Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber

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Background: The efficacy and safety of a 5-grass-pollen sublingual immunotherapy (SLIT) tablet (Stallergènes SA, Antony, France) have been evaluated in clinical studies during the pollen season. The allergen challenge chamber (ACC) has been developed as a pharmacodynamic assessment tool to control the environmental allergens and to avoid all problems associated with unpredictable pollen seasons.
Objective: We sought to evaluate the onset of action and efficacy of 300-IR (index of reactivity) SLIT tablets by using an ACC.
Methods: Patients with grass pollen–induced rhinoconjunctivitis were randomized into the active or placebo groups. A standardized allergen challenge with grass pollen and symptom evaluation every 15 minutes was performed at baseline, 1 week, and 1, 2, and 4 months of treatment. The primary end point was the average rhinoconjunctivitis total symptom score (ARTSS). Allergen-specific basophil activation, T-cell proliferation, and plasmatic IgE and IgG responses were assessed before and after treatment.
Results: In the intention-to-treat population (n = 89) a significant treatment effect was achieved after the first month ($P = .0042$) and second month ($P = .0203$) and was maintained through to the fourth month ($P = .0007$). In the active group the ARTSS (means ± SDs) decreased at each challenge: week 1, 7.40 ± 2.682; month 1, 5.89 ± 2.431; month 2, 5.09 ± 2.088; and month 4, 4.85 ± 1.999. An improvement (vs placebo) of 29.3% for the mean ARTSS (median, 33.3%) was observed at end point. Furthermore, the induction of grass pollen allergen–specific IgGs was associated with clinical response. The most frequent adverse reactions were local: oral pruritus, ear pruritus, and throat irritation.
Conclusions: In this ACC study the 300-IR 5-grass-pollen SLIT tablets had a significant effect on rhinoconjunctivitis symptoms (vs placebo) from the first month of treatment onward.
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Key words: *Grass pollen, tablets, sublingual immunotherapy, allergen challenge chamber, Vienna Challenge Chamber*

A 5-grass-pollen 300-IR (index of reactivity) sublingual immunotherapy (SLIT) tablet (Stallergènes SA, Antony, France) has demonstrated its efficacy and safety in a series of multicenter clinical trials in adult and pediatric populations with seasonal allergic rhinoconjunctivitis (SAR) triggered by grass pollen.[1-3] These standard outdoor clinical trials evaluated the symptoms of SAR during the pollen season and, as such, were inevitably influenced by unpredictable variations in pollen levels, antigenicity, and exposure. In fact, variations in the patients' degree of pollen exposure occur through both local variations in pollen counts and differences in individuals' daily routines and pollen-avoidance strategies (eg, staying indoors during the pollen peak). The lack of standardized exposure and natural year-to-year variations in the dates of pollen season onset and peaks makes it difficult to perform outdoor studies designed to measure the onset of action of SLIT and thus determine the optimal preseasonal treatment duration required for efficacy.

In Europe the main pollination period covers about half the year, from spring to autumn. For grasses, the flowering period starts at the beginning of May for countries in which pollination is early and finishes at the end of July for the latest countries. In Mediterranean areas flowering usually starts and ends 1 month earlier compared with other European areas. Pollination occurs about 2 to 3 weeks earlier at sea level than in mountainous regions. On the whole, in Europe grass flowering notably peaks in June. The pollen season tends to vary from year to year because of fluctuations in climatic factors, but the maximum atmospheric concentration of grass pollen usually occurs 1 to 2 months after the start of the main flowering season.[4,5] The current study assessed the efficacy and onset of action of 5-grass-pollen tablets under controlled conditions provided by an allergen challenge chamber (ACC; also known as an environmental exposure unit) to overcome these variations. An ACC is a specially designed room used to expose study participants to a fixed, predetermined allergen concentration for a set period of time.[6] ACCs also allow identical repeated exposures and thus assessment of changes over time in an individual's response.

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Abbreviations used
ACC: Allergen challenge chamber
AE: Adverse event
ARTSS: Average rhinoconjunctivitis total symptom score
IR: Index of reactivity
ITT: Intention-to-treat
PP: Per-protocol
RTSS: Rhinoconjunctivitis total symptom score
SAR: Seasonal allergic rhinoconjunctivitis
SLIT: Sublingual immunotherapy
TEAE: Treatment-emergent adverse event
VCC: Vienna Challenge Chamber

In recent years, ACCs have been used in a variety of studies evaluating different aspects of SAR therapeutics, such as the onset of action of antiallergic treatments[7-9] and the efficacy and safety of drug candidates.[6,10,11] The current draft guideline on the clinical development of specific immunotherapy products for the treatment of allergic diseases published by the European Medicines Agency's Committee for Medicinal Products in Human Use cites the ACC as a pharmacodynamic assessment tool that can potentially be used to provide supportive evidence of clinical efficacy.[12] ACC studies investigating the effect of various antihistamines (desloratadine, cetirizine, azelastine, and fexofenadine) have shown that symptom scores with placebo and active treatments are similar to those obtained in outdoor clinical trials. Additional information from ACC trials might significantly contribute to a better determination of a medication's clinical profile, especially in terms of onset and duration of action.[12-14]

A Cochrane collaboration meta-analysis of SLIT in patients with rhinitis demonstrated evidence of efficacy with reduction in symptoms and use of symptomatic medication.[15] It has been previously shown that a preseasonal and coseasonal treatment with sublingual grass pollen tablets is effective and safe in the treatment of grass pollen SAR.[1,2,16,17] The aim of this study was to demonstrate the placebo-controlled efficacy of a 5-grass-pollen 300-IR SLIT tablet and provide the first ever determination of the onset of action of SLIT tablets under the controlled, stable conditions found within an ACC.

