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ORIGINAL RESEARCH

Immunogenic Yeast-Based Fermentation Product Reduces Allergic Rhinitis-Induced Nasal Congestion: a Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Introduction: Allergic rhinitis (AR) impacts around 25% of the worldwide population. However, cost, safety, and a high dissatisfaction rate with numerous conventional medications continues to be an issue in the largest patient surveys, due primarily to a lack of efficacy on nasal congestion. Our previously published randomized trial demonstrated a significant reduction in cold and flu-like symptoms, and a secondary potential observation of a decrease in nasal congestion with an oral yeast-derived compound; therefore, the objective of this study was to test the effects of this same product on nasal congestion and other notable AR symptoms. ***Methods:*** A 12-week, randomized, double-blind, placebo-controlled clinical trial of 96 healthy subjects with a recent clinically documented history of seasonal allergies and AR was conducted. Participants received once-daily supplementation with 500 mg of a dried, modified *Saccharomyces cerevisiae* oral fermentation product (EpiCor®, Embria Health Sciences, Ankeny, Iowa, USA) or placebo during the 12-week period of the highest recorded concentrations of total pollen counts for this Midwest geographic area. Clinical outcome measurements included in-clinic examinations, validated questionnaire and standard diary, and serologic analysis at baseline, 6 and 12 weeks. ***Results:*** During the highest pollen count period (weeks 1-6), EpiCor significantly reduced the mean severity of specific AR symptoms, including a significant reduction in nasal congestion (P=0.04), rhinorrhea (P=0.005), and a nonsignificant reduction in ocular discharge symptoms.

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A significantly (*P*=0.04) reduced total number of days with nasal congestion (12.5 fewer days) favored EpiCor compared with placebo, as did the nasal congestion section of the quality of life questionnaire (*P*=0.04). Subjects receiving the intervention also experienced significantly (*P*=0.03) higher salivary IgA levels. Adverse events were similar to placebo. ***Conclusion:*** This yeast-derived product appeared to be safe and efficacious, and should receive more clinical research with and without standard medications to reduce the impact of seasonal allergies, especially AR-induced nasal congestion.

Keywords: allergic rhinitis; dietary supplement; EpiCor®; nasal congestion; *Saccharomyces cerevisiae*; seasonal allergy

INTRODUCTION

Allergic rhinitis (AR) is a common condition in the United States and throughout the world with reported prevalence rates of at least 10%-25%, and in some countries as high as 20%-50%.[1-4] AR is the sixth most common chronic health condition in the US, occurring in 10%-30% of adults and up to 40% of children.[5-6] It is the most prevalent chronic allergic disorder and is one of the ten most common medical conditions documented in the ambulatory care setting.[7] Costs from direct care and medications are a minimum of $3 billion annually in the US, with almost 80% spent on prescription medications.[8] Workplace productivity losses per employee with AR surpass those for workers with diabetes, migraine, respiratory infection and depression.[9] AR causes 3.8 million days lost annually from school and work in the US alone.[9]

Seasonal AR has a current estimated prevalence of 40% and perennial AR affects at least 10%-20% of the population, but both types of AR have increased over the past 40 years.[4,10-12] It is estimated that 40% of AR patients actually have both seasonal and perennial symptoms.[4] However, these numbers may represent a gross underestimation of the problem, because as many as one third of the individuals with either condition do not seek medical attention.

AR is notable for producing rhinorrhea; sneezing; pruritus of the nose, eyes, ears, and palate; and nasal congestion.[1] However, data from two of the largest patient surveys demonstrated that nasal congestion is usually the primary and dominating of all the symptoms, the one that is most concerning and bothersome, and it is the principal symptom that leads to medical attention and over-the-counter (OTC) or prescribed interventions.[13,14] For example, nasal congestion has been known to increase the risk of sleep disturbances, lower quality of life scores, increase absenteeism, and reduce productivity in the workplace and school.[15-17] Patient surveys also suggest that nasal congestion is not adequately controlled by currently available medications.[13,14]

A once-daily oral immunogenic fermentation product (EpiCor®, Embria Health Sciences, Ankeny, Iowa, USA) and dietary supplement partially derived from *Saccharomyces cerevisiae* (*S. cerevisiae*) has previously demonstrated the potential for adjuvant immune enhancement in a randomized, double-blind, and placebo-controlled trial of vaccinated subjects for influenza.[18] Significant reductions occurred in both the incidence and duration of cold and flu symptoms. One notable finding in this clinical trial was the significant reduction in nasal congestion with this intervention compared with placebo.[18] This observation, along with previous laboratory and clinical findings,[19] suggested the potential for this product to provide immune balance and activity against some of the common symptoms of AR, especially nasal congestion. Any

intervention that is safe, competitively priced, and potentially effective for nasal congestion specifically, and also for other AR issues, would be of interest because of the burden of this condition and the high rate of dissatisfaction with the current treatment options.[20]

