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Add-on Probiotics in Patients With Persistent Allergic Rhinitis: A Randomized Crossover Clinical Trial

Mir Mohammad Jalali, MD; Robabeh Soleimani, MD; Ali Alavi Foumani, MD; Hooman Ganjeh Khosravi, MD

Objectives: Current medications for allergic rhinitis (AR) may have undesirable side effects that could affect quality of life (QoL). Probiotics could be an alternative in these patients. The aim of this study was to assess the impact of add-on probiotics on symptoms and QoL of patients.

Methods: In this randomized crossover clinical trial, patients with persistent AR were included. Each subject received budesonide with probiotic supplements (BP) or budesonide with placebo for 8 weeks (B), then vice versa for a further 8 weeks. There was an 8-week washout. The primary outcome was the change of the Short Form 36-Item Health Survey (SF-36) score. The secondary outcomes were assessed by the Sinonasal Outcome Test-22 (SNOT-22) and the Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaires.

Results: A total of 152 subjects (30.1 ± 7.5 years) completed the study. The SF-36 score in both groups showed improvement compared with baseline values. Treatment BP was more effective than that of B. The Cohen’s d and the number needed to treat for Physical Component Scales of SF-36 were 0.40 and 10.77, respectively. These values for Mental Component Scales were 0.33 and 12.61, respectively. Also, treatment BP showed more reduction in the score of SNOT-22 and CARAT.

Conclusion: This study showed that the addition of probiotics to budesonide significantly improved QoL in persistent AR patients. However, the clinical situation of these patients may be not very representative of AR patients in general population. Further studies are recommended.

Key Words: Probiotics, allergic rhinitis, quality of life, SF-36, SNOT-22, CARAT.

Level of Evidence: 1b

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INTRODUCTION

The prevalence of allergic diseases is a serious problem in the field of modern medicine and public health. Estimates suggest that 10% to 30% of adults and up to 40% of children suffer from allergic rhinitis (AR), and the prevalence of the disorder is increasing.1 Symptoms can have significant negative impact on the patients’ quality of life (QoL), sleep quality, mood, learning achievement, and sexual dysfunction.2

Treatment for AR continues to be based on allergen avoidance, medications that provide symptomatic relief, anti-inflammatory therapies, and allergy immunotherapy. Current medications for allergies may have undesirable side effects (e.g., dry mouth, drowsiness, sleeplessness),3 some of which may affect QoL. It is of interest to continue to look for alternatives. Then, the use of probiotics as an alternative in the world is increasing. Probiotics can activate or inhibit type 1 T-helper cell and cause proinflammatory or anti-inflammatory effects. Probiotics may also stimulate interleukin-10, which acts primarily to inhibit the inflammatory response.4,5 It is expected that consuming probiotics could establish a more balanced intestinal flora in AR patients, lead to milder reactions to inhaled allergens in these patients, and limit damages resulting from the inflammation. Thus, the use of probiotics is a popular strategy to prevent or treat AR.

A recent meta-analysis4 provided evidence of a potential benefit of probiotics in the treatment of AR. Although probiotics significantly improved the total scores of QoL questionnaires, the degree of heterogeneity was high. The researchers recommended more high-quality studies to prove the efficacy of probiotics with validated QoL tools and objective measurements.

Initially, a single probiotic strain was intensively investigated in the studies of the treatment of AR. However, recent studies have begun to evaluate the treatment effect by using more than one strain of probiotics. The potential benefits of using multistrain probiotics over single-strain probiotics were suggested in several reviews.5–10 These works point to various explanations: additive effect, synergistic effect, and symbiosis. There is a body of evidence that various lactobacilli and bifidobacteria exert a high interleukin (IL)-10/IL-12 ratio, which lead to anti-inflammatory profile and associated with protection from allergy.11,12 However, there is concern that the antagonistic effects of multi-strain probiotics result in reduced efficacy. The efficacy of multistrain probiotic in

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Jalali et al.: Add-on Probiotics in Allergic Rhinitis
persistent allergic rhinitis (PAR) is unclear. It is worth stressing the paucity of such studies reporting the efficacy of multistrain probiotics on the QoL of patients with AR, particularly the persistent type of AR.

Familact (Zist Takhmir Co., Tehran, Iran) is a probiotic mixture supplement that has shown efficacy in several diseases. Therefore, we conducted this randomized crossover clinical trial. The aim of this study was to assess the impact of add-on probiotic supplement on PAR symptoms and on the QoL of patients.

