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Current Issues on Immunotherapy in Children

Ivana Djuric-Filipovic, Snezana Zivanovic,
Gordana Kostić, Djordje Filipovic,
Marco Caminti and Zorica Zivkovic

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Abstract

Therapy of allergic diseases in children implicates avoidance of allergens, standard pharmacotherapy, and immunotherapy. Immunotherapy is the only treatment for allergic diseases with the ability to change the natural course of the disease, thus stopping its further progression as well as the development of new allergic diseases and new sensibilizations. The objective of this chapter is to give insight into the latest data on immunotherapy in treating children with allergic diseases. Methods: The study involved a search for relevant articles on the MEDLINE and PubMed up to 2017. Results: Numerous studies have shown that the sublingual application of allergen-specific immunotherapy is adequate, safe, and efficient in the therapy of immunoglobulin E (IgE)-mediated allergic diseases of the respiratory tract in children, but there are still some questions to be solved concerning the usage of SLIT in children younger than 5 years old, SLIT for polysensitized patients, duration of SLIT, long-lasting effects of SLIT. Conclusions: In order to improve the clinical efficacy of SLIT, we are looking for new routes of administration, new allergens, new protocols as well as combination of SLIT with other immune modulatory treatments.

Keywords: allergen immunotherapy, children, asthma, allergic rhinitis

1. Introduction

1.1. Epidemiology of asthma and rhinitis

With a global prevalence of 6.9% (ranging from 3.8 in Asia-Pacific and Northern and Eastern Europe to 11.3% in North America), asthma is one of the most common chronic diseases in children, adolescent, and adults [1]. 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 study included around 14,000 from 5 regional centers different geographical and urban characteristics (children both from urban and rural areas participated). Investigators analyzed the prevalence of allergic diseases in two age groups (the first one preschool children aged 6–7 years old and the second one children between the age of 13–14 years old). The prevalence of asthma was 6.59% in younger age group, whereas the prevalence in older age group was around 5.36%. Note that 7.17% of preschool children and 14.89% of school children were diagnosed allergic rhinitis. Overall, asthma prevalence was 5.91%, rhinitis 11.46%, and eczema 14.27% [2]. The growing worldwide burden of allergic diseases is properly defined as the “allergy epidemic.” The German epidemiological Multicenter Allergy Study (MAS) suggested an age-related evolution of atopic and allergic diseases, usually named “atopic march.” In fact, on epidemiological bases, infantile eczema and food allergy usually precede the onset of allergic airway disease (rhinitis and asthma). It is also interesting to point out that unlike other common chronic diseases such as diabetes mellitus or hypertension, it is well established that the development of allergic diseases start just after birth or according to some authors maybe earlier in prenatal period [3]. The incidence of asthma is the highest in preschool and early school age with an improvement in symptoms and a decrease in prevalence afterwards, but with one more pic in incidence in adolescents’ period especially in female teenagers mainly due to hormone disturbance. It is well known that allergic diseases are multi factorial which means that in their pathophysiology both genetic and environmental factors are included. Atopic family history is one of the most important risk factors for the development of asthma. MAS cohort study analyzed the main risk factors for persistent asthma/wheeze in an early adolescent’s period. According to the results from this huge study wheezing before the age of 3 as well as wheezing after the age of 6, accompanied with early atopic dermatitis, positive family history of atopic diseases and positive allergy tests, particular to perennial allergens represent the main risk factors [4, 5].

Although according to birth cohort studies data we are aware that genetic burden has an important influence in allergies development and despite lots of efforts, we have still failed to identify responsible genes. Many factors in the environment contribute to the development of allergies (e.g., diet, immunizations, antibiotics, pets, and tobacco smoke), but we do not know how to modify the environment to reduce the risks [6]. According to several epidemiological studies, a decline in microbial diversity was proposed to have an important role in allergic epidemic, best summarized in hygiene hypothesis, and nowadays defined as “biodiversity hypothesis.” Identification of prenatal and early postnatal risk factors is of a great importance for early prevention and successful intervention. Two recent studies showed that reduce food diversity in early childhood can be associated with atopic sensitization and allergic diseases later on. It is also suggested that high “antigen burden” in early life can be a protective factor necessary to “educate” the immune system and to prevent childhood allergic diseases. Early allergy prevention that includes: administrations of probiotics to pregnant mothers and to high-risk children, oral or intranasal extracts, and earlier introduction of foods is still matter of a debate due to conflicting results [7, 8]. Despite many different options are currently available for the diagnostic workup and management, the burden of allergic airway

