Efficacy and perceived satisfaction of 3-year SLIT in children with allergic rhinitis and asthma: A pilot study in real-life .

Sara Manti[1], Giulia Maria Diletta Tropea[1], Caterina Ledda[1], Giuseppe Fabio Parisi[1], Maria Papale[1], Enrico Compalati[2], Franco Frati[2], and Salvatore Leonardi[1]

[1]Universita degli Studi di Catania Scuola Facolta di Medicina
[2]Lofarma SpA

December 27, 2022

Abstract

Background. Despite the presence of robust evidence, very sparse data are available on the efficacy of allergen immunotherapy (AIT) on selected patients in *real-life*. Moreover, the obtained data does not ever fit with the general population; thus, the translation and the use of data obtained from randomized clinical trials (RCTs) in *real-practice* can be questionable. Accordingly, we aimed to evaluate in *real-life* efficacy and perceived satisfaction of 3-year sublingual immunotherapy (SLIT) in a pediatric population with with allergic rhinitis and/or asthma. **Methods.** A pilot, monocenter, retrospective cohort, *real-life* study was performed. 153 children who fulfilled the criteria for allergic rhinitis and asthma and mono- or poly-sensitized were enrolled. A standardized questionnaire on perceived efficacy, rescue medication, disease control, number of exacerbations, quality of life, and perceived satisfaction was administered to each patient. **Results.** 70 patients (49 males, 21 females; mean age, 14.3±1.9 years) were included in the final analysis. All 70 patients received SLIT for up to three years, with 100% treatment adherence throughout the study duration. Significant improvement in symptoms and quality of life was reported ($p<0.01$). A significant decrease in disease severity, rescue medication use, and sleep disturbances was reported ($p<0.01$). A significant improvement was also recorded in school performance ($p<0.01$). 60/70 (85.7%) of all enrolled patients declared themselves *very satisfied*, 6/70 (8.57%) *much satisfied*, and 4/60 (5.71%) *satisfied*. **Conclusions.** We firstly showed the efficacy and perceived satisfaction of 3-year SLIT in a paediatric population, with 100% treatment adherence throughout the study duration, in *real-life*.

Title: Efficacy and perceived satisfaction of 3-year SLIT in children with allergic rhinitis and asthma: A pilot study in*real-life* .

Running title: A *real-life* study on SLIT

Authors : Sara Manti[1,2*], MD, PhD, Giulia Diletta Tropea[1], MD, Caterina Ledda[3], Giuseppe Fabio Parisi[1], Maira Papale[1], Enrico Compalati[4], Franco Frati[4#], Salvatore Leonardi[1#], MD

Affiliations :

[1] Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", University of Messina, Messina, Italy.

[2] Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

[3]Occupational Medicine, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

[4]Medical Department, Lofarma S.p.A., Milan, Italy

Co-last Authors

Corresponding author :

Sara Manti, MD, PhD

Paditric Unit, Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", AOUP "G. Martino", University of Messina, Messina, Italy

Email: saramanti@hotmail.it

Word count: 2896

Number of tables: 2

Number of figures: 0

Conflict of Interest: Enrico Compalati, employer of Lofarma; Franco Frati, employer of Lofarma.

Financial support: The author(s) received no financial support for the research, authorship and/or publication of this article.

Key Message

The novelty and strength of our study were to show the efficacy and perceived satisfaction of 3-year SLIT via a *real-life* design. Despite the presence of robust evidence, very sparse data are available on the efficacy and perceived satisfaction of SLIT on selected patients in *real-life* . We strongly believe that *real-world* studies, using data collected in everyday clinical settings, can hold the promise of providing *real* data to maximize the applicability and generalizability of an intervention. Moreover, the possibility to collect and test everything, and not only data-driven, will give the chance to realize a model analyzing both *internal* and*external data sources* and understand the context and patient behaviour. Furthermore, it becomes crucial especially in the drug approval process. All these fine-grained health data will open the way for personalized medicine to satisfy the unmet needs of a broad range of patients who reflect the diversity of persons and not only those who volunteer for clinical trials or biobanks.

