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Nondaily dosing schedule of allergen-specific sublingual immunotherapy: efficacy and safety

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Purpose: Sublingual immunotherapy is currently promoted by various companies, with administration schedules variable in the different products even though almost all are standardized immunologically. So, this study was planned to examine the efficacy of simple nondaily dosing of sublingual immunotherapy instead of the widely used daily schedule.

Materials and Methods: Fifty-two patients with allergic rhinitis and bronchial asthma were enrolled. Sublingual immunotherapy (manufactured at the allergen immunotherapy preparation unit at Mansoura University) was given in suitable bottles with a dropper mechanism that permits comfortable dosing under the tongue. The physician recommended that the patient put the drops under his/her tongue and leave the drops beneath the tongue for 2 minutes before swallowing. This was repeated every 3 days, with the drop number and concentration gradually rising.

Results: After 2 months of follow-up, 65.8% responded partially to the symptom score and 26.3% responded completely to the medication score. There was a significant decline in the symptom and medication scores from the baseline scores ($p<0.0001$). After 4 months of follow-up, 95.8% responded partially to symptom scores and no one has not responded; 54.2% responded completely to medication scores; and 81% of studied patients had no side effects. However, the most frequent side effect was a sore throat.

Conclusion: Our nondaily schedule of sublingual immunotherapy is tolerable, safe, and effective in patients with allergic rhinitis and bronchial asthma.

Keywords: Sublingual immunotherapy, Schedule, Dosing, Bronchial asthma, Allergic rhinitis

Introduction

Allergen immunotherapy is the lone possible curative treatment for type 1 hypersensitivity-related disorders like allergic rhinitis (AR), and bronchial asthma (BA). It offers long-term alleviation of symptoms. In addition, it may inhibit new sensitizations as well as the development of BA after AR [1].

The mouth is an immune-tolerant space, remaining noninflamed despite being constantly subjected to various extrinsic proteins. Langerhans cells and monocytes are required for the delivery of interleukin 10 and transforming growth factor-β (key providers of tolerance conservation) [2].

The tonsils and neighboring lymphoid tissue are found at the entrance of the digestive and respiratory systems and might be essential for regional stimulation of toler-

ance to food in addition to aeroallergens. Plentiful FOXP3+ Treg cells were identified in lingual and palatine tonsils [3]. Sublingual immunotherapy (SLIT) produces fairly small systemic changes consistent with subcutaneous immunotherapy (SCIT), but its added local mechanisms in the oral mucosa and/or regional lymph nodes are essential. SLIT is accompanied by the detention of allergens in sublingual mucosa for numerous hours [4].

SLIT is painless and safer than SCIT since the number of mast cells is minimum in the sublingual mucosal tissue [5]. Previous experiments have demonstrated that SLIT has a dose-response relationship, and thus it is critical to utilize an established clinically efficient dose from the start of therapy, due to minimal doses being useless and extremely high doses raising the risk of complications [6]. So, this study was planned to examine the efficacy of simple nondaily dosing of SLIT instead of the widely used daily schedule.

Materials and Methods

Ethics statement

This pre- and post-interventional study was performed on patients with airway allergic disorders (BA and AR) attending Allergen Immunotherapy Clinic, Chest Medicine Department, Mansoura University. Comorbid disorders like autoimmune disease and diabetes, as well as smokers, were excluded. This study was performed within the prerequisites of the institutional research board of Mansoura University (code number: PR.20.08.82). Written informed consent was possessed by each patient.

Diagnosis of airway allergic disorders was done according to the Global Initiative for Asthma Guideline 2022 (for BA) and Allergic Rhinitis and Its Impact on Asthma Guidelines 2020 (for AR) [7,8].

Study procedure

All the included patients were subjected to:

A skin prick test

A skin prick test, using the extract of common aeroallergens in our environment, was performed on the studied patients. Skin reactions were interpreted according to European standards [9,10]. *Chenopodium album*, Conyza, and *Tamarix aphylla* pollen combined in one bottle (pollen 1). *Polypogon monspeliensis, Cynodon dactylon*, and *Arundo donax* are mixed in another bottle (pollen 2).

