Patient characteristics associated with allergen immunotherapy initiation and adherence

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Allergen specific immunotherapy (SIT) is the treatment of choice for patients with systemic allergic reactions to *Hymenoptera* insects and is an important treatment option for patients with allergic rhinitis (AR), asthma, or both.[1] Compared with pharmacologic therapies, which provide temporary relief of allergy symptoms, SIT is the only potentially allergic disease-modifying treatment.[2] SIT reduces health care costs within 3 months of initiation,[3] decreases the risk of developing asthma and new allergies,[2] and produces sustained clinical benefits after completion of a treatment course of 3 to 5 years.[2] SIT may be administered subcutaneously or locally.[4] Subcutaneous delivery is the only US Food and Drug Administration–approved SIT formulation[5] and the predominant route of administration in the United States,[5] and is therefore the focus of this editorial.

Specific immunotherapy typically involves injections administered at the physician's office at least every 6 weeks for a duration of 3 to 5 years[4] and does not usually confer immediate symptom relief. Consequently, patients must weigh the deferred but potentially long-term curative benefits of treatment against the immediate and prolonged demands of therapy. Because successful clinical outcomes require strong patient commitment to treatment initiation and adherence, patient characteristics such as demographics, illness burden, and insurance coverage are likely to influence the ultimate success of treatment. However, little is known about the characteristics of US patients who receive and adhere to SIT.

PATIENT CHARACTERISTICS ASSOCIATED WITH RECEIVING SIT

Although several studies outside the US have examined the effects of patient demographic and illness characteristics on the likelihood of receiving SIT, their relevance to US practice is unknown. Studies conducted in Italy, Denmark, and Germany, which included more than 3500 adults, used a variety of methods to assess patient characteristics associated with initiating SIT (see this article's Table E1 in the Online Repository at www.jacionline.org).[6-8] Two studies found that higher levels of education,[6,7] and another[8] that higher social status among women, significantly increased the likelihood of receiving SIT. Patients with comorbid asthma were significantly more likely to initiate SIT than those without comorbid asthma in 2 studies.[7,8] Other variables significantly associated with receiving SIT were younger age,[7] greater severity of rhinoconjunctivitis,[7] lower quality of life because of allergic illness,[7] and living in a large city versus the countryside (among women only).[8] Demographic variables with no effect on the likelihood of receiving SIT were household income and sex in one study,[7] and, among men, town size and social status in another.[8]

We are aware of only 1 US study that examined patient characteristics associated with initiating SIT. This retrospective claims analysis of children (<18 years) enrolled in Florida Medicaid from 1997 to 2004 identified over 100,000 (3%) who were newly diagnosed with AR, of whom 3048 (3%) subsequently received SIT.[9] Whereas the only study outside the US to examine sex as a predictor of receiving SIT found no effect,[7] this study of US children showed that boys were 25% more likely than girls to receive SIT ($P < .0001$). Because the multivariate analysis controlled for the effects of other independent variables (including comorbid asthma) when examining the influence of each predictor, the preponderance of asthma in boys versus girls[10] is not likely to explain this sex difference. Furthermore, because research suggests that boys and girls experience equivalent asthma severity and morbidity,[11,12] sex differences in asthma-related burden also cannot adequately account for this finding. Regarding the influence of diagnosis on SIT initiation, the presence of comorbid asthma and atopic dermatitis in US children with AR significantly and independently increased the likelihood of receiving SIT (both $P < .0001$).[9] Comorbid asthma also was significantly related to SIT initiation in studies of adults[7] and men performed outside the US.[8] No study outside the US has examined the effect of patient race/ethnicity on the likelihood of receiving SIT. In the United States, Hispanic children were significantly more likely to receive SIT than non-Hispanic black or white children ($P < .0001$).[9] This disparity may be explained by greater asthma-related morbidity among Hispanic than black or white children reported in other research.[13]

PATIENT CHARACTERISTICS ASSOCIATED WITH SIT ADHERENCE

Comparisons of SIT adherence across studies are problematic because "adherence" has been variously defined. Among women but not men receiving SIT in Germany, diagnoses of AR and lichen simplex chronicus (neurodermatitis) significantly increased, and diagnosis of food allergy significantly decreased, the likelihood of self-reported SIT completion.[8] Town size, social status, age, and former East or West Germany residency had no effect on SIT completion for men or women. A case-control study of 100 patients receiving SIT in India found no effect of sex, age,

