Treatment with grass allergen peptides improves symptoms of grass pollen–induced allergic rhinoconjunctivitis

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Background: Synthetic peptide immunoregulatory epitopes are a new class of immunotherapy to treat allergic rhinoconjunctivitis (ARC). Grass allergen peptides, comprising 7 synthetic T-cell epitopes derived from Cyn d 1, Lol p 5, Dac g 5, Hol l 5, and Phl p 5, is investigated for treatment of grass pollen–induced ARC.

Objective: We sought to evaluate the efficacy, safety, and tolerability of intradermally administered grass allergen peptides.

Methods: A multicenter, randomized, double-blind, placebo-controlled study evaluated 3 regimens of grass allergen peptides versus placebo in patients with grass pollen–induced allergy (18-65 years). After a 4-day baseline challenge to rye grass in the environmental exposure unit (EEU), subjects were randomized to receive grass allergen peptides at 6 nmol at 2-week intervals for a total of 8 doses (8x6Q2W), grass allergen peptides at 12 nmol at 4-week intervals for a total of 4 doses (4x12Q4W), or grass allergen peptides at 12 nmol at 2-week intervals for a total of 8 doses (8x12Q2W) or placebo and treated before the grass pollen season. The primary efficacy end point was change from baseline in total rhinoconjunctivitis symptom score across days 2 to 4 of a 4-day posttreatment challenge (PTC) in the EEU after the grass pollen season. Secondary efficacy end points and safety were also assessed.

Results: Two hundred eighty-two subjects were randomized. Significantly greater improvement (reduction of total rhinoconjunctivitis symptom score from baseline to PTC) occurred across days 2 to 4 with grass allergen peptide 8x6Q2W versus placebo (−5.4 vs −3.8, respectively; $P = .0346$). Greater improvement at PTC also occurred for grass allergen peptide 8x6Q2W versus placebo ($P = .0403$) in patients with more symptomatic ARC. No safety signals were detected.

Conclusion: Grass allergen peptide 8x6Q2W significantly improved ARC symptoms after rye grass allergen challenge in an EEU with an acceptable safety profile. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Allergen challenge, allergen peptides, allergy, allergic rhinoconjunctivitis, allergic rhinitis, environmental exposure unit, epitope, grass, immunotherapy, synthetic peptide immunoregulatory epitope*

Allergic rhinoconjunctivitis (ARC) is common and costly and has a negative effect on well-being and quality of life. In the third United States National Health and Nutrition Examination Survey (NHANES III; 1988-1994), 16% of respondents aged 6 to 59 years reported allergy-related nasal symptoms alone, 6% reported ocular symptoms alone, and 30% reported both nasal and ocular symptoms.[1] Pollen was the most common environmental trigger for combined nasal and ocular symptoms (60%); pollen-induced nasal symptoms (42%) and pollen-induced ocular symptoms (44%) occurred with similar frequency.[1]

Fifty-four percent of the US population participating in NHANES III had a positive skin test result for at least 1 of 10 indoor or outdoor allergens; this included 27% with a positive skin test result for perennial rye grass.[2] NHANES 2005-2006 found that 45% of participants had positive serum IgE test results for at least 1 of 19 allergens.[3] Positive IgE-specific test results for rye grass, ragweed, and tree pollens occurred in 20%, 16%, and 21% of NHANES respondents, respectively. For rye grass pollen sensitivity in the United States, NHANES respondents had the highest prevalence of positive IgE test results in the west (25%). The next highest prevalence of positive IgE test results for rye grass occurred in the south (20%), followed by the northeast (17%), and the Midwest (14%).[3]

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Abbreviations used

AE: Adverse events
AIT: Allergen immunotherapy
ARC: Allergic rhinoconjunctivitis
BC: Baseline challenge
EEU: Environmental exposure unit
mITT: Modified intent-to-treat
NHANES: National Health and Nutrition Examination Survey
4x12Q4W: Grass allergen peptides at 12 nmol at 4-week intervals for a total of 4 doses
8x6Q2W: Grass allergen peptides at 6 nmol at 2-week intervals for a total of 8 doses
8x12Q2W: Grass allergen peptides at 12 nmol at 4-week intervals for a total of 4 doses
PEFR: Peak expiratory flow rate
PNIF: Postnasal inspiratory flow
PTC: Posttreatment challenge
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SPIRE: Synthetic peptide immunoregulatory epitope
SPT: Skin prick test
TEAE: Treatment-emergent adverse event
TNSS: Total nasal symptom score
TNNSS: Total nonnasal symptom score
TRSS: Total rhinoconjunctivitis symptom score

