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Clinical Implications and Facts About Allergic Rhinitis (AR) in Children

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1. Introduction

The upper airways symptoms in childhood are the most frequent reasons that make children and their parents to seek the doctor's help. The truth is that the symptoms occur as viral infections of the upper airways specially in preschool age children. Up to 30% of preschool age children with acute upper airway problems will suffer at least one wheezing episode, which brings them to the pediatrician for treatment. (Asher et al., 2006) It means that for the first 6 years of life every 3rd child will be treated by bronchodilators, antibiotics or even anti-inflammatory therapy such as corticosteroids.

However, data from hundreds of papers and from our experience as well, shows that it is "normal and expected for a healthy child". What is not expected is more than 3 wheezing episodes in early life that coexists with numerous upper airways diseases. (Lemanske et al., 2005) Children with such a history should be observed more carefully and if the symptoms gradually get worse, should be referred to a specialist for further investigations. (Sigurs et al. 2000; Sigurs et al., 2005) Frequently, these children are atopic with the family history of atopy or some comorbid condition that may confirm the allergic background, even if the skin prick tests on aeroallergens remains negative. (Ng Man Kwong et al., 2001) Usually, child with recurrent wheezing episodes will be suspected of having childhood asthma and successfully treated by antiasthma drugs (inhaled corticosteroids and/or leukotriens antagonists) not taking into account her/his recurrent or chronic upper airways problems. Despite the lack of severe asthma symptoms in these patients, they still suffer from blocked, congested upper airways, runny, itchy nose and eyes, reactive cough and mild wheezy episodes particularly during the physical activities. This is the scenario that we are facing in our everyday practice and this is the reason for involving the investigation and subsequent treatment of the upper airways problem in our work. We cannot expect to solve the childhood asthma problem completely if the allergic rhinitis persists.

2. Quality of life and allergic rhinitis (AR) in childhood

Although it is frequently seen as a mild and intermittent AR is capable of changing and disturbing the quality of life of the children, as well as their well-being, learning and physical activity. Apparently, the severity, and not necessarily the duration of the AR, has a more relevant effect on the quality of life of the patients with AR, with main consequences on sleep quality and learning ability. (Juniper et al., 1999) The impact that AR severity had on quality of life-sleep, activities of daily living and school performance was more significant than was the duration of the disease. (Craig et al., 2004) More than 80% of the patients with more severe forms reported impairment in their activities due to the disease, compared with only 40% of those with mild forms. Disease-specific questionnaires are the instruments most widely used in order to "measure the quality of life". In the case of allergic rhinoconjunctivitis, the disease-specific questionnaire most commonly used is the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). (Nascimento Silva et al., 2001; Santos et al., 2006) It is fundamental to highlight that AR-related physical, psychological and social impairments are experienced not only by adults but also by children and adolescents. Although adolescents experience problems similar to those of the adults, they present greater difficulty in concentrating, particularly on their school work. Younger children, however, present a slightly different profile: they feel unhappy and unsatisfied, however, they tend to experience less limitation in their activities of daily living and do not exhibit the emotional disturbance experienced by adults and adolescents. Our experience in assessment of quality of life of children with AR alone or associated with asthma, basically shows disturbances in physical domen specially during the pollen season in children suffering from hay fever. (Cerovic et al., 2009) It was shown by other authors that quality of life (QOL) in individuals with perennial chronic rhinitis was worse in relation to persons with mild to moderate asthma. (Bousquet 2008a, 1994b, 1994c) Our results on quality of life in children with asthma revealed bad score only for physical activities in children while very bad score for parents and very high level of anxiety related to their children's asthma. (Cerovic et al., 2009) Our survey didn't divide patients with asthma and allergic rhinitis from patients with only one condition, and definitely children are less susceptible to QOL disturbances independently of their real condition. However, untreated and undertreated symptoms of allergic rhinitis in children, definitely impair overall quality of life mainly due to persistent nasal congestion and subsequent feeling of fatigue, headache, cognitive impairment and school problems. (Walker et al., 2007) Nasal congestion has been defined as the most troublesome condition since it may affect negatively sleep time, resulting in reduced daytime activities and particularly sports involvement that is the most important and popular among children and adolescents. (Sundberg et al., 2007; Broide 2007) Occasionally, recurrent upper airways diseases and clearly allergic rhinitis are the conditions that precede or progress to asthma, while in the other cases these are the causes of worsening of already existing asthma symptoms. Both conditions lead to continuous usage of drugs, from symptomatic once (decongestive medications, antitussive drugs) to evidence-based antiallergic, antiasthmatic drugs. Even more, in children with or without obvious signs of complications (otitis media, bronchitis, pneumonia) antibiotics are frequently advised in every respiratory episode. Overtreatment of these children exists in all cases of children hospitalized due to an acute severe bronchiolitis in the first 12 months of age or hospitalized due to repeated acute asthmatic attacks. (Rodić et al., 2006; Radić et al., 2009) So far, not only

