Chapter 4

Present and Future of Subcutaneous Aero-Allergen Immunotherapy

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Additional information is available at the end of the chapter

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Abstract

The present review summarizes the literature-acquired knowledge as well as author's own experience in conducting aero-allergen immunotherapy, particularly in subcutaneous route of administration (SCIT) of all modalities of respiratory allergy disease from allergic rhinosinusitis, bronchial asthma to united airway disease. Because of the better adherence resulting in appropriate efficacy in connection with satisfactory safety, the author favours conventional schedules of subcutaneous route of therapeutic intervention. Given the lack of specific biomarker in monitoring treatment course, the main control mechanism of efficacy is the evaluation of quality of life using simple evaluation scale as visual analogue scale or standardized respiratory allergy questionnaires. The future of allergen immunotherapy should be focused on new routes of allergen administration (e.g. oral, epicutaneous, intradermal, intralymphatic) and on the searching potential biomarkers which could be objectively measured and easily accessible from body fluids (blood, nasal secretion, sputum). The combination of estimated biomarkers obtained from biological samples in conjunction with evaluation of quality of life could lead to the generation of the overall satisfactory monitoring protocol.

Keywords: allergen immunotherapy, routes of administration, adjuvants, compliance, future treatment

1. Introduction

Allergic diseases are considered as major global public health issue. Among them, respiratory allergies represent 1 of 10 most common diseases of affluence. At present, IgE sensitization to foreign proteins in the environment is rising up to 40% of the worldwide population, especially in highly industrialized countries [1]. Only in the United States, prevalence of

asthma reported in 2014 was 8.6% (6.3 million) and 7.4% (17.7 million) among children and adults, respectively. Mortality on asthma in 2013 reaches 1.1 deaths per 100,000 of the United States population [2, 3]. At least similar percentage rate could be reported in European countries also. Approximately, one-fifth of the world population suffers from upper respiratory allergies (hay fever, allergic rhinosinusitis).

Prevalence of asthma is still rising in many high as well as low income countries, likewise impact of allergic diseases continue to grow. According to the World Health Organization (WHO), the number of patients having asthma is 300 million, and with the rising trends, it is expected to increase to 400 million, by 2025. Even though in majority of cases respiratory allergies are not life-threatening diseases, it is necessary to say that patients with asthma and/or other respiratory allergies have reduced quality of life [4] which is comparable to moderate chronic coronary ischemia.

Asthma and allergic rhinosinusitis are linked by epidemiological, physiological, and pathological characteristics. The genetic predisposition to develop IgE-mediated sensitivity to common aero-allergens is the strongest predicting factor for the development of both diseases [5]. Facts are supported by the concept of unifying the management of these disorders. The united airway disease (UAD) hypothesis proposes that upper and lower airway disease, both are manifestations of a single inflammatory process within the respiratory tract.

First-line treatment includes avoidance and minimization of exposure when possible. Medication, including antihistamines, bronchodilators, leukotriene inhibitors, and steroids, may be used to reverse some of the symptoms of allergic reactions. Pharmacotherapy alone has no effect on the progression of the disease and treatment has to be administered repeatedly as long as symptoms prevail, which often means life-long [6]. It can be postulated that allergen avoidance and pharmacotherapy alone cannot control the disease. Only allergen immunotherapy has the disease-modifying potential and should be included in the algorithm of optimal therapeutic strategy.

Allergen immunotherapy is a form of parenteral (subcutaneous) or oral (sublingual) medication, designed to prevent or lessen an allergic reaction. Its mechanism of action is based upon the body's production of different antibodies to an antigen depending on how the antigen is introduced into the body. Allergy immunotherapy induces immunological tolerance and changes the course of disease. It is typically used in individuals after a trial of conservative treatment, when avoidance and medications has been found to be inadequate.

In 2000, American College of Allergy, Asthma and Immunology (ACAAI) organized an international conference "Immunotherapy in Allergic Asthma" where key board of the meeting summarized that allergen immunotherapy is an effective treatment for allergic asthma and also it prevents the early onset of asthma in children with allergic rhinitis. These conclusions were subsequently confirmed by The Preventive Allergy Treatment (PAT) study published in February 2002 [7]. The study concluded that pollen immunotherapy significantly reduces the development of asthma in children with seasonal allergic rhinoconjunctivitis, and also methacholine-induced bronchial hyper responsiveness was improved. Allergen immunotherapy can also prevent the development of sensitization to new allergens [8]. Active

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therapy resulted in a statistically significant reduction in rhinitis, conjunctivitis, and bronchial reactivity, showed a reduction in the need for medication, a reduction in bronchial hyperresponsiveness, and improvement in forced expiratory volume in 1 s (FEV1) [9].

Allergen immunotherapy does not cure allergies; immunotherapy aims to make a person less sensitive to allergens. In some cases, allergic symptoms may be controlled to the point of disappearance, allowing a person to avoid allergen reactions. Both forms of allergen immunotherapy (subcutaneous, sublingual) are used for the management of allergic rhinitis, allergic conjunctivitis, and allergic asthma, however, subcutaneous administration route is used for hymenoptera sensitivity only [10].

