Commentaries

Coadministration of Sublingual Immunotherapy Tablets and Management of Potential Adverse Effects: Austrian, German, and Swiss Expert Recommendations

Gunter Johannes Sturm, MD, PhD[1,2]; Christian Vogelberg, MD[3]; Miriam Marchon, MD[4]; Andreas Horn, MD[5]; Hans-Georg Vitzthum, MD[6]; Marco-Parwis Memar-Baschi, MD[7]; and Jörg Kleine-Tebbe, MD[8]

[1]*Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria;* [2]*Outpatient Allergy Clinic, Vienna, Austria;* [3]*Department of Pediatric Pulmonology and Allergy, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany;* [4]*Praxis um Bern, Gurmels, Switzerland;* [5]*HNO Praxis Am Neckar, Heidelberg, Germany;* [6]*ENT-Practice, Magdeburg, Germany;* [7]*ENT Practice, Essen, Germany; and* [8]*Allergy & Asthma Center Westend, Berlin, Germany*

ABSTRACT

Sublingual immunotherapy (SLIT) is currently available as liquid drops and tablets for treatment of allergic patients. Because several allergens are available and many patients are polyallergic, it is possible to treat patients with multiple clinically relevant allergies by >1 SLIT product. Austrian, German, and Swiss medical experts discussed the available data on allergen uptake at the oral mucosa and recently published data on coadministration of a grass and a ragweed tablet. The experts agreed on a schedule considering data from a North American trial on sequential administration of 2 SLIT-tablets with different allergens and their own experiences made during initiation of treatment with >1 SLIT-tablet in their clinics and subsequent self-administration by the patient and discussed the handling and management of potential adverse drug reactions (ADRs). According to the medical experts' opinion, tolerability at each phase of administration and patient preference should be taken into consideration to ensure a high level of adherence to treatment. Local ADRs that are uncomfortable for the patient may be alleviated by a 2- to 4-week course of antihistamine pretreatment. ADRs with severe swelling and/or systemic ADRs need the physician's particular attention and a decision together with the patient on continuation of treatment with SLIT or possible alternative routes of administration. (*Clin Ther*. 2019;41:1880–1888) © 2019 Published by Elsevier Inc.

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INTRODUCTION

Allergy immunotherapy (AIT) is currently the only causal treatment option for respiratory allergies that induce symptoms of allergic rhinitis and/or conjunctivitis and allergic asthma in a subgroup of patients that usually occurs concomitantly with allergic rhinitis.[1]

Sublingual immunotherapy (SLIT) products are available in drop-based and tablet-based formulations. In 2006, the first sublingually applied SLIT-tablets obtained marketing authorization from European regulatory bodies for treatment of grass pollen allergy because of a safety profile that allowed self-administration at home by the patient. In the following years, SLIT-tablets for other allergens, including ragweed

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and house dust mites, have been clinically developed and approved for clinical use. In addition, a SLIT-tablet for tree pollen allergy has successfully completed Phase III clinical investigation in Europe. Because many patients present with >1 clinically relevant allergy and, thus, fulfill the indication for AIT for >1 allergen, practical recommendations are needed for how to treat patients with ≥2 different SLIT-tablets at the same time. At treatment initiation, patients receiving SLIT may experience local adverse drug reactions (ADRs) that can be the reason for discontinuation of treatment. Therefore, a practical recommendation for how to manage these side effects with the aim of increasing patient adherence to therapy is needed.

Limited evidence is available on these topics, but how to treat patients with ≥2 different SLIT tablets at the same time and how to manage local ADRs are frequent questions that come up in the physician's daily routine. Experienced allergists from Austria, Germany, and Switzerland who are all treating patients, if indicated, with >1 SLIT-tablet product at the same time attended a meeting to produce a consolidated opinion based on clinical data and their own experience.

A literature search was performed by the academic members of the group of participants, and the respective results were presented at the beginning of the meeting. Subsequently, by using the metaplan technique,[2] the treatment schedules applied by every member of the group for administration of 2 SLIT-tablets were described and discussed. For each treatment schedule, pros and cons were collected and discussed to come to an agreed-on recommendation of the group. The same technique was applied to create practical recommendations for the management of ADRs. This article summarizes the results of the expert meeting and provides recommendations of the experts as answers to the 2 following questions from physicians routinely treating allergic patients by AIT: (1) How can I treat a polyallergic patient with >1 allergen with SLIT? and (2) How can I manage ADRs after SLIT administration that typically occur at the initiation of treatment?