SLIT schedule

The SLIT manufactured according to Abu El-Enin et al. [11], was given in suitable bottles with a dropper mechanism that permits comfortable dosing under the tongue. Dosing must be done in the morning. The starting concentration in most patients was 1:10,000 weight per volume. More dilution was done for severe cases.

The physician recommended that the patient put the drops under the tongue and leave the drops beneath the tongue for 2 minutes before swallowing. This was repeated every 3 days, gradually raising both the drop number and the SLIT concentration during the whole treatment schedule. Each concentration (which lasts for 2 months) had a build up phase and a maintenance phase (10 drops/3 days) (Fig. 1).

Assessment of response

Every 2 months, symptom and medication scores were used to assess SLIT response. Symptom scores were graded from 0 (no symptoms) to 3 (severe symptoms) for each AR symptom and BA symptom. The medication score was assigned a value of 0 for no medications, 1 for B-2 agonists and antihistamines, 2 for inhaled or intranasal steroids, and 3 for one tablet of corticosteroid [12].

The global response was assessed as follows: complete response; patients with lack of symptoms and withdrawal of medicines (both symptoms as well as medication scores=0), partial response (decline in symptom and/or medication scores but not reaching 0), and no response in both symptom and medication scores.

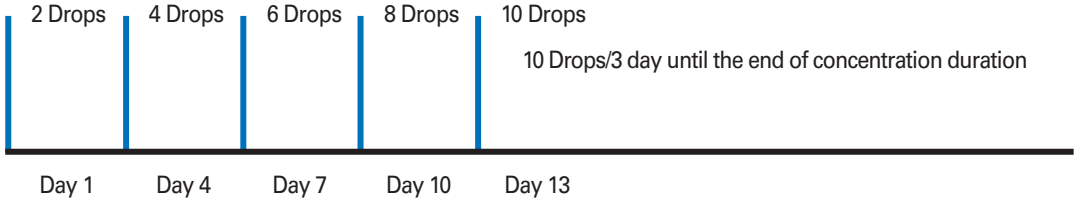

Fig. 1. Sublingual immunotherapy schedule for each concentration.

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Assessment of complications

Both systemic and local side effects of SLIT were recorded.

Statistical analysis

Analysis of variables was done utilizing SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were shown as numbers and percentages. A comparison of paired ordinal data (pre- and post-therapy symptom score and pre- and post-therapy medication score) was performed by the Wilcoxon signed ranks test. The p-value was set at 0.05.

Results

A total of 52 patients with AR and BA were enrolled (the mean age was 26.9±10.5 years). Among them, 30.8% had AR alone, 21.8% had BA alone, and 48% had both AR and BA. Most of the studied patients were females (65.4%). The most frequent allergen sensitization pattern was mold (67.3%), followed by house dust mites (57.6%). Of the studied patients, 59.6% had a baseline symptom score of 3, and 71.2% had a baseline medication score of 2 (Table 1). Thirty-eight patients came for follow-up after 2 months of SLIT and 24 patients came after 4 months of SLIT (Fig. 2).

After 2 months of follow-up, 65.8% responded partially to

Table 1. Characteristics of studied patients (N=52)

Characteristic	Value
Age (yr)	26.9±10.5
Sex	
Male	18 (34.6)
Female	34 (65.4)
Diagnosis	
Allergic rhinitis alone	16 (30.8)
Bronchial asthma alone	11 (21.2)
Allergic rhinitis and bronchial asthma	25 (48.0)
Sensitization pattern[a]	
Molds	35 (67.3)
mp1	19 (36.5)
mp2	17 (32.6)
CD	11 (21.1)
Feather	11 (21.1)
Straw	17 (32.6)
Mite	30 (57.6)
Cat	16 (30.7)
Pigeon	10 (19.2)
Wheat	19 (36.5)
Hay	28 (53.8)
Wool	5 (9.6)
Baseline symptom score	
0	0
1	3 (5.8)
2	18 (34.6)
3	31 (59.6)
Baseline medication score	
0	0
1	5 (9.6)
2	37 (71.2)
3	10 (19.2)

Values are presented as mean±standard deviation or number (%).
CD, cotton dust pollen.
[a]Not mutually exclusive, CD.

