Probiotics and Allergic Rhinitis: A Simon Two-Stage Design to Determine Effectiveness

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Abstract

Background: Allergic rhinitis (AR) is a chronic upper respiratory disease affecting 10–30% of the population worldwide. It is associated with significant economic and medical burden. Probiotics have received attention in recent years as a novel strategy to treat infectious/immune conditions, including AR. However, substantiation of these health claims by regulatory bodies has been rejected due, in part, to inadequate clinical trial design. While randomized controlled trials are considered the gold standard for assessing clinical efficacy, such trials require a priori preclinical data on effect size, which may be a reason for the conflicting results in the probiotic and AR literature. Progressive clinical trial designs, such as the Simon Two-Stage Design, are showing promise within the area of integrative and alternative medicine, particularly in relation to probiotic supplementation, to obtain empirical data for the design of clinical trials that meet regulatory requirements.

Methods: This Phase II study uses a Simon Two-Stage Design to determine the response rate of patients with AR to a probiotic supplement. Patients will consume a multispecies probiotic supplement twice daily for 8 weeks, and will attend an allergy clinic at the beginning and end of the intervention period for assessment. Symptom improvement following probiotic supplementation will be measured by the mini-Rhinoconjunctivitis Quality of Life Questionnaire. Secondary outcomes include twice-weekly symptom and medication diaries, objective determination of nasal congestion via Nasal Rhinomanometry, and change in frequency of medication usage.

Discussion: This study provides an exemplar of the value of using a progressive study design in the complementary and alternative medicine setting. A Simon Two-Stage Design was adopted to investigate whether a multispecies probiotic supplement, not yet trialed in the context of AR, has promise as a therapeutic intervention and warrants the design of larger placebo-controlled studies.

Keywords: Simon Two-Stage Design, mini-Rhinoconjunctivitis Quality of Life, probiotics, allergic rhinitis
Allergic rhinitis (AR) is a chronic upper respiratory disease estimated to affect between 10% and 30% of the population worldwide. The disease is responsible for significant economic and medical burden worldwide. The disease manifests symptomatically as rhinorrhea, nasal congestion, sneezing, and pruritus. House dust mites, animals, and mold spores are major triggers responsible for perennial presentation of symptoms. Intermittent or seasonal symptoms are typically initiated by exposure to pollens. Total avoidance of the common environmental allergens underpinning AR is not possible, and therapeutic options are typically focused on achieving symptomatic relief. Intermittent treatment with oral antihistamines and nasal sprays are costly, may not completely resolve symptoms, and can cause varying degrees of sedation. Immunotherapy to induce desensitization by modifying the allergic response to allergens may offer long-term resolution of symptoms. However, it requires continuous and expensive medical treatment and is not always effective.

The findings of studies that have examined the use of probiotics for AR symptoms remain mixed. A key limitation is the lack of preclinical data utilized to base sample size/power estimates for placebo-controlled trials examining effectiveness. There is growing emphasis on good clinical practice to prevent the unnecessary exposure of patients to potential treatments with minimal effect. Given that there is also a need to design randomized controlled trials with adequate preclinical data consistent with regulatory requirements, there may be benefit in utilizing progressive designs that provide early evidence that an intervention is worthy of continued investigation. This study provides an exemplar of the value of using a progressive study design in the integrative medicine setting. The present study uses a Simon Two-Stage Design to investigate whether a probiotic supplement has promise for AR. This design requires the identification of clinically unimportant (p₀) and important thresholds (p₁), which accounts for natural variation in the course of disease symptoms evident with seasonal allergies. This makes it a practical design for use in probiotic studies to build early-phase clinical evidence prior to embarking on large-scale randomized controlled trials.

Materials and Methods

Study design and setting

This is a prospective non-randomized Phase II study using a Simon Two-Stage Design protocol with $p₁ - p₀ = 0.18$, where $p₀$ (non-effective treatment) was selected as a response in ≤15% of participants and $p₁$ (effective treatment) was as a response in least 33% of participants. The primary objective of this trial design is to determine if the probiotic supplement is worthy of further investigation by determining the proportion of patients reporting a clinically beneficial change in the mini-Rhinoconjunctivitis Quality of Life questionnaire (mRQLQ). This design protocol allows for the recruitment of patients in two stages. In the first stage, a fixed proportion of patients are required to exhibit a pre-specified change in a clinical response rate to warrant further recruitment for the second stage. Following the second stage, the intervention is deemed as having sufficient activity should a fixed number of patients in two stages. In the first stage, a fixed proportion of patients are required to exhibit a pre-specified change in a clinical response rate to warrant further recruitment for the second stage. Following the second stage, the intervention is deemed as having sufficient activity should a fixed number of the total cohort experience a beneficial clinical response.

Participants in the study will be required to consume a probiotic supplement twice daily for 8 weeks and to attend an allergy clinic at the beginning and end of the intervention period for clinical evaluation of nasal congestion, allergic response, and presentation of symptoms through completion of questionnaires. The trial will be conducted at the Queensland Allergy Services Clinic in Southport, Gold Coast, Australia, and completed within the peak pollen season running from September to March.

