



Letter

Systemic reaction to timothy grass pollen sublingual immunotherapy

Allergen immunotherapy is an effective way of treating allergic rhinitis and allergic asthma. It can be performed by sublingual or subcutaneous administration of allergens. Currently, tablet formulations have been approved in the United States for grass pollen and ragweed pollen.¹ Even though sublingual immunotherapy (SLIT) has a better safety profile than subcutaneous immunotherapy (SCIT) with mostly local reactions, there is a risk of systemic reaction that must be considered.¹ This case report discusses a systemic reaction to timothy grass (*Phleum pratense*) pollen tablets.

A 42-year-old white woman with significant allergic rhinitis and allergic conjunctivitis symptoms presented for initiation of SLIT to northern pasture grass pollen. She had no other significant medical conditions and did not want to start SCIT because of the inconvenience of the build-up schedule. Her symptoms included nasal pruritus, sneezing, congestion, postnasal drainage, and ocular pruritus. Her symptoms typically occurred during the local grass pollen season from middle April to early June each year. She did not want to discontinue antihistamine therapy for allergy skin testing, so specific IgE testing was performed. Specific IgE test results were positive to timothy grass (7.30 kU/L). Her symptoms were not associated with any asthma symptoms, such as dyspnea, wheezing, or cough. The symptoms were only partially controlled with oral antihistamines, nasal steroid and nasal antihistamine sprays, and antihistamine eye drops.

The patient had been using daily oral levocetirizine and bepotastine eye drops for 4 weeks before the initiation of SLIT. She was given one dose of timothy grass pollen tablet (2,800 BAU) sublingually in April, during the local grass pollen season. She had mild clear outward rhinorrhea and mild ocular pruritus before the dose but no pulmonary or cutaneous symptoms. She was not anxious and did not have any throat symptoms before the dose. As per pharmaceutical recommendations, the patient was advised not to swallow for 1 minute after tablet administration.² She also did not eat or drink for 5 minutes after administration.

Within 10 minutes of taking the sublingual tablet, she experienced a mild scratchy throat, but the symptoms soon resolved, and she did not notify office staff or physician. However, the throat pruritus recurred 5 minutes later. She then started to have throat tightness and lightheadedness. When the patient notified office staff of these symptoms, she was actively clearing her throat on examination and was in moderate distress with dyspnea and difficulty speaking. She had pruritus on her arms and legs and was visibly seen by staff scratching these areas. Initial blood pressure was 122/72 mm Hg. Oral cavity examination revealed postnasal drainage with slight erythema but no angioedema. No significant rash or hives were noted on

cutaneous examination, except for mild excoriations on the legs, presumably caused by scratching. Lungs were clear to auscultation. Clinically, the patient had definite new-onset symptoms after the sublingual dose compared with baseline, which were deemed not attributable to anxiety. A World Allergy Organization grade 2 systemic reaction to the timothy grass tablet was diagnosed, and 0.3 mg of 1:1,000 epinephrine was administered intramuscularly in the thigh.³ After the epinephrine, 50 mg of diphenhydramine orally and 62.5 mg of solumedrol intramuscularly were administered. The patient's symptoms improved after a few minutes. The patient was observed for 45 minutes, and she was discharged in stable condition with complete resolution of symptoms. Vital signs remained stable throughout her evaluation. She was counseled on self-administration of auto-injectable epinephrine. Timothy grass tablet SLIT was discontinued, and her allergic rhinitis symptoms were treated with antihistamines and nasal sprays.

Per the prescribing information of the timothy grass pollen tablets, there is a warning of severe allergic reactions that can occur.² However, many studies with SLIT have few or no cases of systemic reactions. In a study of sublingual timothy grass tablets with 253 children ages 5 to 16 years, Bufer et al⁴ reported no episodes of anaphylaxis. A study by Nelson et al⁵ of sublingual timothy grass tablets involving 439 adults had only 1 individual treated with epinephrine for rash, local site reaction, and chest discomfort. A study with sublingual house dust mite involving 509 adults by Bergmann et al⁶ had no episodes of systemic reactions. In 2012, Dunskey et al⁷ reported the first case of SLIT anaphylaxis administered in the United States. The case involved a 31-year-old woman with a history of perennial and seasonal allergic rhinitis, tree nut allergies, and well-controlled asthma who had begun SLIT at home, using extracts at a 1:100 dilution (Greer, Lenoir, North Carolina).⁷ The extract contained cat, dog, grass mix, and weed mix.⁷ She developed systemic allergic symptoms on days 2 and 3 of self-administered SLIT, and her symptoms consisted of angioedema, hives, pruritus, and dyspnea.⁷ Calderon et al⁸ described 11 published case reports of nonfatal anaphylaxis to SLIT. Cochar and Eigenmann⁹ reported 2 cases of anaphylaxis to SLIT in Switzerland. According to the 2010 World Allergy Organization Grading System, grade 1 systemic reactions involve symptoms and signs from one organ system, including cutaneous, upper respiratory, or conjunctival organs.³ Grade 2 reactions, as in our patient, involve symptoms and signs from 2 or more of these organ systems and can include lower respiratory tract (responding to bronchodilator) or gastrointestinal organ systems.³ Grade 3 reactions involve lower respiratory tract symptoms not responding to bronchodilator or laryngeal, uvula, or tongue edema.³ Grade 4 reactions involve respiratory failure or hypotension, and grade 5 reaction is death.³ Our patient received her initial sublingual dose during the local grass

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pollen season and had mild rhinitis and ocular symptoms just before the dose. These may be potential risk factors for systemic reactions to SLIT, and it may be beneficial for the clinician to be more aware of these potential risk factors when administering SLIT. In addition, our case illustrates a systemic reaction to one of the few SLIT formulations that is currently approved by the US Food and Drug Administration. Thus, despite the overall improved safety profile of SLIT over SCIT, the clinician should be aware of the very real risk of systemic reactions involving SLIT.¹⁰ Appropriate precautions are warranted, including providing patients with self-administered autoinjectable epinephrine.

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