diseases still represents a major health problem in childhood. It is a very well known that allergic diseases are multifactorial in terms that both genetic and environmental and risk factors are involved in its pathogenesis. Taking about different endo- or phenotype is very common when we analyze these diseases. Looking for a better quality of life (QOL) and disease of overall morbidity and mortality rate seek further investigation on every single individual risk factor that can have even the smallest impact on the disease development. Searching for a new and more individualized treatment for allergic diseases most of current research is focusing on the identification of biological and clinical predictive markers of allergy and asthma onset [9].

2. Diagnostic tools and monitoring

Despite many different diagnostic tools for allergic disease it still remains a challenge especially in infants and toddlers. Skin tests represent an important diagnostic tool in workup of many allergic diseases. These tests are mainly used for the diagnosis of inhalant allergies, but nowadays there are more and more tendencies to use this kind of tests for allergies to food, venom, occupational agents, and drugs. Skin prick tests (SPTs) and intradermal tests still represent the cornerstone of the diagnosis of IgE-mediated (type I) allergies. They are easy to perform, cheap and allow a fast reading, usually performed in outpatient clinics. Performing skin prick tests needs a specific training, especially for intradermal and epicutaneous tests with nonstandard allergens, that are not usually performed in children population. Special precautions that have to be considered before performing skin prick tests include the usage of some drugs, skin conditions and in adolescents and adults pregnancy. Before performing *in vivo* skin prick tests patients are not allowed to take drugs such as antihistamines at least several days because it is well known that these kinds of drugs could mask positive results of type I reactions, on the other side conditions like pressure urticaria or dermatographism are able to provoke false positive results. For that reason using positive control histamine and negative control saline solution are crucial for results interpretations. Skin prick tests (SPT) are one of the most important diagnostic tools in asthma and AR diagnosis with sensitization to inhalant allergens. They can get prompt information on sensitization to inhalant allergens such as pollen, house dust mites, pets, to a lesser extent molds. Recommendation for SPTs is available with more or less variation in many climate and geographical areas. As they are very cheap and easy to perform SPTs are of a great importance especially in undeveloped or developing countries. Here, it is also interesting to mention that in tropical areas standard SPTs battery should include typical tropical allergens such as *Blomia tropicalis*. In southeastern and Western Europe standard allergens for performing SPTs usually include following allergen solutions: tree, ragweed, and grass pollen, house dust mite, molds, cockroach, dogs, and cats dander. Before starting allergen-specific immunotherapy SPTs have to be performed [10–14]. Nasal and bronchial provocation test are indicated for patients with typical clinical symptoms and signs of allergic rhinitis and/or asthma but with negative *in vivo* skin prick tests [15]. Those tests should be performed

