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ADVERSE REACTIONS TO VACCINES AND WAYS OF ITS PREVENTION

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Vaccines have had a tremendous impact on public health by reducing morbidity and mortality from a variety of virulent pathogens, including diphtheria, pertussis (whooping cough), tetanus et al. [1]. Efforts to generate collaboration between state and local governments and public and private health care providers have resulted in record rather high levels of vaccination coverage in the Ukraine. But the high rate of vaccinations could be paralleled by growing concerns about the safety of their delivery [2]. Unintended side effects continue to pose a potential risk that may outweigh the vaccine's protective attributes [1].

General physicians, pediatricians and parents realize that serious adverse events occur with an extremely rare incidence, but have no information on the incidences of vaccine-associated adverse events. A proper understanding of vaccine adverse events would be helpful in promoting an immunization strategy [3].

The variety of substances used in vaccines sometimes causes the development of adverse reactions in susceptible adults and children [2].

Adverse reactions to vaccines are highly varied, ranging from mild local reactions to fatal outcomes. In the last few years many adverse reactions have been attributed to vaccines, often without justification. In agreement with the World Health Organization, these reactions can be classified as follows, depending on the cause: vaccination-induced reactions (due to an effect of the vaccine itself or to an idiosyncrasy); reactions due to errors in storage, manipulation and/or administration; and coincidental reactions (no causal relationship with the vaccine). Hypersensitivity reactions fall into six categories, depending on the causative agent: reactions due to some component of the infectious agent or one of its products; reactions due to adjuvants: aluminium hydroxide; reactions due to stabilizers: gelatin; reactions due to preservatives: thiomersal; reactions due to antibiotics: neomycin; and reactions due to a biological culture medium: chicken embryo cells [4, 5, 6].

Causal association with immunization can rarely be determined in adverse events through laboratory examinations [3].

Hepatitis B and bacillus Calmette-Guerin vaccines are the most frequently incriminated products. Cutaneous adverse effects are less frequently encountered following administration of vaccines against diphtheria/tetanus/pertussis (primary and booster doses). The adverse effects can occur at the site of or at a distance from the injection. The pathological mechanisms of local adverse cutaneous reactions include predominantly nonspecific lymphoid or granulomatous reactions. Allergic reactions to the vaccine strain, adjuvants, conservatives or other components are less frequently involved in local vaccine adverse effects [6, 7].

Systemic reactions are mainly mediated by immediate type or immune complex-related allergic reactions to toxoid-, ovalbumin-, gelatin- or pneumococcal-containing vaccines. Systemic reactions are sometimes related to a specific vaccine strain. Other cutaneous reactions may also occur through unknown pathological mechanisms. No vaccine type or strain is specifically associated with a particular type of cutaneous adverse effect [6, 7].

It's examined the cases reported in the post-marketing surveillance of the Kitasato Institute, categorizing them into two groups: allergic reactions and severe systemic illnesses [3]. Anaphylactic patients with gelatin allergy after immunization with live measles, rubella and mumps monovalent vaccines have been reported since 1993, but the number of reported cases with anaphylaxis dramatically decreased after 1999 when gelatin was removed from all brands of DPT. The incidence of anaphylactic reaction was estimated to be 0,63 per million for Japanese encephalitis virus (JEV) vaccine, 0,95 for DPT and 0,68 for Influenza vaccine, but the causative component has not yet been specified. Among 67,2 million immunization practices, 6 cases with encephalitis or encephalopathy, 7 with acute disseminated encephalomyelitis (ADEM), 10 with Guillain-Barré syndrome and 12 with idiopathic thrombocytopenic purpura (ITP) were reported. The wild-type measles virus genome was detected in a patient with encephalitis and in two of four bone marrow aspirates obtained from ITP after measles vaccination. Enterovirus infection was identified in two patients after mumps vaccination (one each with encephalitis and ADEM), one patient with encephalitis after immunization with JEV vaccine, and one with aseptic meningitis after immunization with influenza vaccine. The total estimated incidence of serious neurological illness after vaccination was 0,1-0,2 per million immunization practices. We found that enterovirus or wild-type measles virus infection was coincidentally associated with vaccination in several cases suspected of being vaccine adverse events [3].