MATERIALS AND METHODS

Population and Study Design

Inclusion criteria were as follows: generally healthy male and female subjects who were willing to sign informed consent and participate in all study activities; 18 years or older; self-report and also tested positive (ARUP Laboratories, Salt Lake City, Utah, USA) for grass allergy, which is indicative of seasonal allergies in the upper Midwest; experienced at least nasal symptoms and/or ocular symptoms on a seasonal basis; females who were not breastfeeding; and females who were of childbearing potential if they tested negative for pregnancy at the time of screening based on a serum test, intended not to become pregnant during the study, and agreed to utilize a reliable method of birth control. A past history of asthma was permitted and a total of 12 participants (seven on the intervention, and five on placebo) fit this profile.

Exclusion criteria were as follows: immune dysfunction and/or utilizing a prescribed immunosuppressive medication; uncontrolled asthma; nasal polyps; use of an intranasal steroid spray 1 month or less prior to randomization or during the study; HIV-positive; abnormal laboratory values; females who were pregnant, breastfeeding, or planning to become pregnant during the study; history of drug abuse; unable or unwilling to comply with the study protocol (ingesting study interventions, blood draws, completing diaries, and medical visits); current participation in another research study; comorbidity/concomitant disease; allergies to yeast or yeast-derived products; and chronic sinusitis and/or recent (within the last 6 weeks) episode of acute sinusitis.

A double-blind, placebo-controlled trial of 500 mg of EpiCor, a dietary supplement, was conducted to evaluate seasonal allergy symptoms in subjects 18 years or older. The placebo was of similar shape, size, consistency, and smell compared to the intervention. Each participant was asked to attend five clinical visits over a 12-week time period. Visit 1 included informed consent, standard serum analysis, and grass allergy screening by standard skin testing and/or serum analysis. At visit 2, all subjects that tested positive for grass allergies (n=96) that were asymptomatic and in good health were randomized to 500 mg once-daily EpiCor (n=48) or placebo (n=48). A licensed pharmacist, independent from the trial, utilized a random and blinded numerical and sequential distribution method, and assigned each participant to the intervention or placebo group. Medical history and examination was conducted along with standard blood analysis, saliva, inclusion and exclusion criteria, and the clinically validated Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),[21,22] along with a standardized symptom and adverse events diary[22] that was given to all participants to be completed daily. The RQLQ has seven domains: activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional dimension.[21,22] Each domain inquires about quality of life of the participant with a specific reference to the past week. The responses range from 0 to 6, with 0 indicating not troubled by the symptom and 6 as extremely troubled by the symptom. A lower overall score per symptom or domain is tantamount to a better quality of life.

The daily diary given to participants included the most common nose and eye

allergy symptoms. Subjects rated the presence or absence of their individual symptom on a daily basis, using a standard scale of 0-3, with 0 indicating the absence of the symptom and 3 indicating the most severe experience of this symptom.[22] The nasal symptoms were congestion, rhinorrhea, and sneezing. The eye symptoms included discharge, wateriness, and pruritus. Analysis of symptoms was done on two variables: the mean severity of the symptom and the mean total number of days the subject experienced the symptom (primary endpoints). Severity was defined as the average rating for the symptom only when the subject experienced it; therefore responses of 0 were excluded. Number of days with the symptom was defined as the total number of days the subject experienced the symptom. The days did not need to be continuous.

Visit 3 included collection of saliva samples, serum, quality of life, and review of adverse events and information from symptoms and adverse events diary. Visit 4 and 5 were similar to the third visit but also included nasal smear data collection. There was an approximate 6-week time period between visit 2 and 3, and 3-week time period between visit 3 and 4, and between visit 4 and 5 (12-week total interventional duration). Pollen counts (low, medium, and high) were based on the number of grains of pollen per cubic meter over a 24-hour period from diverse sources (trees, grasses, weeds, and mold) specific to this Midwest region of the country, and were monitored from Pollen.com, which provides daily monitoring of total pollen counts for every region of the US, utilizing comprehensive data from several hundred monitoring stations (http://www.pollen.com/allergy-weather-forecast.asp).

Participants were permitted to utilize OTC and prescription allergy antihistamine/decongestant medications, with the exception of steroids (exclusion criteria), on an "as needed" basis for allergy symptoms. Subjects were asked to record medications in the study diary. This was taken into consideration for statistical analysis. Allowed medications utilized during the study included the following: loratadine, fexofenadine, certirizine, montelukast, diphenhydramine, desloratadine, and sudafed.

