Original Article

Safety Review of 5-Grass Pollen Tablet from Pooled Data of Clinical Trials

Thomas B. Casale, MD[a], Linda S. Cox, MD[b], Ulrich Wahn, MD[c], David B.K. Golden, MD[d], Brigitte Bons, MD[e], and Alain Didier, MD[f] *Tampa and Fort Lauderdale, Fla; Berlin, Germany; Baltimore, Md; and Antony and Toulouse, France*

What is already known about this topic? The 300 Index of Reactivity 5-grass pollen sublingual tablet has been proven safe and well tolerated in patients with grass pollen–induced allergic rhinitis associated or not with intermittent asthma in several clinical trials.

What does this article add to our knowledge? Pooling of safety data collected over the clinical development program in 1514 actively treated subjects provides better knowledge of the safety profile of the 5-grass pollen sublingual tablet over time and in patients of special interest.

How does this study impact current management guidelines? The pooled safety results in the overall population and in subgroups such as patients with asthma will help health care professionals in improving their management and educating the patients receiving this treatment.

BACKGROUND: The 5-grass pollen sublingual tablet has been approved for the treatment of grass pollen–induced allergic rhinoconjunctivitis in subjects with or without intermittent asthma.
OBJECTIVE: To provide a comprehensive analysis of the safety profile of the 5-grass tablet on the basis of pooled data from 8 clinical trials.
METHODS: Subjects (5-65 years old) with medically confirmed grass pollen–induced allergic rhinoconjunctivitis were included in the double-blind studies. Those with intermittent asthma not requiring treatment other than inhaled beta-2 agonists could participate. Randomized subjects received a 5-grass or placebo tablet daily 2 or 4 months preseasonally and coseasonally (5 single-season studies, over 3 years in a long-term study) or outside the season (phase I studies). Adverse events were pooled and analyzed descriptively.
RESULTS: Among 2,512 subjects enrolled, 1,514 received the 5-grass tablet. A total of 1,038 adults and 154 pediatric (5-17 years old) subjects were treated with the 300 Index of Reactivity dose (vs 840 and 158 placebo recipients, respectively); 17% had intermittent asthma, and 62% were polysensitized. Adverse reactions (ADRs) reported in more than 10% of actively treated subjects were mild or moderate application-site reactions, for example, oral pruritus 25% (placebo 4%) and throat irritation 21% (placebo 3%). These generally occurred during the first week of treatment and decreased over time. They led to discontinuation in less than 2.5% of subjects. None of the 3 serious ADRs were reports of anaphylaxis. No notable differences were detected in terms of incidence, nature, and severity of ADRs between adult and pediatric populations, nor between subjects with or without asthma.
CONCLUSIONS: The pooled analysis in 1,514 subjects from 8 clinical studies demonstrates that the 5-grass pollen sublingual tablet has a similar good safety profile in adult and pediatric patients with or without mild, intermittent asthma. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *5-Grass pollen tablet; Grass pollen; Allergic rhinoconjunctivitis; Asthma; Sensitization; Allergy immunotherapy; Allergen-specific immunotherapy; Sublingual immunotherapy; Safety; Clinical trial*

[a]Division of Allergy & Immunology, University of South Florida, Tampa, Fla
[b]Allergy and Asthma Center, Fort Lauderdale, Fla
[c]Pediatric Pneumology and Immunology, Charité, Berlin, Germany
[d]Allergy & Immunology, Medstar Franklin Square Medical Center, Baltimore, Md
[e]Stallergenes Greer, Antony, France
[f]Service de Pneumologie – Allergologie, Hôpital Larrey, CHU de Toulouse, Toulouse, France

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Corresponding author: Thomas B. Casale, MD, Division of Allergy & Immunology, University of South Florida, 12901 Bruce B. Downs Blvd, MDC 19, Tampa, FL 33612. E-mail: tbcasale@health.usf.edu.

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Abbreviations used
AE- Adverse event
ARC- Allergic rhinoconjunctivitis
AIT- Allergen-specific immunotherapy
IR- Index of Reactivity
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy
TEAE- Treatment-emergent adverse event

Allergic rhinitis with or without conjunctivitis is a globally prevalent disease affecting between 10% and 30% of adults and up to 40% of children, totaling more than 500 million people worldwide.[1,2] Grass pollens specifically are among the most prevalent and clinically relevant sources of aeroallergens that trigger this disease.[3,4] Depending on the severity of allergic rhinoconjunctivitis (ARC) symptoms, the patient's physical or psychological conditions, quality of life, family and social interactions, and work/school performances may be considerably affected.[2] Moreover, patients affected by ARC are at increased risk for the development of asthma and other comorbidities.[1]