For patients with ARC, a significant reduction in ARC symptom scores is evident for several products for specific allergen immunotherapy (AIT) administered subcutaneously and with sublingual tablets.[4] In addition, immunotherapy can reduce asthma development.[5-10] Existing evidence also suggests that AIT can prevent the acquisition of new allergic sensitizations.[11,12] Allergists have used AIT to treat allergies for more than 100 years.[13] Subcutaneous immunotherapy (SCIT) was the first available mode of this treatment; sublingual immunotherapy (SLIT) tablets and drops have become available more recently in Europe, the United States, and Canada.[14-16] Systemic allergic reactions are a risk for SCIT and SLIT because intact allergens in these treatments can cross-link IgE molecules on the surfaces of mast cells and basophils, causing activation and degranulation and resulting in systemic allergic reactions. Other limitations of SCIT and SLIT include marked local side effects (eg, injection-site swelling with SCIT, which can be prolonged, impressive, and dose limiting, and oral pruritus with SLIT),[15,17-19] the risk of systemic allergic reactions (higher with SCIT than with SLIT[16]) along with the need to provide patients with "rescue" epinephrine in the United States, lengthy (≥3 years) treatment necessary to achieve disease modification,[20,21] and the cost of long-term treatment.[22-24] Systematic reviews and meta-analyses show grass SLIT and SCIT to have a modest treatment benefit for symptom and medication score reduction in patients with seasonal ARC.[25,26]

Concerns in the AIT field include high levels of nonadherence (in one study 23% of patients continued SCIT and 7% of patients continued SLIT for a minimum period of 3 years)[27] and the belief that these forms of AIT are either too costly, too risky, too inconvenient, or ineffective.[21] A new class of synthetic peptide immunoregulatory epitope (SPIRE),[28] which has targeted immunoregulatory properties and the potential to transform allergy treatment, is being developed to address issues of efficacy, safety, and adherence. Possible mechanisms for allergen SPIRE therapy include induction of specific T-cell anergy, differentiation of naive T cells to regulatory T cells, immune deviation (ie, decreased T_H2/T_H1 ratio), and allergen-specific T_H2 cell deletion.[28-30] Cyn d 1, Lol p 5, Dac g 5, Hol l 5, and Phl p 5 grass allergen peptides, members of the SPIRE class, have been designed as a short course of treatment with reduced potential to cross-link IgE on the surface of mast cells and basophils. The allergenic molecules of grass pollens have been classified into 13 distinct groups based on their structure and biologic and immunologic properties. However, it has been demonstrated that major contributors to allergic sensitization and hence induction of symptoms are the allergens belonging to groups 1 and 5, both of which are contained in grass allergen peptides.[31-34] Group 1 allergens are recognized by approximately 95% of grass pollen–sensitive patients, followed by group 5 allergens, which are recognized by up to 85% of these patients.[32]

Clinical development programs for antiallergic medications and AIT have included studies performed in environmental exposure units (EEUs)/allergen challenge chambers,[35-39] which have preceded clinical trials in uncontrolled outdoor and indoor settings in which exposure to allergens (eg, pollens, animal salivary proteins, or glandular secretions) occurs naturally. Advantages of this model include control over all environmental variables, consistent allergen delivery, and the ability to conduct studies outside a specified pollen season.[40]

The EEU used in the current grass allergen peptide study is located in Kingston General Hospital, Ontario, Canada, and allows for the reliable exposure of up to 140 participants to predetermined levels of allergen, which remain consistent regardless of outside weather conditions, to determine the efficacy and onset of action of new therapies for ARC.[36] The EEU setup, including location of chairs, feeder, fans, and Rotorod (IMS Health, Plymouth Meeting, Pa) sampling equipment, is illustrated in Fig E1 in this article's Online Repository at www.jacionline.org.

Grass allergen peptide, a SPIRE for grass allergy, is a combination of 7 T-cell epitope–based peptides (each of 10-18 amino acids) derived from major grass allergens.[41,42] The purpose of the present study was to evaluate the efficacy, safety, and tolerability of 3 regimens of grass allergen peptides in subjects allergic to grass pollen after challenge with rye grass allergen in an EEU.

METHODS

Peptides

Grass allergen peptides contain 7 peptides, 3 conserved in group 1 allergens and 4 conserved in group 5 allergens across a range of different grasses, including rye, timothy, Kentucky bluegrass, orchard, velvet, canary, and Bermuda grasses. The individual peptide sequences were as follows: SGKAFGAMAKKGQED, FIPMKSSWGA, KSSWGAIWRID PKKPLK, KYDAYVATLTEALR, LKKAVTAMSEAEK, KKIPAGELQIIDKIDA, and KPEVKYAVFEAALTKAIT. The peptides were synthesized by Bachem (Bubendorf, Switzerland), according to current Good Manufacturing Practice; formulated, filled, and finished by Nova Laboratories (Leicester, United Kingdom), also according to current Good Manufacturing Practice; tested at Gen-Probe (Livingston, United Kingdom); and released in accordance with the EU Clinical Trials Directive.

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group phase 2 dose-finding study to evaluate the