QUESTION 1: HOW CAN I TREAT A POLYALLERGIC PATIENT WITH >1 ALLERGEN WITH SLIT?

Is coadministration of SLIT well tolerated according to published data?

Polysensitized, polyallergic patients may be identified by in vivo testing (skin prick test) or detection of specific IgE. Especially in case of unclear results in-vitro testing of IgE sensitization, including highly purified natural and recombinant single allergenic molecules for identification of specific IgE against cross-reacting molecules, such as profilin, lipid transfer proteins, and calcium-binding proteins, or against genuine molecules allow to distinguish between true and false polysensitization.[3]

Data on the tolerability of treatment with single and multiple allergens (grass and various other pollen species) of liquid SLIT mixed in the same product were reported from postmarketing studies performed in Italy with adults and children treated for pollen allergy.[4,5] The authors concluded that SLIT with a limited number of mixed allergens does not increase the risk of side effects if the treatment is correctly prescribed and standardized extracts are used. For optimal potency of the SLIT product used, the administration of a single SLIT product for each allergen is required.[6] In another postmarketing study performed in Germany, data on tolerability were recorded in patients who were primarily treated with a grass SLIT-tablet and received concomitantly SCIT or SLIT with another allergen.[7] In this study, 30 patients were concomitantly treated with a liquid SLIT product, and ADRs were reported in 1 patient.

In a more recent Phase IV, multicenter, open-label trial conducted in North America, the tolerability of coadministration of 2 SLIT-tablets was investigated.[8] Treatment with a timothy grass and a ragweed SLIT-tablet was initiated in 102 patients by a sequential schedule. First, the timothy grass SLIT-tablet was administered in the clinic and, subsequently, treatment continued by daily self-administration by the patient in the evening during the first 14-day period. Second, the ragweed SLIT-tablet was administered in the clinic in the morning and continued by daily self-administration in the morning in the second 14-day period, while the patient continued to take the timothy grass SLIT-tablet in the evening. In the beginning of the third 14-day period, patients received both the ragweed SLIT-tablet and the timothy grass SLIT-tablet within 5 minutes under supervision in the clinic and subsequently self-administered the 2 tablets daily within 5 minutes until the end of the 14-day period.[8]

The primary end point of the trial was the proportion of patients with local swellings with the potential to compromise the upper airway. No severe

swellings in the mouth or throat were reported. All swelling reactions were of mild or moderate severity and of short duration. No severe swelling, systemic allergic reactions, asthma attacks, or reactions that required treatment by adrenaline were reported, and 99% of adverse events (AEs) were graded mild to moderate. The trial found that swellings may occur later than the first day of administration and will typically be present for approximately 20 minutes and usually reoccur for <15 days. The authors noted that the introduction of the ragweed tablet appeared to influence new-onset swellings related to the grass SLIT-tablet taken in the evening, possibly because of increased tissue hyperreactivity related to the administration of ragweed allergen in the morning. However, no increase in local swelling were observed when comparing the 2 tablets for administration in the morning and evening in the second 14-day period, separately, and no worsening of the intensity of local swellings. Whether the risk of AEs or more severe AEs would still be increased if 2 tablets are introduced simultaneously from the start was also discussed.[8] However, the trial was not powered for rare systemic events; therefore, it is unknown whether the risk of systemic allergic reactions may increase with dual tablet administration.

Are Local Langerhans Cells of the Human Oral Mucosa Able to Absorb Different Allergens at the Same Time?

Allergen uptake at the human oral mucosa has been studied with the help of mucosal biopsy specimens as an ex vivo model of the oral mucosa using the major allergen of grass Phl p 5 as a representative allergen.[9] Oral Langerhans cells (oLCs) are antigen-presenting cells that have been identified to play a central role for allergen uptake. They bind and process antigens and induce allergen-specific T-cell responses involved in tolerance induction by SLIT. Transforming growth factor β—mediated T-cell suppression may be an important mechanism in the first 6 months of SLIT.[10] Expression of the high-affinity receptor for IgE may also be involved in the uptake of allergen.