Current recommendations to clinicians for the management of ARC now include a combination of patient education, allergen avoidance, symptomatic pharmacotherapy, and allergen-specific immunotherapy (AIT) through a stepwise therapeutic approach.[2,5,6] AIT is a therapeutic option for patients whose symptoms are not adequately controlled by avoidance measures or standard medications, those experiencing unacceptable adverse effects with standard medications, or those who wish to reduce the long-term use of medications.[7] AIT is the only therapy that has been shown to be disease modifying, with benefits persisting for several years after treatment discontinuation in most patients.[8]

In the United States, subcutaneous immunotherapy (SCIT) serves as the primary delivery method for AIT and has a demonstrated therapeutic benefit in both short-term symptom management and longer-term disease modification.[9] Potential risks and use limitations associated with SCIT are the potential of near-fatal or fatal anaphylaxis and while not as serious, the discomfort and inconvenience of frequent injections. Recent availability of sublingual immunotherapy (SLIT) tablets represents a viable alternative with similar efficacy and a favorable safety profile.[2,9] Importantly, SLIT may be proposed as an early treatment in the therapeutic strategy for respiratory allergy according to scientific societies.[8]

The 5-grass pollen sublingual tablet has been developed during the last decade for the treatment of patients with grass pollen—induced ARC confirmed by positive skin test result or *in vitro* testing for pollen-specific IgE to any of the 5 grass species included in the product. Randomized, double-blind, placebo-controlled trials have been conducted showing the product efficacy.[10-16] The purpose of the present article was to provide a comprehensive and thorough review of the safety profile of the 5-grass pollen tablet from the clinical development program.

METHODS

Design overview

The overall clinical safety experience with 5-grass pollen sublingual tablet (Stallergenes, Antony, France) is based on pooled data from all subjects enrolled in 8 studies regardless of the dose or treatment regimen, treatment duration, subject age, or study duration. A tabulated summary of the studies is presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org. The studies included in the development program were VO33.04DK (Safety and tolerability study), VO34.04 (European study; NCT00367640), VO40.05 (Extension of European study), VO52.06 (Pediatric study; NCT00409409), VO53.06 (Long-term study; NCT00418379), VO56.07A (Allergen exposure chamber study; NCT00619827), VO60.08 (2-month preseasonal regimen study; NCT00803244), and VO61.08USA (US study; NCT00955825).[10-16] All studies were randomized, double-blind, placebo-controlled and were conducted globally between 2004 and 2011. Ethics committees or institutional review boards approved all study protocols and all subjects signed informed consent before any study procedure was performed.

Settings and participants

All subjects (5-65 years old) enrolled in the development program had a clinical history of grass pollen—associated ARC for at least 2 years, confirmed by positive skin prick test to 5-grass pollen mix (ex-US) or timothy grass (US) and timothy grass—specific serum IgE level of 0.7 kU/L or more (except in the US study). Their Retrospective Rhinoconjunctivitis Total Symptom Score evaluated on the most severe days of the pollen season preceding enrolment was at least 12 out of 18. Polysensitized subjects, that is, demonstration of antigen-specific IgE to 2 or more allergens by skin prick testing or *in vitro* testing,[17] could be enrolled as long as they did not have significant clinical symptoms of ARC due to allergens other than grass pollen during the season. Subjects with asthma requiring treatment other than with inhaled beta-2 agonists and those receiving continuous therapy with corticosteroids or beta-blocker therapy were excluded.

Randomization and interventions

Active treatment consisted of sublingual tablets containing an allergen mixture obtained by concurrent extraction from 5 different grass pollens in equal amounts (sweet vernal grass, *Anthoxanthum odoratum* L.; cockfoot/orchard, *Dactylis glomerata* L.; perennial rye grass, *Lolium perenne* L.; timothy, *Phleum pratense* L.; and meadow/Kentucky blue grass, *Poa pratensis* L.) at doses of 100IR, 300IR, and 500IR. The Index of Reactivity or "IR" is the potency unit used by Stallergenes to quantify the allergenic activity of the 5-grass pollen extract. An in-house reference standard for potency measurement was established on the basis of titrated skin prick testing of allergic subjects.[16,18] The mean dosage of 300IR/mL corresponds to 20 to 25 μg/mL of the group 5 major allergens[12,16] and is equivalent to approximately 9000 bioequivalent allergy units.[19] Active and corresponding placebo tablets were matched in packaging, shape, taste, color, and appearance to ensure blinding. In all studies, subjects were randomized to receive either active treatment or placebo through a computer-generated scheme. The European study (VO34.04) tested different doses of active treatment ranging from 100IR to 500IR. The selected dose, 300IR, was further investigated in subsequent studies.

Various administration schedules were used in the clinical studies. In the Safety and tolerability study and the Allergen exposure chamber study, subjects were treated for 10 days and 4 months, respectively, outside the pollen season. The other 6 clinical trials were natural field studies in which treatment was administered beginning either 4 months or 2 months before the grass pollen season and continued throughout the season. In addition,