Abstract

Background. Despite the presence of robust evidence, very sparse data are available on the efficacy of allergen immunotherapy (AIT) on selected patients in *real-life* . Moreover, the obtained data does not ever fit with the general population; thus, the translation and the use of data obtained from randomized clinical trials (RCTs) in *real-practice* can be questionable. Accordingly, we aimed to evaluate in *real-life* efficacy and perceived satisfaction of 3-year sublingual immunotherapy (SLIT) in a pediatric population with with allergic rhinitis and/or asthma.

Methods. A pilot, monocenter, retrospective cohort, *real-life* study was performed. 153 children who fulfilled the criteria for allergic rhinitis and asthma and mono- or poly-sensitized were enrolled. A standardized questionnaire on perceived efficacy, rescue medication, disease control, number of exacerbations, quality of life, and perceived satisfaction was administered to each patient.

Results. 70 patients (49 males, 21 females; mean age, 14.3±1.9 years) were included in the final analysis. All 70 patients received SLIT for up to three years, with 100% treatment adherence throughout the study duration. Significant improvement in symptoms and quality of life was reported ($p<0.01$). A significant decrease in disease severity, rescue medication use, and sleep disturbances was reported ($p<0.01$). A significant improvement was also recorded in school performance ($p<0.01$). 60/70 (85.7%) of all enrolled patients declared themselves *very satisfied* , 6/70 (8.57%) *much satisfied* , and 4/60 (5.71%) *satisfied* .

Conclusions. We firstly showed the efficacy and perceived satisfaction of 3-year SLIT in a paediatric population, with 100% treatment adherence throughout the study duration, in *real-life.*

Keywords: adherence; children; efficacy; follow-up; perceived satisfaction; real-life study; SLIT.

Background

As confirmed by several randomized clinical trials (RCTs), consensus documents, and meta-analyses, allergen immunotherapy (AIT) has led to crucial changes in clinical outcomes compared to standard treatments in selected patients, as it is the only therapeutic approach able to modify the underlying course of the disease and recover from the disease [1-4].

Despite the presence of robust evidence, very sparse data [5] are available on the efficacy of AIT on selected patients in*real-life* , a research method that takes into account *real*factors of daily clinical life, and aims to evaluate the true effectiveness of innovative therapies.

With the aim to fill this gap, we performed a pilot, monocenter, retrospective cohort study to evaluate *real-life* data on efficacy and perceived satisfaction of 3-year sublingual immunotherapy (SLIT), measured by a validated questionnaire, in a population of mono- or poly-sensitized patients with allergic rhinitis and/or asthma.

Materials and Methods

Study design

A pilot, monocentre, retrospective, open, *real-life* study was designed.

Objectives of the study

To evaluate, in *real-life* , data on the efficacy and perceived satisfaction of 3-year SLIT in a population of mono- or poly-sensitized patients with allergic rhinitis and/or asthma.

Efficacy

The efficacy of 3-year SLIT will be expressed as 1) perceived efficacy in patients; 2) rescue medication use; 3) disease control and impact on quality of life; 4) number of disease exacerbations.

Satisfaction

The satisfaction of 3-year SLIT will be expressed as 1) perceived satisfaction in patients; 2) quality of life in using patient-reported measures.

Subjects and eligibility criteria

153 children who fulfilled criteria for allergic rhinitis and asthma [5, 6] who had been referred to the Department of Clinical and Experimental Medicine, University of Catania between January 2016 and May 2022, were enrolled in the study.

Inclusion criteria were: patients of both sexes; in ages 6-18 years old; who are diagnosed with allergic rhinitis; allergic asthma; allergic rhinitis and allergic asthma according to ARIA [7] and GINA's [8] criteria, respectively; mono- or poly-sensitized to ambrosiae, artemisiae, betulaceae, dermatophagoides farinae and pteronyssinus, cat epithelium, grasses, olive and parietaria; who were treated preseasonally and coseasonally or continuously with grass pollen (ambrosiae, artemisiae, betulaceae, dermatophagoides farinae and pteronyssinus, cat epithelium, grasses, olive and parietaria) tablets up to three years; who stopped SLIT at least three years.

Exclusion criteria included: children younger than 6 years or older than 18 years; patients who are diagnosed with chronic disease; patients who had stopped SLIT for less than three years.

Immunotherapy

SLIT was performed using a preparation of carbamylated allergoid (Lais®, Lofarma SpA, Milan, Italy), biologically standardised in allergenic units (AU, 1:1000 AU), prepared as orosoluble tablets (allergoid SLIT), and administered according to the recommendations by the manufacturer. The patients started with the

maintenance 1000 AU dose, taken regularly twice a week for house-dust mites and 5 times a week for pollens.

