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Allergen-specific immunotherapy in allergic rhinitis

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ABSTRACT

The review focuses on allergen-specific immunotherapy (AIT), a treatment method for atopic diseases, including allergic rhinitis. The theoretical and practical basics, development prospects, indications and contraindications to AIT, peculiarities of AIT execution in allergic rhinitis, and tolerogenic effects of immunotherapy are considered. Advantages and disadvantages of each of the two preferable routes of allergen administration in AIT, subcutaneous and sublingual, are described. The main goals of further AIT advancement include shortening of treatment protocols with no significant loss of efficacy, creation of a safer adverse effect profile, and distribution of AIT in developing countries.

Keywords: allergen-specific immunotherapy, allergen administration routes, allergic rhinitis, allergen tolerance

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Аллерген-специфическая иммунотерапия при аллергическом рините

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РЕЗЮМЕ

Настоящий обзор фокусирован на аллерген-специфической иммунотерапии (АСИТ), методе лечения атопических болезней, включающих аллергический ринит. Рассматриваются теоретические и практические основы, перспективы развития, показания и противопоказания к АСИТ, особенности выполнения процедур АСИТ при аллергическом рините и толерогенные эффекты иммунотерапии. Отмечены преимущества и недостатки каждого из двух предпочтительных методов введения аллергенов, подкожного и подъязычного. Главной целью дальнейшего усовершенствования АСИТ является укорочение продолжительности протоколов лечения без существенной потери эффективности, создание более надежного профиля безопасности и распространение АСИТ в развивающихся странах.

Ключевые слова: аллерген-специфическая иммунотерапия, пути введения аллергенов, аллергический ринит, толерантность к аллергенам

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INTRODUCTION

Allergen-specific immunotherapy (AIT) was invented by an outstanding British researcher Leonard Noon (1877–1913) (Fig.1), who published his revolutionary article “Prophylactic inoculation against hay fever” in The Lancet in 1911 [1]. Throughout all his life, L. Noon was involved in research; he stayed at the laboratory till past midnight and often worked till three or four in the morning and sometimes till dawn. Dying from tuberculosis, he continued to think about his remarkable invention long before allergy medications appeared [2].

AIT has been used in healthcare for over 100 years, helping millions of atopic patients, children, females, and males and creating novel unexpected trends in medicine. Currently, AIT efficacy and safety have been demonstrated in multicenter, placebo-controlled, double-blind studies, and protocols of AIT execution and clinical comments to them have been approved in the international position papers [3]. AIT, the only available disease-modifying method for atopic conditions, is classified as a treatment modality with the highest level of evidence-based medicine with advantages exceeding those in pharmacotherapy. In particular, AIT can halt the allergic march in patients with allergic rhinitis [4–6].

BASICS AND FUTURE PROSPECTS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

There are at least five described routes of allergen administration into the body: subcutaneous [7–9], sublingual [10–12], oral [13–15], epicutaneous [16, 17], and intralymphatic [18, 19]. Currently, two main, well-studied, and documented routes of AIT are being used in clinical practice: subcutaneous [7] and sublingual [10]. The third route, oral AIT, is being developed and standardized.

The main indications to AIT are atopic diseases, allergic rhinitis, allergic asthma, and atopic dermatitis. The additional indications include [20]: failure to effectively control the symptoms by pharmacotherapy; serious adverse events caused by pharmacotherapy; reluctance of patients to receive continuous or long-term pharmacotherapy.

AIT is contraindicated in relapses of atopies, uncontrolled and severe asthma, severe cardiovascular disorders, psychoses, malignant tumors, severe systemic autoimmune diseases, pregnancy at the start of immunotherapy, and acute infections [21]. Adverse events in the course of AIT are divided into systemic and local ones. Systemic adverse events occur extremely rarely and are monitored by World Allergy Organization (WAO) [22, 23].

The recommended age to start AIT ranges in different countries from 3 to 5 years [7, 20]. The efficacy and patient-relevant benefits of AIT are proven and evident [24]. Unfortunately, low compliance with treatment in some children and their parents results in violation of conventional AIT protocols and decreased treatment efficacy.

Fig. 1. Leonard Noon (1877–1913)

Subcutaneous AIT [7–9] is a classical therapeutic method for atopic diseases that has been used for a long time. However, there is an enormous potential to improve this administration route by using combinations of allergens or allergoids with biologics like omalizumab and a great number of adjuvants (recombinant allergens, hypoallergenic variants, conformational variants, deletion mutants, allergen fragments and oligomers, as well as hybrid and mosaic antigens) [25]. Although clinical developments were mainly focused on sublingual AIT, interest in the subcutaneous route of administration has increased over the past decade. However, the need for repeated injections and the risk of serious adverse events associated with subcutaneous AIT limit wide use of this method in clinical practice. In the opinion of some researchers, the future of immunotherapy may belong to sublingual AIT [26].