Significant uptake of Phl p 5 was observed after an incubation time of 5 minutes. Dose-dependent binding of Phl p 5 to oLCs was saturated at a concentration of 100 μg/mL of Phl p 5, suggesting a receptor-mediated process, and was found to be comparable in grass pollen allergic patients and nonatopic persons[9] Preliminary unpublished data indicate that oLCs are capable of taking up 2 different allergens at the same time as well as after sequential application. In conclusion, from the data described above, it can be expected that allergens released from 2 SLIT preparations that contain different allergens administered concomitantly may be efficiently bound by oLCs as a prerequisite for clinical efficacy.

Is Coadministration of 2 SLIT Products Feasible at 2 Different Mucosal Regions?

Studies on expression of T-cell cytokines and transcription factors at different oral mucosal regions found that the highest number of T cells was located in the vestibular and buccal region. In this region, significantly higher transforming growth factor β1 mRNA expression was detected compared with the sublingual region, revealing a protolerogenic cytokine micromilieu and a higher expression of Toll-like receptors 2 and 4 by oLCs, which might serve as a target structure for adjuvants.[11]

In biopsy specimens of the oral mucosa from different areas in the mouth, the ratio of oLCs and oral tryptase-positive and chymase-positive mast cells was higher for the vestibular region compared with the sublingual region. The highest density of oLCs was detected within the vestibular region, with lowest density in the sublingual region. The lowest density of oLCs was detected at the sublingual region and the highest density in the vestibular region. The strongest expression of high-affinity receptor for IgE was observed in the vestibular region. The vestibular region could, therefore, be an alternative application site to the established sublingual region.[12] The clinical effect of vestibular administration of AIT remains to be established by randomized, placebo-controlled efficacy trials.

In a pilot study, 71 individuals were treated by a SLIT product in a liquid formulation that was administered sublingually and at the vestibulum oris. The vestibulum forms a pocket surrounded by buccal and gingival mucosa and the teeth alignment. In this study, noninferiority of the vestibular administration in respect to primary immunologic parameters compared with the sublingual administration was observed, and significantly higher levels of IgE-blocking factor at week 4 of treatment indicated a faster immunologic response. No significant difference in the occurrence of AEs between the 2 application sites was observed.[13] No major salivary glands drain

into the vestibular region so that production of saliva is stimulated by the administration of allergens; thus, at this site, allergens may be less diluted and/or swallowed within the recommended holding time for the SLIT. It may therefore be feasible to coadminister SLIT at the sublingual and vestibular region, but currently no data are available.

Which Schedules for Coadministration of 2 SLIT Tablets Are Recommended by Experts According to Their Own Experiences?

The medical experts at the meeting, agreed on a schedule for coadministration of 2 SLIT-tablets based on their own experience in clinical practice and considering the data from the North American trial investigating sequential administration of 2 SLIT tablets (Figure 1).

According to this schedule for a sequential administration of 2 different allergens with SLIT-tablets, SLIT 1 may be administered at a visit in the clinic under medical supervision and, subsequently, self-administered by the patient for 2 to 4 weeks. At a second visit in the clinic, preferably at the follow-up prescription visit for SLIT 1, SLIT 2 may be administered under medical supervision followed by daily self-administration of SLIT 1 in the morning and SLIT 2 in the evening or by taking the 2 SLIT-tablets with a 30-minute interval for the next 4 to 8 weeks when it fits best in the daily routine of the patients. An interval between the 2 SLIT applications was recommended to allow the allocation of potential AEs to 1 SLIT. At the first follow-up prescription of the second SLIT tablet, it should be discussed with the patient if the 30-minute interval for self-administration of the 2 SLIT-tablets may be maintained or even shortened to a 5- to 30-minute interval or taking the 2 SLITs without any interval if tolerability is considered acceptable by physician and

