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Objective approach for fending off the sublingual immunotherapy placebo effect in subjects with pollenosis: double-blinded, placebo-controlled trial

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ABSTRACT

Background: Symptom scoring for the assessment of allergen immunotherapy is associated with a substantial placebo effect.
Objective: To assess the ability of exhaled breath temperature (EBT), a putative marker of airway inflammation, to evaluate objectively the efficacy of grass pollen sublingual immunotherapy in a proof-of-concept study.
Methods: This was a double-blinded, placebo-controlled clinical trial in 56 subjects (mean ± SD 30 ± 12 years old, 33 men) sensitized to grass pollen. The objective measurements were EBT, spirometry, and periostin and high-sensitivity C-reactive protein in blood. Overall discomfort scored on a visual analog scale was used as a proxy for subjective symptoms. Evaluations were performed before, during, and after the grass pollen season.
Results: Fifty-one subjects (25 and 26 in the active treatment and placebo groups, respectively) were assessed before and during the pollen season. The mean pre- vs in-season increase in EBT was significantly smaller (by 59.1%) in the active treatment than in the placebo group ($P = .030$). Of the other objective markers, only the blood periostin level increased significantly during the pollen season ($P = .047$), but without intergroup differences. Subjectively, the mean pre- vs in-season increase in the visual analog scale score was 32.3% smaller in the active treatment than in the placebo group, although this difference did not reach statistical significance ($P = .116$).
Conclusion: These results suggest that the efficacy of grass pollen sublingual immunotherapy can be assessed by EBT, a putative quantitative measurement of airway inflammation, which is superior in its power to discriminate between active and placebo treatment than a subjective assessment of symptoms assessed on a visual analog scale.
Trial Registration: clinicaltrials.gov Identifier: NCT01785394.

Introduction

Allergen immunotherapy (AIT) for atopic airway diseases has gone through a long and difficult period of doubt and skepticism.[1] This is due largely to the fact that evidence of the efficacy of AIT is based mainly on the subjective assessment of symptoms. The European Medicines Agency has recommended that the preferred primary outcome measurement for AIT clinical trials should be a total combined score taking into account symptom scores and medication usage scores.[2] In turn, symptom scoring is known to be associated with a substantial placebo effect in blinded studies.[3] This shortcoming also affects alternatives to conventional subcutaneous AIT routes for allergen administration, such as sublingual immunotherapy (SLIT).[4] This implies that to prove the efficacy of AIT, large placebo-controlled clinical trials need to be performed involving hundreds of patients and large amounts of data collected by the patients in diaries for the entire duration of the treatment period. Thus, the ever stricter standards for the quality of outcome reporting mean that traditional clinical research in the field of AIT is increasingly challenging and expensive to perform.[5]

Grass pollen–induced allergic respiratory disease (also known as *pollenosis*) is a classic atopic condition in which the inhalation of pollen grains by sensitized patients triggers a sequence of inflammatory events in the airways. At least 1 clinical manifestation (such

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as rhinitis, conjunctivitis, and asthma) subsequently affects various target organs and is influenced more by immediate hypersensitivity than by significant inflammatory events.[6] As a potentially disease-modifying treatment, AIT is thought to modulate the aberrant immune response associated with the inflammatory cascade.

Grass pollen–induced allergic respiratory disease is common in many parts of the world and is certainly the most prevalent pollen-induced allergy in Europe.[7] From a research point of view, pollenosis provides a convenient, natural model of atopic respiratory disease for approximately 2 to 3 months during the late spring and early summer, so that different pathogenetic aspects and treatment modalities can be studied before, during, and after the pollen season. The authors took advantage of this particular feature of the disease to assess a novel noninvasive method for evaluating inflammation of the airways.

Measurement of exhaled breath temperature (EBT) has been suggested as a new method for detecting and monitoring disease processes in the respiratory system.[8–10] This approach is based on the hypothesis that blood flow changes in the conducting airways are characteristic of different disease states and influence the temperature of the exhaled gases. This influence is minimal and requires high-precision gauging devices to assess it reliably so as to provide ground for clinical inferences. Similarly to fractional nitric oxide in conjunction with which the first measurements of EBT were made, EBT captures the signal related to eosinophil-driven inflammation. Different open and closed circuit systems using a single breath or continuous breathing have been used by different research teams. A handheld device has been developed, representing an isolated thermal chamber with a valve system ensuring the accumulation of heat from multiple breaths until a temperature plateau is reached.[11,12] It is user friendly and allows accurate and reproducible EBT measurements within a very narrow temperature range. In a previous study with this instrument, the authors documented a highly significant increase in EBT during the pollen season in patients sensitized to grass pollen with upper airway symptoms (irrespective of whether they experienced signs of asthma).[13]

The next logical step was to determine whether the initiation of AIT before the pollen season could affect the in-season EBT values. The authors reasoned that if AIT created tolerance to the disease-inducing allergen, the subsequent inflammatory response would be dampened.[14] Thus, a study was designed to test this hypothesis.