Study procedures

After to identify the patients meeting the inclusion criteria, a physician administered a structured questionnaire. The interview could be conducted in person or with the telephone.

The questionnaire included an explanatory cover letter reporting the aim of the study. Experts designed the questions in the field.

The structured questionnaire was prepared as a specific form to be fulfilled online (open-ended format questions) on the website. Responses were anonymous, but general information (initials of name and surname, age, gender, allergen for which SLIT was administered, drug administration schedule) was requested.

In accordance with the diagnosis (allergic rhinitis, allergic asthma, allergic rhinitis and asthma), three different questionnaires were administered. Patients who have practiced multiple cycles of SLIT were evaluated for each treatment, *via* a specific questionnaire for the allergen taken.

Each questionnaire included twenty questions in a multiple-choice format. Moreover, each questionnaire was split into four timing: T0: period prior to the start of therapy with monomeric carbamyl allergy; T1: first year of therapy with monomeric carbamyl allergy; T2: conclusion of the treatment with monomeric carbamyl allergoid; and T3: period following the suspension of treatment with monomeric carbamyl allergy. Specifically, each questionnaire contained questions on:

1. perceived efficacy: measured using a visual analog scale (VAS) that has been proven to be a valid tool in evaluating allergic rhinitis for patient satisfaction [9]. Using the VAS, patients assessed their level of satisfaction by indicating a position along a continuous line between two points from 0 (absence of symptoms) to 10 (bothersome or severe symptoms). VAS was referring to T0, T1, T2, and T3.

2. rescue medication (antihistamines, inhaled or systemic corticosteroids) use in patients with allergic rhinitis measured using a VAS [9]. Using the VAS, patients assessed the rescue medication use by indicating a position along a continuous line between two points from 0 (never used) to 10 (widely used). VAS was referring to T0, T1, T2, and T3.

3. perceived efficacy: measured using a visual analog scale (VAS) that has been proven to be a valid tool in evaluating asthma for patient satisfaction [8, 10, 11]. Using the VAS, patients assessed their level of satisfaction by indicating a position along a continuous line between two points from 0 (absence of symptoms) to 10 (bothersome or severe symptoms). VAS was referring to T0, T1, T2, and T3.

4. allergic rhinits control and its impact on quality of life assessed through standardized questionnaire according to ARIA guidelines [7]. The questionnaire was referring to T0 and T3.

5. asthma control and its impact on quality of life assessed through standardized questionnaire according to GINA guidelines [8]. The questionnaire was referring to T0, T1, T2, and T3.

6. number of asthma exacerbations requiring the use of rescue therapy (salbutamol or systemic corticosteroids) or hospitalization in the last 12 months. This item was numerically measured by a scale ranging from 0 to 8.

7. perceived satisfaction expressed in terms of “very dissatisfied”, “dissatisfied”, “satisfied”, and “very satisfied”. The perceived satisfaction was referring to T0, T1, T2, and T3.

One answer for each question was provided. The questionnaire was administered in Italian and translated into English for publication. The English version of the questionnaire is enclosed in Appendix 1 (a, b, a and b).

Safety was defined as the number and the type (mild, moderate, and severe) of adverse events (AEs) recorded by physician and/or children’s parents and/or patients.

Collected data were securely stored and managed using the electronic data capture tools (server: PHP; Web: HTML, CSS, JS; Framework: Bootstrap; Libraries JS: jquery, noUiSlider).

Written informed consent was obtained before entering the study, and in the case of minors was obtained from next of kin, caregivers, or guardians [12]. Patient privacy was protected in compliance with the European Union General Data Protection Regulation (GDPR). Institutional Review Board of University of Catania approved the study.

Data analysis

The data collected were statistically analyzed by the statistical computer software SPSS, version 15.0. A *post hoc* analysis of temporal trend was performed. Descriptive statistics were calculated for all demographic and clinical variables. Continuous variables were presented as mean and standard deviation (SD), and categorical variables as frequency and percentage. The normality assumption was verified using the Shapiro-Wilk test. T-student and χ^2 tests were adopted for comparisons between categorical variables. T-test and non-parametric Mann-Whitney tests were adopted for comparisons between continuous variables. Kaplan-Meier curves estimated the survival function. Statistical significance was set at levels of $P < 0.05$.

