Development of cockroach immunotherapy by the Inner-City Asthma Consortium

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Background: Cockroach allergy is a key contributor to asthma morbidity in children living in urban environments.
Objective: We sought to document immune responses to cockroach allergen and provide direction for the development of immunotherapy for cockroach allergy.

Methods: Four pilot studies were conducted: (1) an open-label study to assess the safety of cockroach sublingual immunotherapy (SLIT) in adults and children; (2) a randomized, double-blind biomarker study of cockroach SLIT versus placebo in adults; (3) a randomized, double-blind biomarker study of 2 doses of cockroach SLIT versus placebo in children; and (4) an open-label safety and biomarker study of cockroach subcutaneous immunotherapy (SCIT) in adults.
Results: The adult SLIT trial (n = 54; age, 18-54 years) found a significantly greater increase in cockroach-specific IgE levels between the active and placebo groups (geometric mean ratio, 1.92; $P < .0001$) and a trend toward increased cockroach-specific IgG_4 levels in actively treated subjects ($P = .09$) but no evidence of functional blocking antibody response. The pediatric SLIT trial (n = 99; age, 5-17 years) found significant differences in IgE, IgG, and IgG_4 responses between both active groups and the placebo group but no consistent differences between the high- and low-dose groups. In the SCIT study the treatment resulted in significant changes from baseline in cockroach IgE, IgG_4, and blocking antibody levels. The safety profile of cockroach immunotherapy was reassuring in all studies.
Conclusions: The administration of cockroach allergen by means of SCIT is immunologically more active than SLIT, especially with regard to IgG_4 levels and blocking antibody responses. No safety concerns were raised in any age group. These pilot studies suggest that immunotherapy with cockroach allergen is more likely to be effective with SCIT. (J Allergy Clin Immunol 2014;133:846-52.)

Key words: *Cockroach, immunotherapy, sublingual immunotherapy, subcutaneous immunotherapy, inner city asthma*

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It has been convincingly demonstrated over the past 2 decades that the combination of cockroach allergy and cockroach exposure is one of the most important factors contributing to the high morbidity seen in inner-city children with asthma.[1,2] Consequently, one of the major initiatives of the National Institute of Allergy and Infectious Diseases–sponsored Inner-City Asthma Consortium (ICAC) has been to develop treatment strategies that target cockroach allergy as an immune-based therapeutic approach to asthma. To accomplish this goal, a standardization trial of German cockroach allergen extracts compared 3 cockroach extracts to establish biological potency and to determine an optimal surrogate *in vitro* test of biological potency.[3] An eventual ICAC goal is to conduct multicenter efficacy trials of cockroach immunotherapy for inner-city asthma. Treatment of children with asthma living in the inner city poses a number

Abbreviations used
BioCSI: Biomarkers of Cockroach Sublingual Immunotherapy
BioCSI2: Biomarkers of Cockroach Sublingual Immunotherapy 2
FAB: Facilitated allergen binding
ICAC: Inner-City Asthma Consortium
SCIT: Subcutaneous immunotherapy
SCITCO: Subcutaneous Immunotherapy in Cockroach-sensitive Adults
SCSS: Sublingual Cockroach Safety Study
SLIT: Sublingual immunotherapy
SPT: Skin prick test

of significant risks, one of which is the potential for anaphylaxis during immunotherapy. Given these concerns, sublingual immunotherapy (SLIT) has been the focus of this program because of the growing body of literature supporting its efficacy and safety profile with other common allergens.[4-6] However, before a definitive trial could be designed and implemented, it was deemed essential to gather data on the safety of cockroach SLIT, as well as on the dose and route of administration needed to achieve the greatest likelihood of efficacy. In addition, the ICAC has chosen to examine how the SLIT approach would compare with subcutaneous immunotherapy (SCIT), at least at the level of immunologic activity. To that end, 4 pilot clinical trials have now been conducted and involve a total of 190 children and adults. We now report the findings of these 4 phased studies, focusing on both safety and the capacity of SLIT and SCIT to generate immune responses and the direction for future trials.

METHODS

Study design

An overview of each study is provided in Table I, and a protocol synopsis for each study is provided in the Methods section in this article's Online Repository at www.jacionline.org. In brief, the studies were designed as follows.

The Sublingual Cockroach Safety Study (SCSS) was an open-label, phase I safety study conducted at a single site using glycerinated German cockroach extract (Greer). It was designed and divided in 3 phases, first studying a group of 9 adults, followed by groups of nine 8- to 17-year-olds and nine 5- to 7-year-olds, with Data and Safety Monitoring Board review after each group. Within each group, 3 subjects with low cockroach sensitivity, which was defined as a skin prick test (SPT) wheal size of less than 6 mm, were first studied, followed by a group of 6 high-sensitivity subjects defined as having a cockroach SPT wheal of 6 mm or larger (greater than that elicited by the negative control). SPTs for each study were performed with Greer German cockroach extract and the GreerPick device (Greer). All participants had perennial allergic rhinitis, and each group was required to include at least 3 participants with mild-to-moderate persistent asthma. Only subjects with well-controlled asthma were eligible, which was defined as an FEV_1 of 80% of predicted value or greater and less than 4 puffs of albuterol use in the prior 2 weeks.