Most allergic (like) reactions to vaccines are reported in patients immunized with diphtheria and tetanus toxoid-containing vaccines. Local inflammatory reactions are the most frequent, but most of them are non-specific [8]. Adverse cutaneous events consistent with hypersensitivity reactions to the following ingredients in vaccines: aluminum, thimerosal, formaldehyde [2]. Diagnosis of Arthus-type reactions is based on clinical history and specific IgM/IgG anti-toxoid determination. For other local reactions (persistent nodules, sterile abscesses, etc.), diagnostic value of non-immediate responses in skin tests varies with clinical symptoms and substances involved. Immediate responses in skin tests and specific antibody determination have good diagnostic and/or predictive value in anaphylaxis and immediate and accelerated urticaria and angioedema. Although a few generalized non-immediate reactions may result from toxoid-specific semi-late or delayed-type hypersensitivity, most reactions are non-specific. Withholding booster injections is advised if specific IgM/IgG levels are high. If the levels are low, sequential intramuscular injections of mono- or multi-partial vaccines are usually tolerated. However, injections of the vaccine should be performed using a "desensitization" procedure in patients reporting anaphylaxis and immediate or accelerated urticaria or angioedema [8].

Replacement of cellular with acellular pertussis (aP) vaccines has considerably reduced the systemic reactions observed with diphtheria-tetanus toxoids-pertussis vaccine but has not eliminated the extensive swelling (sometimes involving an entire limb) observed after the fifth injection of diphtheria-tetanus toxoids-aP (DTaP) vaccine [9]. Diphtheria-tetanus-acellular pertussis vaccine (DTaP) developed in Japan is now widely used worldwide. DTaP is safer than the diphtheria-tetanus-whole-cell pertussis vaccine (DTwP) and has fewer severe side effects, but local reactions such as redness, swelling, and induration are still reported [10]. This local reaction, which is likely an Arthus hypersensitivity reaction caused by high levels of antibodies reacting with DTaP vaccine, could discourage its use in adults, who serve as the major reservoir of pertussis for infants [9].

The pathophysiological mechanism of these reactions is controversial. To clarify the cause of local reactions, it's conducted studies using the mouse model. After administering either one or two abdominal subcutaneous DTaP inoculations, they are observed changes in histopathology at the injection site at 24h, 48h, and 7 days. The control group, inoculated with physiologic saline, showed no significant changes either pathologically or with the naked eye. All mice after DTaP vaccination showed indurations at the injection site. Pathologically, they watched leukocyte invasion into or around the site, especially neutrophils and eosinophils. After the first vaccination, the extent of the invasion was strong 24h and 7 days later. At 24h following the second vaccination, a dramatic leukocyte invasion seen persisted at 7 days. At 7 days after the first vaccination, peripheral fibrosis had begun, and when a second vaccination was administered, it began even earlier at the second site. These histopathological changes show that local reactions are caused by both inflammatory and allergic responses. Because this mouse study resulted in the same pattern of reactions observed in humans, this method will be useful for studies focusing on local reactions [10].

In rare circumstances, certain vaccines may cause acute exacerbations of allergic diseases, but the contention that vaccination causes allergic disease is not substantiated by any available evidence [11].

It's considered that in children at heightened risk for atopy, common childhood immunization in the first year is not associated with an increased risk of more severe eczema or allergic sensitization. Parents of atopic children should be encouraged to fully immunize their children [12, 13]. Currently available data, based on observational studies, do not support an association, provocative or protective, between receipt of the BCG or whole-cell pertussis vaccine and risk of asthma in childhood and adolescence [14]. The DTP-IPV vaccination was not related to reported atopic disorders at primary school age [15].

Multi-variable analyses revealed no associations between the presence of atopic diseases and all of the three vaccine-specific antibody titres against tetanus, diphtheria and hepatitis B in adults with atopic diseases. There is no reduced immune response related to antibody production following immunizations [16].