Results

Globally, we evaluated 70 patients (49 males, 21 females; mean (SD) age, 14.3 ± 1.9 years; age range 10-18). The patients' demographic and clinical characteristics and sensitization are reported in Table 1. All 70 patients received SLIT up to three years, with 100% treatment adherence for SLIT throughout the study duration. 62 (89%) out of 70 included patients received SLIT continuously, 8 (11%) out of 70 patients received SLIT pre-coseasonally. No AEs were reported during the study.

Patients with allergic rhinitis with or without asthma

Of the 70 patients, 6 subjects reported allergic rhinitis, 4/6 (75%) had moderate to severe intermittent allergic rhinitis, and 2/6 (25%) had moderate to severe persistent allergic rhinitis. 34 out of 70 experienced allergic rhinitis with asthma. With the exception of 2 patients, 32 out of 34 subjects (94.11%) reported moderate to severe intermittent allergic rhinitis.

At T3 a significant clinical improvement, expressed in terms of nasal and eye symptoms, was reported: T0: 7.7 ± 1.5 vs. T3: 2.4 ± 2.7 ($p<0.01$). In parallel, a significant decrease was found in disease severity (T0: 8/40 (20%) vs. T3: 0/40 (100%), $p<0.01$), rescue medication use (T0: 6.4 ± 2.7 vs. T3: 2.4 ± 3.2 ($p<0.01$)), and sleep disturbances (T0: 19/40 (47.5%) vs. T3: 9/40 (22%), $p<0.01$).

A significant improvement was also recorded in school performance: T0: 9/40 (22%) vs. T3: 2/40 (5%), $p<0.01$.

No significant changes were reported in frequency of symptoms *([?] 4 days/week or [?] 4 weeks* : T0: 26 (65%) or 14 (35%) vs. T3: 21 (52.5%) or 19 (47.5%); *[?] 4 days/week o [?] 4 weeks* : T0: 20 (50%) or 20 (50%) vs. T3: 28 (70%) or 12 (30%).

Patients with allergic asthma or allergic asthma and rhinitis

Of the 70 patients, 64 subjects reported asthma or allergic asthma with rhinitis.

At T3 a significant clinical improvement was reported: T0: 7.6 +- 2.1 vs. T3: 0.9 +- 1.8 ($p<0.01$). In parallel, a significant decrease was found in frequency of symptoms (> 2 days/week: T0: 42/64 (66%) vs. T3: 1/64 (2%), $p<0.01$); rescue medication use (salbutamol: T0: 36/64 (56%) vs. T3: 1/64 (2%) ($p<0.01$); systemic corticosteroids: T0: 36/64 (56%) vs. T3: 1/64 (2%) ($p<0.01$)); and sleep disturbances (T0: 39/64 (61%) vs. T3: 64/64 (100%), $p<0.01$).

A significant improvement was recorded in school performance: T0: 15/64 (23%) vs. T3: 2/64 (3%), $p<0.01$.

Perceived satisfaction for all enrolled patients

60/70 (85.7%) of the all enrolled patients declared themselves*very satisfied* , 6/70 (8.57%) *much satisfied* , and 4/60 (5.71%) *satisfied* .

Discussion

We performed a pilot, monocenter, retrospective cohort study to evaluate the efficacy and perceived satisfaction of 3-year SLIT in*real-life* , measured by a validated questionnaire, in a population of mono- or poly-sensitized patients with allergic rhinitis and/or asthma. As expected, the SLIT significantly contributed in modifying the disease course in patients suffering from allergic rhinitis and asthma as well asthma with rhinitis. The positive impact of treatment has been assessed by significant changes in perceived efficacy in patients, rescue medication use; perceived satisfaction in patients; disease control and impact on quality of life; and number of disease exacerbations. Significant changes have also been recorded in the frequency of symptoms of patients suffering from asthma and asthma with allergic rhinitis; however, no changes were reported in the allergic rhinitis group. The absence of significant changes has been related to the small sample size: only six patients were suffering from allergic rhinitis.