usual predictive or risk factors for developing asthma should be taken into consideration. We suggest the hypothesis that individuals with the early life upper airways problem similar to so called "common cold symptoms", should attract our attention for earlier and better investigations in terms of proper diagnosis and treatment as early as possible. Basically, the possibility of developing asthma after 6 years of age after having allergic rhinitis from 3rd to 6th year of life, has been estimated at about 30% in children (not administered allergen specific hyposensitization). (Meltzer 2005; Martinez et al., 1995) In real life, detailed investigations (that have to be performed before the decision on immunotherapy) in children of preschool ages are difficult due to weak cooperation of a child and parents as well. Secondly, the lack of information and standardized protocols on allergen specific immunotherapy (ASIT) among pediatricians, allergologists and all relevant subspecialties make this situation even more complicated.

Our aim is to present some numbers on prevalence of allergic rhinitis in childhood and some considerations about ASIT in children. Long-term benefits have also been seen with the use of immunotherapy, although some patients, especially children, resist the injections used in subcutaneous immunotherapy. Recent studies with sublingual immunotherapy have indicated that it might be an effective and well-tolerated alternative to immunotherapy injections.

3. Epidemiology of allergic rhinitis in children

Reference list of the articles dealing with the prevalence and epidemiology of childhood atopic diseases, mainly asthma, dermatitis and rhinitis, is extremely long and extended. The numbers from thousands of surveys varied from too low to too high, rarely can rely on approved methodological and statistical background and cannot deserve enough attention for valid conclusions. However, the International Study of Asthma and Allergies (ISAAC) Phase Three has valuable power involving 98 countries worldwide and 236 Phase Three Centers, in other words around 1 059 053 children of 2 age groups from 236 centres in 98 countries.(Ait-Khaled et al., 2009) (Obviously, this multicentric, multiethnic, multicultural study present "a new and greatly enlarged world map of symptom prevalence". The average prevalence of current symptoms of allergic rhinoconjunctivitis across all centres was 14.6% for the 13- to 14-year old children. However, extensive variation in the prevalence of diagnosis of allergic rhinitis within regions, countries and centres was observed (values range from 1% in India to 45.1% in Paraguay). The highest regional prevalence rates of current rhinoconjunctivitis were observed in Africa (18.0%) and Latin America (17.3%) and the lowest in Northern and Eastern Europe (9.2%). In each region, there were major differences in prevalence between countries. Variation in the prevalence of severe rhinoconjunctivitis symptoms was also observed between regions (range 0.4% in Western Europe to 2.1% in Africa), and between countries within regions. The prevalence of severe rhinoconjunctivitis symptoms was generally the highest (more than 1%) in centres from middle and low income countries. These are important and valuable observations that socio-economic impact of the country and regions have been related to the severity of the AR. In the 13- to 14-year age group, the prevalence of current AR was substantially lower in centres in low income countries compared with those in high income countries. From the other hand, centres in low income countries had an increased prevalence of severe AR related to the centres in high income countries. (Ait-Khaled et al., 2009)

These results are sufficient for conclusion that economic burden of allergic rhinitis worldwide is enormous and directly related to high morbidity in countries with poor health resources.

