td>
<td>24 (77)</td>
</tr>
<tr>
<td>Oral glucocorticoids (%)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Intraarticular glucocorticoids (%)</td>
<td>2 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>DMARD (%)</td>
<td>8 (25)</td>
<td>10 (31)</td>
</tr>
<tr>
<td>Sulfasalazine (%)</td>
<td>6 (19)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Methotrexate (%)</td>
<td>2 (6)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.
serious adverse events reported and none required discontinuation of the study drug. The most common adverse event was a change in bowel habit, reported by 7 of those in the probiotic group and 6 in the placebo group. In the probiotic group there were also reports of nausea (4), increased flatus (2), abdominal pain (2), flu-like illness (1), headache (1), diarrhea and vomiting (1), upper respiratory tract infection (1), and gastroesophageal reflux (1). In the placebo group there were reports of increased flatus (3), flu-like illness (2), nausea (1), abdominal pain (1), headache (1), diarrhea and vomiting (1), bloating (1), and vertigo (1).

While nausea was reported by 4 (12.5%) patients in the probiotic group and only 1 in the placebo group, this was not a statistically significant difference (p = 0.173). Of those reporting nausea in the probiotic group, 2 patients were taking sulfasalazine and had resolution of their symptoms with a reduction in sulfasalazine dose. A third patient, taking methotrexate, had spontaneous resolution of nausea, as did the fourth patient, who was not receiving DMARD therapy. The patient reporting nausea in the placebo group was not taking DMARD and also had spontaneous resolution of symptoms.

### DISCUSSION

Our study aimed to determine whether probiotics are an effective and safe therapy for spondyloarthritis. It is the first randomized double-blind placebo-controlled trial with defined entry and activity criteria and using ASAS core outcome measures to assess the efficacy of probiotic therapy in this context. The study was adequately powered to detect a significant difference in one of the primary outcome domains. Probiotic therapy did not improve disease activity, function, or quality of life in patients with SpA treated over a 12-week period. A strong placebo response was evident, with both groups demonstrating an improvement in the majority of measures over the course of the trial. A potent placebo effect has been noted in other clinical trials in SpA and may in part reflect the paucity of effective treatments, prior to the recent introduction of anti-TNF therapy.

The narrow 95% confidence intervals for the majority of individual measures preclude any clinically significant benefit from the probiotic preparation. The minimum clinically important difference (MCID: the smallest change in a measure that is considered to represent clinically relevant improvement) was not achieved even at the outermost limits of the confidence intervals for the majority of outcome measures employed. This makes the chance of a type II error (failing to observe a difference when in truth one exists) very low. When the composite ASAS20 criteria were applied, there was no evidence of a probiotic benefit, with 6/32 (18.8%) in the probiotic group and 9/31 (25.8%) in the placebo group achieving an ASAS20 response at the end of
the 12-week intervention period (p = 0.338). This precludes any clinically significant benefit of probiotics on an individual patient basis.

There are 4 possible principal explanations for these findings: probiotics are not an effective treatment of spondyloarthritis, the probiotic preparation trialed was not effective, a longer duration of therapy is required, or probiotic treatment should be given at an earlier stage of disease. The results of the trial may reflect a true absence of clinical effectiveness for probiotics in the treatment of SpA. In support of this explanation, the only other clinical trial addressing this question also failed to demonstrate significant benefit. Brophy, et al conducted an Internet-based trial, randomizing 147 patients with SpA to probiotic or placebo for 12 weeks. Limitations of their study included possible selection bias, absence of active disease as an entry criterion, and high dropout rate.

In further support for a true lack of efficacy, measures of intestinal inflammation — fecal calprotectin and the bowel symptom questionnaire (DISQ) — did not reveal any probiotic benefit. The hypothesis for a probiotic benefit in SpA is based on effects on intestinal inflammation. At Week 12, mean calprotectin concentrations were essentially unchanged in both groups, with no significant probiotic effect observed. Further, while the DISQ scores improved in both groups, again there was no probiotic benefit demonstrated. This suggests that probiotics did not have an effect on ileocolitis that was measurable by changes in calprotectin or bowel symptom score (DISQ).

There are very limited data to guide the choice of probiotic strain for clinical trials. It can be argued therefore, that an alternative probiotic preparation to the one chosen may confer benefit in SpA. The choice of probiotic strains used in our study was based as much as possible on published in vitro, animal, and clinical trials. S. salivarius K12 has exhibited antimicrobial properties and has been shown to down-regulate the inflammatory response in epithelial cells by inhibiting the nuclear factor-kB pathway, and to stimulate beneficial pathways including type I and II interferon responses. Further, other probiotic preparations, most notably VSL#3, have incorporated S. salivarius strains and demonstrated an ability to prevent relapsing pouchitis in patients with ulcerative colitis. B. lactis has also been used in combination probiotic preparations, demonstrating clinical benefit in IBD. Bifidobacteria species show evidence of antibacterial activity and enhanced innate and acquired immunity in both animal and in vitro experiments. L. acidophilus is used in the production of commercial yogurts and is a component of VSL#3. Lactobacillus species have shown promising results in animal models of collagen-induced arthitis, with modified cellular and humoral immune responses and attenuated development of arthritis. Given the chronic course of SpA and the deformities associated with longstanding disease, it could be argued that a longer duration of probiotic therapy than undertaken in our study may be needed to demonstrate benefit. Further, if probiotics exert their effects by ameliorating intestinal inflammation it might be expected that some time might elapse before improvement was evident in activity of SpA, and particularly in function. A longer duration of probiotic therapy of 24–48 weeks would have helped to address these concerns. However, since there was no measurable effect on bowel symptoms over the period of the study, it is unlikely that this was the sole reason for a lack of efficacy. Probiotic treatment has demonstrated benefit in patients with IBD over a period as short as 12 weeks, suggesting that beneficial effects of probiotic therapy are attainable in a 12-week study period.

In our study the mean disease duration was 8.9 years with mean BASFI of 3.5. Many clinical trials in SpA have excluded patients with severe longstanding disease. Patients with greater duration of disease are more likely to have radiographic evidence of extensive fusion and ankylosis of vertebral and sacroiliac joints. These structural changes are irreversible; however, there is evidence that treatment can still be effective at this late stage of disease and can offer substantial improvements in quality of life and disease activity.

Our study demonstrates the safety of the probiotic preparation used. No significant differences between the active and placebo groups were noted in the incidence or type of adverse events. All events were rated as minor and most were self-limiting. None required cessation of the study agent. The lack of adverse events in other clinical studies for which various probiotic treatments have been investigated is consistent with our findings. Trials in IBD have reported no significant difference between probiotic and placebo groups, and large multicenter trials for childhood gastroenteritis also found no increase in side effects attributable to probiotics.

Our randomized controlled trial of a probiotic agent in the treatment of active SpA demonstrated no significant benefit over placebo in terms of gastrointestinal symptoms, disease activity, pain, function, or quality of life. Probiotic therapy was not associated with an increase in adverse events. Based on these findings, this particular probiotic combination cannot be recommended for the treatment of SpA; however, future research could investigate alternative probiotic strains and a longer duration of therapy.

ACKNOWLEDGMENT
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REFERENCES