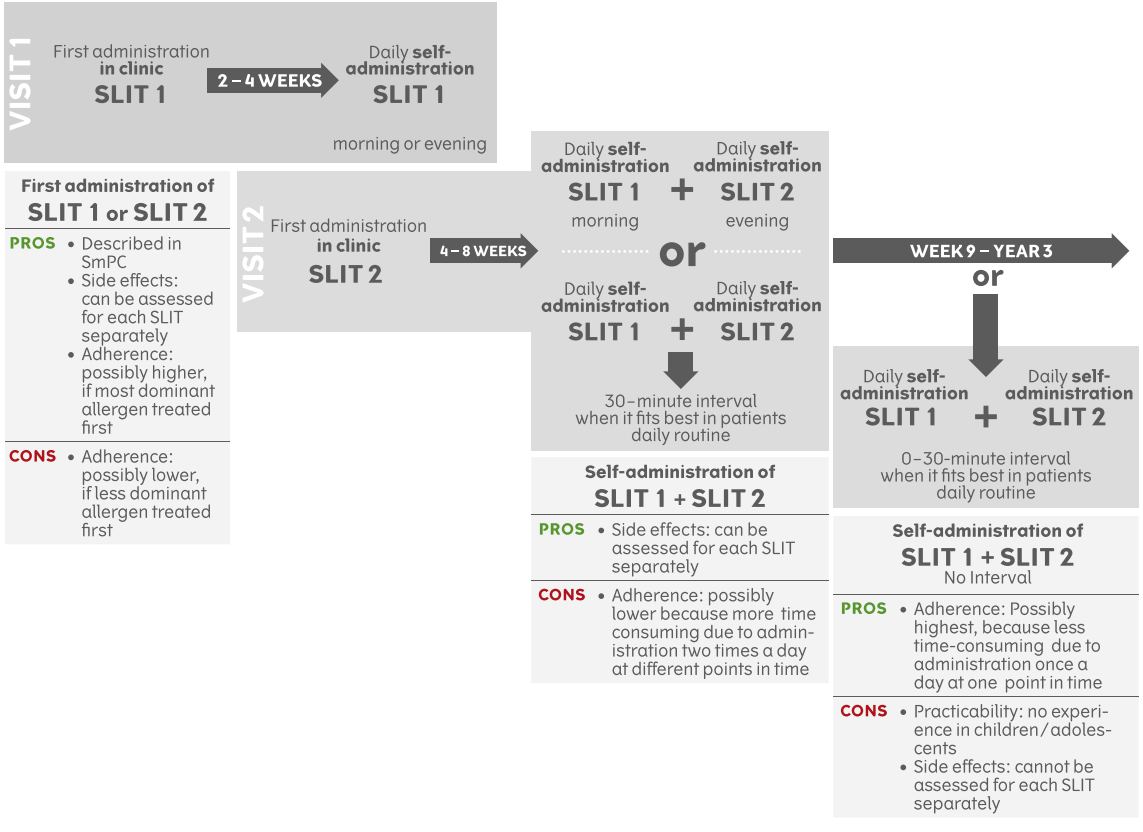

Figure 1. Proposed schedule for sequential administration of 2 sublingual immunotherapy (SLIT) tablets with different allergens. SmPC = summary of product characteristics.

patient over the scheduled treatment period of 3 years. To achieve the highest possible acceptance by the patients, the schedule that fits best into patient's daily routine should be used and, if possible, the schedule should be adapted accordingly.

Also discussed was a schedule starting treatment with first intake of 2 SLIT-tablets at the same day with a 5- to 30-minute interval. However, such a schedule is not supported by any prospective clinical data, and it might be possible that ADRs accumulate for the 2 SLIT-tablets (ie, with no or a very short interval between the 2 SLIT administrations). Therefore, such schedules should be used with caution in experienced centers only.

QUESTION 2: HOW CAN I MANAGE SIDE EFFECTS OF SLIT THAT TYPICALLY OCCUR AT THE INITIATION OF TREATMENT?

Typical ADRs of SLIT and Local ADRs

Clinical data out of double-blind, placebo-controlled clinical trials are available for SLIT-tablets. The administration of SLIT-tablets that contain grass, house dust mite, and ragweed allergens is generally well tolerated in patients with allergic rhinitis and/or conjunctivitis and with or without concomitant mild to moderate asthma.[14–20] However, approximately 50% of the patients reported ADRs.[14–27] These ADRs normally last several minutes to hours after the intake and tend to decrease within the first 2 to 4 weeks of treatment as a first sign that the immune system develops tolerance against the allergen. The most frequent ADRs are oral pruritus, throat irritation, ear pruritus, and mouth edema of mild to moderate severity. These ADRs may be uncomfortable for the patient but usually do not impair daily activities or require medical treatment and do not affect the tolerability of treatment.[28,29] Because of the high frequency of these ADRs, it is important to discuss options for how to handle these initial ADRs with the patients to secure adherence to treatment.