2. History of allergen immunotherapy

The first known historical remark about perception of immunity is dated to 430 B.C. when Thucydides recorded "recovery from plague-endowed protection from repeated attacks" [11]. Other pre-Christian reference by Plinius described the "principle" of allergen-specific immunotherapy when King Mithridates VI from Pontos (132–163 B.C.) tried to protect himself against poisoning. He had used increased doses of snake venom to make himself immune against the toxin. Plinius did not report the result of such procedure [12].

The real development in immunological treatment started approximately at the end of nineteenth and at the beginning of the twentieth century, but research was mostly orientated on how to protect humans against infective diseases. Parallel with these trends, scientists as Besredka, Pirquet, Dunbar, Holbrock-Curtis experimented with induction of "tolerance" by administration of various sera (hyper immune animal sera, mixtures of various pollens) in animal experiments as well as on treatment of human beings. However, due to significant side-effects of treatment (including one report of death), procedures were discontinued [12].

In the year 2011, worldwide allergy-immunology community celebrated 100 years of allergen immunotherapy, since the first successful use of this form of treatment by Leonard Noon (1878–1913) at St. Mary's Hospital in London in 1911. It is interesting to say that in 1928 in the same hospital one floor above Alexander Fleming discovered penicillin, the first antibiotic which has broad consequences for mankind.

Noon and Cantab published, in 10 June 1911 in Lancet [13], successful desensitization with pollen extract (*Phleum pratense*). In this first use of parental immunotherapy, they administered very low, increasing doses of the pollen extract by intradermal injections at intervals of 3–4 days. Following this therapy, the researchers demonstrated an improvement in hay fever symptoms. They monitored the reactivity of their hay fever patient with conjunctival provocation tests and observed that a single drop of highly diluted grass pollen extract prepared according to Dunbar's method was still sufficient to trigger a conjunctival reaction in sensitive patients. Noon left his work for following hay fever seasons in hands of his colleague and close friend John Freeman, while he knew his advanced tuberculosis would keep him from finishing his work. In February 1913, only 2 years after the discovery, Leonard Noon died from florid pulmonary tuberculosis at the age of only 35 [14].

Noon's immune-pathologic interpretation of possible mechanisms which was strongly influenced by Dunbar's thought was incorrect in claiming that the disease is caused by the exposure to a toxin, present in pollen, which could even induce antitoxin when injected into rabbits or horses. Administering little quantities of pollen extract to patients would actively immunize them [15].

John Freeman (1877–1962) continued in pending work and he had published early results in the same year 1911 [16]. After 3 years of treatment in 1914 (1 year after Noon's death), he summarized their results in the paper "Vaccination against hay fever: report of results during the last three years" in the same medical journal [17].

On the opposite coast of the Atlantic Ocean, the pioneer publication concerning the allergen immunotherapy appeared in 1913. George Cloves reported on the treatment of autumnal hay fever by vaccination with aqueous extract of the pollen of ragweed. He concluded all eight treated cases experienced improvement of general symptoms [18]. In 1915, Robert Cooke, the founding director of one of the first allergy clinics in the United States: "The Institute of Allergy Roosevelt Hospital, New York" published his own experience in Laryngoscope "The treatment of hay fever by active immunization" [19].

In years 1918–1922, Robert Cooke introduced a suggested mechanism of action for allergen injections as a "desensitization or hyposensitization," analogous to tolerance achieved in experimental anaphylaxis induced in animals. This concept suggested that the injections of an increasing amount of allergen or antigen slowly neutralized those antibodies responsible for the allergic reaction [11]. Cooke together with Mary Loveless have introduced the concept of specific blocking antibody: "the development under treatment of a peculiar blocking or inhibiting type of immune body that prevents the action of allergen on the sensitizing antibody" [20]. Twenty years later, Cooke confirmed his assumption that "serum factor" for inhibition was most likely gamma globulin (IgG) in electrophoretic mobility studies in ragweed-treated patients [21].

Next 30 years were strongly influenced by notable socio-economic disturbances as WWI, Wall Street Crash, Great Depression, and WWII. One remarkable publication from that period (1937), which has to be mentioned, was the report about depot allergenic vaccines for delayed absorption: alum adsorption [22]. Aluminum adjuvants function as delivery systems by generating depots that trap antigens/allergen at the injection site, providing slow release in order to continue the stimulation of the immune system (see Chapter 4).

Negative historical conditions slowed down medical and scientific world, so the next important event in the field of allergy was the first DBPC trial of grass pollen subcutaneous immunotherapy published by Alfred Frankland in 1954 in Lancet [23], which proved beyond doubt that subcutaneous immunotherapy was effective. The adequate number of patients (200), the exact description of randomization (four randomization groups), blinding, and of dropouts makes this study even today being rated as of moderately high scientific quality [15]. In 1957 Douglas Johnstone published early results and in 1968 late results of the study which was realized on the same group of paediatric patients. The research was focused on a preventive

and dose–response effect of immunotherapy in terms of bronchial hypersensitivity and development of asthma [24, 25].

