Current issues on sublingual allergen-specific immunotherapy in children with asthma and allergic rhinitis

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SUMMARY
In 1993 the European Academy of Allergy and Clinical Immunology was the first official organization to recognize that sublingual administration could be "promising route" for allergic desensitization. A few years later, the World Health Organization recommended this therapy as "a viable alternative to the injection route in adults." The first meta-analysis showed sublingual allergen specific immunotherapy (SLIT) effectiveness for allergic rhinitis and another study showed SLIT can actually help prevent the development of asthma both in adults and in children. The main goal of this review article is to present insight into the most up-to-date understanding of the clinical efficacy and safety of immunotherapy in the treatment of pediatric patients with allergic rhinitis and asthma. A literature review was performed on PubMed from 1990 to 2015 using the terms "asthma," "allergic rhinitis," "children," "allergen specific immune therapy." Evaluating data from double-blind placebo-controlled randomized clinical trials (DB-PC-RCTs), the clinical efficacy (assessed as the reduction of symptom score and the need of rescue medicament) of SLIT for allergic rhinitis and allergic asthma, has been confirmed in various meta-analysis Outcomes such as rhinoconjunctivitis score and medication scores, combined scores, quality of life, days with severe symptoms, immunological endpoints, and safety parameters were all improved in the SLIT-tablet compared with placebo group. SLIT safety has been already proven in many DB-PC-RCTs and real-life settings. In accordance with all of the above mentioned, the goals for future trials and studies are the development of comprehensive guidelines for clinical practice on immunotherapy, embracing all the different potential participants. The importance of allergen immunotherapy is of special relevance in the pediatric age, when the plasticity and modulability of the immune system are maximal, and when preventative effects can be reasonably expected.
Keywords: allergen immunotherapy; children; asthma; allergic rhinitis

INTRODUCTION AND HISTORICAL BACKGROUND TO SUBLINGUAL IMMUNOTHERAPY

The first data concerning allergen immunotherapy (AIT) dates back to the beginning of the 20th century when Freemen and Noon were the first to use allergen extracts for desensitizing patients [1, 2]. Although the first clinical trials of allergen-specific sublingual immunotherapy to pollen date back to the 1920s [3], it was not used until the 1970s when interest in the mucosal route was re-examined by a group of German investigators who showed the clinical efficacy of sublingual allergen specific immunotherapy (SLIT) in comparison with subcutaneous allergen specific immunotherapy (SCIT) [4]. The next step in SLIT evolution was revealed by Scadding's and Brostoff's [5] double-blind placebo-controlled trial (DB-PCT) on SLIT efficacy [5]. At the same time, a group of Italian allergists investigated the sublingual manner of allergen administration in order to make this kind of therapy more available [6]. Early papers with sublingual allergen immunotherapy demonstrated positive results, and in 1993 the European Academy of Allergy and Clinical Immunology was the first official organization to recognize that sublingual administration could be a "promising route" for allergic desensitization [7, 8]. A few years later, SLIT safety in adults and children (age >5) was shown [9, 10]. Based on eight DB-PCTs on clinical efficacy of SLIT drops, the World Health Organization recommended in 1998 that this therapy can be considered to be "a viable alternative to the injection route in adults" [11]. A recent Cochrane review analyzing symptoms and/or medication scores proved the efficacy of SLIT in 49 randomized control trials (RCTs) with 4,589 children and adults affected by allergic rhinitis (AR) (with or without asthma or conjunctivitis), compared with placebo [12].

The main goal of this review article is to present insight into the most up-to-date understanding of the clinical efficacy and safety of immunotherapy in the treatment of pediatric patients with allergic rhinitis and asthma. A literature review was performed on PubMed up until 2015 using MeSH terms "asthma," "allergic

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rhinitis," "children," "immune therapy." Additional articles were identified by a manual search of the list of references in the initial search.

