Preventive effect of nasal filters on allergic rhinitis: A randomized, double-blind, placebo-controlled crossover park study

Peter Kenney, BSc,[a,b] Ole Hilberg, MD, DMSci,[c] Anne Cathrine Laursen, BSc,[d] Robert George Peel, PhD,[e] and Torben Sigsgaard, MD, PhD[a] *Aarhus and Roskilde, Denmark*

Background: A recently reported small, out-of-season environmental exposure unit study found nasal filters to be efficacious in preventing seasonal allergic rhinitis (AR). However, nasal filters still need to show efficacy in a natural setting in a regular pollen season.

Objective: We sought to evaluate the efficacy of nasal filters (Rhinix; Rhinix ApS, Aarhus, Denmark) for the prevention of symptoms related to seasonal AR.

Methods: The trial was a single-center, randomized (1:1), double-blind, placebo-controlled crossover clinical trial (NCT02108574) conducted over 2 days in the main grass pollen season in June 2014 in Aarhus, Denmark, on 65 adults with proven grass allergy. A total nasal symptom score (TNSS) consisting of blocked nose, runny nose, nasal itching, and sneezing was used to evaluate symptoms. The difference in daily$_{\sum}$ TNSS (the sum of 13 ratings) was the primary outcome measure. The difference in maximum TNSS (highest score, 13 ratings) was also evaluated.

Results: The nasal filters significantly reduced daily$_{\sum}$ TNSSs ($P = .03$) and maximum TNSSs ($P = .03$) compared with placebo. Median relative reductions were 40% for daily$_{\sum}$ TNSSs ($P = .02$), 43% for maximum TNSSs ($P = .004$), 83% for daily$_{\sum}$ sneezing ($P = .001$), 75% for daily$_{\sum}$ watery eyes ($P = .02$), and 53% for daily$_{\sum}$ runny nose ($P = .005$) when compared with placebo. The nasal filters were well tolerated, and no serious adverse events were recorded.

Conclusion: Statistically significant and clinically relevant reductions were achieved for the primary outcome measure of daily$_{\sum}$ TNSS, for maximum TNSS and for a subset of individual symptoms. The results support the preventive role of nasal filters for managing seasonal AR. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Seasonal allergic rhinitis, nasal filter, placebo controlled, randomized controlled trial, total nasal symptom score, total ocular symptom score, pollen, efficacy, allergen avoidance, prevention*

Allergic rhinitis (AR), a symptomatic disorder of the upper airway tract affecting more than 500 million persons globally, occurs when exposure to environmental allergens triggers IgE-mediated inflammation.[1] AR has been linked to a general impairment in quality of life,[2,3] emotional problems and poorer mental well-being,[3] daytime sleepiness,[4] and loss of productivity.[5,6] Consequently, AR is associated with significant direct and indirect costs to an economy.[7]

As part of an overall management strategy for AR, allergen avoidance is indicated for all patients,[8,9] although it has generally been considered difficult to implement.[9,10] Recently, a study on a new impaction nasal filter showed promising results as an effective and wearable device for the prevention of nasal and throat allergy symptoms during exposure to pollens.[11] However, because that study was conducted out of season in an exposure unit environment, it is essential to investigate the efficacy of the nasal filters in a regular pollen season and in natural settings. This is in line with the US Food and Drug Administration's recommendations for AR clinical trials.[12] One in-season method for achieving this is a park study.[12] Park studies have previously been used to study the in-season effect of antiallergenic treatments under controlled natural settings.[1,13,14]

Also, supporting the relevance of this current study, the exposure unit study did not meet its primary end point. It was argued that this could have been due to a small sample size or a limited symptom severity as a result of the study's out-of-season setting or the lack of priming or because of the choice of pollen levels.[11] Therefore this randomized controlled trial sought to investigate the efficacy, safety, and usability of the nasal filter in a larger population during a regular pollen season in a natural park setting.