Each subject underwent a 1-day, 8-dose escalation to the maintenance dose (see Table E1 in this article's Online Repository at www.jacionline.org), followed by a once-daily administration of the maintenance dose for 14 days. The first 2 days of maintenance dosing were done under observation at the clinic, and the remaining 12 maintenance doses were self-administered at home. The maintenance dose of 0.42 mL was calculated to contain 3685 bioequivalent allergy units, with approximately 4.2 μg of Bla g 2 and 50 μg of Bla g 1 per dose.

The primary outcome was the proportion of participants who discontinued for any reason after initiation of treatment. Secondary outcomes included the proportion of participants who discontinued the study for reasons related to treatment or for a possible systemic reaction, as well as an assessment of adherence with self-administered doses.

Biomarkers of Cockroach Sublingual Immunotherapy (BioCSI) was a double-blind, placebo-controlled, randomized, biomarker-based pilot trial that was conducted at 4 ICAC sites. This trial was designed to assess safety and the effects of 6 months of daily administration of cockroach SLIT versus placebo on a variety of immunologic biomarkers. Although the extract and maintenance dose were the same as in the SCSS trial, the dose escalation was achieved with a 5-dose regimen (see Table E1). BioCSI included adults with cockroach allergy with both a positive SPT response (wheal diameter ≥3 mm greater than the negative control) and a cockroach-specific IgE level of 0.35 kU/L or greater (ImmunoCAP; Phadia, Uppsala, Sweden), as well as a history of perennial allergic rhinitis, asthma, or both. Participants with asthma were required to have an FEV_1 of 80% of predicted value or greater and could not have used albuterol more than 3 days per week in the 2 weeks before enrollment. After the initial dose escalation, subjects self-administered their next 2 daily doses under observation. All subsequent doses were administered at home. Follow-up visits occurred monthly, during which the extract vials were exchanged and blood was collected. Titrated SPTs to German cockroach were conducted at baseline and after 6 months of treatment by using seven 3-fold dilutions of a 1:20 glycerinated German cockroach extract.

The BioCSI primary outcome was the change over baseline in German cockroach-specific serum IgE levels. The expected effect size, based on a Timothy grass SLIT study by Dahl et al,[7] was a 3-fold group mean difference in cockroach-specific IgE levels between the active and placebo groups measured over the 6 months of treatment. Secondary outcomes included German cockroach–specific serum IgG_4 levels and IgE-facilitated allergen binding (FAB) activity, end point cockroach skin test titration, and measures of safety.

Biomarkers of Cockroach Sublingual Immunotherapy 2 (BioCSI2) was a follow-up study to BioCSI in a pediatric population in which a third arm with a higher dose of cockroach SLIT was evaluated. This was a multicenter, randomized, double-blind, placebo-controlled trial comparing 3 months of treatment with 2 doses of cockroach SLIT versus placebo in children 5 to 17 years of age with a history of perennial rhinitis, asthma, or both and sensitivity to German cockroach (a positive SPT response and a cockroach-specific IgE level ≥0.35 kU_A/L). The choice of 3 months of treatment in this trial was based on the fact that the cockroach-specific IgE response had plateaued at 3 months in BioCSI. Subjects were equally randomized to the same dose of German cockroach extract used in the BioCSI study (low dose, 0.42 mL daily), a 4-fold higher dose (0.84 mL twice daily), or placebo (consisting of uncolored 50% glycerinated saline or caramelized color-matched 50% glycerinated saline, with half receiving 0.42 mL daily and half receiving 0.84 mL twice daily; see Table E1). The high dose of extract contained approximately 16.8 μg of Bla g 2 and 202 μg of Bla g 1 every day. Study outcomes included changes in cockroach IgE, IgG, and IgG_4 levels and FAB activity, safety assessments, and a more detailed assessment of adherence using both daily diaries and vial weights before and after treatment.

Cockroach Subcutaneous Immunotherapy in Cockroach-sensitive Adults (SCITCO) was a biomarker-based pilot study. It was an open-label single-site trial of subcutaneous German cockroach immunotherapy conducted in 10 adults age 18 to 55 years with inclusion criteria identical to those of the BioCSI study. Glycerinated German cockroach extract was administered subcutaneously over a 6-month period with twice-weekly dose escalations over approximately 11 weeks (maximum, 18), followed by weekly maintenance injections of 0.6 mL of 1:20 wt/vol extract (see Table E1) containing approximately 6 μg of Bla g 2 and 120 μg of Bla g 1 per maintenance dose. The primary SCITCO end point was safety, as assessed by the number of reported adverse events and serious adverse events. Secondary outcomes included changes in cockroach-specific IgE and IgG_4 levels and FAB activity.

Laboratory assessments

In both BioCSI studies and SCITCO, German cockroach-specific IgE and IgG_4 levels were measured at baseline and monthly by using the ImmunoCAP system (Phadia).

The IgG-associated inhibitory capacity to prevent IgE and German cockroach allergen interaction (blocking antibody activity) was assessed by