At the 1987 meeting of the EAACI on Mallorca, 40 specialists formed a subcommittee on immunotherapy and decided to create some guidelines for indications of allergen immunotherapy, monitoring of effect and side effect, practical information, and requirements for allergen extracts. The new common guidelines would serve for all specialists not only in the European countries, but also on a worldwide basis. So the first position paper was published in 1988 as Supplement of Journal Allergy [26]. New insights into the pathogenesis of allergic diseases and new publications on immunotherapy have called for its revision. Immunotherapy position paper was introduced to public in 1993 [27].

In 1996 in the United States, AAAAI together with ACAAI published practice parameters for allergen immunotherapy [28]. After the great discussion at the level of World Health Organization (WHO) and various allergy, asthma, and immunology societies throughout the world specialists took the decision to prepare common guidelines and in 1998 WHO position paper "Allergen immunotherapy: therapeutic vaccines for allergic diseases" was published [29]. Practice parameters for allergen immunotherapy in the United States were updated in 2007 and 2011 under the principal editor Linda Cox. In the preparation of these updates, the comprehensive search of the literature, information from articles known to the authors were considered. Published clinical studies were rated by category of evidence and used to establish the strength of a clinical recommendation. Published updates represent an evidence-based, broadly accepted consensus opinion [30, 31]. All these clinical guidelines are designed to assist clinicians by providing a framework for the evaluation and treatment of patients and are not intended to replace a clinician's judgment or establish a protocol for all patients [31].

3. Mechanisms of subcutaneous allergen immunotherapy

WHO position paper defines allergen immunotherapy as the administration of gradually increasing quantities of an allergen vaccine to an allergic subject, reaching a dose which is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen [29]. The ultimate goal of the therapy is to induce immune tolerance, a change in the immune response to specific antigens so that discontinuation of the therapy results in sustained long-lasting therapeutic benefits.

Allergen immunotherapy modifies the response to allergen exposure by inducing tolerance, but the mechanisms by which immunotherapy mediates its anti-inflammatory effects remain incompletely defined because of the use of heterogeneous medicaments, treatment protocols, routes of administration, and outcome measures in different studies. However, several common features emerge from the multiple studies show that allergen immunotherapy modifies the responses of antigen-presenting cells, T-cells and B-cells, as well as both the number and the function of effector cells. So allergen immunotherapy regulate regulate the local and systemic allergic inflammation [32].

Successful immunotherapy in respiratory allergy is associated with the immunodeviation of Th2 response to a more protective allergen-specific Th1 cells and with the induction of IL-10-/TGF-β-producing T regulatory cells in blood and also locally in inflamed airways. In subcutaneous route of administration (SCIT), allergen-specific T-cell proliferation has been reduced because of peripheral tolerance mechanisms. Immunoregulatory activity of T regulatory cells has been claimed to be the main mechanism for clinical efficacy of SCIT [33]. Production of IL-10 and TGF-b from an expression of cytotoxic T-lymphocyte-associated protein-4 by T regulatory cells have importance in immune regulation in SCIT.

3.1. Immunological processes

Four groups of immunological processes can be classified during the course of allergen immunotherapy [34]:

3.1.1. Group 1

An initial event is desensitization of FcεRI-bearing mast cells and basophils by allergen. The mechanism of this desensitization is not fully elucidated, although its major role is assigned to a rapid upregulation of the histamine 2 receptor, which is a major suppressor of basophil activation. At the beginning of treatment, decreases in mast cell and basophil activity, degranulation and tendency for systemic anaphylaxis degranulation take place within the first hours. Histamine 2 receptor strongly suppressed FcεRI-induced activation and mediator release of basophils, including histamine and leukotriene sulphides, as well as cytokine production *in vitro* [35].

3.1.2. Group 2

Second group represents generation of allergen-specific T and B regulatory cells and suppression of allergen-specific Th1 and Th2 cells. T regulatory cells are a diverse group of T cells that are active in the regulation of immune responses, and allergen-specific T regulatory cells (CD4+CD25+) have been demonstrated after allergen immunotherapy [36]. T regulatory cells have distinct cytokine profiles other than Th1 and Th2 cells, are characterized by IL-10 and TGF-β secretion capacity, and express suppressor molecules, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) [37].

IL-10 is the leading cytokine, which in T regulatory cell/B cell interaction suppresses specific IgE production. In addition, IL-10 induces specific IgG4 production. IgG4 and probably IgG1 compete with IgE on the surface of mast cells and basophils for allergen binding [37]. They produce interleukin IL-10 and transforming growth factor TGF-β, and have the potential to suppress local Th2 cell responses and redirect antibody class switching in favour of IgG4 (IL10 isotype switch factor), and IgA (TGF-β isotype switch factor) [5].