Systemic ADRs

In contrast to the frequent local ADRs, systemic ADRs are rare. These reactions may include but are not limited to urticaria, rhinorrhea, sneezing, dyspnea, cough, wheezing, bronchospasm, chest discomfort, rash, pruritus, flushing, syncope, hypotension, and tachycardia.[29–31] Eosinophilic esophagitis has been reported in isolated cases with grass and house dust mite SLIT-tablets. Patients should be educated to contact thephysician in case of new-onset and persistent symptoms of dysphagia, dyspepsia, and/or heartburn, if experienced, discontinuation of treatment should then be considered.[32]

Possible Measures and Instructions to Manage Side Effects

Most local ADRs begin at the first treatment day, resolve approximately 30 to 60 minutes after the intake, and recur for <2 weeks.[29] Figure 2 shows possible measures and instructions to patients to alleviate symptoms after application of SLIT; these recommendations are based on the clinical experience of the medical experts and have not been formally assessed regarding effectiveness in clinical studies. In general, comprehensive education of the patients at the first intake in the physician's office was recommended to secure a good adherence to treatment. Patients need to know that SLIT contains the allergens that they are allergic to and that local ADRs are thus to be expected. They also need to know that the immune system should be trained by regular exposure to the allergens by SLIT and will, thereby, develop tolerance, leading to a successive decrease of ADRs within the first weeks of treatment.

ADRs are expected to occur with highest frequency at the first administration and can be assessed by the physician at the 30-minute surveillance period after first intake. The first administration should be performed without any antihistamine premedication to allow the judging of the untreated reaction of the patient toward the SLIT administration. ADRs that occur during self-administration by the patient may be distinguished to primarily impair the patient's comfort (intolerable for the patient but not necessarily assessed as requiring discontinuation of treatment by the physician). In case of severe systemic ADRs, such as severe asthma exacerbation, angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension, or feeling of fullness in the throat, the treatment should be discontinued and a physician should be contacted immediately.[28] According to the opinion of the experts, in these cases, an individual decision on later continuation of treatment should be made together with the patient. Additional information may be

Do´s	Consider?	Don't's
• Demonstration of SLIT intake at first intake in the office	• Caution if lips are inflamed, in case of severe oral inflammation, rhagades or perioral symptoms, discontinue treatment and contact physician	• Do not dilute SLIT in water before intake
• Written information and description of actions in case of side effects	• Cooling by licking of ice cube (itching or swelling)	• Do not chew or swallow
• Contact of physician before discontinuation of SLIT intake (by telephone or visit)	• Spit after 5 minutes sublingual holding time of SLIT (swelling, esophageal or gastrointestinal symptoms)	• Avoid intake of food cross–reacting with the allergen(s) treated close to SLIT intake
	• Antihistamine pretreatment	
	• Avoid intake of SLIT after teeth brushing (because of possible induction of gingiva lesions, no data available)	
	• Vestibular application (Caveat: off-lable use)	

Figure 2. Possible measures and instructions to patients to alleviate symptoms after application of sublingual immunotherapy (SLIT).

obtained from the prescribing information (summary of product characteristics) of the SLIT product used and/or from the medical service of the manufacturer.

If local ADRs are considered intolerable by the patient but without objective swellings that affect the airway in clinical examination, the medical experts recommended, according to their clinical experience, the use of an antihistamine premedication to alleviate the symptoms as shown in Figure 3. Because no airway obstruction is present, patients can start taking the antihistamine premedication at home. To be effective, antihistamine premedication should be taken by the patient at least 1 hour before the SLIT administration.[33] If intolerable local ADRs continue despite antihistamine pretreatment, actions as mentioned in Figure 2 may be recommended in addition (eg, cooling, spitting after 5 minutes). If no or tolerable ADRs occur with antihistamine premedication, administration of SLIT with the antihistamine premedication may be continued for 2 to 4 weeks, depending on the type of reaction (eg, itching shorter, swelling longer), and subsequently possibly continued without the premedication. If intolerable local ADRs continue or return after withdrawal of antihistamines, actions as mentioned in Figure 2 (eg, cooling, spitting) may be recommended, and antihistamine pretreatment may be prolonged for additional 4 weeks, while the patient is reassessed more frequently.