EPIDEMIOLOGY OF ASTHMA AND RHINITIS IN SERBIA

The list of articles analyzing the prevalence and epidemiology of childhood atopic diseases, mainly asthma, dermatitis, and rhinitis, is extremely long and extensive. The numbers varied from too low to too high mainly due to a great heterogeneity in the methodological and statistical background. However, the International Study of Asthma and Allergies Phase Three has valuable influence, involving 98 countries worldwide and 236 Phase Three Centers – in other words, it encompasses around 1,059,053 children of two age groups from 236 centers in 98 countries [13, 14]. The prevalence rate of allergic rhinitis, asthma, and eczema in Serbia has been investigated as a part of the International Study of Asthma and Allergies Phase Three. The survey was conducted in five regional centers with different geographical and urban characteristics. Around 14,000 children were enrolled, aged six to seven years and 13–14 years. Prevalence rate of asthma has been 6.59% in the six to seven years age group, and 5.36% in the 13–14 years age group. Prevalence of allergic rhinitis has been 7.17% in six to seven years age group, and 14.89% in the 13–14 years age group. In total, we found asthma in 5.91%, rhinitis in 11.46%, and eczema in 14.27% of the children [15].

CLINICAL EFFICACY

Evaluating data from DB-PC-RCTs, the clinical efficacy (assessed as the reduction of symptom score and the need of rescue medicament) of SLIT for allergic rhinitis and allergic asthma has been confirmed in various meta-analyses (Tables 1 and 2) [12, 16–19].

However, significant clinical and methodological heterogeneity was shown among studies and some issues are still a matter of debate. Recently, a study by Nelson et al. [20], in addition to confirming clinical efficacy of SLIT in reducing nasal and ocular symptoms and the use of rescue medications, also observed no differences in clinical efficacy in mono- and poly-sensitized patients. The effect of disease modification of an SQ-standardized grass SLIT-tablet two years after three years of treatment has been shown in a randomized trial in patients with moderate-to-severe grass pollen induced rhinoconjunctivitis. Outcomes such as rhinoconjunctivitis score and medication scores, combined scores, quality of life, days with severe symptoms, immunological endpoints, and safety parameters were all improved in the SLIT-tablet, compared with placebo group [21]. Results from a 15-year-long prospective study by Marogna et al. [22] show that long-lasting effects of SLIT are in direct correlation with the treatment's duration. Analyzing 59 adult patients on SLIT, the authors concluded that four years of SLIT treatment is optimal to achieve long lasting effects. Duration of five years or more adds only non-additional benefits [22]. The SLIT approach in very young children has raised skepticism concerning the use of soluble allergen drops in an age group that cannot sufficiently hold sublingual allergen long enough under the tongue to deliver allergens to mucosal immune cells [23]. The current study might provide evidence that preventive SLIT over a treatment period of one to two years would deliver enough allergen as to mediate immunologic changes [24]. Nevertheless, optimizing allergen dosing and treatment duration for the use of preventive immunotherapy (sublingual or subcutaneous) in very young children is one of the main questions to be solved. Overall, the current pilot study underlines that the approach of immunomodulation by preventive allergen-specific immunotherapy in early infancy is feasible, and larger studies should delineate more details of optimal application modalities [25]. Literature data showed that SLIT can prevent the development of new sensitization, comparing with the standard pharmacotherapy, even six years after cessation of the treatment [26]. A study of sublingual immunotherapy done by Malling et al. [27] showed that the allergen used for immunotherapy is historically the predominant cause of symptoms, the beneficial effect of SLIT in polysensitized

Table 1. Comparison between SLIT studies

Symptom scores	Reference	Study population	Studies (N)	Active participants (n)	Placebo (n)	Heterogeneity (I^2)
Rhinitis	Wilson D, 2003	Adults and children	21	484	475	73%
Rhinitis	Penagos M, 2006	Children	10	245	239	81%
Rhinitis	Radulović S, 2011	Adults and children	49	2,333	2,256	81%
Asthma	Calamita Z, 2006	Adults and children	9	150	153	64%
Asthma	Penagos M, 2008	Children	9	232	209	94%

Heterogeneity (I^2) = 0–40%: might not be significant; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity

Table 2. Medication score

Medication scores	Reference	Study population	Studies (N)	Active participants (n)	Placebo (n)	Heterogeneity (I^2)
Rhinitis	Wilson D, 2003	Adults and children	17	405	398	44%
Rhinitis	Penagos M, 2006	Children	7	141	138	86%
Rhinitis	Radulović S, 2011	Adults and children	38	1,737	1,642	50%
Asthma	Calamita Z, 2006	Adults and children	6	132	122	92%
Asthma	Penagos M, 2008	Children	7	192	174	95%

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participants is similar to that observed for monosensitized patients. This is of importance particularly in patients with respiratory allergies [27].