Sublingual AIT is currently widely used. Allergens can be administered in the form of tablets and liquid formulations (drops). Both allergen forms are administered under the tongue and held there until swallowed or spit out. The potential for development of sublingual AIT is associated with its safety, low risk of systemic adverse reactions, long-term post-treatment benefits, and a lack of necessity to visit the hospital and consult allergists frequently [10, 11]. Therefore, treatment can be quickly modified in terms of allergen composition, if necessary.

Currently, oral AIT in food allergy is extremely relevant, however, it has not been proven, whether this route really results in desensitization to food allergens. The method involves regular oral administration of small but gradually increasing amounts of food allergens. Mild adverse reactions during oral AIT are frequent, for example, mouth or throat itching and abdominal pain. Today, oral AIT has been standardized only for peanuts [13–15], but preliminary clinical trials have shown substantial benefits of this method in treating cow's milk, hen's egg, and peanut allergies.

Epicutaneous AIT is based on high density of professional antigen-presenting cells in the epidermis that are administered with an allergen for a greater impact on immunity. At the same time, it is possible to use both allergens and tolerogenic adjuvants [16]. A modification of the method consists in applying interchangeable skin patches for daily maintenance of the allergen dose [17]. Since the epidermis is not vascularized, the risk of systemic adverse events is lower than in routine AIT. Epicutaneous AIT demonstrated a more prolonged treatment effect in food allergy.

Intralymphatic AIT includes three ultrasound-guided injections of indoor, pollen, and animal allergens in the inguinal lymph nodes at 4-week intervals, making it possible to receive the entire treatment within two months. However, in total, AIT typically takes approximately three years [19]. Continuously increasing numbers of published trials on intralymphatic AIT are promising, but still insufficient for its routine use [27].

Before the start of AIT, the allergist prescribes a medication, a route of administration, and a treatment schedule. The trained nurse performs subcutaneous injections in the allergist's office [28]. After that, the patient must remain under observation for at least 30 minutes following the injection. Monthly patient visits to the hospital for these procedures are mandatory. Sublingual formulations (drops or tablets) are taken by the patient at home daily. In case of adverse events, the patient should inform the allergist about them.

The prospects of AIT include development of alternative application routes, immune-modulating adjuvants, allergoids [29, 30], recombinant vaccines [18, 31–33], and containers for allergens, such as virus-like particles and liposomes. The principal aim of AIT development is to shorten existing long protocols without a significant loss of efficacy, create a better adverse effect profile, and distribute AIT in developing countries [3].

ALLERGEN-SPECIFIC IMMUNOTHERAPY IN DIFFERENT POPULATIONS OF PATIENTS WITH ALLERGIC RHINITIS

In allergic rhinitis, AIT has been used for over 100 years, showing high efficacy. Sublingual AIT is generally recommended for treating seasonal and perennial allergic rhinitis in adults and children, with some limitations in perennial allergic rhinitis due to house dust mite (HDM) allergens [34]. However, due to heterogeneity of allergens, different approaches to publishing study reports, and a lack of the established dose, standardization of sublingual AIT in HDM sensitized patients is being approved. The study [35] reported long-term effects, which lasted for up to 7 years, after 2-year sublingual AIT in mono- and polysensitized children. In the monosensitized children, a more sustained benefit was observed.

In another study [36], the efficacy and safety of 300 index of reactivity HDM allergen extract tablets were assessed in 5–16-year-old children with allergic rhinitis in a randomized, double-blind, placebo-controlled study. The HDM sublingual tablets significantly improved symptoms of HDM-induced perennial allergic

rhinitis, caused the required immune response, and their safety profile in pediatric patients was consistent with that in adults, with no new safety concerns.

In adults with HDM-induced perennial allergic rhinitis who suffered from other atopic diseases, such as asthma, conjunctivitis, and atopic dermatitis, the sublingual AIT efficacy was studied [37]. It was demonstrated that the therapy improved not only the outcomes for allergic rhinitis, but also its comorbid conditions. A prolonged positive effect after 3-year sublingual AIT was observed in elderly patients with HDM-induced allergic rhinitis [38]. In another study [39], 41.9% of elderly patients with HDM-induced allergic rhinitis discontinued treatment within 2 years of sublingual AIT, and the most frequent reasons for that included unavailability of medications and persistent symptoms of the disease.

In the study [40], most patients with allergic rhinitis (average age – 27.3 years) were satisfied with 3-year sublingual AIT, as the therapy reduced the severity of symptoms and improved the quality of life. There has been no significant difference in the efficacy between subcutaneous and sublingual AIT in recent meta-analyses, but the sublingual route had more local adverse effects though less systemic ones [41]. The cost minimization analysis indicated that HDM tablets were a cost-minimizing alternative to subcutaneous AIT with HDM allergen extracts, when considered from a societal perspective [42]. For the treatment of persistent moderate to severe HDM-induced allergic rhinitis, HDM tablets, in addition to pharmacotherapy, had cost efficiency of Î2,276 over the 9-year time period compared with pharmacotherapy plus placebo which cost 7,519. Besides, persistent moderate to severe HDM-induced allergic rhinitis was not well controlled by allergy medications [43].