Allergen-specific IgG4 antibodies interrupt allergen presentation to Th2 cells and, in addition, block allergen-induced activation of mast cells and basophils, thereby significantly weakening the allergic reaction [5]. Although multiple factors contribute, it could be supposed that the tolerant state of specific cells essentially results from increased IL-10 secretion [38]. IL-10

particularly originates from activated and antigen-specific T regulatory and B regulatory cell populations and increases during allergen immunotherapy as well as in natural allergen exposure [39].

3.1.3. Group 3

These processes include regulation of antibody isotypes demonstrating an early increase in specific IgE levels, which later decrease, and an early and continuous increase in specific IgG4 levels. Natural exposure to a relevant allergen is often associated with an increase in IgE synthesis. Similarly, allergen immunotherapy often induces a transient increase IgE levels in serum, followed by a gradual decrease over months or years of continued treatment [40].

Allergen immunotherapy decreases allergen-specific IgE production and promotes allergen-specific IgG4 production, which competes with IgE by blocking the binding of allergens to FcεRI on the surface of mast cells and basophils [41]. IL-10 reduces allergen-specific IgE production through IL-4-induced IgE switching and enhances allergen-specific IgG4 production by inducing IL-4-induced gamma 4 transcript expression [42]. Grass pollen SCIT has reduced seasonal increases in serum allergen-specific IgE, whereas 60- to 80-fold increases in allergen-specific IgG and 100-fold increases in allergen-specific, IgG4 have been observed [43]. Thus, measuring IgG4 levels could be a good indicator of clinical efficacy of AIT during follow-up [44].

Mechanisms of innate immunity are also stimulated during the course of allergen immunotherapy. Human blood dendritic cells from allergic subjects have impaired IFN-α production following toll-like receptor-9 (TLR9) dependent innate immune stimulation. Tversky et al. [45] found out subcutaneous allergen immunotherapy resulting in a fivefold increase in IFN-α production and thus increases dendritic cell TLR9-mediated innate immune function, which is impaired in allergic subjects.

3.1.4. Group 4

The fourth group of events takes place after several months from the beginning of the treatment and these processes are characterized with decreases in tissue mast cells and eosinophils and release of their mediators. The phase is referred as the late-phase response and is localized in the peripheral tissues such as mucous membranes of respiratory organs (nose, bronchi) or in the skin. When comparing immediate reactions mediated by mast cells, last-phase response involves activation of T cells and the recruitment, activation and persistence of eosinophils at sites of allergen exposure. Chronic exposition to inhalant allergens causes immunopathologic changes seen during the late-phase. Mucosal changes are associated with positivity of nasal and bronchial provocation tests and suggest the pathologic conditions of chronic allergic inflammation. Van Bever and Stevens [46] postulated that allergen immunotherapy may resolve and/or reduce the severity of the late-phase reaction in treated children. Rak et al. reported reduction in plasma levels of eosinophil cationic protein, a marker of eosinophil activation, and chemotactic factors for eosinophils and neutrophils correlate with decreased bronchial hyperreactivity and clinical improvement [47]. After grass

pollen allergen immunotherapy decreased eosinophil and mast cell infiltration in nasal and bronchial mucosa correlates with an anti-inflammatory effect [48, 49].

3.2. Involved cells

When describing above mentioned immunological processes, the expected role of many immunological cells can be deduced (**Figure 1**). All these cells are involved in regulatory processes and might contribute to the control of allergen-induced immune responses.