If ADRs are still intolerable, discontinuation of treatment with the SLIT-tablets or administration of AIT by an alternative route should be discussed with the patient. Cheilitis and chronic or acute infection of the mouth should be considered as other risks and cofactors for ADRs after SLIT administration. In these cases, patients should interrupt the SLIT treatment until the oral wound has healed.

Potential Alternative Application Site

If local ADRs continue to be intolerable or measures such as cooling of the application site by an ice cube or spitting after the recommended sublingual holding time are ineffective, the panel of medical experts discussed the possibility of using an alternative oral application site. According to data from mucosal biopsies,[12] the vestibular region may be promising, and some of the experts have made positive experience with application of SLIT at that site. The administration of SLIT at the vestibulum is not listed in the approved summaries of product characteristics of SLIT products and is, therefore, an off-label use. It only should be introduced at the clinical discretion of the

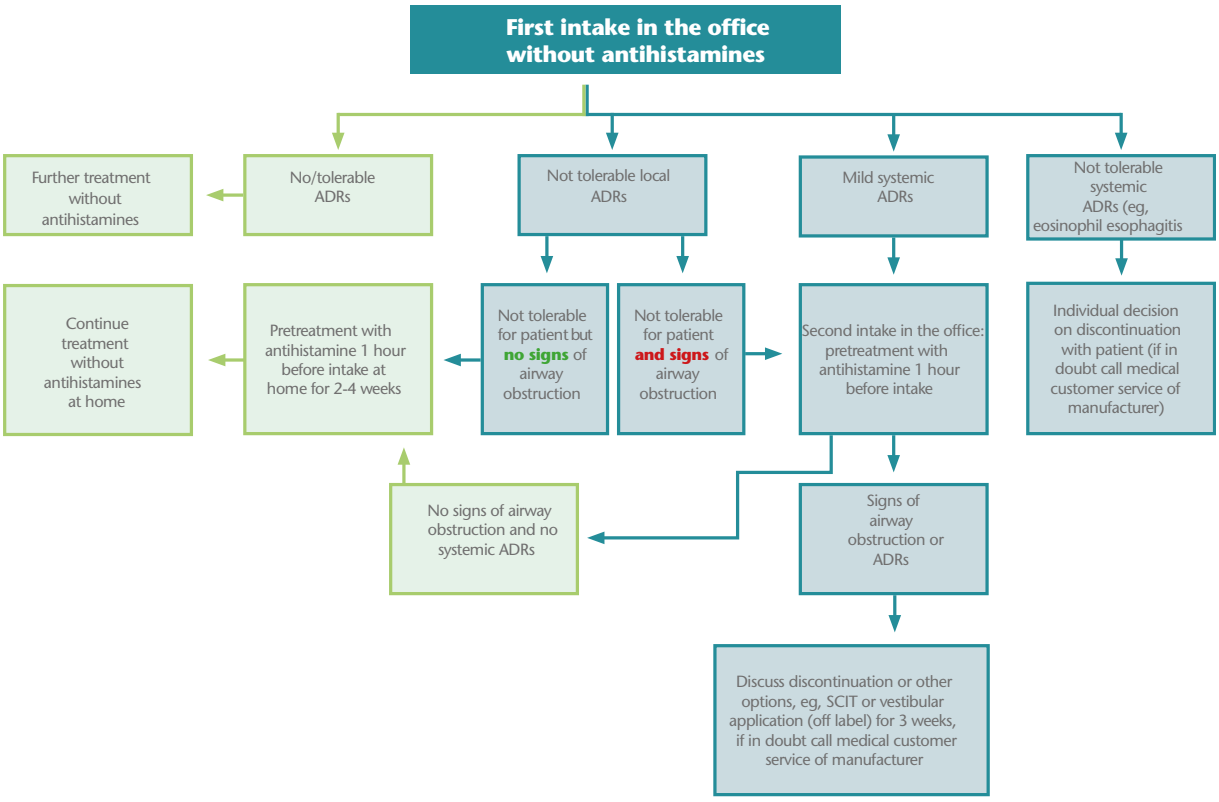

Figure 3. Practical recommendation for management of adverse drug reactions (ADRs). If any systemic or local ADRs are compromising the airway, pretreatment with antihistamine should be weighed against the risk of masking symptoms possibly impeding the assessment of the further course, an individualized decision with patients should be made, and an individualized action plan developed or discontinuation be considered. If treatment is continued, patient education and close follow-up are important. The individualized actions should be adapted according to severity of the ADR, patient input, patient understanding, and access to emergency services. The prescription of an adrenaline autoinjector should be considered. For the vestibular administration of sublingual immunotherapy, only limited data are available. In case of prolonged systemic ADRs or compromised airway, discontinuation of treatment should be strongly considered. Mild systemic reactions: reactions at the nose, eyes, or skin. SCIT = subcutaneous immunotherapy.

responsible physician after careful consideration and with close monitoring and follow-up. The experts agreed on the importance of educating the patient about contacting the physician before a permanent discontinuation of SLIT, either by personal conversation or telephone call, so that the continuation of treatment can be discussed.

CONCLUSIONS

Treatment of patients with multiple clinically relevant allergies by coadministration of >1 allergen with SLIT by tablets has become possible as already practiced with SCIT.[34] Coadministration of ≥2 SLIT-tablets is expected to be effective according to results from investigations of allergen uptake in ex vivo biopsies. A Phase IV clinical trial with freeze-dried timothy grass and ragweed SLIT-tablets found that coadministration by a sequential schedule of 2 SLIT-tablets was well tolerated. The panel of medical experts discussed possible schedules for coadministration of 2 SLIT tablets that may be applicable in clinical practice, including their pros and cons. Recommendations for