METHODS

Patients

Eligible patients were men and women aged between 18 and 50 years with a documented history of moderate-to-severe seasonal grass pollen–related allergic rhinoconjunctivitis for at least the 2 previous pollen seasons. At screening, patients were required to demonstrate grass pollen sensitization through a positive specific skin prick test response (wheal diameter >3 mm) to a 5-grass pollen extract (Stallergènes SA) and a specific serum IgE level of at least 0.70 kU/L for timothy grass (assayed with the UniCAP system; Phadia, Uppsala, Sweden). In addition, patients had to show a symptomatic reaction to an allergen challenge test at baseline (ie, before the administration of any study treatment), which was defined as a rhinoconjunctivitis total symptom score (RTSS) of at least 7 (of 18) within the 2-hour challenge (see the "Efficacy variables" section for more details of the RTSS). The main exclusion criteria were as follows: allergic rhinoconjunctivitis caused by a cosensitization likely to significantly influence symptoms throughout the study and asthma requiring treatment other than rarely a short-acting inhaled β_2-agonist. All patients provided written informed consent before study entry. The study was carried out in accordance with the Declaration of Helsinki (1964, as amended in 2004) and good clinical practice (CPM/ICH/135/95) and was approved by the appropriate independent ethics committee and regulatory authorities.

Study design

This was a randomized, double-blind, parallel-group, placebo-controlled, single-center trial performed between the 2007 and 2008 grass pollen seasons. After an initial screening visit and a baseline allergen challenge, eligible patients were randomized 1:1 to receive either a 300-IR SLIT tablet or placebo. Patients underwent an allergen challenge in the chamber with grass pollen before treatment (the baseline challenge). A 2-hour baseline challenge was chosen, which was sufficient for qualification, to avoid unnecessary priming and to keep the patients' burdens as low as possible (no rescue medication was allowed). Additional challenges were performed after 1 week and 1, 2, and 4 months of treatment (each lasting 4 hours, Fig 1).

Immunotherapy

The investigational product was a 300-IR 5-grass-pollen SLIT tablet, (orchard, meadow, perennial rye, sweet vernal, and timothy grasses; Stallergènes SA) taken once daily. The IR is a measure of the biologic potency of an allergen extract assessed based on skin reactivity. The dosage of the 300-IR tablet corresponded to approximately 20 μg of group 5 major allergens.

Patients were told to take the sublingual pollen extract or placebo tablets once a day before eating or drinking and, preferably, at the same time of day throughout the 4-month treatment period. The patients were further instructed to leave the tablet under the tongue and not to swallow until the tablet had completely dissolved. Treatment was taken daily at the dose of 300 IR from day 1 and for 4 months. The doses were administered under medical supervision on every scheduled visit in the study. Patients were observed for 30 minutes to check for any local or systemic reactions. Antihistamines, decongestants, antileukotrienes, cromones, corticosteroids, and topical nasal or ocular treatments were prohibited during the treatment period. There was no necessity for rescue medication because the trial was performed out of season.

Allergen challenge and study measurements

The allergen challenge was carried out in the validated Vienna Challenge Chamber (VCC) at the department of the Allergy Center of Vienna West (Vienna, Austria). The methods for the VCC are described in this article's Methods section in the Online Repository at www.jacionline.org.

During the challenge the patients scored the 6 individual rhinitis and conjunctivitis symptoms every 15 minutes on computer keypads. Nasal airflow was measured every 30 minutes by means of active anterior rhinomanometry. Nasal secretion was determined every 30 minutes by collecting and weighing used tissues; patients were given preweighed packs of paper tissues, which they used to blow their noses as necessary. FEV_1 was measured every hour by using standard spirometric procedures (with reference values given by the European Community for Coal and Steel).

Initial measurements (except nasal secretion weight) were performed before patients entered the chamber. Blood was taken before treatment initiation and after 2 and 4 months of treatment. This biologic sample was subjected to a range of prespecified immunologic analyses (see the "Assessment of immunologic changes" section in the Methods section of this article's Online Repository).

Efficacy variables

The RTSS includes the 6 most common symptoms of allergic rhinoconjunctivitis: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and tearing. Each symptom was evaluated by the patient with a score ranging from 0 to 3, as follows: 0, absent symptoms (no sign/symptom evident); 1, mild symptom (sign/symptom is clearly present/minimal awareness and easily tolerated); 2, moderate symptom (definite awareness of sign/symptom that is bothersome but tolerable); and 3, severe symptom (sign/symptom that is hard to tolerate and causes interference with daily activities). The RTSS is the sum of the 6 individual symptom scores and thus varies from 0 to 18. The RTSS was recorded every 15 minutes during the 4-hour allergen exposure challenge (2 hours at baseline). The average rhinoconjunctivitis total symptom score (ARTSS) for each patient was calculated for each challenge as