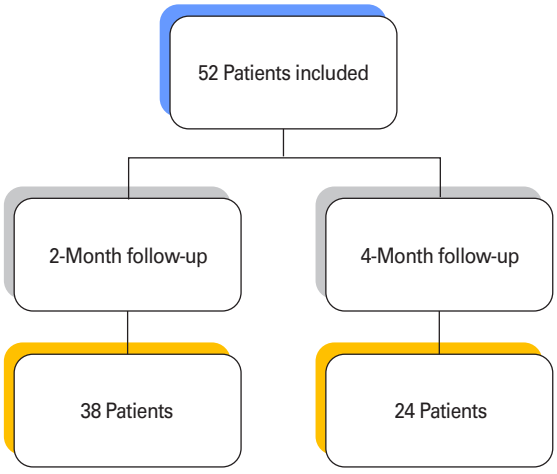

Fig. 2. Flow chart of the studied patient.

Table 2. Assessment of response after 2 months of sublingual immunotherapy (N=38)

Variable	No. (%)	Z (p-value)
Symptom score		-4.7[a] (<0.0001)
0	0	
1	13 (34.2)	
2	17 (44.7)	
3	8 (21.1)	
Medication score		-4.1[a] (<0.0001)
0	10 (26.3)	
1	11 (28.9)	
2	14 (36.8)	
3	3 (7.9)	
Response (symptom score)		
Complete response	0	
Partial response	25 (65.8)	
No response	13 (34.2)	
Response (medication score)		
Complete response	10 (26.3)	
Partial response	12 (31.6)	
No response	16 (42.1)	

[a]By Wilcoxon signed ranks test.

the symptom score, and 26.3% responded completely to the medication score. There was a significant decline in the symptom and medication scores from the baseline scores ($p<0.0001$) (Table 2).

After 4 months of follow-up, 95.8% responded partially to symptom scores, and no one has not responded. And 54.2% responded completely to medication scores. There was a significant decline in the symptom and medication scores from the baseline scores ($p<0.0001$). Also, there were significant differences in response within 2 months of follow-up ($p=0.007$ in symptom score and $p=0.01$ in medication score) (Table 3).

Of the studied patients, 81% had no side effects. However, the most frequent side effect was sore throat (7%) followed by vomiting in 5% of the studied patients. These side effects were minor and were dealt with, and the patients completed the treatment schedule (Fig. 3).

Table 3. Assessment of response after 4 months of sublingual immunotherapy (N=24)

Variable	No. (%)	Z (p-value)
Symptom score		-4.4[a] (<0.0001)
0	1 (4.2)	
1	16 (66.7)	
2	7 (29.1)	
3	0	
Medication score		-3.6[a] (<0.0001)
0	13 (54.2)	
1	3 (12.5)	
2	8 (33.3)	
3	0	
Response (symptom score)		-2.7[a] (<0.007)
Complete response	1 (4.2)	
Partial response	23 (95.8)	
No response	0	
Response (medication score)		-2.4[a] (<0.01)
Complete response	13(54.2)	
Partial response	4 (16.7)	
No response	7 (29.1)	

[a]By Wilcoxon signed ranks test.