Methods

Study Design

This was a double-blinded, placebo-controlled, parallel-group, proof-of-concept study of AIT-naive patients with grass pollen–induced allergic respiratory disease who were randomized 1:1 to SLIT with a 5-grass pollen extract or placebo (Fig 1). Objective measurements and subjective assessment using visual analog scale (VAS) scores as a proxy for the classic approach for an evaluation of the efficacy of AIT were performed before the grass pollen season (when atmospheric grass pollen counts were well below critical levels), during the season (when high atmospheric grass pollen counts triggered symptoms in the sensitized population), and after the season (when atmospheric grass pollen counts had decreased). The study's objectives and protocols were approved by the local investigational review board (Medical University Sofia, Sofia, Bulgaria; reference number 86/01/06/2011) and the study was conducted in accordance with good clinical practice and the tenets of the Declaration of Helsinki (as amended in Edinburgh in 2000). All participants gave their prior, written, informed consent to participate in the study.

Subjects

Fifty-six AIT-naive patients referred to Clinic of Allergy & Asthma of Medical University Sofia were invited to participate in the study. The study population's demographic characteristics are presented in Table 1. Participants were sensitized to grass pollen (as evidenced by a wheal diameter >3 mm larger than the negative control in a skin prick test with a mix of 5 grass allergens: *Anthoxanthum odoratum, Dactylis glomerata, Lolium perenne, Phleum pratense, and Poa pratensis*; Stallergenes, Antony, France). According to the study's main inclusion criteria, participants had to be 7 to 55 years old and have displayed documented symptoms requiring symptomatic medication for at least the preceding 2 grass pollen seasons. The main exclusion criteria were moderate to severe asthma (as defined by the Global Initiative for Asthma guidelines[15]), symptoms related to or strong skin test positivity to other seasonal or perennial allergens, immunosuppression, malignancies, autoimmune diseases, intake of β blockers, pregnancy, and lactation at the time of initiation of immunotherapy. The investigating physicians also were asked not to include patients in whom (in their clinical judgment) comorbidities could affect the study results. At least 3 months before the expected start of the grass pollen season, 53 patients (3 patients revoked their informed consent) underwent the preseason visit and were randomized to SLIT with a 5-grass pollen extract that contained the same components as the mixture used for skin prick testing (Staloral 688; Stallergenes) or to placebo. Once-daily treatment was continued throughout the pollen season. The AIT induction phase was carried out with preparations with 10 and 300 indices of reactivity (Stallergenes) using the doses specified in the summary of product characteristics. The daily maintenance dose was 10 squirts under the tongue before breakfast from the preparation with a 300 index of reactivity, corresponding to approximately 25 μg/mL of the

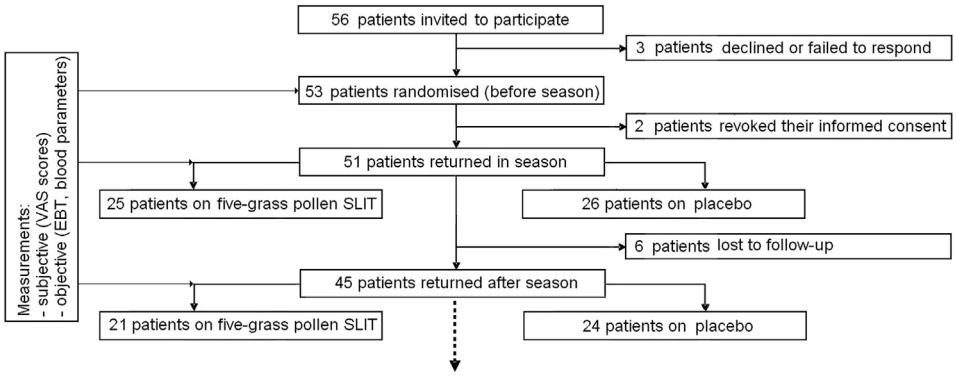

Figure 1. Flow diagram summarizing study protocol. EBT, exhaled breath temperature; SLIT, sublingual immunotherapy; VAS, visual analog scale.