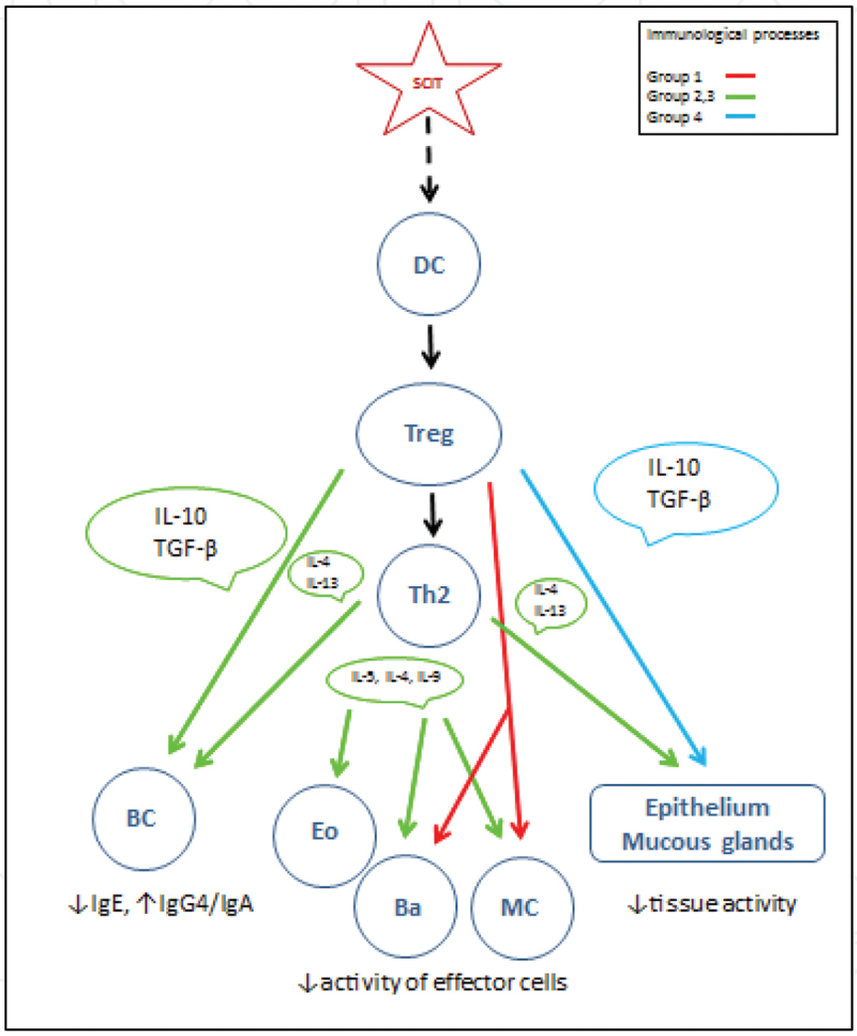

Figure 1. Cells and processes during allergen immunotherapy. DC, dendritic cell; Treg, T regulatory cell; Th2, Th2 cell; BC, B-cell; Eo, eosinophil; Ba, basophil; MC, mast cell; SCIT, subcutaneous allergen immunotherapy.

3.2.1. Antigen presenting cells (APCs)

APCs, particularly DCs, control both peripheral tolerance and immunity through the interpretation of environmental signals that are associated with antigen encounter (such as pathogen-associated molecular patterns). DCs in the airways control the pulmonary immune

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response and determine tolerance and immunity to newly encountered antigens. Several studies support a role for DCs in the induction of T cells with a regulatory phenotype and function, particularly IL-10-secreting T regulatory cells. These T regulatory cells are involved in the inhibition of subsequent inflammatory response as well in protection against sensitization to allergen and development of asthma in a mouse model, so T regulatory cells might be important mediators of the beneficial action of allergen immunotherapy [32].

3.2.2. T cells

Allergen immunotherapy has been shown to modify T-cell responses to allergen in several ways. The main role is in switching Th1/Th2 ratio by increasing the allergen-induced Th1 cytokines to Th2 cytokines [50]. In other way, allergen immunotherapy can induce epitope-specific T-cell anergy, generate allergen-specific T regulatory cells that can suppress the responses of effector T cells following delivery of either whole allergen extracts or synthetic peptides that contain or consist of a T-cell epitope and increase the production of cytokines with regulatory activity [51]. Regulatory T cells also play an important role in controlling allergic inflammation. The transcription factor Foxp3 regulates the development and function of natural and adaptive CD4(+)CD25(+) T regulatory cells. Radulovic et al. detected the presence of local Foxp3(+)CD25(+)CD3(+) cells in the nasal mucosa, their increased numbers after immunotherapy, their association with clinical efficacy and suppression of seasonal allergic inflammation. In conclusion, they supported a putative role for T regulatory cells in the induction of allergen-specific tolerance in human subjects [52].

3.2.3. B cells

It is now generally accepted that peripheral tolerance is essential for a normal immune response and successful immunotherapy of allergic disorders. As seen above, the tolerant state essentially results from increased IL-10 secretion by T regulatory cells. Similar to Th cells, B cells can be classified into subsets according to the cytokines they produce. One functional B-cell subset, B regulatory cells, has recently been shown to contribute to the maintenance of the fine equilibrium required for tolerance. B regulatory cells control excessive inflammatory responses through IL-10, which inhibits proinflammatory cytokines and supports T regulatory cell differentiation [53]. IL-10 not only generates tolerance in T cells, but it also regulates specific isotype formation and skews B cells specific response from an IgE to an IgG4-dominated phenotype. In addition to IgE/IgG4 switching, recent studies have also provided evidence for increases in the amount of TGF-β driven allergen-specific IgA following allergen immunotherapy, indicating that other B cell production (antibody classes) might contribute to clinical efficacy [54].

3.2.4. Effector cells (mast cells, basophils, eosinophils) and indirect influences

Late-phase reaction involves the recruitment, activation, and persistence of eosinophils, mast cells, and activation of T cells at sites of allergen exposure. It is usually associated with increased bronchial and nasal hyper responsiveness and suggests the pathologic conditions present in chronic allergic inflammation. It has been postulated that the effect of allergen

immunotherapy on the late-phase reaction is relevant to its clinical efficacy [46]. After a few months, a decrease in tissue mast cell and eosinophil numbers and release of their mediators is observed, as well as a decrease in the late-phase response. These effects are partially demonstrated in SLIT and are rather weak compared with those seen in SCIT [55].