management of ADRs were discussed, including antihistamine premedication to alleviate the inconvenient frequent oral application site reactions (ie, itching and discomfort), which may have an influence on patients' adherence and persistence to treatment when taking SLIT across the scheduled 3-year treatment period.

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REFERENCES

1. Pfaar O, Alvaro M, Cardona V, Hamelmann E, Mösges R, Kleine-Tebbe J. Clinical trials in allergen immunotherapy: current concepts and future needs. *Allergy*. 2018;73:1775–1783.
2. Schnelle E. *The Metaplan Method; Communication Tools for Planning and Learning Groups*. Hamburg: Quickborn; 1979. Metaplan series No. 7.
3. Savi E, Peveri S, Cavaliere C, Masieri S, Montagni M. Laboratory test for allergy diagnosis. *J Biol Regul Homeost Agents*. 2018;32:25–28.
4. Agostinis F, Foglia C, Landi M, et al. The safety of sublingual immunotherapy with one or multiple pollen allergens in children. *Allergy*. 2008;63:1637–1639.
5. Lombardi C, Gargioni S, Cottini M, Canonica GW, Passalacqua G. The safety of sublingual immunotherapy with one or more allergens in adults. *Allergy*. 2008;63:375–376.
6. Passalacqua G. The use of single versus multiple antigens in specific allergen immunotherapy for allergic rhinitis: review of the evidence. *Curr Opin Allergy Clin Immunol*. 2014;14:20–24.
7. Reiber R, Keller M, Weller W, Wolf H, Schnitker J, Wüstenberg E. Tolerability of the SQ-standardised grass sublingual immunotherapy tablet in patients treated with concomitant allergy immunotherapy: a non-interventional observational study. *Clin Transl Allergy*. 2016;6:9.
8. Maloney J, Berman G, Gagnon R, et al. Sequential treatment initiation with timothy grass and ragweed sublingual immunotherapy tablets followed by simultaneous treatment is well tolerated. *J Allergy Clin Immunol Pract*. 2016;4:301–309.
9. Allam JP, Würtzen PA, Reinartz M, et al. Phl p 5 resorption in human oral mucosa leads to dose-dependent and time-dependent allergen binding by oral mucosal Langerhans cells, attenuates their maturation, and enhances their migratory and TGF-β1 and IL-10–producing properties. *J Allergy Clin Immunol*. 2010;126:638–645.
10. Hoseini RF, Jabbari F, Rezaee A, et al. House dust mite sublingual-swallow immunotherapy in perennial rhinitis: a double-blind, placebo-controlled Iranian study. *J Biol Regul Homeost Agents*. 2018;32:83–88.
11. Allam JP, Duan Y, Winter J, et al. Tolerogenic T cells, Th1/Th17 cytokines and TLR2/TLR4 expressing dendritic cells predominate the microenvironment within distinct oral mucosal sites. *Allergy*. 2011;66:532–539.