Concerns about possible allergic reactions to immunizations are raised frequently by both patients/parents and primary care providers. Estimates of true allergic, or immediate hypersensitivity, reactions to routine vaccines range from 1 per 50 000 doses for diphtheria-tetanus-pertussis to approximately 1 per 500 000 to 1 000 000 doses for most other vaccines [17].

In a large study from New Zealand, data were collected during a 5-year period on 15 marketed vaccines and revealed an estimated rate of 1 immediate hypersensitivity reaction per 450 000 doses of vaccine administered. Another large study, conducted within the Vaccine Safety Datalink, described a range of reaction rates to >7,5 million doses. Depending on the study design and the time after the immunization event, reaction rates varied from 0,65 cases per million doses to 1,53 cases per million doses when additional allergy codes were included. Although these per-dose estimates suggest that true hypersensitivity reactions are quite rare, the large number of doses that are administered, especially for the commonly used vaccines, makes this a relatively common clinical problem [17].

But there is another opinion about an association with development allergic diseases after vaccination. For some vaccines, particularly when allergens such as gelatin are part of the formulation (e.g., Japanese encephalitis), higher rates of serious allergic reactions may occur.

Early childhood immunizations have been viewed as promoters of asthma development by stimulating a Th2-type immune response or decreasing microbial pressure, which shifts the balance between Th1 and Th2 immunity [18]. Differing time schedules for childhood immunizations may explain the discrepant findings of an association with asthma reported in observational studies. There is a retrospective longitudinal study of a cohort of children born in Manitoba in 1995. This research was undertaken to determine whether timing of diphtheria, pertussis, tetanus (DPT) immunization has an effect on the development of childhood asthma by age 7 years. The complete immunization and health care records of cohort children from birth until age 7 years were available for analysis. The adjusted odds ratio for asthma at age 7 years according to timing of DPT immunization was computed from multivariable logistic regression. Among 11 531 children who received at least 4 doses of DPT, the risk of asthma was reduced to (1/2) in children whose first dose of DPT was delayed by more than 2 months. The likelihood of asthma in children with delays in all 3 doses was 0,39 (95 % CI, 0,18-0,86). They found a negative association between delay in administration of the first dose of whole-cell DPT immunization in childhood and the development of asthma; the association was greater with delays in all of the first 3 doses. The mechanism for this phenomenon requires further research [18].

The adverse reactions to vaccines are between 0,6 % and 1,3 % of first visits in the beginning of 2000 year [4]. 92 % of recorded adverse reactions to vaccines were attributed to the tetanus vaccine. Clinical features consisted of urticaria, urticaria with angioedema, pseudo-shock, fever and urticaria, local reactions, persistent crying with exanthema, giant local reactions with angioedema of the limb, anaphylaxis, fever more than 39,5 °C, bronchospasm, and severe atopic dermatitis. A regimen of hyposensitization to tetanus toxoid was required in 45 % patients and all the patients presented protective titers with diluted vaccine [4].

It's necessary to take into account that nowadays allergic diseases constitute a major health issue worldwide. For example, allergic respiratory diseases affect approximately 15 % of the US population [19]. In Latin America, allergic diseases have a very high prevalence, comparable to that of many other countries of the world, and that prevalence is constantly increasing [20]. Allergic rhinitis and asthma have a very high prevalence and constitute a health problem with a relevant burden of disease, concerning medical and economical issues [21].

Immunologically, allergic individuals are more susceptible to infection and to microbial and viral diseases, which often play an aggravating role. Rubella, whooping cough, and influenza usually exacerbate respiratory allergies. Non-vaccination carries a marked risk of contracting serious diseases such as poliomyelitis, tetanus, and diphtheria, etc. [4]. Therefore children with allergic or atopic diseases require immunization just like non-atopic children and they should not be excluded from the normal vaccine calendar [4]. However, vaccination of such children requires some special considerations and precautions. Children who have suffered an apparent allergic reaction to a vaccine should be evaluated by an allergist to determine the culprit allergen and to make recommendations regarding future vaccination [10].

Mainstay treatment of such individuals constitutes allergen avoidance and pharmacotherapy for symptom relief, but allergen immunotherapy offers advantages of specific treatment with long lasting efficacy, and being able to modify the course of the disease [22].