In addition, allergen immunotherapy exhibits indirect inhibition of Th2 cell-associated phenomena (such as mucus production, and endothelial cell activation and cellular influx) and Th1 cell-associated phenomena (such as epithelial cell activation and apoptosis).

In conclusion, when comparing clinical significance of SCIT and SLIT, due to well-established safety profile, SLIT is considered an alternative to SCIT [55]. However, immunologic mechanisms of SLIT are less well-elucidated than those for SCIT. All potential mechanisms seem to be similar in both forms of allergen immunotherapy—in induction of T-cell tolerance, generation of T regulatory cells, in the role of IL-10 and TGF-β as well as in the late-phase response (decrease the presence of mast cells, eosinophils and release of their mediators). Furthermore, subcutaneous administration in contrast to sublingual immunotherapy modifies the immune response also in very early phase of desensitization, generates B regulatory cells and shows clearly decrease in IgE and increase in blocking IgG4 [34].

4. Aluminium—basic adjuvant in subcutaneous allergen immunotherapy

Mineral adjuvant molecules such as calcium phosphate or aluminium hydroxide are broadly used in human immunization as adjuvants in parenteral route of administration. While aluminium salts are commonly included in vaccines against infectious pathogens with the aim to elicit proinflammatory responses following activation of the inflammasome, in subcutaneous allergen immunotherapy, allergen extracts are adsorbed on aluminium hydroxide or calcium phosphate as adjuvants in Europe, whereas in North America only soluble allergens are used.

Like any vaccines, adjuvants to be associated with allergens are expected to allow simplifying immunization regimens, and reaching efficacy faster and for a longer duration. Mechanisms involved include both a depot effect (slow release of the allergen, formulation of the allergen as particles to target antigen presenting cells) as well as interaction with the innate immune system (activation of the inflammasome) [56].

Although allergy vaccines are usually well-tolerated, an additional expected benefit of adjuvants in this field is to help lowering the allergen dose, thus improving the safety profile with less local reactions to the site of administration. On the other side, none of commercially available noninvasive sublingual products, which are considered as a safe and efficacious alternative, contain any adjuvant. These vaccines are based on high-dose aqueous allergen extracts presented either as drops or more recently as fast dissolving tablets or lyocs [57].

History shows that aluminum salts are being used as adjuvants in allergen immunotherapy for many years. Aluminum is validated as safe adjuvant with few established side effects. Biological potential of aluminum lays on its reactivity not only at injection site, but also

elsewhere in the body. Aluminium hydroxide modifies the immune response to a range of allergens and is generally used in multiple injections over extended time periods. Incidence of adverse events increases more likely in the subsets of individuals predisposed to such reactivity. Susceptibility to adverse events grows with the high body burden of aluminum, in which allergen immunotherapy is the most probable source of the adjuvant molecule. But neither the safety nor the toxicity of aluminum as adjuvant in subcutaneous allergen immunotherapy preparations have been confirmed [58].

Threshold values for foodstuffs established by authorities are regularly exceeded and aluminum compounds are routinely used as adjuvants in vaccinations. A big challenge for pharma industry is to conduct clinical trials which confirm the benefit–risk relationship of long-term use of aluminum as adjuvant in SCIT according to good pharmacovigilance practice. Long-life time of accumulation of aluminum in every individual human body has undoubtedly the potential to exert chronic toxic side effect, such as neurotoxicity. In the literature, one serious disease, a neuromuscular disorder called *macrophagic myofasciitis*, is attributed to the persistence of aluminium salts at injections sites in muscle [59].

However, there is still a lack of studies examining the possible relationship among the development of such diseases, which may have a latency period of many years after the application of SCIT. Predisposing an individual to an unnecessary high body burden of aluminium should be avoided and could reasonably be considered [60]. Adverse events associated with aluminium adjuvants in allergen immunotherapy could be also connected with other more common conditions such as chronic fatigue syndrome or and autoimmune diseases [61]. More common but less critical are local reactions, such as discolouration of skin, urticaria, foreign body granulomas, subcutaneous sarcoidosis, progressive circumscribed sclerosis, subcutaneous nodules, and pseudo-lymphoma. When indicating subcutaneous route of administration, we have to consider aluminium as strong potent adjuvant in stimulating or modifying immunity. However, on the other side, the toxicity, antigenicity, and in a long-term possible body burden of aluminium have to be considered.

The other potent adjuvant used in subcutaneous allergen immunotherapy is calcium phosphate. Many studies have compared the effects and adverse effects of immunologic adjuvants, and in most studies, it was reported that allergen immunotherapy that contained calcium phosphate causes fewer reactions [62]. Nacaroglu et al. reported no association between adjuvant content and the incidence of adverse effects. They also concluded that the frequencies of local and wide local reactions during SCIT were lower than expected, and although systemic reactions were frequently seen, no fatal reaction was observed in the published study. House dust mite SCIT and multiple allergen use increased the risk of reaction [63].