12. Allam JP, Stojanovski G, Friedrichs N, et al. Distribution of Langerhans cells and mast cells within the human oral mucosa: new application sites of allergens in sublingual immunotherapy? *Allergy*. 2008;63:720—727.
13. Allam JP, Wuestenberg E, Wolf H, et al. Immunologic response and safety in birch pollen sublingual versus oral vestibule immunotherapy: a pilot study. *J Allergy Clin Immunol*. 2014;133, 1757—1759.e3.
14. Maloney J, Durham S, Skoner D, et al. Safety of sublingual immunotherapy timothy grass tablet in subjects with allergic rhinitis with or without conjunctivitis and history of asthma. *Allergy*. 2015;70:302—309.
15. Nolte H, Amar N, Bernstein DI, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol*. 2014;113:93—100.e3.
16. Bernstein DI, Kleine-Tebbe J, Nelson HS, et al. SQ house dust mite sublingual immunotherapy tablet subgroup efficacy and local application site reaction duration. *Ann Allergy Asthma Immunol*. 2018;121:105—110.
17. Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol*. 2014;133:1608—1614.e6.
18. Didier A, Bons B. Safety and tolerability of 5-grass pollen tablet sublingual immunotherapy: pooled analysis and clinical review. *Expert Opin Drug Saf*. 2015;14:777—788.
19. Larenas-Linnemann D. How does the efficacy and safety of Oralair® compare to other products on the market? *Ther Clin Risk Manag*. 2016;12:831—850.
20. Okamoto Y, Fujieda S, Okano M, Yoshida Y, Kakudo S, Masuyama K. House dust mite sublingual tablet is effective and safe in patients with allergic rhinitis. *Allergy*. 2017;72:435—443.
21. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablet for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;118:434—440.
22. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129:717—725.
23. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*. 2016;137:444—451.
24. Mosbech H, Deckelmann R, de Blay F, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2014;134:568—575.
25. Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA*. 2016;315:1715—1725.
26. Nolte H, Bernstein DI, Nelson SH, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2016;138:1631—1638.
27. Nolte H, Hébert J, Berman G, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol*. 2013;110:450—456.
28. Epstein TG, Calabria C, Cox LS, Dreborg S. Current evidence of safety and practical considerations for administration of sublingual immunotherapy (SLIT) in the United States. *J Allergy Clin Immunol Pract*. 2017;5:34—40.
29. Bernstein DI, Bardelas Jr JA, Fogh BS, Kaur A, Li Z, Nolte H. A practical guide to the sublingual immunotherapy tablet adverse event profile: implications for clinical practice. *Postgrad Med*. 2017;129:590—597.
30. Passalacqua G, Baena-Cagnani CE, Bousquet J, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. *J Allergy Clin Immunol*. 2013;132:93—98.
31. Cox LS, Sanchez-Borges M, Lockey RF. World allergy organization systemic allergic reaction grading system: is a modification needed? *J Allergy Clin Immunol Pract*. 2017;5, 58—62.e5.
32. Jaiganesh T, Wiese M, Hollingsworth J, et al. Acute angioedema: recognition and management in the emergency department. *Eur J Emerg Med*. 2013;20:10—17.
33. Simons FER, Simons KJ. Histamine and H_1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol*. 2011;128:1139—1150.
34. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. *Allergy Asthma Clin Immunol*. 2016;12:2.

Address correspondence to: Gunter Sturm, Department of Dermatology and Venerology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria. E-mail: Gunter.Sturm@medunigraz.at