MATERIALS AND METHODS

Patients

Included patients were 18 to 45 years of age with a diagnosis of moderate-to-severe PAR (according to the Allergic Rhinitis and Its Impact on Asthma classification) for at least 1-year duration. Allergic rhinitis was confirmed by positive findings on physical examination and a positive skin prick test (weal diameter ≥3 mm) at initial screening visit. Volunteers were excluded from the study when presenting any medical condition, such as pregnancy, respiratory tract infection, that could influence the study; uncontrolled asthma (peak expiratory flow <20% of volunteer’s best personal value); taking antihistamine, leukotriene receptor antagonist, and decongestant within the week prior to the study; consumption of corticosteroids within the month prior to the study; or having no medical compliance.

The trial was registered at the Iranian Registry of Clinical Trials (IRCT) (IRCT201501251138N13). The survey protocol was approved by the ethical committee of Guilan University of Medical Sciences (GUMS), Rasht, Iran (1930459703) and complied with the rules delineated in the Helsinki Declaration. Written informed consent was obtained from each subject before the start of the study.

Study Design

This was a randomized, double-blind, placebo-controlled, crossover study was conducted in Rasht, Iran, between April 2015 and October 2015. The subjects were recruited from patients...
already receiving treatment at the outpatient clinics of Amiralam-menin and Razi Hospitals.

All participants were evaluated in five visits (Fig. 1). Visit 1 (screening) determined inclusion and exclusion status. A medical history was taken, and nasal endoscopy and skin prick tests were performed. In addition, forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) responses were measured. Participants stopped any usual therapy with antihistamines, antileukotrienes, decongestants, and nasal steroids, and were given cromolyn sodium nasal spray as rescue medication. Participants attended visit 2 after 2 weeks without their usual treatments to washout periods and throughout the study, cromolyn sodium was an 8-week washout between treatments. During the run-in and washout periods and throughout the study, cromolyn sodium (Nasocrom, Sina Darou) was used as required for symptomatic relief. The symptomatic use was recorded on a diary card, and the number of puffs was considered. Visit 3 was conducted after the first treatment. Visits 4 and 5 were conducted before and after the second treatment, respectively.

Each probiotic supplement—Familact (500 mg capsule, Zist Takhmir Co.)—contains seven different gram-positive organisms: 9 * 10^6 colony-forming units (CFU) of viable, lyophilized lactobacilli (L. acidophilus, L. casei, L. delbrueckii subsp. L. bulgaricus, and L. rhamnosus), 1.25 * 10^10 of bifidobacteria (B. longum, and B. breve), and 1.5 *10^9 of Streptococcus salivarius subsp. thermophilus and 38.5 mg fructooligosaccharide. Rhincourt (AstraZeneca AB Company, Sodertalje, Sweden), an intranasal corticosteroid spray (INCS), is a micronized suspension of budesonide in an aqueous medium. At each visit, the subjects’ diary cards were reviewed, and a physical examination and spirometry were conducted. The primary endpoint was mean total score of the Short Form 36-Item Health Survey Questionnaire (SF-36) on week 8 of treatment following budesonide with probiotic supplement versus budesonide and placebo. The secondary outcomes were the effect on AR symptoms at the Sinonasal Outcome Test-22 (SNOT-22) and the Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaires. In addition, asthma control in subjects who had coexisting asthma was estimated based on the Global Initiative for Asthma (GINA) recommendations.19

### Measurements

The SF-36 is a general QoL instrument measuring eight health-related concepts, including physical function (PF), role physical (RP), body pain, general health (GH), vitality (VT), social function (SF), role emotional (RE), and mental health (MH). The interval level scoring for all eight scales ranges from 0 (for worse health) to 100 (best possible health as measured by the questionnaire). These eight scales can be aggregated into two summary measures: the Physical (PCS) and the Mental (MCS) Component Summary scores. The component scores are standardized with a mean of 50 and a standard deviation (SD) of 10.
A difference of 3 to 5 points has been proposed as the minimal clinically important difference (MCID).  

The SNOT-22 questionnaire is a validated tool to assess nasal symptoms as well as their impact on psychological status, sleep, ear and facial symptoms. The range of the total score is 0 to 110, with lower scores implying a better QoL.  

The CARAT questionnaire is a validated tool to measure disease control of asthma and AR in the last 4 weeks. It is composed of 10 questions divided into two scores: upper airway (U) and lower airway (L). Each score includes four questions. All the questions are scored on a Likert scale of 4 points. The CARAT (U) score >8, is indicative of good control.

