Original Article

Epinephrine Use in Clinical Trials of Sublingual Immunotherapy Tablets

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What is already known about this topic? Allergy immunotherapy can result in systemic allergic reactions and even life-threatening anaphylaxis requiring epinephrine administration.

What does this article add to our knowledge? Epinephrine administrations in response to timothy grass, ragweed, and house dust mite sublingual immunotherapy (SLIT)-tablet-related events are uncommon, typically occur within the first week of treatment, and are rarely self-administered. SLIT-tablet events treated with epinephrine were nonserious.

How does this study impact current management guidelines? Systemic allergic reactions and severe swellings may occur at first SLIT-tablet administration and are manageable with conventional treatment, including epinephrine. Rarely, systemic allergic reactions occur after the first dose.

BACKGROUND: Allergy immunotherapy can result in systemic allergic reactions and even life-threatening anaphylaxis requiring epinephrine administration.

OBJECTIVE: The objective of this study was to describe epinephrine use in the clinical trial development programs of 3 rapidly dissolving sublingual immunotherapy tablets (SLIT-tablets; Merck & Co., Inc., Kenilworth, NJ/ALK, Hørsholm, Denmark/Torii Pharmaceutical Co., Ltd., Tokyo, Japan).

METHODS: Data on epinephrine use were collected from 13 timothy grass SLIT-tablet trials (MK-7243; ≤2800 bioequivalent allergen units/75,000 SQ-T dose, n = 2497; placebo, n = 2139), 5 short ragweed SLIT-tablet trials (MK-3641; ≤12 Amb a 1-U, n = 1725; placebo, n = 770), and 11 house dust mite (HDM) SLIT-tablet trials (MK-8237; ≤12 SQ-HDM; n = 3930; placebo, n = 2246).

RESULTS: In grass SLIT-tablet trials, epinephrine was used 13 times (grass SLIT-tablet, n = 10; placebo, n = 3). Eight administrations were for grass SLIT-tablet-related adverse events (AEs): 4 for systemic allergic reactions and 4 for local mouth and/or throat swelling. In ragweed SLIT-tablet trials, epinephrine was used 9 times in 8 subjects (ragweed SLIT-tablet, n = 7; placebo, n = 1 [2 administrations for protracted anaphylaxis]). Four administrations were for ragweed SLIT-tablet-related AEs: 1 for systemic allergic reaction and 3 for local mouth and/or pharynx/throat swelling. In HDM SLIT-tablet trials, epinephrine was administered 13 times (HDM SLIT-tablet, n = 8; placebo, n = 5). Four administrations were for HDM SLIT-tablet-related AEs: 1 for systemic allergic reaction and 3 for local events. Of the 16 epinephrine administrations for events related to SLIT-tablet treatment, 11 occurred within the first week of treatment (7 administrations on day 1) and 5 were subject self-administered.

CONCLUSIONS: Epinephrine administrations in response to SLIT-tablet-related reactions in clinical trials are uncommon, typically occur within the first week of treatment, and are rarely self-administered. All SLIT-tablet-related events treated with epinephrine were nonserious. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)**

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Allergy immunotherapy can result in systemic allergic reactions and even life-threatening anaphylaxis.[1-3] Specifically for sublingual immunotherapy (SLIT), swelling of the oral or

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Conflicts of interest: H. Nolte is employed by Merck & Co, Inc. T. B. Casale has received money for his institution from Stallergenes; is employed by the American Academy of Allergy, Asthma & Immunology as the Executive Vice President; and his institution has also received grants from Merck and Stallergenes. R. F. Lockey has received money for consultancy from Merck and AstraZeneca; is an employee at the University of South Florida College of Medicine; is on the board for The Journal of Allergy Clinical Immunology: In Practice and Allergy, Asthma & Immunology Research; has received payments for lectures from Merck and AstraZeneca; receives royalties from Informa Publishing; has received travel/accommodations/meeting expenses unrelated to the activities listed from national and international congresses for presentations. B. Svanholm Fogh is employed by ALK-Abello A/S. A. Kaur and S. Lu are employed by Merck & Co, Inc. H. S. Nelson has received money as a consulting fee or honorarium from Merck; and has received money for consultancy and grants/grants pending from Circassia.

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Abbreviations used
AE- Adverse event
AR/C- Allergic rhinitis with or without conjunctivitis
BAU- Bioequivalent allergen units
HDM- House dust mite
ICS- Inhaled corticosteroid
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy

laryngeal pharynx is an additional safety concern. To date, all fatal anaphylactic events associated with allergy immunotherapy have been with subcutaneous immunotherapy (SCIT). No fatal cases of anaphylaxis have been associated with SLIT, and only a few nonfatal systemic allergic reactions defined as anaphylactic events have been reported.[4] The rate of anaphylaxis, as defined by the World Allergy Organization,[5,6] with SLIT has been estimated at 1 case/100,000,000 administrations.[4]

First-line treatment for anaphylaxis is intramuscular administration of epinephrine.[6] In the United States, prescription of autoinjectable epinephrine along with a prescription for approved SLIT products is mandatory.[7-9] However, an epinephrine prescription with SLIT is not required in non-US trials by regulatory agencies or institutional review boards and is not generally provided with SLIT products outside of the United States.[10]

The overall safety and tolerability of 3 rapidly dissolving SLIT-tablets for the treatment of timothy grass (and related grasses), short ragweed, and house dust mite (HDM) allergic rhinitis with or without conjunctivitis (AR/C) has been established in multiple double-blinded, placebo-controlled trials,[11-33] but the treatment of adverse events (AEs) with epinephrine has not been systematically evaluated. The objective of this analysis was to describe epinephrine use in the clinical trial development programs of these SLIT-tablets.