exclusively by a well-trained staff at the allergy departments. They are very important for distinguishing allergic and nonallergic rhinitis as well as for the diagnosis of local allergic rhinitis (LAR)—typical clinical history of allergic rhinitis with positive nasal provocation test, usually with elevated eosinophils in nasal smear, but with negative skin prick or/and *in vitro* allergy tests [16]. *In vitro* allergy tests are cornerstone of allergy diagnostic especially in the pediatric population. All children with positive clinical history of allergic diseases (atopic dermatitis, allergic rhinitis, and/or asthma) should be evaluated, particularly those with positive uni- or bilateral family history of atopic diseases. Determinations of total IgE, followed with evaluation of the allergen-specific antibody levels are precede the introduction of allergen-specific immunotherapy. It is also a very important to be mentioned that the interpretation of the allergy tests should be strictly done in the light of clinical history of a certain patients. Novel diagnostic tools are also capable to determine sensitization to a specific pure or recombinant allergens that is of a great importance for individualized treatment approach. Sometimes this kind of tests are the most relevant to confirm the diagnosis of allergy sensitization. To data, the most commonly used system to determine allergen-specific IgE is the ImmunoCAP system that are considered as a goal standard for *in vitro* diagnosis of allergen condition. Despite great technological improvements in *in vitro* diagnostics of allergies, several problems still remain. Although elevated IgE is a marker of IgE-mediated allergy, this is not sufficient for the induction of symptoms. According to the data, more than 20% of patients with elevated IgE are in fact asymptomatic. Elevated serum IgE level is irrelevant as long as it does not bind to Fcε receptors on effectors cells (mastocytes, eosinophils, and basophils). Positive allergen-specific IgE in serum is not sufficient to confirm allergy in all cases [17–19]. At the current state of art it is a very important to be a little bit septic about allergy diagnostic test results only based on determination of allergen-specific serum IgE levels and to consider clinical history, accompanied by adequate skin prick tests or provocation tests, which drive the diagnosis before considering allergen-specific immunotherapy inclusion. During the last decades, there has been a huge improvement in *in vitro* allergy diagnosis due to novel approaches that include molecular components. It has been already mentioned that allergen-specific tests are not enough sensitive and specific for allergy diagnosis, through the advent of molecular technology, some weaknesses, and shortcomings of classical approach that used only natural extracts could be solved. Component resolved diagnosis (CRD) of the specific IgE response provides more individual approach in diagnosis of allergic patients and better selection of patients for allergen-specific immunotherapy. It is also of a great value for monitoring of the efficacy, immunogenicity and safety of allergen-specific immunotherapy [20, 21]. Cellular allergy testing represents one more *in vitro* allergy diagnostic tool. It expands the tools of allergist to diagnose and monitor allergic diseases. The basophil activation test (BAT) is the most common used cellular allergy tests in routine clinical practice and in research. That test is able to document type I sensitization to a specific allergen, as fraction of blood basophils activated by soluble allergen. Basophil sensitivity can be used for identification the main sensitizer among cross-reacting allergens or allergen preparation as well as for monitoring progress of allergen-specific immunotherapy and anti-IgE therapy [22–24].

3. Biomarkers and prediction

Determination of a certain biomarkers that are known to be important in pathophysiology of allergic diseases can be a very useful in primary prevention, early intervention and disease course modification [25]. Currently reliable tools that can adequately predict which children will develop asthma are still lacking [26]. Nowadays identification and determination of biomarkers in diagnosis of allergic diseases represent an important step toward better understanding of a great number of different endotypes. Biomarkers are also very important for increasing drug effectiveness through a more individualized therapeutic approach. Discovering novel biomarkers or combining them with the existing one and better understanding of different asthma endo- and phenotypes are important goals in allergy research improving both allergy diagnosis and treatment [27–29]. Fractional exhaled nitric oxide FeNO is considered a very good biomarker of eosinophilic inflammation of lower airways. Many data showed that FeNO is a reliable predictor of corticosteroids responsiveness [30]. The results from the most recent studies indicated that allergen-specific immunotherapy has also an impact on the decrease of eosinophilic airway inflammation [31]. Periostin is a downstream molecule of interleukin (IL)-4 and/or IL-13 has been recently marked as a surrogate biomarker of type 2 inflammation and tissue remodeling in bronchial asthma. It has been shown that serum periostin can predict the efficacy of anti-IL-13 antibody (lebrikizumab) and anti-IgE antibody (omalizumab). Sputum eosinophils are useful for estimating the efficacy of anti-IL-5 antibody (mepolizumab) [32, 33].

4. Therapy of allergic airway disease in childhood

Although there are numerous studies, management of allergic disease is still a matter of a debate. According to the data management of allergic diseases, consider avoidance of the risk factors, treatment, and induction of tolerance. In that light the management of allergic diseases depends on how easy is to avoid the triggers, whether there are multiple triggers and how easy is to induce tolerance. The possibility to avoid certain allergen mainly depends on the nature of that allergen. For ubiquitous allergens such as house dust mites or pollens it is usually impossible to avoid, unlike for animal dander [34]. There are also some studies suggest that food allergen avoidance in pregnancy, lactation, and infancy have preventive role in the development of food allergy, and possibly other allergic diseases. The only current recommendations to prevent allergic disease are exclusive breastfeeding at least 4–6 months and if breastfeeding is insufficient or not possible, hypoallergenic formula for the high-risk infants [35–37]. The most common approach used in allergic diseases treatment is symptomatic therapy in step management strategies. Pharmacologic therapy is tailored to the primary symptom or symptoms and to the severity of symptoms without modifies the long-term outcome of allergy. The optimal utilization of pharmacologic therapies varies among regions and countries and varying preference of therapies in different populations [38, 39]. According

to the clinical data, more targeted therapies include monoclonal antibodies against IgE and against various proallergic cytokines (e.g., anti-IL-5, anti-IL-13, and anti-IgE). Although expensive, these therapies are useful in the management of selected patients who are usually unresponsiveness to standard pharmacological treatment [40].