Approvals

The institutional Human Research Ethics Committee provided ethical approval for this study (Ref# 2015/564). All study procedures are in keeping with the Declaration of Helsinki, and all subjects will provide written informed consent prior to participation. The trial was registered prior to commencement with the Australia New Zealand Clinical Trials Registry (ACTRN12615001103550).

Participant selection

Interested participants will be sourced from the community, via dissemination of study information through local media (newspapers, television and radio), and from among the existing patients of the Queensland Allergy Services Clinic. Eligible participants are both males and females aged 17–65 years with >2-year history of moderate to severe persistent AR and who test positive to either skin prick test or radio-allergosorbent test (RAST; QML Pathology, Murarrie, Australia) to Bermuda (couch) grass or both.

Individuals will be excluded from participating if they: suffer from non-AR; test negative on skin prick test and RAST to Bermuda grass; have consumed probiotics or prebiotics within the previous 12 weeks; have undergone treatment with systemic corticosteroids within the previous 6 months or antibiotics within the previous 30 days; use other anti-inflammatory or immune modulating medications; have existing respiratory disease including asthma, nasal polyposis, or chronic obstructive pulmonary disorder; have illness or infectious disease at time of enrolment; or are pregnant at the time of enrolment or intend to become pregnant during the trial period.

Intervention

Participants will consume one sachet of 2 g freeze-dried multispecies probiotic food supplement (Ecologic® AllergyCare; Winclowe Probiotics, Amsterdam, The Netherlands) twice daily. The probiotic mixture contains bacterial strains Bifidobacterium bifidum W23, Lactobacillus acidophilus W55, Lactobacillus casei W56, Lactobacillus salivarius W57, and Lactococcus lactis W58 (total cell count $1 \times 10^{7}$g) and vitamin B2, biotin, maize starch, and maltodextrins. Participants will be instructed to take one sachet in the morning and one sachet in the evening, preferably at least 15 min before a meal, mixed with water and ingested. Compliance will be encouraged with a daily checklist and monitored through reporting via an online symptom and medication diary and return of unused supplements at the end of the intervention period.

During the supplementation period, participants will be permitted to use a topical nasal steroid sprays (e.g., Mometasone furoate, Budesonide, or Fluticasone propionate) and/or...
a non-sedating antihistamine (e.g., Ceterizine hydrochloride, Fexofenadine hydrochloride, or Loratadine) for symptomatic relief. Medication use will be recorded by self-report twice weekly. Use of antihistamines will be discouraged in the 72 h prior to clinical assessment.

Clinical assessment

Clinical assessment will be completed prior to enrolment to the supplement phase of the study (week 0) and again at the end of the supplementation period (week 8). Participants will complete a skin prick test to assess the degree of allergy specific to Bermuda grass (couch). Allergic reactions will be assessed after 15 min, and the size of the wheal recorded to the nearest millimeter. A wheal size ≥3 mm will be considered a positive Bermuda grass allergy, and these participants will be recruited into the study. Participants with a wheal size of <3 mm will be excluded from participation. A venous blood sample will be collected from an antecubital vein using standard venipuncture techniques and used for determination of a full blood count, including white-cell differential, and confirmation of the skin prick test result by measurement of immunoglobulin E antibodies specific to Bermuda grass using a radio-allergosorbent test. Nasal congestion will be assessed objectively by determination of unilateral nasal resistance, which will be measured with a Nasal Rhinomanometer (NR6 Rhinomanometer; GM Instruments) as a secondary outcome.

Sample size calculation and statistical analysis

The primary endpoint of this study is based on the mRQLQ and the proportion of participants reporting an improvement in quality of life. To provide 80% power with a 95% confidence, a sample size of 46 participants is required, with ≥10 of these participants required to demonstrate the defined clinically beneficial change in the primary endpoint to be considered a worthy response. The aim was to recruit a total of 50 participants to allow for up to a 10% dropout rate. Reported symptom improvement was addressed by Juniper et al, who reported that mean changes in raw score from the mRQLQ of >0.7 can be considered of clinical importance and would justify a change in the patient’s treatment in the absence of troublesome side effects or excessive cost. Descriptive statistics (proportion, median, and/or range) will be determined for all outcomes and demographic variables. Changes in the primary outcome (mRQLQ scores) and nasal resistance measures from pre to post supplementation will also be assessed using a paired samples t-test. Data distributions will be assessed and variables transformed, as appropriate, to approximate conditional normality as required. Changes in weekly symptom scores will be assessed using a one-way repeated measures analysis of variance. Self-reported medication use will be reviewed, categorized, and scored for each individual, and changes over the study assessed using a one-way repeated measures analysis of variance. Statistical significance will be accepted at $p < 0.05$.

Discussion

The health effects of probiotics were traditionally thought to be localized to the gastrointestinal tract. However, recent evidence now suggests that probiotics also play an important role in promoting health effects beyond the gut. In the context of AR, data support the potential for clinical effects beyond those locally in the gut, with a number of randomized placebo-controlled trials demonstrating improvement in AR symptoms following probiotic supplementation. Despite this, not all studies have reported beneficial effect and the consensus of their efficacy remains unclear, likely due to a myriad of variables across studies. Two-stage designs in early clinical development provide an avenue for assessing the response to an intervention, and they provide stringent rules for stopping where there is no evidence of an effect. The utilization of these design protocols provides key evidence for larger-scale clinical trials, and avoids the pitfalls of small underpowered clinical trial studies.