METHODS

Injectable epinephrine use in all of the phase 1, phase 2, and phase 3 double-blinded, placebo-controlled trials conducted for timothy grass SLIT-tablet (MK-7243; GRASTEK/GRAZAX; Merck & Co., Inc., Kenilworth, NJ/ALK, Hørsholm, Denmark), short ragweed SLIT-tablet (MK-3641; RAGWITEK; Merck/ALK), and SQ HDM SLIT-tablet (MK-8237; ACARIZAX/MITICURE; Merck/ALK/Torii Pharmaceutical Co., Ltd., Tokyo, Japan) was evaluated.[11-36] Characteristics for these trials are reported in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org), and specific details for most of these trials have been previously described.[11-33] Some of the phase 1 trials were dose-ranging trials; however, for this report only epinephrine use in subjects receiving any dose evaluated up to the approved dose for timothy grass (2800 bioequivalent allergen units [BAU]/75,000 SQ-T in North America and Europe), short ragweed (12 Amb a 1-U in North America), and SQ HDM SLIT-tablets (up to and including 12 SQ-HDM in Europe) was evaluated. In Japan, 6 SQ-HDM is the approved dose although any epinephrine use up to and including 12 SQ-HDM was evaluated.

The tablets were administered once daily. In the Japanese phase 2/3 SQ HDM SLIT-tablet trials, an up-titration sequence was performed beginning with the 2 SQ-HDM dose for 1 week, followed by the 6 SQ-HDM dose for 1 week (or through the end of the trial for the 6 SQ-HDM group), followed by escalation to the 12 SQ-HDM dose for subjects in the 12 SQ-HDM group.[35,36] Up-titration was not performed in any of the other trials. In all the trials, administration of the first dose (and the second dose in a few of the phase 1 trials) was under medical supervision in an office setting, followed by self-administration at home. Epinephrine autoinjectors were provided to subjects in most of the trials conducted in North America (see Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Site personnel, investigators, and subjects were educated regarding the possible signs and symptoms of systemic allergic reactions in the trials that provided epinephrine. It was clearly instructed in the protocols that self-injectable epinephrine is intended for immediate self-administration for a severe systemic allergic reaction. The investigator or designee was requested to properly educate the subject/parent/guardian on administration of the epinephrine and provide informational materials including an Anaphylaxis Emergency Action plan. Subjects were given a written Anaphylaxis Emergency Action Plan adapted from an American Academy of Allergy, Asthma & Immunology position statement and Simons et al.[37,38] No epinephrine autoinjectors were provided in the European and Japanese trials.

Eligible subjects had a primary diagnosis of AR/C or asthma to the respective allergens, and demonstrated sensitivity to the allergens by the skin prick test and serum-specific IgE. Most of the trials included subjects with a primary diagnosis of AR/C (with or without asthma), whereas 7 trials only included subjects with a primary diagnosis of asthma (with or without AR/C). No epinephrine autoinjectors were provided as emergency rescue medication to subjects in the asthma trials as they were conducted outside of the United States.

The rate of SLIT-tablet treatment-related events with epinephrine administration by number of tablets was calculated by dividing the number of total SLIT-tablet treatment-related events with epinephrine administrations by the total number of exposure days. Daily exposure was considered equivalent to a tablet intake as subjects were required to take a tablet every day. Total exposure was calculated for the phase 2, phase 2/3, and phase 3 trials only, as the phase 1 trials were small, of short duration, and did not have any reported occurrences of treatment-related events with epinephrine administrations.

For this analysis, systemic allergic reactions were defined as investigator-reported "anaphylactic reaction," "hypersensitivity," "systemic allergic reaction," "anaphylaxis," and "allergic reaction." A serious AE was defined as an AE that resulted in death, a life-threatening event, persistent or significant disability/incapacity, congenital anomaly or birth defect, required hospitalization or prolonged existing hospitalization, or was a medically important event as determined by the investigator. According to the protocols, other important medical events may be considered a serious adverse experience when, based on appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the "serious" outcomes of death, life-threatening event, persistent or significant disability/incapacity, and so on. Grading of the intensity of an AE was conducted by the investigator. Mild intensity was defined as awareness of sign, symptom, or event, but was easily tolerated. Moderate intensity was defined as discomfort enough to cause interference with usual activity and may have warranted intervention. Severe intensity was defined as incapacitating with inability to do usual activities or significantly affected clinical status and warranting intervention.