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Esophageal dysfunction and immunological changes induced by grass sublingual immunotherapy

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Key words
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Summary
Sublingual immunotherapy frequently causes local oropharyngeal adverse events which are usually of mild severity, and tend to be self-limited and disappear within the first weeks of therapy. The mechanism of action involves changes in the specific humoral response to allergens, with increases in allergen-specific immunoglobulin G4 (IgG4) and blunting of the seasonal increase in allergen-specific IgE.
We describe the case of a 25-year-old man diagnosed with grass pollen induced allergic rhinoconjunctivitis, who was treated with a lyophilisate of Phleum pratense *by sublingual route. After 5 weeks of therapy he developed repeatedly intense symptoms of esophageal dysfunction immediately after the administration. Symptoms recurred every day, subsided in some hours without treatment and disappeared with the termination of therapy. The episode coincided with a marked elevation of total and specific IgE. The immunological changes gradually declined during the three years of follow up.*
The reported case suggests the need to evaluate the role of the immunological changes detected after the first weeks of sublingual therapy with Phleum pratense*, in the induction of esophageal disorders.*

Introduction

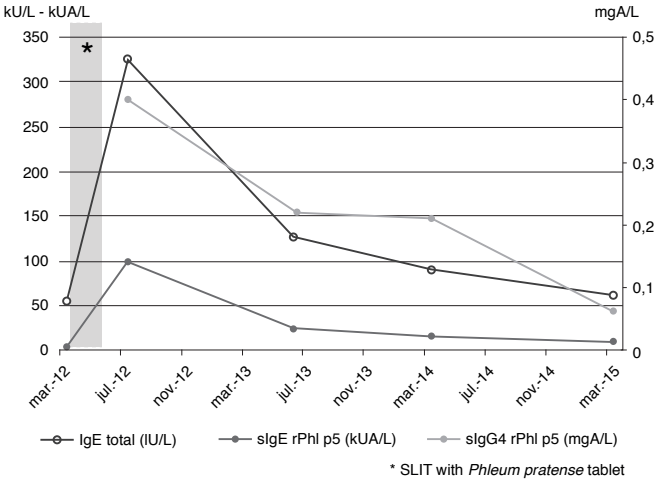
Sublingual allergen immunotherapy (SLIT) shows a high tolerability, allowing self-administration at home. A significant percentage of patients show minor local side effects (oral pruritus and/or edema, throat irritation) which usually disappear within a few days of treatment (1). In the two forms of SLIT allergen preparations, drops or tablets, the aim is sublingual absorption. Therefore, patients are instructed to avoid swallowing it.
Esophageal involvement is not an expected consequence of SLIT and there is no scientific evidence linking esophageal dysfunction (such as reflux or esophagitis), with SLIT (2). However, there are several reports of eosinophilic esophagitis (EoE) in children after oral desensitization with food allergens (milk, egg) (3,4), and there are two cases of early EoE after a month of pollen SLIT. The first case, reported in 2013, was related to the administration of liquid SLIT containing pollens (5). The second case occurred in a patient receiving sublingual tablets with timothy grass (6). In both cases EoE was confirmed by biopsy and disappeared after SLIT was withdrawn.
The immunological effects of SLIT include the capture by the mucosal dendritic cells and the presentation to T cells, which bias the response to a TH1 profile, away from a pro-IgE TH2 profile. However, during the first month of therapy the sublin-

gual administration of a *Phleum pratense* tablet induces a TH2 immune response characterized by increased levels of allergen specific IgE, IL-4, IL-5 and IgG4. This phenomenon is followed by a TH1 response with reduced levels of IL-4, IL-5 and IgE; and increase of IgG4 and a CD4+ cell response (7).
We describe a case of marked immunological changes occurring in a patient treated with a sublingual grass pollen tablet who developed esophageal dysfunction symptoms.

Case report

A 25-year-old man was referred to our allergy clinic with grass pollen moderate-severe allergic rhinoconjunctivitis refractory to standard therapy with antihistamines and intranasal corticosteroids. The patient's medical history included seasonal allergic rhinoconjunctivitis treated for 2 years with subcutaneous immunotherapy (*Lolium perenne, Phleum pratense* and *Chenopodium album*) in 2007, without significant improvement. He denied any history of food allergy, gastrointestinal symptoms or esophageal pain. The initial allergy evaluation was positive for grass pollen (specific IgE to *Phleum pratense*: 5.41 kUA/L) with a normal serum level of total IgE (54.7 kU/L). Sensitization to dust mites, molds, animal dander, other pollens and foods was ruled out by skin prick-tests and/or specific IgE (*Derm pteronyssinus*: 0.16 kUA/L, *Derm. farinae*: 0.13 kUA/L, dog dander: 0.18 kUA/L, cat dander: 0.14 kUA/L, olive pollen: 0.67 kUA/L, peach lipid transfer protein 0.48 KU/L, phleum profilin: 0.03 kU/L).
Treatment with a daily oral lyophilisate (tablet) of grass pollen from Timothy (*Phleum pratense*), 75,000 SQ by sublingual administration (GRAZAX®, ALK) was initiated in April 2012 without immediate complications after the first doses. Five weeks later he turned up referring a significant improvement of the nasal symptoms and no need of antihistamines. However, he complained of an intense esophageal burning sensation and epigastric pain increasing by trunk flexion immediately after the intake of the tablet and persisted for about 30 minutes until gradually calming down. These symptoms appeared after four weeks of therapy and reappeared the following four days after the tablet administration. SLIT was discontinued and therapy with omeprazole 20 mg/day initiated with a rapid resolution of symptoms.
At the moment of SLIT discontinuation, total and specific *Phleum pratense* IgE were markedly increased (**figure 1**). The patient was monitored during three years observing a gradual decrease in the levels of specific IgE and IgG4. Symptoms of allergic rhinoconjunctivitis were milder and well controlled with few doses of antihistamines during the following three grass pollination seasons. No gastric or esophageal symptoms reappeared.