5. History of sublingual allergen-specific immunotherapy

Although all story of immunotherapy seems to be a new one, the first routes of immunotherapy dates back to 1911 when two English researchers used water solution of hay fever pollen extracts for treating hypersensitized patients. They noticed that hypodermal inoculation of specific allergen could have some benefit. Without a sound knowledge of basic and clinical immunology immunotherapy was pure empiric, not so widely used treatment for decades [41, 42]. The second very important step in the history of sublingual immunotherapy was the findings of a group of German researchers who showed that sublingual route of allergen-specific immunotherapy could be equally clinical effective as subcutaneous route [4, 43]. They performed a small double-blind placebo control crossover trail. The maximum subcutaneous tolerated dose of a house dust mite (HDM) extract was given sublingual as drops three times daily [44]. They showed an improvement in symptoms and improvement in nasal inspiratory peak flow. A few years later Scadding's and Brostoff proved a clinical efficacy of low dose sublingual immunotherapy in patients with allergic rhinitis sensitized to house dust mites in a double-blind placebo-controlled trial (DB-PCT) [45] whereas Italian allergist were the first one who showed clinical efficacy of SLIT for patients with allergic rhinitis and/or asthma sensitized also to house dust mites. Those study included both adults and children population [46]. In early 1990s, the first commercial available sublingual immune drops were developed. Since the introduction of sublingual immune drops, the scientific community has been seeking for improvement. When evaluating the findings from clinical trials with sublingual immunotherapy drops, it became clear that this therapy was more likely to be effective when administered once daily and higher doses. Moreover, pharmacokinetic studies of SLIT showed that only a very small proportion of liquid extracts was taken up into superficial layer of sublingual mucosa. Searching for a way to augment local allergen uptake sublingual rapidly dissolving tablets were developed. These tablets facilitated the delivery of high concentration of allergen in a small volume. This concept led to the clinical and commercial development of high-dose sublingual AIT using fast-dissolving tablets [47]. 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. Two studies from 1999 to 2001 showed a satisfied safety profile of sublingual route for both children and adults [48–51]. From 1998, the World Health Organization recommended SLIT as an "a viable alternative to the injection route in adults" [52]. Wilson Cochrane review from 2003 analyzed 49 randomized control trials (RCTs) with 4589 children and adults affected by allergic rhinitis (with or without asthma or conjunctivitis)

and proved clinical efficacy of SLIT over placebo [53]. To date, over 70 double-blind, placebo-controlled trials and several meta-analyses of sublingual allergy immunotherapy drops have been reported. It is important to note that many trials with SLIT drops or tablets were small and/or had an open label design. Over the last 10 years, however, several adequately designed and powered trials have been conducted with grass pollen, as well as with *Dermatophagoides pteronyssinus* (DP) in both adults and children, and have demonstrated efficacy and safety with this therapeutic approach [10, 54].