5. Treatment protocols in subcutaneous allergen immunotherapy

Although allergen specific immunotherapy represents the only immune-modifying and curative option available for patients with respiratory allergy, the optimal schedule for specific subcutaneous immunotherapy is still unknown. All injections are given in the doctor's surgery,

because there is a small risk of inducing allergic reactions, which can become severe or even life-threatening if not treated promptly and appropriately. Two major groups of parenteral treatment courses are used in clinical praxis: intermittent (pre-seasonal) or continual (year-long) course.

Intermittent treatment course is considered as pre-seasonal treatment with pollen allergens (trees or grasses). The allergens are prepared by conversion into allergoids by treatment with glutaraldehyde and are adsorbed onto L-tyrosine. The course should be completed before the onset of the tree/grass pollen season. The three graduated doses constitute a complete dose for 1 year and can be followed by the pre-seasonal extension injections with three highest-dose vials for continued clinical improvement. It is recommended that the treatment course should be given in each of 3 successive years [64, 65].

Continuous all-year courses are used in the treatment of allergy to pollens, dust mites, moulds, animal epithelia as well as in the treatment of insect venom allergy (bee/wasp). Duration of such course lasts from 3 to 5 years and the course is divided into a build-up and a maintenance phase. In the initial (build-up) phase, four administration schedules of immunotherapy have been reported: conventional and three accelerated (cluster, rush, and ultra-rush) schedules (**Table 1**). Conventional subcutaneous immunotherapy for allergy treatment needs one injection per week. The duration of the conventional build-up phase varies but typically ranges from 3 to 8 months to reach the maintenance dose. Maintenance treatment continues at constant dosing and in the case of airway allergy, the duration of all treatment should be at least 3 years [66, 67].

	Conventional	**Cluster**	**Rush**	**Ultra-rush**
Time consumption	1 injection/week	2–3 injection/ week	2–3 full days	1 full day (+night)
Build-up phase	14–25 weeks	6 weeks	2–3 days	1 day
Arrangements	Check after 20 min	Check after 30 min	Premedication/2–3 consecutive day stay	Premedication/day stay (or + overnight)

Table 1. Administration schedules of subcutaneous allergen immunotherapy.

Accelerated immunotherapy build-up schedules allow the patient to achieve the benefits of immunotherapy more rapidly, as the maintenance dose is reached sooner. Shorter up-dosing schedules are desired, provide earlier clinical improvement and improved convenience, though they introduce increased risk of adverse reactions. However, many cluster schedules have similar adverse reaction rates to conventional schedules, and premedication significantly decreases side effects. Additionally, there may be cost savings by reduced patient visits and medication requirements [68]. To assess the safety of cluster SCIT, meta-analysis showed that no differences existed in the incidence of either local adverse reaction or systemic adverse reaction between the cluster group and control group. Based on the current limited evidence,

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this meta-analysis could not conclude affirmatively that cluster subcutaneous immunotherapy was a safe and efficacious option for the treatment of patients with allergic rhinitis [69].

It is important to conclude that accelerated build-up schedules have advantages over conventional schedules. They bring better compliance, cost effectiveness, and a reduction in dosage errors since most patients can reach the maintenance dose in shorter time. The introduction of premedication provides a safety profile similar to that of conventional schedules [70–72]. But main decision in favouring the treatment course lies on the clinician who is the only responsible person also in considering possible side effect of preferring the route of administration and the chosen protocol.

At present, it is also unclear whether subcutaneous or sublingual allergen immunotherapy has better outcomes. Subcutaneous protocols seem to be more effective in reducing symptoms for dust mites and grass allergy, but no one could declare any conclusive evidence of superiority of SLIT or SCIT because of a lack of true head-to-head studies. However, trend has favoured SCIT as more effective therapy [73].

6. Future of subcutaneous allergen immunotherapy

Recent research of the cellular and molecular basis of allergic reactions has advanced contemporary understanding of the mechanisms involved in allergic diseases. Newly discovered mechanisms have also helped the development of innovative approaches that are likely to further improve the control of allergic responses in the future. Only allergen immunotherapy induces immunological tolerance and changes the course of disease. Novel vaccines should meet increasing needs for reduction in adverse effects, costs, and duration of treatment [74]. The vaccines have to induce long-term tolerance to allergens.

The efficacy of allergen immunotherapy for the treatment of respiratory allergy (allergic rhinoconjunctivitis with or without bronchial asthma) has been clearly demonstrated in numerous well-designed, placebo-controlled trials. One of the most important studies was the PAT study. PAT study was conducted on children with allergic rhinoconjunctivitis and followed for 10 years with asthma development as the primary outcome. It showed that three years of continuous subcutaneous allergen immunotherapy reduced the risk of developing asthma in comparison to the control group. The difference was maintained at follow-up after 10 years [75].