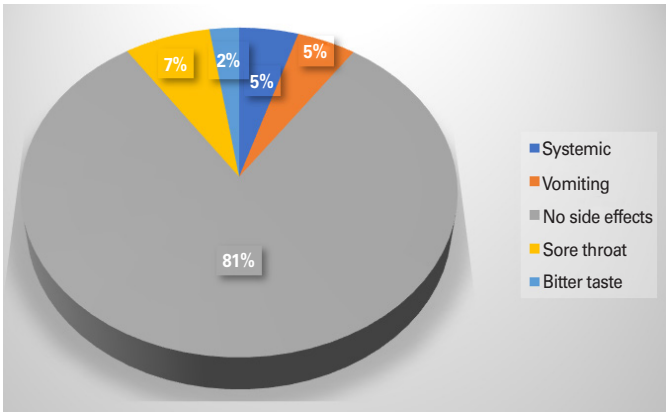

Fig. 3. The reported side effects in the studied patients.

Discussion

The most presently confirmed ways of giving allergen immunotherapy are SCIT and SLIT (which consist of daily dosing). Both are supplied over a duration of 3–5 years [6]. A significant difference between the two methods of administration is that SLIT requires at least 50–100 times more allergen than SCIT to produce a comparable level of effectiveness, and thus low-dose SLIT is frequently ineffective [13].

Strong evidence has demonstrated that SLIT requires a dose-response relationship [14], and it is crucial to utilize an established clinically efficient dose. Researches utilizing grass pollen or house dust mite in the form of tablets [15,16] or drops [17,18] for the management of respiratory allergies have established that the daily 300 index of reactivity dose approaches optimal efficiency and tolerability.

Inadequate tolerability, particularly the appearance of local complications, is one of the key factors affecting SLIT adherence and lastly influencing its efficiency [19]. So, new treatment schedules emphasizing improved tolerability and patient adherence were developed. There are possible associations between the administration schedule, the maintenance dose of allergen, and clinical efficiency [20]. A proper cumulative dose of allergen could be remarkable, but is it the daily unit dose or the cumulative dose which matters the most? After setting up a tolerated dose range, the studies needed to prove a dose response [21].

The safety, efficacy, and tolerability of our schedule examined in this study are in line with those stated in earlier studies. The results of this study showed that 65.8% responded partially to symptom scores and 26.3% responded completely to medication scores after 2 months of follow-up. Also, there was a significant decline in the symptom and medication scores from the baseline scores. Also, there was a significant improvement in response after 4 months of follow-up compared to 2 months of follow-up.

Of the studied patients, 81% had no side effects. The reported side effects in this study were minor and were dealt with, and the patients completed the treatment schedule.

Like our results, Tripathi et al. [22] used a nondaily schedule (every other day) of SLIT and reported a significant re-

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duction in symptoms and medications. Only two patients in Tripathi et al. [22] developed a mild sore throat, which was self-limited and mild vomiting. Various researchers have examined rush up-dosing schedules and have reached differing conclusions, with a few researchers finding such schedules poorer [23,24] while other experiments declare them to be non-inferior [25,26] to traditional up-dosing schedules. Mösges et al. [1] compared three up-dosing schedules to examine whether the shortened up-dosing schedule might be established with similar tolerability as the previously known schedules. Mösges et al. [1] found that the therapy given by using the rapid home-based up-dosing schedule was safe and well tolerated.

The no-up dosing method would result in a therapy that is more patient-pleasing and accessible to do. The latter studies were achieved with the no-up-dosing schedule and their results in terms of safety were as beneficial as the experiments achieved with the conventional up-dosing method [26]. SLIT is currently promoted by various companies, with administration schedules and several allergen(s) variables in the different products, even though almost all are standardized immunologically [27].

In conclusion, our nondaily schedule of SLIT is tolerable, safe, and effective in patients with AR and BA.