The prevalence rate of allergic rhinitis, asthma and eczema in Serbia has been investigated as a part of the ISAAC phase 3. The survey was conducted in five regional centers with different geographical and urban characteristics. Around 14000 children were enrolled, aged 6- to 7-year and 13- to 14- years. Prevalence rate of asthma has been 6,59% in 6- to 7- year group and 5,36% in 13- to 14- year group respectively. Prevalence of allergic rhinitis has been 7,17% in 6- to 7- year age group while 14,89% in the 13- to 14- year age group. We found statistically significant difference between groups. Prevalence of eczema has been 14,04% in younger and 14,45% in older children. When counted prevalence rate in total we found asthma in 5,91%, rhinitis in 11,46% and eczema in 14,27%. From the whole number of children around 40% presented repeatedly for upper airway problems, 26% presented at least once with symptoms of upper and lower airways simultaneously and 11% more than 4 times for the both conditions for the last 12 months. It means that expenses only for their acute episodes highly cross over the expected annual budget for outpatients clinics. In addition, AR is commonly associated with other respiratory diseases, and the cost resulting from these comorbidities increases even more the socioeconomic impact of the disease. (Zivkovic et al., 2010) Not less important conclusion that we made has been that prevalence rate has been higher in urban than rural areas except in certain villages near by large air-pollutants (power stations and chemical industry). This is the conclusion that leads us to multifactorial origin of the rhinitis in childhood and particularly for the youngest ages seems to be difficult to distinguish allergic from nonallergic rhinitis.

Our special clinical interest was association of allergic rhinitis in children and wheezing episodes or asthma. The majority of children suffer from both conditions from the early childhood. From the infancy they experience waterish nasal discharge or congestion all over the year, frequently unrelated to day care respiratory infections. Later in childhood they present with wheezing episodes, cough or asthma that deserve more attention and investigations. (Brand et al., 2008; Zivkovic et al., 2009) Usually, the allergic background of the nasal symptoms has been revealed many years after their occurrence. From our study it is evident that delay in diagnosis of asthma is around 4,5 years and of allergic rhinitis more than 5,7 years. (Zivkovic Z et al., 2009) Analysing the course of allergic symptoms of upper and lower airways we found allergic rhinitis frequently associated with pollen allergy, long-term usage of medication, unsatisfaction of patient and parents and deterioration of quality of life. The important effort in the literature was made in assessment of allergic inflammation in children with comorbid conditions in regard of treatment of clinically silent forms or inappropriate response on therapy. (Pijnenburg et al., 2005; Arnal et al., 1997) We measured exhaled NO in children with asthma and allergic rhinitis, 6 to 16 years of life, in September – December 2009. (Zivkovic et al., 2009) Clearly, the higher was fraction of exhaled NO, the more symptoms allergic rhinitis we detected in children as well as higher levels of nasal eosinophils. In conclusion, we stated importance of follow up of a child with asthma and AR through the seasons are mostly valuable since atopic conditions are developing in terms of season or years. (Zivkovic et al., 2008) What is the main result of our studies and clinical surveys? The AR in children is an early life presenting problem, recurrent or persistent during the early childhood, frequently associated with the lower airway diseases, over treated or maltreated, and finally completely confusing and disturbing

in terms of quality of life of children and their families. So far, the various aspects of treatments might be successful but over time they become bothersome and hardly acceptable for young persons and adolescents. Obviously, we are looking for efficient, easy to use and inexpensive treatment, but it is probably not possible. (Mçsges et al., 2007) Therefore, we were searching through the literature and clinical practice for the benefits of the allergen specific immunotherapy, particularly sublingual immunotherapy (SLIT) as the causative way of treatment and would like to present in the other part some of our findings and comments.

SLIT is widely known as an effective treatment for children requiring immunotherapy who normally prefer oral administration compared to subcutaneous therapy. (Mahr et al., 2007; Canonica et al., 2003) Concerns and dilemmas still remain in relation to the optimal dose and treatment protocol . In addition, there are no standardized code for administration of SLIT therapy. Studies are underway to evaluate an FDA-approved product for SLIT. Hopefully these studies will assist clinicians in clarifying the role of SLIT therapy in the management of AR. (Cox et al., 2006; Hankin et al., 2010)

There are many studies on clinical effectiveness of sublingual immunotherapy and we would like to point out one of the meta-analyses. Meta-analysis of SLIT for AR in children 4–18 years of age involved 10 trials and 484 subjects. The results of this meta-analyses showed that SLIT was significantly more effective than placebo, by improving AR symptom scores and usage of rescue medication. Related to the possible, mainly local side effects it seems that SLIT is better tolerated than subcutaneous route of administration of allergen specific immunotherapy. Despite many clinical studies confirming the clinical efficacy there are still unmet needs for SLIT in children : the optimal dose and dosing frequency of allergen administration, time of administration of SLIT in patients unresponsive to pharmacotherapy, duration of SLIT, long-term efficacy, preventive capacity, other allergic processes beyond respiratory allergy, usage of SLIT in children in preschool ages etc. (Moingeon et al., 2006; Penagos et al., 2008)

