Systemic Reactions to Subcutaneous Allergen Immunotherapy

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KEYWORDS

- Subcutaneous immunotherapy • Systemic reactions
- Anaphylaxis

The prevalence of asthma and allergic rhinitis associated with aeroallergen sensitization have increased over the past 40 years, especially in "westernized" developed countries. Thus, much attention has been focused on treatment modalities that may prevent or mitigate clinical expression of severe allergic disorders including asthma.[1] One such therapy, subcutaneous allergen immunotherapy (SCIT), has been practiced for 100 years.[2] Placebo-controlled trials of seasonal allergic rhinitis (SAR) with single pollen allergens have demonstrated that SCIT is effective in reducing symptoms of SAR and in preventing seasonal allergic asthma in children with SAR.[3] Placebo-controlled trials with single allergens (ie, grass pollen, cat, and house dust mite) have also established the efficacy of SCIT in reducing symptoms of asthma due to aeroallergens.[4] SCIT with purified Hymenoptera venoms is effective in preventing anaphylaxis in patients with previous life-threatening systemic allergic reactions.[5] However, the clinical benefits of SCIT are tempered by risks of injection-related systemic reactions and life-threatening anaphylaxis.

In 1916, Robert Cooke reported that 3.5% of subcutaneous grass pollen injections were followed by systemic reactions. As early as 1932, 9 fatal reactions (FRs) after SCIT injections were reported in the United States, including one who failed to respond to epinephrine.[6] A review of fatal reactions to SCIT injections conducted in the United Kingdom identified 26 anaphylactic deaths occurring from 1957 to 1986, all of which occurred among allergic patients with asthma.[7] This report resulted in the institution of a mandatory 2-hour postinjection waiting period in Great Britain, virtually creating a moratorium on administration of SCIT for many years.

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In the last 40 years, a series of surveys and descriptive studies have been conducted to define the incidence, prevalence, and factors contributing to injection-related fatal anaphylactic and near-fatal systemic reactions (SRs) in North America. Nearly all such information has been collected from retrospective surveys with the cooperation of practicing allergists in the United States, or reports from individual clinics.[8–10] Limitations of these retrospective studies include the potential for recall bias, lack of comparator populations, and low participation rates among groups of surveyed physicians. Therefore, data collected in this manner may underestimate the true incidence of fatal and near-fatal injection related to SRs and obviate the ability to define risk factors for severe SRs. Nevertheless, a national reporting program designed to capture adverse events related to SCIT does not exist and, if it did, would rely entirely on nonsolicited voluntary reporting of events.

Three retrospective surveys have been performed to identify FRs, and one of these evaluated near-fatal reactions (NFRs) associated with SCIT injections.[11] In the first 2 surveys capturing FRs occurring between 1973 and 1989, members of the American Academy of Allergy Asthma and Immunology (AAAAI) were contacted to report FRs occurring after SCIT or skin testing in their practices as well as FRs in other clinical practices in their communities.[9,10] A third survey was conducted to capture events between 1990 and 2001.[8] Here, short surveys were sent to all physician members of the AAAAI to inquire about NFRs and FRs associated with either SCIT or skin testing. Physicians were contacted by email, fax, and phone to optimize response rates. Those who reported NFRs (n = 273) or FRs (n = 41) on the brief survey were contacted again to provide further details about the events in a longer itemized questionnaire. Completed questionnaires were returned for 68 NFRs and 17 FRs.[11] Subsequently, a longitudinal annual surveillance study of FRs and all SCIT-related SRs, cosponsored by the AAAAI and American College of Allergy Asthma and Immunology (ACAAI), was initiated in 2008.[12]

In this article, the authors review data derived from the aforementioned retrospective surveys and recently initiated longitudinal surveillance studies of SCIT reactions in clinical allergy practices.

FREQUENCIES OF FATAL SCIT REACTIONS IN NORTH AMERICA

There were 76 direct or indirect reports of FRs after SCIT injections occurring between 1973 and 2001.[13] In the survey conducted between 1985 and 1989, it was estimated that a FR occurred once in every 2 million injection visits and once in every 2.5 million injection visits from 1990 to 2001.[8,10] From 1985 to 2001, this averaged to 3 to 3.4 reported deaths per year. Of interest, these incidences were quite similar between surveys despite different methods used for estimating total numbers of injections administered. Subsequently, an additional 6 FRs were identified that had transpired during 2001 to 2007.[12] Based on data collected from the aforementioned longitudinal surveillance study of SRs, no additional FRs related to SCIT occurred between 2008 and 2010.

CLINICAL MANIFESTATIONS OF SCIT-ASSOCIATED FATAL AND NEAR-FATAL ANAPHYLACTIC REACTIONS

Amin and colleagues[11] reported results from a long questionnaire regarding details of NFRs and compared these findings with detailed reports of FRs occurring between 1990 and 2001. In this study, one NFR was estimated to occur in every million injections, or 4.7 NFRs per year. Long survey responses were available for 68 of 273 NFRs and 17 of 41 FRs. The clinical manifestations of FRs and NFRs reported in this survey are summarized in **Figs. 1** and **2**. A NFR was defined as respiratory compromise,