In the pediatric age range, allergic diseases represent a special problem, with specific aspects, that include their possible evolution (allergic march) [28–30], the problems related to the long-term pharmacotherapy [31], the compliance (which is in charge of caregivers), and the objective difficulties in correctly deliver inhaled drugs. In addition, the quality of life of the children themselves and of their parents (drug treatment, emergency unit visits, impaired school performance and absenteeism), is usually affected [32, 33].

On the other side, quality of life in children with asthma revealed poor score only for physical activities in children, while very poor score for parents and very high level of anxiety related to their children's asthma [34].

Many clinical trials and meta-analyses have convincingly demonstrated that AIT is effective in reducing symptoms and drug consumption, with a consequent improvement of the overall quality of life [35].

CLINICAL INDICATIONS

Recommendations from various allergy organizations to minimize risk and improve efficacy suggest the following considerations for initiating immunotherapy: 1) demonstrating the presence of IgE-mediated disease – atopic constitution in early childhood; 2) documentation that specific sensitivity is involved in symptoms – positive *in vivo* tests on aeroallergens and *in vitro* tests minimum class three on aeroallergens; 3) documentation of the severity and duration of symptoms of allergic rhinitis and asthma [7]. The first dose should be taken in the presence of a doctor (observation period of 30–60 minutes). In this way, patients are reassured about the safety of SLIT, their follow-up can be organized, and compliance structured. SLIT drops or tablets are recommended to be taken usually for three years as continuous treatment during the year or pre- and co-seasonal treatment.

SAFETY OF SLIT IN ALLERGIC CHILDREN

SLIT safety has been already proven in many DB-PC-RCTs and real-life settings [36].

Life-threatening and non-life-threatening severe systemic adverse events (SAEs) related to SLIT for allergic asthma, allergic rhinitis, or allergic rhino-conjunctivitis involving pediatric population are very rare even in DB-PC-RCTs. The prevalence of SAE was lower than 20%, whereas the prevalence of severe SAEs was between 1% and 2%, with only one study reported epinephrine use [37–39]. In real-life settings, most of the systemic reactions reported by post-marketing surveys were mild and resolved spontaneously without any treatment [40–45]. Potential risk factors for systemic adverse reactions are still confusing. Concerning the vaccine-related risk factors, the most relevant are the use of non-standardized extracts, administration of products containing a mixture of many allergens, and overdosing [46]. On the other side, cardiovascular diseases and long-term therapy with non-cardio selective beta-blockers, as well as uncontrolled asthma, oral lesions, and infections can be marked as potential triggers of SAEs related to the patient [47, 48].

The most common SLIT-related local adverse events include oropharyngeal signs and symptoms and gastrointestinal reactions with great variability of their prevalence, rated between 50% and 85% [49, 50, 51].

ORAL TOLERANCE

The immunological effects of SCIT have already been described in a great number of studies. Nevertheless, the questions on SLIT immune modulatory effects are strongly debated. It is well known that SLIT affects both humoral and cell-mediated immune responses. Concerning the allergen specific IgG4, it is proven that SLIT increases its level, although this effect is less intensive comparing with SCIT. The most important immunological effects of SLIT are reduction in mucosal infiltration by effector cells (neutrophils and eosinophils), increase in allergen-specific IL-10 production, and modulation in Th1 and Treg activity in the oral mucosa. The oral mucosa is described as a site of natural immune tolerance induction. Antigen presenting cells (APCs) in the oral mucosa were suggested to be the main actors for the modulation of IL-10 and TGF-β-secreting Tregs observed following sublingual immunotherapy. After allergen uptake by specialized APCs in the oral mucosa, they migrate to regional lymph nodes. These professional APCs are characterized by the expression of high levels of MHCclass I and II, costimulatory molecules such as CD40, CD80, CD86, and high levels of the IgE receptor FcεRI. As mentioned before, these cells are able to release IL-10 in a TLR4-dependent manner and induce T-cells with a regulatory phenotype *in vitro*, after contact with allergen [52, 53].