4. More about immunotherapy and sublingual immunotherapy in children

The first data concerning immunotherapy dated from the beginning of 19th century. The main aim of the immunotherapy was to redirect inappropriate immunological response in atopic patients. It has proven to be efficacious to treat type I allergies to a variety of allergens. (Pichler et al., 2001; Moller et al., 2002) Since Food Drug Agency (FDA) reported more seriously adverse reaction post subcutaneous immunotherapy new routes of administration (sublingual and intranasal) have been widely considered. (Canonica et al., 2003) After more than 500 million doses of SLIT administered to humans SLIT is proven to be much safer than subcutaneous immunotherapy (SCIT), with no evidence of anaphylactic shock recorded. (Wilson et al., 2003; Frew et al., 2001; Agostinis et al., 2005; et al., 2002) SLIT was firstly accepted as a viable alternative to SCIT in the World Health Organization (WHO) position paper, published in 1998, and then included in the ARIA guidelines. (Sub-Lingual Immunotherapy World Allergy Organization Position Paper 2009) The main targets for using SLIT are patients of all ages with good correlation between clinical symptoms of allergy and positive allergen specific IgE. Monosenzitized patients are the best candidates for SLIT. Recent studies have investigated using SLIT for the patients with food allergy, latex allergy, atopic dermatitis and allergy on insect venoms. (Sub-Lingual Immunotherapy World Allergy Organization Position Paper 2009) SLIT is also a good choice for patients

uncontrolled with optimal pharmacotherapy (SCUAD), patients in whom pharmacotherapy induces undesirable side effects, patients refusing injections, patients who do not want to be on constant or long-term pharmacotherapy. (Sub-Lingual Immunotherapy World Allergy Organization Position Paper, 2009).

Allergens using in SLIT persist in tablets and drops forms. (Casale , 2004) The most frequent schedule for using SLIT considers induction (build up) and retention phases. The best time for starting SLIT is 4/5 months before pollen season. (Allergy and Immunology Society of Serbia and Montenegro, Position Paper, 2005).

Optimal allergen extracts dose is a dose which is sufficient for improving clinical symptoms in a great number of patients without adverse reaction. (Moingeon et al., 2006). Despite excellent clinical experience in using SLIT the exact immunological mechanism is still undefined. The central paradigm for successful immunotherapy has been to reorient the pattern of allergen-specific T-cell responses in atopic patients from a Th2 to Th1 profile.

There is currently a growing interest in eliciting regulatory T cells, capable of down regulating both Th1 and Th2 responses through the production of interleukin (IL)-10 and/or transforming growth factor (TGF)-β. SLIT induces three categories of immunological changes: modulation of allergen-specific antibody responses; reduction in recruitment and activation of proinflammatory cells and changes in the pattern of allergen specific T-cell responses.

5. Modulation of allergen-specific antibody responses

SLIT was shown to increase allergen-specific IgG4 levels compared with placebo, with a more limited impact on specific IgE responses. A decrease in the IgE/IgG4 ratio has been observed in a number of SLIT studies (Bahceciler et al., 2005), with some exceptions. (Rolinck-Werninghaus et al., 2005).

A meta analysis of six SLIT studies with detailed analysis of antibody responses concluded on a consistent increase in allergen-specific IgG4 levels. (Torres Lima et al., 2002) Such changes in the IgE/IgG4 ratio were found to correlate with a decrease in the late-phase skin reaction to the allergen and with the overall clinical efficacy of the vaccine in some studies (Torres Lima et al., 2002). In a recent phase I/II trial with grass pollen tablets, SLIT was shown to elicit allergen-specific seric IgAs in a dose-dependent fashion (Malling et al., 2005) and a small up regulation of IgA responses was also observed when SLIT was used in house dust mite allergic patients. Altogether, allergen-specific IgG (and IgA) antibodies induced by immunotherapy are thought to contribute to the positive clinical response through distinct and nonexclusive mechanisms: these antibodies can compete with IgEs for binding to the allergen, thereby preventing both basophil or mastocyte deregulation (Mothes et al., 2003; Niederberger et al., 2004), as well as allergen capture and presentation to T lymphocytes by FcεRI+ and CD23+ antigen-presenting cells (APCs). and such antibodies may act as blocking antibodies by engaging low-affinity Fc receptors for immunoglobulins (e.g. FcγRII) expressed by B lymphocytes, basophils, or mast cells. FcγRII receptors contain immunoreceptor tyrosine-based inhibitory motifs (ITIM), they transduce, as a consequence, negative signals preventing cellular activation and release of soluble pro-inflammatory mediators following co-aggregation with FcεRI receptors. (Wachholz et al., 2003; Flicker et al., 2003) SLIT prevented the recruitment of eosinophils in the eyes or in the nose after allergen challenge. (Marcucci et al., 2001; Marcucci et al., 2003; Silvestri et al., 2002) SLIT with grass pollen extracts was shown to decrease local or systemic levels of eosinophil cationic protein (ECP), without any increase in tryptase. (Marcucci et al., 2001).