6. Clinical efficacy of SLIT still matter of a debate

Although a great number of various meta-analyses and DB-PC-RCTs have showed clinical efficacy of SLIT in children population diagnosed allergic rhinitis and/or asthma [55], due to significant clinical and methodological heterogeneity, some issues are still a matter of debate. One of the main issues to be solved is long-term efficacy, particularly after cessation of the treatment. Results from several European clinical trials in pediatric and adult patients with grass pollen-induced rhinoconjunctivitis have shown that grass AIT reduces daily rhinoconjunctivitis symptom scores compared with patients receiving only symptomatic medications. The proportion of days with minimal or no symptoms increase in patients on SLIT. The same study also showed the improvement of quality of life in children on SLIT. The beneficial effects were observed for three consecutive years of treatment as well as during the first year following cessation period, indicating a disease modifying effect and persistence of efficacy despite discontinuation of therapy [56–60]. Due to the fact that majority of atopic patients are poly sensitized, one of the most important issues to be answered is SLIT efficacy in those patients. Recent study confirmed 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 [61]. However, the cross-protection against unrelated allergens seems to be limited [62]. Although it passed more than a decade of proven clinical efficacy of SLIT, data of long-lasting effects are still missing. Results from a 15-year-long prospective study by Marogna et al. [63] show that long-lasting effects of SLIT are in direct correlation with the treatment's duration. Some study suggested that 4 years of SLIT may be associated with more favorable effects than 3 years of treatment [64]. As the only immune modulatory treatment for allergic diseases, preventive role of AIT is of a great interest. Some authors are very doubtful concerning the adherence and tolerability of the treatment particularly in the pediatric population [65], whereas the other one claimed that even 1 or 2 years of treatment is sufficient to mediate immunological response [66, 67]. The second important issue on SLIT is long-lasting effects. After a 12 years of follow-up period Eng et al. showed preventive effects of SLIT 6 years after the treatment termination comparing with the standard pharmacotherapy [68]. Although the best candidates for allergen-specific immunotherapy are mono sensitized patients Malling et al. in their study showed that desensibilization with the predominant allergen in polysensitized participants can be similar effective [69]. In the light of preventive effects of immunotherapy and possibility to have impact on further evolution of allergic diseases (atopic march), the opportunity to use this kind of

treatment in very young children is of a great importance, but several issues have to be answered [70–72]. Immunotherapy can overcome problems related to the long-term pharmacotherapy [73], adherence and compliance to the standard treatment. Low-adherence and bad compliance to a long-term pharmacotherapy, both drug (problems with the usage of inhaled drugs) and non/drug-related factors can be overcome with the introduction of immunotherapy. All chronic diseases have an impact on quality of life due to high score of school absenteeism, impaired school performance, frequent emergency unit visits. Children with allergic diseases especially those with asthma showed low physical activity performance [74, 75]. High level of anxiety as well as higher incidence of depression and other physiological disorders can be seen in children and adolescents with asthma, allergic rhinitis and atopic dermatitis. A certain number of studies confirmed the impact of SLIT on all previous mentioned aspects of quality of life [76, 77].

7. Safety and tolerability of SLIT in allergic children

Over the last 20 years, sublingual allergen immunotherapy has gained popularity based on controlled trials that have demonstrated a favorable safety profile [78, 79]. Although a great number of DB-PC-RCT showed clinical efficacy of SCIT since the British Committee on Safety of Medicines in the UK reported 26 SCIT-related anaphylactic deaths between 1957 and 1986, the interest for alternative routes constantly grows. The risk of subcutaneous immunotherapy (SCIT)-related systemic adverse events (SAEs) still represent a major concern that may, sometimes limit the use of this effective treatment, especially in the pediatric population. On the other side the overall safety of SLIT has been widely proven and accepted [80]. Moreover, Nichani study showed that SLIT can be safely administered to patients who previously experienced systemic reactions in response to subcutaneous allergen immunotherapy.

According to double-blind placebo-controlled-randomized clinical trials (DB-PC-RCTs) for allergic asthma, allergic rhinitis or allergic rhinoconjunctivitis [80–84] and real-life studies only several life-threatening and nonlife-threatening severe systemic reaction related to SLIT are reported [50, 85–87]. Overall prevalence of systemic adverse events was lower than 20% in DB-PC-RCT, whereas the prevalence of severe systemic reactions was between 1 and 2% of total recorded events [88–93]. Most commonly postmarketing surveys reported mild to moderate usually self-resolved systemic reactions [94, 95]. A very important issue concerning SLIT particularly in the pediatric population is to define risk factors for developing systemic reactions. Up to now several potential risk factors are defined: inadequate administration conditions (use of non-standardized extracts, administration of products containing a mixture of many allergens, overdosing [92]), and/or patient-related nonspecific risk factors (include cardiovascular diseases and long-term therapy with noncardioselective beta-blockers) that are very uncommon in children [96]. Those conditions are considered as special precaution, but not contraindication for SLIT introduction. On the other side uncontrolled asthma or severe asthma, oral lesion, or acute infections can represent temporary contraindication for SLIT. Although previous systemic reaction due to SCIT were considered as absolute