Confirming the efficacy of SLIT, the perceived satisfaction for all enrolled patients was high, and it is reasonable to hypothesize that these data were related to the improvement in clinical outcome. Sparse studies investigated the efficacy/perceived satisfaction ratio, which is crucial in obtaining a high treatment adherence [13-15]. Moreover, when this issue was investigated, several biases were affecting the results, such as conflict of interests [13, 14]. In our study, all patients reported a high rate of satisfaction, more probably as a consequence of efficacy treatment. It has been reported that the reasons for premature cessation of AIT are the inability to reach the clinical centre, the ineffectiveness of therapy, and the long course of treatment [16]. Herein, the nature study allowed us to enrol patients that were highly motivated to start treatment as well as to participate in a study in the absence of a strict protocol. All these factors resulted in high treatment adherence as 60/70 (85.7%) of all enrolled patients declared themselves very satisfied, 6/70 (8.57%) much satisfied, and 4/60 (5.71%) satisfied. Adherence is the key to ensure SLIT effectiveness, as poor adherence is a potential factor affecting negatively the efficacy of AIT. In line with this finding, all enrolled patients completed at least three years of treatment, showing 100% spontaneous adherence to the prescribed treatment. Contrary to other studies in which a high treatment adherence was obtained thanks to the help of nurse interventions, frequent scheduled visits and telephone calls [17-19], herein, our patients showed 100% *spontaneous*adherence to the prescribed treatment. In this regard, we believe that patients were obtaining real benefit from the treatment probably since the first year of the therapy; thus, a good efficacy achieved during the first year of treatment could be considered as a favourable prognostic factor for treatment adherence for the next two years with long-lasting positive effects in real-practice. Also, only a continuous AIT for a period of at least 3 years modifies the course of the disease and ensures the long-term remission of symptoms for several years [20-23]. RCTs and observational studies on treatment adherence reported that the discontinuation rate for SCIT is approximately 22%, 34%, and 26% from one to three treatment years, respectively; and, for SLIT is 42%, 29%, and 27% from one to three treatment years [24, 25]. Herein, we firstly reported that the treatment adherence for SLIT was 100% troughtout the study duration. Similar to other chronic conditions, allergic diseases require ongoing care to minimize their impact, improve health outcomes, prevent clinical worsening and comorbidities, and reduce healthcare costs [26]. Nevertheless, it has been estimated that only the half of patients with chronic conditions take their medications as prescribed; since several factors affect the patients'ability to follow treatment recommendations correctly [26, 27]. We strongly believe that the complete treatment adherence in our population can primarily be attributed to the study design. In RCTs, patients are strictly selected and monitored over time to limit bias; and, when patients differ from that set out, they are excluded from the final study results. Conversely, more reliable data can be derived from real-life studies, since a combination of strategies, such as educational plans and regular assessments, can be more easy applicable [28].

Moreover, the novelty and strength of our study were also to show the efficacy and perceived satisfaction of 3-year SLIT via a*real-life* design. Although the health sciences community selects RCTs as the main tool able to investigate and evaluate clinical interventions with the lowest risk of bias, the obtained data

does not ever fit with the general population; thus, the translation and the use of data obtained from RCTs in real-practice can be questionable. Looking specifically at RCTs performed in AIT, several issues could explain the inadequacy of RCTs in AIT. The studies generally have short duration and are limited to one pollen season, and it is well known that the potential of AIT in preventing new sensitization and onset of allergic diseases is strictly correlated with the duration treatment, and at least 3-year treatment course is recommended [29, 30].

The RCTs are designed to test if the selected treatment is working, but they do not evaluate if the treatment *works in real-life.* Aiming to limit any factor that could potentially influence final results, RCTs are designed in compliance with a *rigid and strict*protocol; however, the latter is not the same adopted by all RCTs; thus, a "within-study" and "between-study" heterogeneity is extensively reported among different trials [6]. Moreover, the RCTs are investigating an experimental treatment in a selected group of patients who must respect the study's inclusion criteria [6]. Any protocol modification is foreseen for patients who do not strictly meet the inclusion criteria or unforeseen events [6]. Thus, it can happen that, due to several reasons (e.g., age, disease severity, comorbidities, use of concomitant medications, etc), a cluster of patients, from which it could be possible to extract potential and interesting data, must be excluded from the study with a gap in knowledge of the investigated treatment *in real-practice.*

Whether on one hand the "one-size-fits-all" approach can provide the opportunity to apply a treatment for a large population; on the other hand, it does not work for everyone. A treatment defined as "effective" in an *ideal* clinical setting can not give specific quantifiable answers under individual cases in a *routine* clinical setting. Tailor healthcare approach and treatment to meet the specific needs of each patient. is urgently needed as only a "sartorial" approach can provide an individual's unique molecular, lifestyle, and clinical information.