Statistical Measurements

A power analysis was conducted based on data reported from a previous clinical trial with this intervention,[19] and for 85% statistical power at a significance level of 0.05 the required subjects would be approximately 40-50 per group, which set the optimal goal for recruitment. The analysis of symptoms was done in two parts: part 1 used the time factor as a grouping variable, and part 2 considered pollen counts. Comparison of the intervention and placebo groups was accomplished with the Mann-Whitney *U* test procedure at alpha equal to 0.05. All statistical analyses were done using version 9.1 of the SAS software. A *P* value of <0.05 was considered statistically significant.

RESULTS

Mean age of the EpiCor (intervention) group was 39 (SD±11.5) years with a maximum age of 62 and a minimum age of 18 years. Mean age of the placebo group was 38 (SD±12.5) years with a maximum age of 70 and a minimum age of 21 years. A total of 49% of the participants were female. Smoking status was as follows: 61% were nonsmokers in the EpiCor group and 56% in placebo. No statistical differences were noted for any of the baseline characteristics between the intervention and placebo groups. All of the subjects were Caucasian with the exception of one African-American in the placebo group.

Groups were divided into the three clinical visit periods after the intervention or placebo was utilized, and included weeks 1-6, weeks 7-9, and weeks 10-13. A significant difference occurred in pollen counts during these three different time intervals. A comparison of weeks 1-6 and weeks 7-9 resulted in a *P* value of 0.007, indicating a significantly higher pollen count on weeks 1-6 versus 7-9. Comparison of weeks 1-6 and weeks 10-13 also resulted in a highly significant ($P<0.0001$) difference in favor of a greater pollen count for weeks 1-6. Comparing weeks 7-9 and 10-13 demonstrated a significantly ($P=0.03$) higher pollen count during weeks 7-9. When comparing weeks 1-6 and 7-13 there was a significantly ($P=0.001$) higher pollen count for weeks 1-6 compared with any other time interval, whether or not that time interval was grouped (weeks 7-13) or separated in time (7-9 or 10-13).

During weeks 1-6 subjects given the intervention demonstrated significantly less mean severity of nasal congestion ($P=0.04$) and running nose ($P=0.005$) (see Tables 1 and 2). The median severity for nasal congestion was 1.14 with the intervention compared with 1.33 with placebo, and for rhinorrhea it was 1.24 versus 1.53. Total number of days with nasal congestion significantly ($P=0.04$) favored EpiCor with a median of 16.5 days of nasal congestion compared with 29 days with the placebo. Similar results and significance levels occurred regardless if median or

Table 1. The mean and median severity of symptom comparisons between the intervention (EpiCor) and placebo group over the period of highest pollen counts (weeks 1-6).

	Mean severity		Median severity		
Symptom	Intervention group (SD)	Placebo group (SD)	Intervention group (IQR)	Placebo group (IQR)	*P* value
Nasal congestion	1.29 (0.33)	1.43 (0.37)	1.14 (0.54)	1.33 (0.56)	0.040
Rhinorrhea	1.38 (0.39)	1.61 (0.41)	1.24 (0.56)	1.53 (0.54)	0.005
Sneezing	1.63 (0.44)	1.66 (0.42)	1.63 (0.78)	1.85 (0.74)	0.320
Ocular discharge	1.26 (0.32)	1.29 (0.40)	1.14 (0.38)	1.20 (0.47)	0.350
Ocular wateriness	1.31 (0.32)	1.37 (0.48)	1.19 (0.30)	1.18 (0.48)	0.440
Ocular pruritus	1.44 (0.51)	1.43 (0.36)	1.31 (0.67)	1.39 (0.48)	0.280

IQR=interquartile range; SD=standard deviation.

Table 2. The mean and median total number of days with the specific symptom comparisons between the intervention (EpiCor) and placebo group over the period of highest pollen counts (weeks 1-6).