METHODS

Clinical trial design

A detailed methodology is given in the Methods section in this article's Online Repository at www.jacionline.org. Briefly, this trial was a single-center, randomized (1:1), double-blind, placebo-controlled crossover clinical trial (clinicaltrials.gov ID: NCT02108574) conducted over 2 days (day 1 on June 4th and day 2 on June 16th) in 2014 during the main grass pollen season in a park in Aarhus, Denmark. Seventy-six adults with a history of grass pollen–induced AR confirmed by a positive specific IgE level and a positive

From [a]the Department of Public Health, Section for Environment, Occupation and Health, Aarhus University, Aarhus; [b]Rhinix ApS, Aarhus; [c]the Department of Respiratory Diseases and Allergology, Aarhus University Hospital, Aarhus; [d]Aarhus University, Aarhus; and [e]Department of Environmental Science, Aarhus University, Roskilde.

Supported by Rhinix ApS, Aarhus, Denmark, and designed to be consistent with recommendations provided in the US Food and Drug Administration document for clinical development of drug products for allergic rhinitis (Guidance for Industry, US Department of Health and Human Services, US Food and Drug Administration Center for Drug Evaluation and Research, April 2000).

Disclosure of potential conflict of interest: P. Kenney is founder and part owner of, is a board member for, has a patent with, has stock/stock options in, and receives a monthly salary from Rhinix ApS. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 4, 2015; revised April 30, 2015; accepted for publication May 13, 2015.

Corresponding author: Torben Sigsgaard, MD, PhD, Department of Public Health, Section for Environment, Occupation and Health, Aarhus University, Bartholins Allé 2, Building 1260, 8000 Aarhus C, Denmark. E-mail: ts@ph.au.dk.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.05.015

Abbreviations used
AR: Allergic rhinitis
Daily$_{\sum}$: Sum of ratings from minute 90 to minute 450
SAR: Seasonal allergic rhinitis
TNSS: Total nasal symptom score
TOSS: Total ocular symptom score

skin prick test response were included (see Table E1 in this article's Online Repository at www.jacionline.org).

The nasal filters (Rhinix; Rhinix ApS, Aarhus, Denmark), placebo filters, and method for insertion are described in the Methods section in this article's Online Repository.

Trial protocol

An overview of the trial protocol is presented in Fig 1. Both days, subjects arrived at the park before 9 AM and left just after 5 PM. Baseline was recorded at 9 AM. The run-in period started at 9:30 AM, and the assessment period started at 11 AM. Assessments were made every 30 minutes by using a total nasal symptom score (TNSS) consisting of blocked nose, runny nose, nasal itching, and sneezing.[12] The primary outcome measure was the difference between placebo and the nasal filter evaluated by the difference in daily$_{\sum}$ TNSS (the sum of the 13 ratings from minute 90 to minute 450). Difference in maximum TNSS (the highest score of the 13) was also evaluated. Other prespecified secondary and tertiary analyses included difference in daily$_{\sum}$ throat irritation and difference in daily$_{\sum}$ total ocular symptom score (TOSS).

Exploratory analyses were performed for the groups with a baseline TNSS of 0 or 1 and the groups with a baseline TOSS of 0 or 1. Also, exploratory analyses of drowsiness and global discomfort were performed. Finally, the device was evaluated on usability, and FEV_1 served as a safety measure.

All crossover analyses were done with Wilcoxon rank sum tests for 2-period crossover studies.[15] For each of the 2 study days individually, reductions (Tables I-IV) were calculated as follows:

$$\frac{Placebo - Rhinix}{Placebo} \times 100.$$

Also, statistical analyses for each day individually were carried out for the parallel groups by using Wilcoxon rank sum tests. All analyses, including exploratory analyses, were prepared before unblinding. A P value of less than .05 was used to measure significance in all analyses. P values of .10 or less were considered to indicate tendencies. For information on sample size determination, randomization, blinding, and pollen measurements, see the Methods section in this article's Online Repository.

RESULTS

A total of 76 subjects were randomized. Of these, 7 did not show up at all, 3 were discontinued after day 1 for reasons unrelated to the study, and 1 was excluded because of an inappropriate nasal filter fit. This left 65 subjects for the analyses. See Fig 2 for a diagram of the study flow.