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or education on SIT adherence, but a diagnosis of conjunctivitis and absence of a family history of allergic disease significantly increased the likelihood of nonadherence.[14]

Four US studies have reported aggregated findings for adults and children,[15-18] and results generally parallel those reported in studies outside the US. Two studies reported that older patients were significantly more adherent than younger patients,[15,18] and 3 studies found no effect of sex on adherence,[15-17] with 1 reporting better (unspecified significance) adherence among females.[18] Unlike findings reported for patients in Germany and India,[8,14] the type of allergic disease had no effect on SIT adherence among patients receiving care at a military clinic or a private allergy practice.[15,16] However, a retrospective claims analysis of patients in a health maintenance organization reported that patients diagnosed with both AR and asthma treated with ragweed allergen and with an identified allergen were significantly more likely to be adherent than those diagnosed with either AR or asthma alone, treated with allergens other than ragweed, and treated with an unknown allergen type ($P < .01$ for all).[17]

In a study of Florida Medicaid-enrolled children who received SIT, even though Hispanic children were significantly more likely to initiate SIT than black or white children ($P < .0001$), they had a significantly shorter duration of treatment ($P = .003$).[9] In addition, Hispanic children were 1.5 times more likely to discontinue SIT within 2 years of initiation than white children (Cox proportional hazard, 1.53; $P = .001$). This finding parallels the poor adherence to long-term preventive asthma medications seen among Hispanic versus white children[13] and may be explained, in part, by cultural beliefs among caregivers of Hispanic children that may affect medication use.[19] In another US study, among children receiving SIT in a university-based allergy clinic, girls, nonwhite subjects, and those with nonprivate insurance were significantly more likely to be nonadherent than boys, white subjects, and those with private insurance ($P < .01$).[20]

As SIT approaches its 100th anniversary, more information on patient characteristics associated with successful treatment in the United States is needed. In contrast with burgeoning, high-cost, high-tech allergy treatments yielding temporary symptomatic relief, SIT is a more traditional approach and the only available potentially curative treatment. In striking contrast, considerably more is currently known about patient characteristics in the United States that predict adherence to allergy medications. In support of this contention, a MEDLINE search of patient adherence to SIT using the following terms was conducted: ((“Allergens”[MeSh] AND “Immunotherapy”[MeSh]) OR “Desensitization, Immunologic”[MeSh]) AND (“Patient Compliance”[MeSh] OR “Health Resources”[MeSh] OR “utilization”[Subheading])). Among 86 references, 18 (21%) referred to care in the United States. Among these 18 articles, only 7 were original studies reporting compliance to subcutaneous SIT, 1 of which did not include patient factors associated with adherence. In contrast, a MEDLINE search to identify research on patient adherence to allergy medications ((“Anti-Allergic Agents”[MeSh] OR “Anti-Allergic Agents”[Pharmacological Action]) AND (“Patient Compliance”[MeSh] OR “Medication Adherence”[MeSh])) yielded 136 references, 45 (33%) of which referred to care provided in the United States. Twenty-six of these 45 articles assessed patient factors associated with adherence of drug therapy. Thus, whereas 7% (6/86) of identified articles examined patient factors associated with SIT adherence in the United States, 19% (26/136) described patient factors associated with allergy medication.

Why is comparably so little known about the characteristics of US patients with allergic disease who receive SIT? One possible explanation is that funding for large-scale research may be more readily available for treatments developed by the pharmaceutical industry than for patient-specific treatments that are formulated within specialty practice. For example, the widely cited Allergy in America studies, sponsored by pharmaceutical companies,[21,22] comprehensively characterize patient patterns of allergy medication use but entirely disregard SIT.

This is not to say that industry-sponsored research is necessarily flawed or biased. In fact, robust health economics and outcomes research methods developed by the pharmaceutical industry could be applied to explore and improve patient adherence to SIT. For example, specialty allergy clinics could analyze claims/billing data to identify current rates of premature SIT discontinuation and patient characteristics associated with patterns of adherence. Targeted interventions, such as reminder phone calls, letters of encouragement, and Web-based educational materials, could then be evaluated to determine whether they improve adherence. On a broader scale, professional specialty allergy associations could establish a collaborative research consortium to examine patterns of care, best practices, comparative effectiveness, and cost-related outcomes of care.

Ample data demonstrate that SIT is an effective treatment that can alter the course of allergic diseases. Although relatively few studies have been conducted to date, available data suggest that treatment initiation and adherence may be substantially influenced by patient demographic, illness, and insurance characteristics.

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