	Mean total days with symptom		Median total days with symptom		
Symptom	Intervention group (SD)	Placebo group (SD)	Intervention group (IQR)	Placebo group (IQR)	*P* value
Nasal congestion	17.21 (14.11)	23.05 (15.65)	16.50 (26.00)	29.00 (31.00)	0.04
Rhinorrhea	21.86 (15.90)	22.74 (16.19)	20.50 (31.00)	29.00 (30.00)	0.50
Sneezing	22.50 (15.15)	21.90 (15.09)	25.00 (28.00)	25.00 (29.00)	0.37
Ocular discharge	7.45 (12.00)	10.69 (12.36)	2.00 (8.00)	7.00 (16.00)	0.06
Ocular wateriness	13.50 (12.93)	13.07 (13.85)	8.50 (22.00)	6.50 (22.00)	0.35
Ocular pruritus	13.26 (12.59)	15.05 (15.14)	10.50 (23.00)	10.50 (32.00)	0.42

IQR=interquartile range; SD=standard deviation.

mean days were compared between groups for weeks 1-6. Other measured symptom parameters (sneezing, ocular discharge, ocular wateriness, and pruritus) did not reach statistical significance. The additional time intervals (weeks 7-9 and 10-13) demonstrated no significance in symptom severity or total days with symptoms when the intervention was compared with placebo, with the exception of rhinorrhea that statistically (P=0.03) favored the intervention compared with placebo over the entire duration of the study period.

The RQLQ demonstrated that the nasal symptom domain, which includes stuffiness/blocked nose, runny nose, sneezing, and postnasal drip was significantly (P=0.04) less or in favor of EpiCor compared with placebo at visit 3. The EpiCor group also experienced significantly (P=0.04) less irritability at visit 4 compared with placebo. No other differences were noted with the RQLQ.

Rescue medication was utilized a median of 1 day with the intervention and 2 days with placebo for a P value of 0.04 in favor of EpiCor. Weeks 7-9 and 10-13 demonstrated no significant difference between the intervention and placebo.

The median IgE levels for the group given the intervention were nonsignificantly lower compared with placebo throughout the study, but did not reach statistical significance from visit 2 to 5. No statistical difference occurred for basophil or eosinophil concentration between groups. Salivary IgA levels were significantly (P=0.03) higher for EpiCor compared with placebo throughout the duration of the study.

Nasal smear data were collected at visit 4 and 5 only as an addendum to the ongoing protocol, and revealed a significantly (P=0.05 and P=0.03) lower number of lymphocytes for EpiCor (median = 18 and 16) compared with placebo (median = 60 and 57) at visit 4 and at visit 5 respectively, but no difference in monocytes. A marginally significant (P=0.056) reduction in eosinophils was observed in the EpiCor group compared with placebo, and a significantly (P=0.01) larger number of neutrophils occurred for the EpiCor group at visit 4 only. A nonsignificant improvement in quality of life scores occurred between visits 2 and 3 and between visits 4 and 5 in favor of EpiCor.

There were no significant differences between the intervention and placebo in terms of adverse events or drop-outs. A total of 10 subjects terminated prematurely including seven for personal reasons, two in the placebo due to side effects, and one participant became pregnant during the trial. A total of eight participants were lost to follow-up and had incomplete data. A total of 78 subjects completed the trial with equal numbers in the intervention and placebo group. Data analysis was completed on participants that had complete information during each time period.

DISCUSSION

Individuals with AR consistently refer to nasal congestion as the most concerning and bothersome symptom, and the one they would most like to prevent or treat due to the impact it has on overall quality of life and/or day-to-day activities.[13,14,23,24] Nasal congestion has a multifactorial etiology that includes inflammatory, neural, and vascular contributions.[25] These multiple pathways probably contribute to the complexity of trying to apply one appropriate individual treatment and may be responsible for the high dissatisfaction rate of the currently available treatments.[13,20] The prevalence and negative impact of AR and nasal congestion, and the limited therapeutic satisfaction of currently available treatments suggests that there is a strong need for novel options for this condition.

Complementary and alternative medicines are utilized in a large number of individuals with AR, but evidence-based recommendations do not exist for numerous reasons including the lack of safety data, and most clinical trials have not been rigorous enough to provide an endorsement of a specific intervention.[26-29] For example, past studies lack appropriate methodology including lack of randomization, not controlled, and not blinded, with no objective quantitative measurement. Also, numerous herbal remedies in this category lack quality control data. Regardless, there is a strong suggestion that a complementary or integrative therapy for AR that proved to have adequate impact through a well-designed clinical trial would ultimately be a welcome addition to conventional medicine. There are several different compounds that have received clinical results, but the strength of the clinical trial design has been questioned as well as the lack of impact on the most severe symptoms of AR, for example nasal congestion. EpiCor has currently completed four clinical trials that have all demonstrated positive immune modulating effects including cold and flu-like symptom reduction and now partial amelioration of some of the more problematic AR-induced manifestations such as nasal congestion.[18,19]

Nasal congestion is the predominant late-phase symptom of AR and results from the infiltration of inflammatory cells such as lymphocytes (T-cells) and eosinophils into tissue, and the subsequent prolonged release of mediators such as histamine, leukotrienes, and prostaglandins.[30] The finding of a consistent significant reduction in nasal congestion favoring EpiCor that translated clinically into approximately 12 fewer days of this symptom is notable and is on par with past studies of conventional prescription medication.[20] Nasal congestion was also analyzed as a separate clinical symptomatic entity in our clinical trial, which is a profound strength of the design. Numerous past studies are limited because this specific symptom has only been a part of a total nasal symptom score and not analyzed as a separate symptom, which questions the true clinical impact of these medications.