Changes in the pattern of allergen specific T-cell responses. Recent studies focused on the impact of SLIT on CD4+ T cells responses. It is well known that allergic patients usually mount strong allergen-specific Th2 cells immune response, characterized by the secretion of high amounts of interleukin IL-4, IL-5 and IL-13 cytokines.

(El Biaze et al., 2003). Concerning that a central goal for immunotherapy has been to reorient allergen specific T-cell responses in atopic patients from a Th2 to Th1 profile [the latter being rather associated with the production of interferon (IFN)-γ and IL-12cytokines]. (Laaksonen et al., 2003; et al., Gabrielsson et al., 2001; et al., 2001; Faith et al., 2003; Oldfield et al., 2002;) Comparing with SCIT there is a less evidence on the impact of SLIT on T-cell responses. In several studies conducted in children or adults with seasonal allergic rhinoconjunctivitis to grass pollen, no significant effect of SLIT on T-cell functions (i.e. cytokine production, proliferation) was observed. (Rolinck-Werninghaus et al., 2005; Torres Lima et al., 2002) SLIT does not induce any detectable changes in the numbers of dendritic cells (DCs) nor T lymphocytes in the epithelium or lamina propria of the oral mucosa. Immunization through the sublingual route was nevertheless shown in other studies to decrease the production of the Th2 cytokine IL-13 and the proliferation of peripheral blood mononuclear cells (PBMCs) from patients allergic to house dust mite. (Ippoliti et al., 2003; Fenoglio et al., 2005) As of today, there is still no firm evidence that SLIT can induce regulatory T cells. A preliminary study suggests that SLIT increases IL-10 production in PBMCs from house dust mite (HDM) allergic patients following in vitro stimulation with Dermatophagoides farinae antigens, but also with recall antigens (e.g. Candida albicans) or PHA, when compared with untreated allergic patients. (Ciprandi et al. 2005) The fact that some IL-10-secreting T cells are not allergen-specific raises the possibility of a bystander immunosuppressive effect of SLIT. Of note, high-dose SLIT regimens with ovalbumin in mice induce specific T cells producing TGF-β in the spleen of sensitized animals.

6. Regulatory T cells and allergy vaccines

Although both anergy and T-cell depletion are known to contribute to the establishment of peripheral tolerance against environmental antigens, it is now broadly admitted that antigen-specific T-cell populations with suppressive/regulatory function play a key role in controlling immune responses to both self- and nonself-antigens. (Blaser et al., 2004; Umetsu et al., 2003; Jonuleit et al., 2003; Hawrylowicz et al.,2005) These cells, termed regulatory T cells, are heterogeneous, and include both: (i) naturally occurring CD4+CD25+ T cells and (ii) cells induced in the periphery following antigen exposure (e.g. Tr1 cells, Th3 cells, and CD8+ regulatory T cells). There is a growing evidence supporting the role of regulatory T cells in controlling the development of asthma and allergic disease in a variety of models , although it is not clear yet which of the various regulatory T cell subsets are the most important in this regard. (Taylor et al., 2004) A revised version of the hygiene hypothesis proposes that a limited exposure to infectious pathogens during infancy, most particularly telluric mycobacteria and parasites, may prevent the establishment of not only a Th1, but also a T reg repertoire, thereby explaining in part the observed increase in prevalence of allergies in developed countries. (Yazdanbakhsh et al., 2002)