The study population was comprised of 34 male and 31 female subjects. Mean age was 24.8 years (SD, 6.1 years), mean wheal diameter for the *Phleum pratense* response was 8.0 mm (SD, 3.4 mm), and mean specific IgE level was 21.7 kU/L (SD, 22.4 kU/L). Five subjects reported having had asthma attacks within the last 12 months.

Grass pollen levels varied substantially between days 1 and 2. Thus the mean pollen level on day 1 was 56.12 grains/m^3 (SD, 56.60 grains/m^3), and the mean level on day 2 was 140.19 grains/m^3 (SD, 115.23 grains/m^3; Fig 3). Mean temperatures between 9 AM and 5 PM were 17.0°C and 17.4°C for days 1 and 2, respectively.

Efficacy

The primary outcome measure of difference in daily$_{\sum}$ TNSS was significantly reduced for the nasal filter when compared with placebo (P = .03), with median reductions on day 2 of 40% (P = .02, Table I). Difference in maximum TNSS was also significantly reduced (P = .03), with median reductions of 43% on day 2 (P = .004, Table I). Sneezing, itching, and runny nose symptoms contributed to the overall differences (Table I).

Restricting the analyses to the groups with a baseline TNSS of 0 or 1 on each study day (33 subjects on day 1 and 22 subjects on day 2), daily$_{\sum}$ TNSS was reduced by 62% (P = .012) on day 2 for the nasal filter compared with placebo (Table II). Also, symptom severity in the nasal filter groups was close to identical for the 2 study days (Table II).

Difference in daily$_{\sum}$ TOSS was insignificant (P = .12), with median reductions on day 2 of 47% (P = .076, Table III). Daily$_{\sum}$ watering eyes was significantly reduced (P = .03), with reductions of 75% on day 2 (P = .016, Table III). For subjects with a baseline TOSS of 0 or 1 on each study day (56 subjects on day 1 and 41 subjects on day 2), daily$_{\sum}$ TOSS was reduced by 73% (P = .031) on day 2 (Table IV).

The difference in daily$_{\sum}$ throat irritation was insignificant (P = .43, Table III) for days 1 and 2, respectively.

Drowsiness was not significant when evaluated by using the crossover design (P = .24). However, on day 2, the nasal filter significantly reduced drowsiness by a median reduction of 54% (P = .046) compared with placebo (Table III). Global discomfort was significantly decreased overall for the nasal filter (P = .037) compared with placebo, with day 2 reductions of 42% (P = .071). For subjects with a baseline TNSS of 0 or 1, global discomfort was reduced by 82% (P = .005) and drowsiness by 83% (P = .076) on day 2 for the nasal filter compared with placebo (Table IV).

For all outcomes, the overall significant differences, as outlined above, were almost entirely a result arising from differences between treatments on day 2 (Tables I-IV).

No difference between placebo and the filter could be detected for the FEV_1 safety measure. Three subjects experienced device-related transient adverse events: a mild nasal burning sensation (placebo), a mild unspecified nasal irritation (placebo), and a moderate nasal itch (the nasal filter). No other device-related adverse events were recorded. For a summary of the usability results and time-point specific mean TNSSs, see the Results section and Figs E1 and E2 in this article's Online Repository at www.jacionline.org.

DISCUSSION

This is the first report of an in-season natural exposure randomized controlled trial comparing this impaction nasal filter with a placebo filter in adults with seasonal allergic rhinitis (SAR).

Results of this trial demonstrated that the nasal filter was significantly more efficacious than placebo in preventing symptoms associated with SAR. These results expand on the suggested preventive effects of the nasal filter found in a small out-of-season environmental exposure unit study,[11] thus strengthening arguments for the filters' relevance in preventing symptoms of SAR during a regular pollen season.[12] Their relevance is also supported by the current body of evidence related to other nasal filters, especially an earlier randomized, double-blind, placebo-controlled