The effects of AIT on local allergic rhinitis have not been documented yet. A randomized, double-blind, placebo-controlled phase II trial was carried out that included *D. pteronyssinus* sensitized patients with local allergic rhinitis receiving subcutaneous AIT [44]. The primary markers included symptoms, medication scores, and medication-free days, whereas the secondary markers included skin testing, serum-specific IgE and IgG4, nasal allergen provocation test, and adverse events. AIT resulted in significant improvements in both primary and secondary markers versus placebo. After 12 months of the AIT, a substantial and pronounced increase in allergen tolerance with negative nasal allergen provocation test in half of the patients and significant serum-specific IgG4 were observed. The immunotherapy was well tolerated; no systemic reactions occurred. This study demonstrated that subcutaneous AIT is a safe and clinically effective treatment method for local allergic rhinitis, confirming that this disease is a new indication for AIT [44].

TOLEROGENIC EFFECTS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

AIT is executed by administering gradually increasing doses of the causative allergen up to the maintenance dosage to achieve long-term tolerance to this allergen [45]. AIT triggers the tolerogenic immune response to the culprit allergen, resulting in the T helper 2 (Th2) cell allergen tolerance and T helper 1 (Th1) cell polarization. Therefore, allergen-specific IgE antibodies switch to IgG_4 and IgA_2 blocking antibodies [46, 47], and allergen-specific memory cells (memory Treg cells, memory T and B cells) are formed [48]. The whole spectrum of tolerogenic cells and molecules is implemented closer to mid-year [49–52], causing stimulation of Th1 cells in terms of upregulating antibody isotype switch. In individuals who respond to AIT, the IgE level is initially elevating but returning to the baseline value by the end of the first year of the immunotherapy. The IgG_4 level is rising, but an increase in IgG_4 stabilizes after the second year of the immunotherapy [51] (Fig.2).

By the end of the first year and later, the levels of immunosuppressive cytokines interleukin (IL)-10, transforming growth factor (TGF)-β, IL-27, IL-35, and IL-10-secreting Breg cells that inhibit Th2, Tfh, Th17, Th22, and ILC2 increase. It is worth noting that the level of Bregs rises earlier than that of Tregs [53], reaching the maximum after the second year of the immunotherapy [51]. However, a medium level of Tregs is observed after 30 weeks of immunotherapy; then it continues to increase, slightly declining by the end of the third year of AIT [51].

Regulatory cells (Tregs and Bregs) play an important role in formation of memory cells (memory Treg cells, memory B and T cells), which are required for long-term efficacy of AIT [48, 50, 52, 54].

CONCLUSION

AIT is disease-modifying treatment for atopic conditions, having the highest level of evidence-based medicine with advantages exceeding those in pharmacotherapy. It is essential that AIT can halt the allergic march in patients with allergic rhinitis [4–6]. AIT has more than a 100-year history after Leonard Noon invented this method. Currently, allergen quality is be-

ing improved and new medication combinations and protocols are being developed and approved, expanding research of allergen tolerance after AIT and accumulating clinical experience.

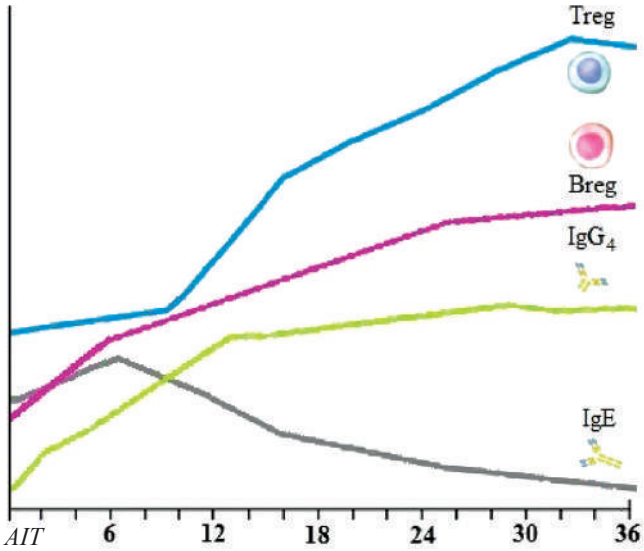

Fig. 2. Sequence of changes in immunological parameters in AIT: blocking IgG_4 antibodies increased by month 12 and stabilized after the second year, whereas IgE antibodies initially increased and diminished after the first year. Regulatory B cells (Bregs) reached a high level at the end of the second year, but regulatory T cells (pTregs) significantly increased from week 30 of the therapy, slightly declining by the end of the third year. According to [51]

AIT showed high efficacy in allergic rhinitis, making it possible to use this method in a new form of pathology, local allergic rhinitis [44]. Among routes of allergen administration, the sublingual AIT is considered preferable due to a better adverse effect profile and efficacy similar to that in subcutaneous AIT. AIT may be combined with allergy medications, including biologics, making this modality perspective in allergy [3].

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