contraindication for all kinds of immunotherapy, results from recent studies showed that they do not represent risk factors for further usage of other kinds of ASIT including sublingual [96]. Local adverse reactions are most common SLIT-related side effects although it is not very easy to record them as it is not usually including in postmarketing analysis nor in DB-PC-RCT [50, 85–88]. Its prevalence varies from 50 to 80% and they include oropharyngeal and gastro-intestinal reactions such as itching, pruritus, and eczema in oral mucosa and/or diarrhoea, vomitus, and abdominal pain [97–99].

The second issue that is also of a great importance is a matter of tolerability that can have a great impact on overall clinical outcomes [100]. Both systemic and local adverse events may have influence on treatment discontinuation as they are most common after the first administration. In order to improve adherence clinicians should be well educated and trained to recognize local and systemic adverse events and to give also patients adequate explanation how to deal with them, although SLIT has much better safety profile compared with subcutaneous allergen-specific immunotherapy. WAO proposal on grading local adverse events can help to achieve better tolerance and adherence [96].

8. Quality of life studies

According to many DB-PC-RCT, real-life studies and meta-analysis quality of life (QOL) is a very important issue for children and adults with allergic diseases. As it has been already mentioned, their quality of life is not so often satisfied particularly in school-aged period [101]. Standard pharmacotherapy treats only symptoms but not the disease itself, nor the quality of life. Although lots of studies proved clinical efficacy of SLIT, only a small part of them take QOL in consideration. One of them is Ciprandi et al. study [102] that has showed the improvement of QOL in polysensitized patients with AR and/or asthma treated with SLIT. Bousquet et al. study of DB-PC-RCT proved that patients on SLIT had a better QOL compared with the group of patients on placebo [103]. However, the results from the studies are controversial. While Bousquet et al. and Ciprandi et al. showed the improvement of the QOL in SLIT groups, Khinchi et al. found no statistical significant difference in QOL scores among three groups, that is, SLIT, SCIT, and placebo, using a 36-item short-form health survey (SF-36) questionnaire [104].

9. Oral tolerance

The mechanism of action of the allergen-specific immunotherapy is very complicated and still remained unexplained. For an easier understanding of the mechanism of action of ASIT, we divided the immune response to early and late immunological response. In the early phase of immunotherapy (induction phase) there is a decrease in the number of tissue mast cells, eosinophils and basophils followed by a decrease in the release of their cell mediators [105]. Reduction of the number of basophils induced by the oral

regulation of the H2 receptor leads to the inhibition of FcεRI-mediated histamine suppression and other mediators. In the first phase of the immune response, the synthesis of IgG4 and IgA is increased [106]. IgG4 blocks the interaction of IgE and allergens as well as the presentation of allergen to T cells. In the late phase, after one to several months, the immune response from Th2 to Th1 is reoriented, as well as the increase in the number and function of both types of T-regulatory cells (T-reg): natural (nT-reg) and inducible (iT-reg) [107]. iT-reg originated from naive CD4⁺ T lymphocytes and they are the most important source of IL-10, which is an important factor in peripheral tolerance [108, 109], because it inhibits IgE production from one, and on the other hand stimulates IgG4 secretion and in this way directly inhibits the activity of allergen-specific T lymphocytes [110]. The nT-reg cells (CD4⁺, CD25⁺ and FOXP3⁺ (Forkhead box protein 3)) are thymus origin and exhibit synergistic effects with iT-reg cells [111] exposing high levels of IL-10 and TGF-beta [112]. T-reg stimulates the proliferation and differentiation of IL-10-secreting dendritic cells, which have a crucial role in the activation and differentiation of different subtypes of T cells. Reducing the number of cell mastocytes, eosinophils, and basophils, increasing IgG4 and IgA synthesis, re-orientation from Th2 to Th1, increasing the number, and function of IL-10 producing T-reg cells play a significant role in the development of immune tolerance and long-lasting immunotherapy effect on the overall immune function and on the immune response to allergens [113–116].