The majority of research trials investigating AR outcomes have been conducted with probiotic preparations containing fewer than three strains with total colony forming units/day ranging from $2 \times 10^7$ to $1.1 \times 10^{12}$ The preparation presented here includes five strains, which may enhance therapeutic benefit and add to the current knowledge. In general, multispecies preparations have been shown to generate increased beneficial health effects compared with single-strain preparations, which is thought to be the result of synergistic effects between strains. To the best of the authors’ knowledge, the cocktail of probiotic strains in the supplement under scrutiny here have not previously been investigated as a
single product in human clinical settings in the field of AR. This particular formulation was selected based on several studies where the individual strains were identified for their ability to suppress Th2 responses in cell-culture models. Furthermore, selected strains contained in this probiotic formulation have also been studied previously in a randomized placebo-controlled trial examining the effect of probiotic supplementation in atopic dermatitis in children. This trial demonstrated significant positive clinical outcomes in participants, supporting the potential of these probiotic strains to influence health outcomes in hypersensitivity conditions. In addition to formulation, length of supplementation was another element considered when designing this study. In published AR clinical trials, the supplementation period varies from 4 weeks to 12 months. However, in a number of studies, significant beneficial effects of supplementation were not seen until after a minimum of 4 weeks of administration, suggesting that supplementation periods in excess of 4 weeks are necessary to assess measurable clinical outcomes. As such, an 8-week supplement period was selected here to allow sufficient time for the supplement to modulate the gut microbiota and to ensure completion of the trial with the peak local pollen season.

Interest in the use of functional foods and supplements has led to increasing focus on the quality of evidence and design of trials used to assess efficacy. With sparse preclinical evidence, initiating large multicenter trials is accompanied by ethical and budgetary implications. Furthermore, regulatory bodies, such as the European Food Safety Authority, have expressly noted the need for information on the estimate of effect of interventions in the design of clinical trials measuring effectiveness, which is consistent with Good Clinical Practice to limit the exposure of patients with a disease to treatments with uncertain effects. The aim of a Simon Two-Stage Design for a Phase II trial is to determine whether a treatment has sufficient biological activity to warrant further development. It is well recognized in oncology and has been used in integrative medicine research. The Simon Two-Stage Design examines the degree of effect of a treatment between an “uninteresting” rate associated with standard therapy or natural variation of disease and an “interesting” rate that warrants further investigation. In the current trial, an uninteresting responder rate of 15% of patients experiencing a change in quality of life through the modulation microbiota to be considered as part of the responder group. A twice-weekly symptom and medication diary was identified as an additional outcome measure to supplement the mRQLQ and to provide assessment of short-term changes in symptoms, as well as any adverse events in response to supplement use.

To provide a level of assessment beyond self-reported outcomes, assessment of nasal congestion via nasal rhinomanometry was identified as a possible tool, given its use as an outcome measure in studies evaluating the therapeutic efficacy of steroid nasal sprays in children with perennial AR and an oral prostaglandin receptor antagonist in adults with seasonal AR. To the authors’ knowledge, this study is one of few to use nasal rhinomanometry as an objective measure to complement data from self-reported symptom questionnaires. However, the relationships between nasal resistance and self-reported symptom severity are unknown, and nasal resistance alone may fail to capture the scope of AR symptom severity across multiple domains. For this reason, nasal resistance is to be considered as a secondary outcome.

There are a number of limitations to this application of the Simon Two-Stage Design and the assumptions for determining a beneficial change in the mRQLQ. As this is an open single-arm study design, the occurrence of placebo effects cannot be quantified. This must, however, be balanced with the principle of putting the well-being of patients first in clinical trial research and limiting exposure of patients to a treatment with unknown benefits. It may be that the threshold of a change of 0.7 in the mRQLQ as a clinically relevant change, along with the difference in the uninteresting and interesting response rates, may not be conservative enough. Under the assumptions of the study design, however, the mean responder rate of 33% is considered a substantial change in clinical research. Furthermore, the “uninteresting rate” was estimated by an allergy specialist based on historical data to reflect change in the quality of life of allergy patients due to natural variation in pollen count. Along with meeting a clinically relevant change in score of the mRQLQ previously published, the decision for a beneficial response is relevant to the disease.

Consistently replicated positive clinical outcomes are required if consensus statements and guidelines for probiotic use in AR are to be developed. As such, additional data are still needed. This study is designed to assess changes in quality of life and AR symptom severity following supplementation with a multispecies probiotic over 8 weeks utilizing a two-stage design protocol. The study will provide preliminary data drawn to inform the subsequent design of larger and placebo-controlled studies to assess the effectiveness of probiotic supplements more rigorously as a tool for managing AR symptoms.
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Author Disclosure Statement

The authors have no competing interests to declare in relation to this study.

References


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