We strongly believe that *real-world* studies, using data collected in everyday clinical settings, can hold the promise of providing*real* data to maximize the applicability and generalizability of an intervention. Nevertheless, we do not aim to fule a war between a "wrong" and "right" research approach rather we want to shift form a*dichotomous* to an *integrated* perspective, able to combine the strengths of each research method -the prospective, randomized, and analytical design of the RCTs with more representative and generalizable data of *real-life* studies- and exceed the limits of restrictive inclusion and exclusion criteria of RCTs and the risk of low-quality control of the surrounding data collection and susceptibility to multiple sources of bias occurring in *real-life* studies.

Limits of the study

Nevertheless, we are aware that our study has limitations, as we designed a retrospective trial and included small numbers of patients. The possibility of designing a prospective study is also evaluated, and we plan to conduct a larger study to increase our sample size. However, the small sample size is due to our choice to include patients with high motivation for the treatment success. AIT works only if it is taken adequately by the patient, and when this occurs, we demonstrated that it works well. This evidence represents a crucial motivation for patients approaching the AIT because they take responsibility for their well-being. If the treatment is taken adequately and constantly, the patient will achieve several advantages, such as improvement of clinical symptoms, quality of life, and sparing of symptomatic therapy.

References

1. Frati F, Incorvaia C, Passalacqua G. Efficacy of sublingual immunotherapy. JAMA 2013;310(6):643-644
2. Calamita Z, Saconato H, Bronhara Pela A, Nagib Atallah A. Efficacy of sublingual immunotherapy in asthma. Systematic review of randomized clinical trials. Allergy 2006;61:1162-72
3. Melaranci C, Matteoli MC. Efficacy of allergoid sublingual immunotherapy in children with asthma and/or allergic rhinoconjunctivitis. JACI 2004;113:S111
4. Cuppari C, Leonardi S, Manti S, Filippelli M, Alterio T, Spicuzza L, Rigoli L, Arrigo T, Lougaris V, Salpietro C. Allergen immunotherapy, routes of administration and cytokine networks: an update. Immunotherapy 2014;6(6):775-86.