Asthma control is defined as the extent to which the various manifestations of asthma are reduced or removed by treatment.

Randomization and Blinding
Randomization and blinding were carried out by an independent pharmacist unrelated to the study. Block randomization (size of four) was conducted with a computer-generated random allocation sequence. This was administered by using sealed envelopes at the Rhino-Sinus, Ear and Skull Base Disease Research Center of GUMS. The probiotic supplement and placebo were made identical in external appearance and content to double blind and double dummy the trial.

Statistical Analyses
According to a previous study, a sample size of 150 subjects allows to detect a 2-point difference in score SF-36, a power of 90%, and a type I error of 0.05. Taking into account a dropout rate of 15%, 172 subjects were planned to be enrolled.

Descriptive analysis of the pattern of distribution of each variable was performed. Qualitative variables were reported as frequencies and quantitative variables as means and SD. Intention-to-treat analyses were conducted. The baseline characteristics and outcomes of interest were compared by Student t test or \( \chi^2 \) test. We carried out analysis of variance to evaluate differences in intraindividual responses between treatments for each response variable. We estimated the sequence and period effects. The sequence effect is the difference between period 1 and period 2 irrespective of treatment order. The period effect is the difference between period 1 and period 2 irrespective of treatment order. This bias may result from a change of patient characteristics during the study that modifies response to different interventions. The pkcross procedure of the Stata 13.0 software (StataCorp LLC, College Station, TX) was used for the crossover analysis.

We calculated Cohen’s d effect size for all primary and secondary outcomes. The Cohen’s d was defined as the difference between the means at postintervention, divided by the pool SD. Cohen defined effect sizes as “small, d = 0.2,” “medium, d = 0.5,” and “large d = 0.8.” Additionally, we calculated the number needed to treat (NNT) for all significant interaction effects.

RESULTS
A total of 172 AR patients were randomized to treatment, and 152 (88%) completed the study as planned (Fig. 1). The mean age of the total population was 30.1 ± 7.6 years; the majority were male (53.9%). About 30% percent of enrolled subjects were current smokers, with an average 9 ± 2 cigarettes per day. The number of smokers in group 1 (BP then B) was more than that of smokers in group 2 (B then BP) \( (P = 0.009) \). Demographic data are presented in Table I. No significant differences existed between baseline values before each randomized treatment for any of the primary or secondary outcome measures evaluated by treatment or sequence. There was no significant difference between patients taking BP or B. Therefore, all analyses were subsequently performed compared with pooled baseline values.

The summary measures of SF-36 (PCS and MCS) showed an insignificant difference between baseline and beginning of the period 2 (paired \( t \) test; \( P = 0.89 \) and 0.11, respectively). The component scores in both groups showed improvement after intervention compared with baseline values. Treatment with BP was more effective than that B (Fig. 2). After supplementary analyses, a
significant higher score was detected in physical function (PF), vitality (VT), and social function (SF) subscales (Fig. 3). The Cohen’s d effect size of PCS between two groups was 0.40, which signifies that about 66% of the BP group had a higher PCS score than the B group. If we assume that 80% of the B group have favorable outcomes, that is, control group’s event rate (CER) is set to 80%, NNT will be 10.77. The Cohen’s d for MCS was 0.33. Given CER 80%, NNT will be 12.61.

The mean of puff number usage of cromolyn sodium as symptomatic relief in BP and B groups was 76.2 (median 72.5) and 81.2 (median 78.5), respectively. After logarithmic transformation of the variable, statistical analysis showed a significant difference between two groups (geometric mean difference 1.11; paired t test, \( P < 0.01 \)). This result is probably not clinically important.

The change score of variables from baseline (i.e., visit point 3 or 5) is illustrated in Table II. Comparing between groups, treatment BP showed more reduction of the SNOT-22 in most items than did treatment B during the both periods. The CARAT (U) subscale measures four items: nasal congestion, sneezing, nasal itching, and runny nose. The mean CARAT (U) score showed a significant decrease in the BP group (\( P \) value: 0.03). The evaluation of CARAT (U) items in BP versus B groups showed that scores of nasal itching and runny nose items were significantly improved after 8-week intervention (Fig. 4).