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References

1. Mosges R, Breitruck NY, Allekotte S, et al. Shortened up-dosing with sublingual immunotherapy drops containing tree allergens is well tolerated and elicits dose-dependent clinical effects during the first pollen season. World Allergy Organ J 2019;12:100012.
2. Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. Allergy 2009;64 Suppl 91:1-59.
3. Palomares O, Ruckert B, Jartti T, et al. Induction and maintenance of allergen-specific FOXP3+ Treg cells in human tonsils as potential first-line organs of oral tolerance. J Allergy Clin Immunol 2012;129:510-20.
4. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J 2014;7:6.
5. Kawauchi H, Goda K, Tongu M, et al. Short review on sublingual immunotherapy for patients with allergic rhinitis: from bench to bedside. Adv Otorhinolaryngol 2011;72:103-6.
6. Demoly P, Passalacqua G, Calderon MA, Yalaoui T. Choosing the optimal dose in sublingual immunotherapy: rationale for the 300 index of reactivity dose. Clin Transl Allergy 2015;5:44.
7. GINA Science Committee. Global strategy for asthma management and prevention 2021 [Internet]. Fontana (WI): Global Initiative for Asthma; 2021 [cited 2022 Mar 20]. Available from: https://ginasthma.org/
8. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.
9. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test: European standards. Clin Transl Allergy 2013;3:3.
10. Abdelwahab HW, El-Maksoud AA, Farrag NS, Fouda AM, Ehab A. Association of allergen sensitization patterns with clinical outcome of subcutaneous allergen-specific immunotherapy in polysensitized allergic patients. Egypt J Chest Dis Tuberc 2022;71:388-94.
11. Abu El-Enin MA, Rabie Shehab El-Din EM, Abdelwahab HW, et al. Preparation of chemically stable allergen-specific sublingual immunotherapy from Egyptian allergens. J Clin Lab Anal 2022;36:e24261.
12. Eifan AO, Akkoc T, Yildiz A, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy 2010;40:922-32.
13. Demoly P, Calderon MA. Dosing and efficacy in specific immunotherapy. Allergy 2011;66 Suppl 95:38-40.
14. Calderon MA, Larenas D, Kleine-Tebbe J, et al. European Academy of Allergy and Clinical Immunology task force report on 'dose-response relationship in allergen-specific immunotherapy'. Allergy 2011;66:1345-59.
15. 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;133:1608-14.
16. Didier A, Malling HJ, Worm M, et al. Optimal dose, effica-

cy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol 2007;120:1338-45.
17. Ott H, Sieber J, Brehler R, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. Allergy 2009; 64:1394-401.
18. Wang L, Yin J, Fadel R, Montagut A, de Beaumont O, Devillier P. House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma. Allergy 2014;69:1181-8.
19. Senna G, Caminati M, Canonica GW. Safety and tolerability of sublingual immunotherapy in clinical trials and real life. Curr Opin Allergy Clin Immunol 2013;13:656-62.
20. Demoly P, Calderon MA, Casale TB, Malling HJ, Wahn U. "The value of pre- and co-seasonal sublingual immunotherapy in pollen-induced allergic rhinoconjunctivitis". Clin Transl Allergy 2015;5:18.
21. Committee for Medicinal Products for Human Use. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. London: European Medicines Agency; 2008.
22. Tripathi DM, Joshi SV, Dhar HL. Efficacy of sublingual immunotherapy with multiple allergens in bronchial asthma. Bombay Hosp J 2008;50:227-31.
23. Cox L. Accelerated immunotherapy schedules: review of efficacy and safety. Ann Allergy Asthma Immunol 2006; 97:126-37.
24. Bernstein DI, Epstein T. Systemic reactions to subcutaneous allergen immunotherapy. Immunol Allergy Clin North Am 2011;31:241-9.
25. Tabar AI, Echechipia S, Garcia BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus. J Allergy Clin Immunol 2005;116:109-18.
26. Moreno C, Fernandez-Tavora L, Acero S, et al. Tolerance of a cluster schedule on the treatment of seasonal allergic respiratory disease with pollen extracts quantified in mass units. J Investig Allergol Clin Immunol 2003;13:221-7.
27. Frati F, La Grutta S, Bernardini R, et al. Sublingual immunotherapy: administration, dosages, use. Int J Immunopathol Pharmacol 2009;22(4 Suppl):13-6.

 https://doi.org/10.7774/cevr.2023.12.2.121