Several studies documented an association between atopy and a defect in T reg functions. For example, children born with a dysfunctional Fox p3 gene presented with a deficit in CD4+CD25+ regulatory T cells, develop severe autoimmune diseases often associated with eczema, elevated IgE levels, eosinophilia and food allergy [the polyendocrinopathy,

enteropathy, and X-linked inheritance (IPEX) syndrome]. (Gambineri et al., 2003) Moreover, for at least some atopic subjects with active disease, the suppressive activity of CD4+CD25+ regulatory T cells is significantly decreased in vitro when compared with nonatopic individuals, potentially explaining the loss of tolerance against allergens. (Ling et al., 2004) Studies showed that DCs from children with allergic rhinitis can be impaired in their capacity to produce IL-10. (Grindebacke et al., 2004) Interestingly, allergen-specific IL-10-secreting Tr1 cells are highly represented in healthy individuals in comparison with allergen-specific IL-4-secreting Th2 cells, suggesting that regulatory T cells are predominant during natural immune responses to environmental allergens in nonatopic donors. (Gentile et al., 2004; Akdis et al., 2004) Regulatory T lymphocytes can control an established allergic response via distinct mechanisms: IL-10 and TGF-β decrease IgE production and enhance IgG4 and IgA production, respectively. Both cytokines lower the release of proinflammatory mediators by downregulating IgE-dependent activation of basophils and mast cells and by decreasing survival and activation of eosinophils. IL-10 and TGF-β also inhibit the production of Th2 cytokines such as IL-4 and IL-5. (Akdis et al., 2004;, Blaser et al., 2004; Akdis et al., 2001) In addition, regulatory T cells exhibit a direct inhibitory effect on Th1 and Th2 T cells, through cell–cell contact, or by decreasing the antigen presenting function of DCs. Regulatory T cells producing IL-10 and/or TGF-b are induced not only in atopic patients by successful immunotherapy, but also during natural allergen exposure in healthy people. As per the hygiene hypothesis, limited exposure to bacteria and parasites in developed countries may result in a poor establishment of a T reg repertoire during childhood, thereby contributing to an increase in the frequency of allergies. Regulatory T cells can control and regulate all effectors mechanisms activated during allergy and Th2 responses through the production of IL-10/TGF- β and/or cell–cell contact. IL-10 is a potent suppressor of total and allergen-specific IgEs, whereas it induces an antibody isotype switch towards IgG4. TGF-β also decreases IgE production and induces immunoglobulin isotype switch towards IgA. IL-10 and TGF- β act directly or indirectly on human airways to decrease both mucus production and airway hyper-reactivity.

7. Oral mucosa and immune responses

7.1 SLIT and induction of peripheral tolerance

Sublingual immunotherapy takes advantage of an important physiological mechanism (i.e. oral tolerance), which has been evolutionarily conserved to ensure immune tolerance to various antigenic stimuli from the environment, especially from food and commensal bacteria. During SLIT, as for immunization at any mucosal surface, the allergen is captured locally (i.e. within the oral mucosa) by Langerhans-like DCs following either phagocytosis, macropinocytosis or receptor-mediated endocytosis. Subsequent to allergen capture, DCs mature and migrate to proximal draining lymph nodes (e.g. submaxillary, superficial cervical and internal jugular), as a consequence of changes in expression of surface receptors (e.g. the CCR7 chemokine receptor) involved in adhesion and trafficking. Those lymph nodes represent specialized microenvironments favoring the induction of mucosal tolerance through the production of blocking IgG antibodies (IgG2b in mice) and the induction of T lymphocytes with suppressive function. (Van Helvoort et al., 2004) Importantly, the magnitude of CD4+ T-cell responses elicited within lymph nodes is directly proportional to the number of allergen carrying DCs that migrate to lymph nodes, which clearly represents a limiting step. (Martin-Fotecha et al., 2003) Eventually, as a consequence of the circulation