Most parents today have never seen a case of diphtheria or other once commonly encountered infectious diseases now preventable by vaccine administration. As a result, some parents wonder why their children must receive shots for diseases that do not seem to exist. Myths and misinformation about vaccine safety abound and can confuse parents who are trying to make sound decisions about their children's health care [23].

In a not too distant future, the techniques of genetic recombination and monoclonal antibody production will allow the creation of vaccines from organisms that cannot be cultivated in the laboratory or that produce small quantities of antigen. These techniques will also lead to identification of the antigens with the greatest immunogenic power and, consequently, to extremely pure vaccines [4].

But today there is a whole number of developments directed to increasing of vaccines safety. It's proposed the genetically inactivated diphtheria and pertussis mutant toxins. They are more immunogenic and, therefore, induce comparable levels of antitoxin at lower protein levels than do the formalin-treated native toxins. Replacement of the diphtheria and aP components with these improved antigens will reduce the amount of protein in DTaP vaccine and, most likely, the incidence and severity of local reactions in teenagers and adults [9].

There could be another way to prevent allergic adverse reactions to common vaccines. New therapeutic approaches to atopic dermatitis, urticaria, and angioedema have been reported, including use of sublingual specific immunotherapy (SLIT), anti-IgE, and a kallikrein inhibitor [24].

Allergen immunotherapy has been a treatment option for allergic diseases for the last 100 years [19]. After several decades of controversies, allergen specific immunotherapy (SIT) was recognized as an effective treatment for respiratory and hymenoptera allergy by the World Health Organization in 1998 [25]. SIT is the only allergen-specific treatment capable of modifying the natural history of the disease. During the last 25 years, there was an impressive development of basic and clinical research in the field of SIT, with the goal of improving the safety, the efficacy and ameliorating the knowledge on the mechanisms of action [25].

Immunotherapy is effective in patients with mild forms of allergic disease and also in those who do not respond well to standard drug therapy. Immunotherapy is properly prescribed for inhalant allergens and hymenoptera venom by allergy specialists, although some non-evidence based forms of immunotherapy (e.g. bacterial extracts, treatment of atopic dermatitis) are still occasionally practiced [20].

Specific immunotherapy (SIT) is indicated for confirmed immunoglobulin E-mediated airway diseases and remains the treatment of choice for patients with systemic allergic reactions to wasp and bee stings and should be considered as an option in patients with allergic rhinitis, asthma, hay fever and so on [25, 26, 27]. SIT involves the administration of standardized allergen extracts with documented clinical efficacy and safety to achieve a hyposensitization, clinical tolerance of those allergens that cause symptoms in patients with allergic conditions [27]. Conventional immunotherapy involves the subcutaneous injection of gradually increasing amounts allergen extract but the use of current whole allergen extracts is restricted by the risk of adverse IgE-mediated events especially for potent allergens such as peanut and latex and for asthmatics [22].

SIT can modify the course of allergic disease by reducing the risk of new allergic sensitizations. It also produces a long-term, antigen-specific, protective immune effect and is the only treatment that offers the possibility of reducing the risk of asthma development in children treated for allergic rhinitis [26, 28].

The precise mechanisms responsible for the beneficial effects of SIT remain a matter of research and debate. An effect on regulatory T cells seems most probable and is associated with switching of allergen-specific B cells toward IgG4 production [26, 28].

The clinical expression of the most common allergic diseases reflects allergic inflammation and underlines that inflammation is the main target of anti-allergic therapies. Allergen specific immunotherapy has a recognized impact on allergic inflammation, which persists after its discontinuation. The traditional, subcutaneous route of administration is effective in altering the phenotype of allergen-specific T cells, switching from a Th2-type response, characterized by the production of IL-4, IL-5, IL-13, IL-17, and IL-32 cytokines to a Th1-type response. This immune deviation is related to an increased IFN-gamma and IL-2 production as well as to the anergy or tolerance of Th2, the latter related to the generation of allergen-specific T regulatory (Treg) cells, which produce cytokines such as IL-10 and TGF-beta [20, 29].