The value of FEV1 and FVC, as well as EV1/FVC ratio, increased in both groups; however, a significant difference in two groups was observed only in FEV1 (\( P < 0.01 \)). It should be noted that only 52 cases were diagnosed comorbid asthma. According to the GINA criteria, asthma conditions were well controlled in 47 subjects in two periods. This finding may attenuate the effect of intervention on the spirometry tests. A planned subgroup analysis was performed for the 52 patients with

**TABLE II.**

Results of Outcome After Budesonide/Probiotic Versus Budesonide/Placebo in AR Patients (\( n = 152 \)).*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Effect</th>
<th>BP</th>
<th>B</th>
<th>Within-Individual Difference</th>
<th>Effect Size</th>
<th>NNT</th>
<th>F</th>
<th>( P ) Value</th>
<th>Sequence Effect</th>
<th>Period Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SF-36</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td></td>
<td>57.14 (5.40)</td>
<td>55.35 (5.64)</td>
<td>1.79 (4.52)</td>
<td>0.40</td>
<td>10.77</td>
<td>23.88</td>
<td>&lt;0.01</td>
<td>0.30</td>
<td>0.38</td>
</tr>
<tr>
<td>MCS</td>
<td></td>
<td>60.21 (6.86)</td>
<td>58.02 (7.59)</td>
<td>2.19 (6.61)</td>
<td>0.33</td>
<td>12.61</td>
<td>16.57</td>
<td>&lt;0.01</td>
<td>0.24</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNOT-22</td>
<td></td>
<td>16.71 (5.92)</td>
<td>27.47 (4.90)</td>
<td>-10.76 (7.61)</td>
<td>1.41</td>
<td>5.32</td>
<td>306.86</td>
<td>&lt;0.01</td>
<td>0.59</td>
<td>0.12</td>
</tr>
<tr>
<td>CARAT(U)</td>
<td></td>
<td>10.33 (0.67)</td>
<td>8.78 (0.53)</td>
<td>1.55 (1.03)</td>
<td>1.14</td>
<td>5.67</td>
<td>20.28</td>
<td>&lt;0.01</td>
<td>0.89</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>FEV1</td>
<td></td>
<td>86.37 (9.02)</td>
<td>85.54 (10.38)</td>
<td>0.81 (5.38)</td>
<td>0.15</td>
<td>25.44</td>
<td>15.44</td>
<td>&lt;0.01</td>
<td>0.96</td>
<td>0.85</td>
</tr>
<tr>
<td>FVC</td>
<td></td>
<td>92.81 (7.29)</td>
<td>92.17 (7.95)</td>
<td>0.64 (5.28)</td>
<td>0.12</td>
<td>31.37</td>
<td>2.27</td>
<td>0.13</td>
<td>0.91</td>
<td>0.36</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td></td>
<td>92.91 (3.97)</td>
<td>92.54 (4.35)</td>
<td>0.37 (3.35)</td>
<td>0.11</td>
<td>34.07</td>
<td>1.82</td>
<td>0.18</td>
<td>0.93</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Mean (SD).

AR = Allergic Rhinitis; B = budesonide/placebo; BP = budesonide/probiotic; CARAT(U) = Control of Allergic Rhinitis and Asthma Test (upper airway subscale); FEV1 = Forced Expiratory Volume in the first second; FVC = Forced Vital Capacity; MCS = Mental Component Summary; NNT = number needed to treat given the control group’s event rate of 80%; PCS = Physical Component Summary; SD = Standard Deviation; SF-36 = Short Form 36-Item Health Survey Questionnaire; SNOT-22 = Sinonasal Outcome Test-22.

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Fig. 4. Mean score of four items of CARAT (U) at baseline and after the intervention. The 95% confidence interval of the mean score is marked with a box bar (subscale 1: nasal congestion; subscale 2: sneezing; subscale 3: nasal itching; subscale 4: runny nose). CARAT(U) = Control of Allergic Rhinitis and Asthma Test (upper airway subscale). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
comorbid asthma. The baseline values of SF-36 (PCS and MCS) in subjects with or without asthma were similar. Similar to the results found in the study population, the treatment BP was more effective than that of B in these patients ($P < 0.01$ and $0.05$, respectively). In addition, subjects who received BP, had a significantly higher value in FEV1, FVC, and FEV1/FVC ratio than did B ($P$ values 0.01, 0.003, and 0.04, respectively).