of allergen-specific activated effector T cells throughout the body and the persistence of memory cells, a local (i.e. sublingual) administration of the allergen during desensitization results in both systemic and mucosal protective immune responses. Dendritic cells in the sublingual mucosa exhibit morphological characteristics of Langerhans cells, including the presence of intracytoplasmic Birbeck granules. (Allam et al., 2003) Interestingly, Langerhans-like cells from the oral mucosa constitutively express both low- (CD23) and high- (FCeRI) affinity receptors for IgEs, which may facilitate IgE-mediated allergen capture in atopic individuals. (Allam et al., 2003) Perhaps, more importantly, upon engagement of such IgE receptors, oral Langerhans-like cells produce IL-10, TGFb and up regulate indoleamine 2-dioxygenase (IDO), a rate-limiting enzyme-metabolizing tryptophan, thereby resulting in a decrease in T-cell proliferation. (Allam et al., 2003; Von Bubnoff et al., 2004) As discussed above, there is still no formal evidence of Treg induction via the sublingual route. Nevertheless, on the basis of its aforementioned characteristics, the immune system in the oral mucosa appears prone to induce active tolerance mechanisms against allergens and antigens from the environment. Consistent with this, there is preliminary evidence that SLIT elicits IL-10-producing T cells in humans (Ciprandi et al., 2005) and antigen-specific TGF-b+ T cells in murine. (Moingeon, et al., 2004).

8. Clinical efficacy

Usually clinical efficacy of SLIT is measured by the Rhinoconjunctivitis Total Symptom Score (RTSS), which included the 6 most common symptoms of pollinosis (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes). A score ranging from 0 to 3, according to the Center for Drug Evaluation and Research guidance (April 2000), was used for each individual symptom: 0/5 no symptoms, 1/5 mild symptoms (symptoms clearly present, but minimal awareness; easily tolerated), 2/5 moderate symptoms (definite awareness of bothersome but tolerable symptoms), and 3/5 severe symptoms (symptoms hard to tolerate and/or cause interference with activities of daily living and/or sleeping).

From approximately a month before and during the pollen season, patients completed a daily diary card to score nasal and ocular symptoms using the RTSS. The average RTSS was calculated during the entire pollen season. In addition, the effect of immunotherapy on the 6 individual symptom scores (sneezing, runny nose, itchy nose, nasal congestion,watery eyes, and itchy eyes) was analyzed as secondary outcomes. The proportion of symptom-free days (%) during the pollen season was also assessed. A symptom-free day was a day on which"0/ 5 absent" was recorded for each of the 6 individual rhinoconjunctivitis symptoms. Allergen specific immunotherapy (ASIT) is very important in pediatric population. It has been shown to have possibility to change natural course of allergic diseases and to prevent new sensibilisation. ASIT is the only therapeutic method with causal effects in children population. Sublingual route of allergen administration is very comfortable, simple and non-traumatic especially for children.

The first evidence of the effect of SLIT in children came from an 18-month study of 2 different doses of SLIT for tree-pollen allergy in 88 children suffering seasonal allergic rhinitis, confirmed by skin prick test, specific serum IgE, and conjunctival allergen challenge. Eighteen months of SLIT with tree pollen extract provided dose-dependent benefits in terms of significantly reduced symptoms and medication use.(Valovirta E et al., 2006) Two adequately powered, well-designed double blind placebo controlled (DBPC)

randomized controlled trial (RCTs) have now been published, both showing a clear effect of allergen tablets in childhood. A statistically significant reduction in rhinitis symptoms (28%) and medication (64%) score was shown during the pollen season in 114 children receiving active grass allergen tablets (with 15g Phl p 5) compared with 120 children in the placebo group.(Wahn U et al., 2009). The other DBPC/RCT evaluated the efficacy of 5-grass tablets (with 25g group 5 major allergen) administered pre- and coseasonally to 227 children with seasonal allergic rhino-conjunctivitis. In those receiving the 5-grass tablets a significant improvement was found in symptom and medication scores.(Roder E et al., 2007) All these studies, clearly show the efficacy of SLIT in reducing the symptom score during pollen season in children with rhinitis; furthermore, there were also a significant reduction in medication use. The allergens that have been used with success in SLIT in the pediatric age group for rhinitis are pollen from *Phleum pratense*, 5-grass mix, *Parietaria* and *Betulaceae* pollens and HDM. SLIT with olive pollen showed only improvement in symptoms and one grass study was negative.(Bufe A et al. 2004)

23 DBPC studies in the period of 1990-2002. documented clinical efficacy of SLIT. Pediatric population was involved in 16 of those studies. SLIT has been shown to reduce bronchial hyperreactivity, symptoms and medication scores in adolescents population treated with SLIT containing extracts of grass pollen. (Robinson et al., 2004)