FUTURE PERSPECTIVES

Despite a great amount of DB-PC-RCTs and meta-analyses, there are no official guidelines on clinical practice on SLIT. In real life, detailed investigations (that have to be performed before the decision on immunotherapy) in children of preschool age are difficult due to poor cooperation of a child and its parents. Secondly, the lack of information and standardized protocols on allergen-specific immunotherapy among pediatricians, allergologists, and all relevant subspecialties make this situation even more complicated. As there is great interest for this kind of treatment, European Academy of Allergy and Clinical Immunology has launched a new project on Guidelines for Clinical Practice on Allergen-Specific Immunotherapy. The main goals for future trials and studies are the development of comprehensive guidelines for clinical practice on immunotherapy, embracing all the different potential

participants (i.e. clinicians, immunologists, GPs, allergen technologists, industry research department representatives, regulatory bodies, allied health representatives, and patient organizations) [54].

CONCLUSION

Subcutaneous immunotherapy (SCIT), which remained the only administration route for several decades, is effective and safe when properly prescribed and administered, but remote risk of severe side effects is present. For this reason, the international guidelines consider the age below five years a relative contraindication to SCIT. In contrast, SLIT seems to be safe and is presently considered as a viable alternative option for traditional subcutaneous route. In addition to the safety profile, SLIT is also convenient because no injection is needed and it can be managed at home. Recently, a number of studies proved the efficacy of simplified schedule (short build-up and once daily dosing) which have been introduced in order to make the SLIT even acceptable.

All of the above mentioned – proven clinical efficacy in a great number of studies in pediatric population, better safety profile comparing with SCIT (with the possibility of using it in children below the age of five years), disease modifying capability with the possibility of having the long-term effects – implicate that if we want to consider modern approach to allergic diseases, we have to take AIT into consideration. These facts take on special relevance in the pediatric age, when the plasticity and modulability of the immune system are maximal, and when preventative effects can be reasonably expected.

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Актуелни проблеми у сублингвалној алерген-специфичној имунотерапији код деце са астмом и алергијским ринитисом

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КРАТАК САДРЖАЈ

Године 1993. Европско удружење алерголога и клиничких имунолога препознало је сублингвални пут примене алрегена као „обећавајући" у процесу десензибилизације на алергене. Неколико година касније Светска здравствена организација (СЗО) препоручује овај вид терапије као „алтернативу" инјекционом путу примене алергена код адултних пацијената. Прва метаанализа показује ефикасност сублингвалне алерген-специфичне имунотерапије (СЛИТ) код пацијената са алергијским ринитисом, док је једна друга студија потврдила да СЛИТ може успешно да превенира развој астме код деце и одраслих са алергијским ринитисом. Главни циљ овог ревијалног рада је да презентује најновија знања и ставове на тему клиничке ефикасности и сигурности имунотерапије у лечењу педијатријских пацијената са алергијским ринитисом и астмом. Истраживање је извршено претрагом радова у базама *MEDLINE* и *PubMed* у периоду од 1990. до 2015. године користећи кључне речи астма, алергијски ринитис, деца и алерген-специфична имунотерапија. Већ од педијатријског узраста АИТ има посебно место у дечјем узрасту када су пластицитет и способност модулације имунског система максимални и када је оправдано очекивати значајан превентивни ефекат. Анализирајући резулате двоструко слепо плацебо контролисаних рандомизираних клиничких студија (на основу смањења симптом скора и употребе спасоносних лекова), ефикасност СЛИТ-а је показана у великом броју метаанализа. Резулати као што су риноконјунктивитис скор, лек скор, симптом-лек скор, квалитет живота, број дана са тешким симптомима, имонолочки параметри, сигурносни профил били су значајно бољи у групи пацијената који су били на сублингвалној алерген-специфичној имунотерапији у односу на пацијенте који су били на плацебу. Сигурност СЛИТ-а је показана у бројним двоструко слепо плацебо контролисаним студијама и *real life* студијама. У складу са свим претходно поменутим, главни циљеви будућих истраживања треба да се фокусирају на развој јасних водича за клиничку примену сублингвалне алерген-специфичне имунотерпије, укључујући знања и потенцијале различитих специјалиста. Алерген-специфична имунотерапија у педијатријском узрасту је нарочито важна зато што је пластицитет и модулабитет имунског система тада највећи, као и очекивани превентивни ефекти ове терапије.

Кључне речи: алерген-специфична имунотерапија; деца; астма; алергијски ринитис

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