**LETTER TO THE EDITOR**
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# The Local and Systemic Reactions Due to Sublingual Immunotherapy: Is Anaphylaxis Associated with Therapy?

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***To the Editor:***

Sublingual immunotherapy (SLIT) is an allergen specific immunotherapy method which has been used extensively instead of subcutaneous immunotherapy (SCIT). Even though it is considered as the last resort, it is often used combined with pharmacotherapy due to simplicity of application. SLIT has been reported to be effective in seasonal allergic rhino-conjunctivitis treatment of adults and it is tolerated well.[1] Although the systemic reviews support using SLIT in the allergic children, the experience is little and not conclusive on efficacy of SLIT. It is shown to be reliable and effective from 2 years of age.[2-4] Nevertheless, SLIT is currently being used worldwide and serious side effects are rarely reported. The risk for systemic side effects is minimal.[5]

The well-known local side effects are intraoral (sublingual) itching, lip-lingual swelling, and gastrointestinal system (GIS) complaints.[4] Oral and GIS side effects are usually seen in those who used SLIT with grass pollen tablets.[6,7] Complaints such as exacerbations of asthma or rhinitis symptoms, urticaria, angioedema etc. are noticed in less than %20 of patients.[8] Fatigue and worsening eczema are rarely reported.

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Frequency of these kinds of complaints is estimated about 1/1.000.[1-5]

In this letter, we describe 2 patients who had local and systemic side effects during SLIT treatment; thus, we aim to raise awareness on the systemic side effects of SLIT.

In our series, there were 44 children (17 girls, 27 boys) and their mean age was 10 years. 15 asthmatic and 29 non-asthmatic patients with allergic rhino-conjunctivitis have been treated with SLIT and followed up for 3 years. These patients have taken both pharmacotherapy and environmental prevention measures as well. The allergic potential of patients has been determined by skin prick tests. SLIT was given for dust mite mixture in 41/44 of the patients, grasses in 5/44, mixed cereals in 3/44 and mixed molds in 2/44 patients.

Two out of 44 patients developed systemic and local side effects during SLIT treatment. In the first patient with asthma and allergic rhinitis, male, 7 years of age, sublingual swelling (Figure 1) was observed at the last dose of initial phase of SLIT (1000 TU/ml) after using the preparation by Novo Helisen ® Oral, Allergopharma GmbH & Co. KG, Reinbek, Germany. As far as we learned from mother, he might have held the preparation more in the mouth, instead of swallowing immediately. However, there was not any inflammatory lesion or aphthous lesion in his mouth. And his sublingual swelling was not associated with itching or other local or systemic symptoms.

This patient seemed to develop well-known local side effect of SLIT of mite mixture (Dermatophagoides farinae: Dermatophagoides pteronyssinus 50%:50%).



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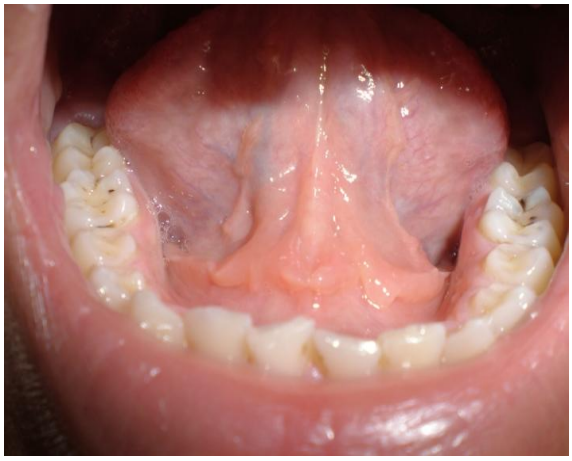

**Figure 1. Sublingual swelling developed during the end of initial phase of sublingual immunotherapy in both patients.**

This side effect can be classified as grade 1 –mild- reaction, according to WAO Grading system for SLIT local adverse events.[9] Local side effects are known to occur frequently in SLIT treatment and this was thought as a mild side effect, according to the literature and communication with Novo-Helisen® medical team. We wished to continue treatment by dose regulation, but the family did not allow us to continue due to recurrent sublingual swellings.

The second patient, 15 year-old, male, was suffering from moderate asthma and allergic rhinitis, and receiving SLIT treatment of a mixture of grass and grain pollens. In the first week of initial phase, he had only sublingual swelling, grade 1 reaction, with the second dose (2 puffs). As said by the family, he later developed immediately (in less than 5 minutes) systemic findings such as facial urticaria and edema, tongue edema, dyspnea and wheezing, suggestive of anaphylaxis, after using the third dose (4 puffs) of APSI Staloral 300® IR/ml (Stallergenes®, France) at home. The patient's arterial blood pressure was measured by the mother and found to be hypotensive (80/50mmHg) at the same time. Hopefully, the patient's condition improved spontaneously in a half-hour and did not require going to emergency. Because of this, laboratory evaluation could not be done. In his past medical and family history, nothing was specific other than his asthma and allergic rhinitis. His asthma was moderate in severity but, not well-controlled with pharmacotherapy. SLIT was not begun at the high pollen season. It was started at the beginning of spring and he was using the dose correctly. He did not receive SCIT before. The size of wheal in the prick test for both grass and grain pollens was ≥3+. He never had a history of anaphylaxis or similar events. Although this reaction did not look like a serious anaphylactic reaction according to the criteria of anaphylactic shock in the position papers; this reaction was supposed by us to be, at least, a severe systemic reaction to SLIT (grade 3 -severe- reaction ). Next day, after discussing the risks of SLIT with the family again, it was decided to discontinue SLIT by the family.

Local and systemic side effects are observed in only 2/44 (4.5%) patients in our series. In general, wrong or overdose application and mixed usage of different and/or multiple pollen allergens are to be blamed.[6] A permanent disease, sequel or fatality has not been occurred so far.[1-4] The first case of SLIT anaphylaxis observed from Turkey in Europe has been reported by Barlan et al.[6] Even severe repeated anaphylactic reactions to SLIT were described in 2013.[10] There have been so far 11 published case reports of nonfatal anaphylaxis, defined according to the World Allergy Organization criteria. These cases were reported from approximately 1 billion SLIT doses administered worldwide since 2000.[5] Only a few cases were agreed on satisfying the criteria for anaphylactic reaction such as the patient received latex by a rush administration protocol.[11] And other reported cases were discussed by the authors whether they developed real anaphylaxis or not.[12] For instance: the patient from the USA reported a severe systemic reaction with no clear evidence of anaphylaxis following SLIT with a mixture of 6 different allergens.[13] In the mean time, many studies have shown the efficacy and safety of SLIT in mono-sensitization with seasonal pollens and perennial allergens in children. In a recent structured analysis of the latest scientific evidence, no anaphylaxis was found among more than 10.000 treated children.[1,2]

In conclusion, SLIT is not a very innocent form of therapy and the SLIT has to be followed by an allergist and be very careful on systemic and/or local side effects. Parents must be informed and taught what have to do especially when a systemic side effect occurs at home.

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