All preparations that are currently available (standardized extract, allergoids, and recombinant allergen) may trigger side effects. A higher risk is detected in subjects with accelerated dosing schedules, and in subjects with asthma [76]. Contemporary research which is focusing on different administration modalities includes epicutaneous and intralymphatic route of administration of allergen extracts. Both novel strategies showed similar efficacy in the treatment of grass pollen allergy. Results gathered from recent studies have shown less demand on numbers of shots as well as on less total dose of allergen [77, 78].

Other way for enhancing desirable immune response of allergens is the biological modification of allergen preparations. Modification can be achieved using recombinant technology resulting in modified proteins and peptides [74]. Such peptide-based allergen preparations which do not bind IgE, induce increase in Il-10 and so consequently reduce the activity of mast cells as well as the modulation of synthesis Th1 and Th2 cytokines [79].

Novel adjuvants, i.e. nucleotide immunostimulatory sequences derived from bacteria CpG or monophosphoryl lipid A could be an alternative strategy in potentiating Th1 response of subcutaneous allergen immunotherapy [79]. The addition of TLR agonists as adjuvants, their use by themselves (TLR4, 8, 9), allergens coupled to virus-like particles or to hepatitis B PreS-fusion peptide also have shown some benefits in the novel treatment strategies [73, 75].

Additive effect to the allergen immunotherapy in the treatment of allergic rhinitis and asthma could be achieved by administration of anti-IgE recombinant humanized monoclonal antibody—omalizumab. Omalizumab which blocks the effects of IgE, improves efficacy, potentiates immuno-modifying effect, and decreases adverse effects when administered along with allergen immunotherapy. Although the cost of the combination of immunotherapy with anti-IgE treatment is high, this should be considered in view of the enhanced benefit/risk ratio and the known long-term benefits of allergen immunotherapy [79].

7. Author's remarks

Subcutaneous allergen immunotherapy seems to be more effective, but still there is lack of true head-to-head studies, favouring it as more effective therapy over sublingual treatment. Accelerated build-up schedules have advantages over conventional schedules due to better compliance, cost effectiveness, and a reduction in dosage errors since most patients can reach the maintenance dose in shorter time. Even though final decision in favouring the treatment course lies on the clinician who is the only responsible person also in considering possible side effect of preferring the route of administration and the chosen protocol.

The author favours conventional schedules of subcutaneous route of therapeutic interventions. Possibly, such view on the treatment process looks very conservative and from the perspective of contemporary knowledge described above, could be "scientifically" unpopular. When starting the treatment process in our office physician provides the patient with an example that "Gaining lean body weight or training for muscle gain is a slow process that takes months and years rather than days and weeks" and so the most efficient treatment with minimum risk lies on application in subcutaneous form and under the conventional schedules.

Other argument using SCIT opposite to SLIT is the personal experience that almost no one (mostly out of season) takes drops/tablets regularly, so the maximal dose-related effect could not be expected. The idea of such non-compliance in common patient community in contrary to patient community underwent the trial treatment with regular follows-up are indirectly confirmed by information obtained from IMS reports (personal communication). Data from IMS reports show the decrease in selling SLIT drugs in the period out of season.

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Given the lack of specific biomarker in monitoring treatment course, the main control mechanism of efficacy is the evaluation of quality of life using simple evaluation scale as visual analogue scale (VAS) or standardized respiratory allergy questionnaires. In evaluation of quality of life-treated patients modified VAS-like questionnaire is used since 2015. Multiple "umbrella" shaped visual analogue questionnaire is not one-parametric as visual analogue scale, but it is not as complicated as many allergy-specific questionnaires either [80].

Allergen upload for 1-year treatment is determined in 10–12 injected doses (one injection in every 4–6 weeks recommended in SPCs). When patient forgets to keep advised dosing due to personal non-compliance, he is kindly asked to hold the regular visits on the ground of reaching highest efficacy after three to five year lasting treatment. It shows us good results of indicated treatment as seen in evaluation of QoL questionnaires after finishing the treatment course (unpublished data).

8. Conclusion

The presented review summarizes the literary-acquired knowledge as well as author's own experience in conducting aero-allergen immunotherapy, particularly in subcutaneous route of administration for all modalities of respiratory allergy disease from allergic rhinosinusitis, bronchial asthma to united airway disease. Because of appropriate efficacy in connection with satisfactory safety the author favours conventional schedules of subcutaneous route of therapeutic intervention.

The future of aero-allergen immunotherapy should be focused on new hypoallergenic molecules/adjuvants, on new routes of allergen administration and on searching potential biomarkers which could be objectively measured and easily accessible from body fluids (blood, nasal secretion, sputum). The combination of estimated biomarkers obtained from biological samples in conjunction with evaluation of quality of life could lead to the generation of the overall satisfactory monitoring protocol. Due to enormous overload seen in the scientific literature, it seems that ongoing research in the field of allergen immunotherapy will bring even brighter future.

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