10. Future perspectives

As it mentioned above clinical efficacy of immunotherapy has been proven in a great number of clinical studies but there are still some issues to be discussed. Recent studies are more focused on the usage of recombinant allergen-based immunotherapy that will possible makes allergy vaccines more safe, convenient, and effective. Recombinant-allergen vaccines also contain defined amounts of the allergen components, and the composition can be tailored according to patient's sensitizations. Both recombinant allergen-diagnostic tests and immunotherapy lead to more personalized and stratified treatment of different allergic entities. Recombinant allergen-based vaccines have been developed and successfully evaluated for several respiratory allergen sources including food allergies [117–120]. The second approach for minimizing side effects and improves compliance is the usage of peptide immunotherapy that has been proven in many studies as effective in treating patients with different respiratory allergies [121]. Data from the studies showed that this kind of immunotherapy is clinical effective for months to years after a short course of treatment. Some studies also investigate new routes of administration such as intralymphatic and epicutaneous. Although it is proven as safe and efficacy, both routes require further clinical investigation [122, 123]. Recently, scientists have exploited the immune system to produce antibodies from single B cell clones, heralding the era of monoclonal antibodies. Biological agents (biologicals or biologics) bring revolution in the treatment of many rheumatic and immunological disorders and are currently being assessed for allergic disorders. Better understanding the endotypes and phenotypes of allergic disease may lead

to specifically targeting the responsible molecular mechanism by a biological. The mechanism of biologicals implies the inhibition of a specific molecule involved in allergic inflammation, without weakening immunity against viruses and bacteria. The design and use of biologicals requires a profound understanding of the mechanisms underlying allergy. Several biologicals are being assessed in clinical trials, including biologicals inhibiting interleukin (IL)-4, IL-5, IL-9, IL-13, and immunoglobulin E, but most of them are still being tested in clinical trials, involving patients with allergic asthma, allergic rhinitis, food allergy, urticaria, atopic eczema, and diseases with high eosinophil counts. It is to be expected that biologicals will replace or reduce the use of the currently prescribed unspecific pharmacotherapy of allergic inflammation. Better understanding of disease endotypes, identification of novel biomarkers, and discovery of novel biologicals are the cornerstones of the modern approach in treating allergic diseases [124–127].

11. Conclusion

According to a great number of clinical studies, allergen-specific immunotherapy in combination with asthma and anti-allergic medication is clinically effective in treating children with respiratory allergies. Respecting the newest data, SLIT can be used not only in children with stable asthma, but also in those with uncontrolled asthma but then in combination with anti-IgE-omalizumab treatment. AIT in children can even bring more benefits. At first, data suggested that SLIT reduced the usage of corticosteroids that can have deep negative impact on child development. The second benefit is the possibility of AIT to change the natural course of allergic diseases in terms of asthma prevention in children with allergic rhinitis. The problem of SLIT, especially in the young population of children and adolescents, is compliance that can be possibly overcome with the introduction of ultra-rush and rush protocols. Investigating the various effects of immunotherapy based on the developmental stage of children and adolescents can help to identify the optimal dose, frequency, treatment duration, and age for starting to treatment. Better selection of well responders based on endotype-driven approach is expected to increase both efficacy and safety.

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Author details

Ivana Djuric-Filipovic^{1*}, Snezana Zivanovic², Gordana Kostić³, Djordje Filipovic⁴, Marco Caminti⁵ and Zorica Zivkovic^{6,7}

*Address all correspondence to: drivanica@yahoo.com

1 Sanofi Pasteur, Vaccine Division of Sanofi Aventis Group, Belgrade, Serbia

2 Faculty of Medicine, University of Nis, Pediatric Internal Diseases Clinic, Clinical Center of Nis, Niš

3 Faculty of Medical Science, University of Kragujevac, Children's Hospital-Clinical Centre Kragujevac, Kragujevac, Serbia

4 Institute for Emergency Medical Care, Belgrade, Serbia

5 Allergy Unit Asthma Center, Verona University Hospital, Verona, Italy

6 Children's Hospital for Lung Diseases and Tuberculosis, Medical Center "Dr Dragiša Mišović," Belgrade, Serbia

7 Faculty of Pharmacy, University Business Academy in Novi Sad, Novi Sad, Serbia

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