5. Pastorello EA, Losappio L, Milani S, Manzotti G, Fanelli V, Pravettoni V, Agostinis F, D'Arcais AF, Dell'Albani I, Puccinelli P, Incorvaia C, Frati F. 5-grass pollen tablets achieve disease control in patients with seasonal allergic rhinitis unresponsive to drugs: a real-life study. J Asthma Allergy 2013;6:127-33.
6. Kabisch M, Ruckes C, Seibert-Grafe M, Blettner M. Randomized controlled trials: part 17 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2011;108(39):663-8.
7. Bousquet J, Khaltaev N, Cruz AA, et al. World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). Allergy 2008;63(Suppl. 86):8-160
8. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Available at: https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. Last Access: July 26, 2022
9. Klimek L, Bergmann KC, Biedermann T, Bousquet J, Hellings P, Jung K, Merk H, Olze H, Schlenter W, Stock P, Ring J, Wagenmann M, Wehrmann W, Mosges R, Pfaar O. Visual analogue scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). Allergo J Int 2017;26(1):16-24.
10. Rhee H, Belyea M, Mammen J. Visual analogue scale (VAS) as a monitoring tool for daily changes in asthma symptoms in adolescents: a prospective study. Allergy Asthma Clin Immunol 2017;13:24.
11. Meltzer EO, Busse WW, Wenzel SE, Belozeroff V,Weng HH, Feng J, Chon Y, et al. Use of the asthmacontrol Questionnaire to predict future risk of asthma exacerbation. J Allergy Clin Immunol 2011;127:167–172.
12. Manti S, Licari A. How to obtain informed consent for research. Breathe (Sheff). 2018;14(2):145-152
13. De Vos C, Mitchev K, Pinelli M-E, et al. Non-interventional study comparing treatment satisfaction in patients treated with antihistamines. Clin Drug Investig 2008;28:221-30
14. Ferrer M, Morais-Almeida M, Guizova M, et al. Evaluation of treatment satisfaction in children with allergic disease treated with an antihistamine: an international, non-interventional, retrospective study. Clin Drug Investig 2010;30:15-34
15. Zicari AM, Indinnimeo L, De Castro G, Incorvaia C, Frati F, Dell'Albani I, Puccinelli P, Scolari M, Duse M; Pediatric SURF Study Group. A survey on features of allergic rhinitis in children. Curr Med Res Opin. 2013;29(5):415-20
16. Wang T, Li Y, Wang F, Zhou C. Nonadherence to sublingual immunotherapy in allergic rhinitis: a real-life analysis. Int. Forum Allergy Rhinol 2017;7:389–392
17. Kiotseridis H, Arvidsson P, Backer V, Braendholt V, Tunsater A. Adherence and quality of life in adults and children during 3-years of SLIT treatment with Grazax-a real life study. NPJ Prim Care Respir Med 2018;28(1):4
18. Ras L, de Groot H, Stengs CH, van Weissenbruch R. Persistence of treatment with 5-grass pollen tablets in patients with allergic rhinitis: a real-life study. Ann Allergy Asthma Immunol. 2016;116(1):52-58.e2
19. Pajno GB, Caminiti L, Crisafulli G, Barberi S, Landi M, Aversa T, Valenzise M, Passalacqua G. Adherence to sublingual immunotherapy in preschool children. Pediatr Allergy Immunol. 2012;23(7):688-9.
20. Halken S, Larenas-Linnemann D, Roberts G, et al. EAACI guidelines on allergen immunotherapy: prevention of allergy. Pediatr Allergy Immunol 2017;28(8):728–745.
21. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sorensen HF, Klink R; GAP investigators. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol 2018;141(2):529–538 e513
22. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006;61(2):198–201.
23. Passalacqua G, Frati F, Puccinelli P, Scurati S, Incorvaia C, Canonica GW, Hilaire C. Adherence to sublingual immunotherapy: the allergists' viewpoint. Allergy 2009;64(12):1796-7.

24. Bruggenjurgen B, Reinhold T. Cost-effectiveness of grass pollen subcutaneous immunotherapy (SCIT) compared to sublingual immunotherapy (SLIT) and symptomatic treatment in Austria, Spain, and Switzerland. J Med Econ 2018;21(4):374-381.
25. Osterberg L, Blashke T. Adherence to medication. N Engl J Med. 2005;353:487–93
26. Sabate E. Adherence to long-term therapies: evidence for action. Switzerland: World Health Organization; 2003. World Health Organization. https://apps.who.int/iris/handle/10665/42682
27. Bidwal M, Lor K, Yu J, Ip E. Evaluation of asthma medication adherence rates and strategies to improve adherence in the underserved population at a Federally Qualified Health Center. Res Soc Adm Pharm 2017;13:759–66.
28. Senna G, Caminati M, Lockey RF. Allergen immunotherapy adherence in the real world: how bad is it and how can it be improved? Curr Treat Options Allergy 2015;2:14.
29. Paoletti G, Di Bona D, Chu DK, Firinu D, Heffler E, Agache I, Jutel M, Klimek L, Pfaar O, Mosges R, DunnGalvin A, Genuneit J, Hoffmann HJ, Canonica GW. Allergen immunotherapy: The growing role of observational and randomized trial "Real-World Evidence". Allergy. 2021;76(9):2663-2672.
30. Di Bona D, Paoletti G, Chu DK, Pepys J, Macchia L, Heffler E, Canonica GW. Allergen immunotherapy for respiratory allergy: Quality appraisal of observational comparative effectiveness studies using the REal Life Evidence AssessmeNt Tool. An EAACI methodology committee analysis. Clin Transl Allergy 2021;11(4):e12033

Table

Table 1. Demographic data and clinical characteristics of the enrolled patients.

Appendix.

Appendix 1. English version of the questionnaire administered to patients with allergic rhinitis (a), asthma (b), rhinitis and asthma (a and b).

Hosted file

`Table.docx` available at https://authorea.com/users/340024/articles/616011-efficacy-and-perceived-satisfaction-of-3-year-slit-in-children-with-allergic-rhinitis-and-asthma-a-pilot-study-in-real-life