The strengths of our study include the randomized, double-blind, placebo-controlled design and the observation of enhanced nasal congestion resolution with this immunogenic fermentation product noted during the period of the highest recorded pollen counts, one of the primary endpoints, which provides the most impressive and consistent finding and suggests that the clinical impact was not due to chance. The quality of life correlations and improvement (less nasal congestion and irritability), and the significant increase in salivary IgA levels consistently in favor of EpiCor also strengthen the clinical observations. Furthermore, the finding of less severe rhinorrhea, and a significantly lower lymphocyte and nonsignificantly lower eosinophil nasal smear count in the EpiCor group, along with an increase in IL-10 from previous studies suggests that this intervention is potentially impacting the early and late-phase response observed with AR.[19] Higher endogenous IL-10 levels for example are partially responsible for resolving inflammation via inhibition of eosinophilia, suppression of nitric oxide production, and is a common mechanism of action whereby steroid therapy and allergen-specific immunotherapy may demonstrate their respective clinical efficacy.[31] Two other indirect observations of potential clinical significance also need mentioning. First a consistent reduction of several points in blood pressure and a reduction in CRP have been observed in past studies with this intervention compared with placebo,[18,19] which may also serve as markers of efficacy of this intervention and the other anti-inflammatory pathways that may be targeted.

Past studies of conventional medicine with allergies and asthma have suggested similar benefits in these two general health areas with effective medications.[32,33] However, the safety of this immunogenic fermentation product is consistently similar or less than placebo, which is notable when compared with common medications for AR.

Limitations of this clinical trial also deserve mentioning. EpiCor was most effective during the highest pollen count periods, but there was no greater perceived benefit compared to placebo during the time period of low pollen counts. IgE levels, although lower, were not significantly different, but in fairness more effective conventional medicines such as prescribed nasal steroids inhibit abnormal seasonal elevations in serum levels of circulating IgE antibodies,[34,35] which was similar to what was observed in our trial. However, unlike nasal steroids,[35] there was no clinically relevant reduction in overall ocular symptoms with the intervention utilized in our study. Eye symptoms, as with most clinical outcomes, favored EpiCor but did not reach significance. Quality of life scores, although improved overall compared with placebo, also did not reach statistical significance. Nasal smears should have been collected at baseline for complete comparative analysis, but a budgetary issue did not permit this ideal scenario. This clinical study also focused on treatment, thus further research in subjects with perennial AR might provide more insight into the preventive capacity of this intervention and should be the subject of further studies. Although, it is possible that many of the seasonal AR participants have perennial AR, and this also exemplifies the challenge in the design of these trials. It is difficult to capture clinical efficacy with AR subjects when predicted timing of pollen concentrations is also an inexact science.

Regardless, the strength of the study design, and the sum of the positive data suggests a true clinical impact in our opinion, especially in the area of nasal congestion, which is the most meaningful clinical endpoint in AR outcome studies. It is important to remember that first-line therapy for AR is based on a medication's ability to resolve nasal congestion, which is why prescribed intranasal corticosteroids fit in this category.[36] However, a multi-modality approach in our opinion would seem to have a higher probability of success in this category because of the complex nature of this condition and the unusually high rate of therapeutic dissatisfaction. For example, a second-generation antihistamine that has efficacy against pruritus in combination with this current intervention and its congestion-reducing properties, would be one of many potential interesting future clinical trials. The unique dual (allergy, and cold and flu-like symptoms) perennial clinical therapeutic efficacy demonstrated from this and past randomized clinical trials also needs to be further emphasized,[18,19] along with the safety profile, because it would certainly provide an argument that this specific intervention could set a novel research standard in the dietary supplement milieu.

CONCLUSION

A once-daily immunogenic fermentation yeast-derived product (EpiCor), significantly reduced nasal congestion by approximately 12 fewer days, and reduced other common symptoms in individuals with AR during the time of highest documented pollen count periods of the year. This dietary supplement should be given more clinical attention as a potential immune modulating intervention for susceptible individuals with and without currently available effective OTC and prescription medications.

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