Figure 1 *- Changes in total IgE and IgG4.*



Discussion

In the present case, symptoms of esophageal dysfunction were related to the sublingual administration of a lyophilisate of *Phleum pratense* after four weeks of treatment. This episode coincided with a marked elevation of total and specific IgE. Symptoms disappeared with the termination of therapy and the immunological changes gradually declined during the three years of follow up. We didn't restart grass tablet SLIT to ethical considerations.
The role of the immune response induced during the first month of SLIT on the esophagus, provoking an acute esophageal inflammation, is not determined. The initial immunological effects, with increased levels of allergen specific IgE and changes in the cellular response might be related to the frequent local application site reactions. As IL-5 is a key mediator in eosinophil activation we hypothesize that allergen exposure may induce esophageal symptoms through the effect of IL-5 on eosinophil activation.
The two published cases of EoE related to the administration of SLIT shows some coincidences with our case. The patients, without previous esophageal or gastric disease, reported esophageal symptoms four weeks after starting SLIT (5,6). Symptoms were mild and resolved after stopping therapy without further need of treatment. No immediate local oropharyngeal adverse events were reported.
In the case we report, the rapid clinical improvement after discontinuation of SLIT and starting a proton pump inhibitor (PPI), avoided the performance of an endoscopy with biopsy which could confirm the diagnosis of EoE. The favorable response should not support the diagnosis of a peptic disorder because PPI have anti-inflammatory effects (8). Two recent studies

showed that PPI inhibit TH2 cytokine-stimulated secretion of eotaxin-3, that this is the primary eosinophilic chemoattractant in EoE, in the esophageal squamous cell (9,10). Thus, therapy with PPI could explain the rapid improvement in our patient.
The esophageal symptoms coincided with the highest levels of specific IgE and probably, IL-5. However, although the esophageal dysfunction disappeared with the discontinuation of SLIT, the levels of total IgE, specific IgE rPhl p5 and specific IgG4 rPhl p5 decreased gradually to previous levels in three years.
We recommend discontinuing therapy in patients receiving SLIT who complain of esophageal symptoms. Analytical and histopathological studies should be performed in order to investigate the role of the specific immunological changes in the induction of esophageal inflammatory processes.

References

1. Passalacqua G, Canonica GW. Sublingual or injection immunotherapy: the final answer? Allergy. 2004;59:37.
2. Bonnin AJ, Zacharias DM. Sublingual immunotherapy. N Engl J Med. 2008:21; 359(8):869-70.
3. Sánchez-García S, Rodríguez Del Río P, Escudero C, Martínez-Gómez MJ, Ibáñez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. J Allergy Clin Immunol. 2012;129(4):1155-7.
4. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. Ann Allergy Asthma Immunol. 2011;106(1):73-4.
5. Miehlke S, Alpan O, Schröder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. Case Rep Gastroenterol. 2013;7(3):363-8.
6. Antico A, Fante R. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. J Allergy Clin Immunol. 2014;133(5):1482-4.
7. Suárez-Fueyo A, Ramos T, Galán A, Jimeno L, Wurtzen PA, Marin A, de Frutos C, Blanco C, Carrera AC, Barber D, Varona R. Grass tablet sublingual immunotherapy downregulates the Th2 cytokine response followed by regulatory T-cell generation. J Allergy Clin Immunol. 2014;133(1):130-8.
8. Dellon ES, Liacouras CA. Advances in Clinical Management of Eosinophilic Esophagitis. Gastroenterology. 2014;147(6):1238-54.
9. Molina-Infante J, Rivas MD, Hernandez-Alonso M, Vinagre-Rodríguez G, Mateos-Rodríguez JM, Dueñas-Sadornil C, Perez-Gallardo B, Ferrando-Lamana L, Fernandez-Gonzalez N, Bañares R, Zamorano J. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. Aliment Pharmacol Ther. 2014;40(8):955-65.
10. Lucendo AJ. Cellular and molecular immunological mechanisms in eosinophilic esophagitis: an updated overview of their clinical implications. Expert Rev Gastroenterol Hepatol. 2014;8(6):669-85.