**DISCUSSION**

Intranasal corticosteroid sprays are first-line therapy for moderate-to-severe AR and are the most effective medication for controlling AR symptoms.28 The most important concern in management of AR is patient’s adherence to treatment. It has been proposed that probiotics improve the intestinal microbial balance and may modulate immune responses. In a recent systematic review and meta-analysis, Guven et al.7 found only five studies29-33 that evaluated the impact of probiotics on patients with PAR. These studies have shown that probiotics may be useful in the treatment or prevention of PAR in children. Only one clinical trial has explored the clinical effects of probiotic administration on PAR in adults.33 However, there are no conclusive studies for the treatment of PAR adults with probiotics.34

We found that during the run-in period, physical and mental health were reduced about 5% and 1% below the norms, respectively. Considerable evidence now exists that the symptoms of AR negatively affect the QoL of patients.35 This study revealed that PCS and MCS improved significantly after adding probiotics to INCS. However, the difference of component summary scores between two groups did not exceed the minimal clinically important difference. The greatest improvements were observed in the subscales that focus more on MH (VT and SF) as opposed to physical health (PF). It is possible that some patients could not discriminate between RP limitations and RE limitations. Thus, we could interpret the results of SF-36 as health conditions rather than those of mental health.

In this study, we used CARAT (U) and SNOT-22 to determine nasal symptom scores and global scores of subjects, as well as lung function tests to assess the lower airway status. We indicated more reduction of AR symptoms in the BP group compared to the B group. These results confirm the study of Bousquet et al.36 We found a significant within-individual difference in SNOT-22 score (mean 10.8, $P < 0.01$, NNT 5.32). The MCID of SNOT-22 is 9-point.37 But, the within-individual difference of CARAT (U) was 1.55, which did not meet the accepted MCID of 3.5 in CARAT.38 However, the Cohen’s d was similar for SNOT-22 and CARAT (U). These questionnaires are disease-specific patient-reported outcome measures (PROMs) for allergic rhinitis. In contrast to disease-specific tools, SF-36 is a generic PROM to assess GH. The generic PROMs allow comparisons between conditions or treatments and therefore can be used to determine not only the impact of different diseases on patient groups but also the relative cost utility of different interventions. However, generic instruments may be unresponsive to small changes in health-related QoL that are important to the patient. It is explained why the effect size of the SF-36 is lower than the values of the SNOT-22 and CARAT (U).

The SNOT-22 items can be divided into four domains (rhinological, ear/facial, sleep, and psychological).39 Hoehle et al.40 pointed out that among the different symptoms of AR, otologic and sleep quality symptoms were most dominantly associated with a decreased QoL; however, there was no association between QoL with nasal symptoms. Considering a significant clinical difference of QoL and SNOT-22 between the two groups, a possible explanation may be that INCS produces the greatest improvement in nasal symptoms in AR patients; thus, more room exists for action of probiotics on extranasal symptoms. In agreement with our finding, Lin et al.31 showed no add-on effect of *Lactobacillus paracasei* as a supplement to levocetirizine in managing PAR children.

The PAR patients with comorbid asthma showed no significant further deterioration of the QoL compared to that of patients without asthma. The results of the pulmonary function tests of FEV1 and FVC indicated that probiotics may have partially improved the effect of budesonide. In our study, only one-third of patients had asthma, and a ceiling effect may exist in the results due to baseline pulmonary function tests of our patients. Therefore, the effect of probiotics on pulmonary function test could be disappeared. Further studies with larger populations are needed to determine the role of probiotics on lung function tests and the QoL of patients with asthma.

There were some limitations associated with this study that must be considered. First, we used the SF-36 and SNOT-22 as PROMs to estimate health-related QoL. There are concerns regarding outcome measures in allergy. Although many researchers used SNOT-22 in research settings, several tools such as Total Nasal Symptom Score exist that have better specificity in allergic conditions. Second, assessments were performed during the intervention, and the stability of these findings was not evaluated through time. Third, this trial was an add-on design without a real control group (no INCS). Because of this, it was difficult to establish the degree to which clinical improvements were due to probiotic supplementation. Fourth, the self-report recall nature of the SF-36 questionnaire is prone to reporting bias and has a ceiling effect that may limit the ability to detect subtle changes in response to the addition of probiotics in subjects. Finally, our sample was comprised of the moderate-to-severe PAR patients. The clinical situation of these patients may be not very representative of AR patients (intermittent and persistent) in the general population.

**CONCLUSION**

This study has shown that the addition of the probiotic compound, Familact (Zist Takhmir), to INCS significantly improved QoL and extranasal symptoms compared with INCS alone in PAR patients. Noteworthy, this finding adds to the growing body of evidence to support the benefits of probiotics in management of AR in adults. We recommend further studies in intermittent and persistent AR to determine the efficacy of probiotics on symptoms and the QoL of these patients.
Acknowledgment

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