9. Safety in children

The sublingual route was introduced with the aim of reducing side effects and increasing the safety of immunotherapy. Recent studies showed that there is no difference in the incidence of adverse events (AE) between children and adults (Passalacqua G, et al., 2007) and SLIT has been shown to be safe. The most frequently reported AEs (mostly self-limiting) are local in the oral mucosa (itching and swelling) and of the digestive system. Just a few cases were considered moderate/severe requiring medical intervention. Experience must be gained in the use of single versus multiple-allergens. SLIT with a single allergen is the most common practice in Europe whereas multiple allergens are used mainly in USA, Latin America and some other parts of the world. In adults, in one study, use of SLIT with multiple allergens was reported to be as safe as SLIT with a single allergen.(Agostinis F et al., 2008)

It is also very important to mention that there are three studies, 2 observational and one postmarketing survey, specifically designed to assess the safety of SLIT in young children. A total of 231 children younger than 5-years-old, who were treated with various pollen and mite allergens (33 patients received allergoid) were included.(Agostini et al, 2005; Fiocchi A,et al. , 2005; Rienzo VD et al. , 2005) AEs were reported in 5 to 15% of patients in a total of 68,975 doses with rates of 0.268, 0.766, and 1.767 AEs per 1,000 doses in the 3 studies. Most reactions appeared to be mild or moderate and resolved without treatment. Dose reduction by changing from a sublingual-swallow to a sublingual-spit method controlled gastrointestinal reactions in one study. One further RCT with HDM SLIT in 138 children aged 2–5 years with asthma or rhinitis showed only mild to moderate local AEs. (Rodriguez-Santos O. Et al., 2008)

10. Our clinical experience

In our practice, we have started using the allergen specific immunotherapy in children more than 10 years ago, however, more frequently for the last 4 to 5 years. Number of children on SLIT is 37, but 31 successfully followed the protocol. The data about the patients, their outcomes and clinical results are about to be analyzed in another article. The youngest child

on SLIT is 7 years old, and the upper age limit doesn't exist. The adolescent patients started at 17 years of age continue the treatment after their pediatric ages. Patients sensitized with Dermatophagoides pteronyssinus are the most frequent cases for SLIT, slightly less frequent is the group of patients sensitized with ragweed pollen (Ambrosia elatior or Artemisia). Predominantly, current symptoms are allergic rhinitis, allergic rhinoconjuncitivitis (hay fever), and 70% of all patients claimed asthma symptoms in the early childhood. At the moment of inclusion to a group for SLIT, asthmatic symptoms were mild or absent. Couple of patients stopped the SLIT from their own reasons, and 2 of the patients had to follow protocol with reduced maintenance doses due to the adverse reactions (sneezing, coughing, tickling of the throat). The final results and outcomes will be announced and published elsewhere, but we have sufficient data to state: good clinical efficacy, lack of hay fever symptoms or diminishing the symptoms after 3 years of therapeutic regime, satisfaction with collaboration and treatment adherence, valuable improvement of patients and their families' quality of life. (Z. Zivkovic: personal communication)

11. Acknowledgment

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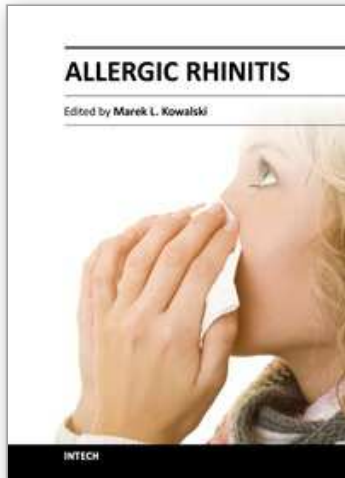
Allergic Rhinitis

Edited by Prof. Marek Kowalski

Allergic rhinitis, while troublesome for a patient, may be also a challenge for the physician. That is why physicians must still learn more on the pathophysiology, clinical spectrum and novel diagnostic and therapeutic approaches to the disease. The chapters of this volume address a variety of important topics related to allergic rhinitis. They begin with a description of innovative translational approaches allowing for unification of animal and human models. Contributing authors provide up-to-date reviews of clinical aspects of allergic rhinitis in children, its association with bronchial asthma and other co-morbid conditions. They also discuss the impact of allergic rhinitis on sleep and sports. Together with articles on diagnostic approaches as well as novel treatments, the book offers a comprehensive and stimulating review of the topic. May this book find a wide readership among allergists and other physicians interested in allergic disease, and also among pediatricians, general practitioners and other specialists who increasingly have to deal with this seemingly benign, but sometimes extremely troublesome, disease.

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