Existing data suggest that the effects of SIT take longer to develop, but once established, SIT achieves long-lasting relief of allergic symptoms, whereas the benefits of drugs only last as long as they are continued [26, 28].

Taking the potential preventive action of immunotherapy into account, there is a case to start treatment early in life. However, the lack of high-quality studies with subcutaneous immunotherapy in children requires new studies to fill the gap [30].

In spite of its validation by abundant experimental data and decades of clinical experience, subcutaneous immunotherapy has not become the mainstay treatment for allergy. Application of this potentially curative treatment is restricted, largely due to the risk of serious adverse events, especially in asthmatics and for potent allergens such as peanut, seafood and latex [31]. The potentially severe side effects associated with this form of immunotherapy limit its widespread use [28].

New insights into immunological mechanisms underlying effective SIT and molecular characterization of allergens and their recognition by the immune system suggest strategies for refinement of SIT. Selective targeting of allergen-specific T cells, especially regulatory T cells, is likely to be pivotal for efficacy. Recombinant allergens lacking IgE reactivity and small T cell epitope-based peptides are being trialled clinically with evidence of efficacy without serious IgE-mediated adverse reactions. Adjuvants, either co-administered or incorporated into a recombinant allergen vaccine to target tolerogenic dendritic cells may also increase efficacy [31].

Defined allergen-derived molecules or peptides offer ease of standardization and, coupled with appropriate targeting of immunoregulatory mechanisms, will result in more widespread clinical use of SIT. Adjunct therapies such as anti-IgE antibody and corticosteroids may minimize the likelihood of adverse reactions in those with severe allergic disease who would most benefit from this treatment [31].

The growing detailed knowledge of the immunological mechanisms of SIT has provided the opportunity to explore new forms of specific hyposensitization. Activation of the innate immune system through Toll-like receptor agonists with and without specific allergens appears to improve the immunologic responses and clinical outcomes in patients with allergic diseases. Diverse preparations are being developed to increase safety of SIT and improve its efficacy [28]. The use of chemically altered allergens, allergoids; alternative routes of administration, particularly the sublingual route; use of novel adjuvants, such as CpG oligonucleotides and mycobacterial vaccines; other approaches, such as allergenic peptides, relevant T-cell epitope peptide immunotherapy; DNA vaccination, recombinant and engineered allergens, chimeric molecules and combined therapy are all approaches that have yielded positive results [19, 25, 28, 32]. The last frontier seems to be the manipulation of genoma with replicons and allergen-encoding plasmids [25].

Finally, alternative modes of delivery hold promise, with sublingual immunotherapy rapidly approaching mainstream use in many countries. One thing is clear: the next century of immunotherapy will be vastly different from today's current standard of care [19].

The sublingual route has become an interesting and novel therapeutic option for the immunotherapeutic management of patients with allergies. Credible evidence exists of both effectiveness and safety of sublingual immunotherapy (SLIT) from several placebo-controlled double-blind studies [33].

Sublingual immunotherapy was proposed for clinical practice about 20 years ago with the main aim of improving the safety and of avoiding the side effects. More than 30 randomized controlled trials have been published so far, in addition to several post marketing surveys. Thus, the literature provides a solid documentation of the safety profile of this treatment. Concerning the randomized controlled trials, the more frequently reported side effect of SLIT is the oral itching or swelling, followed by gastrointestinal complaints. These side effects are invariantly described as mild and easily managed by temporarily adjusting the dose. Systemic relevant adverse events (asthma, urticaria, angioedema) occur sporadically, with their rate not being different from the placebo groups. Moreover, the safety profile seems not to differ in adults and children. More interestingly, the post marketing surveys consistently showed that the occurrence of all side effects is less than 20 % of patients and less than 1 per 1 000 doses, thus being quite insignificant compared to subcutaneous immunotherapy. The most recent surveys showed that the rate of adverse events does not increase in children below the age of 5 years, being traditionally considered as a prudential limit for injection immunotherapy. Finally, it seems that the occurrence of some adverse events, at variance with injection route, does not depend strictly on the dose of allergen administered [34].

Treatment and compliance experiences been gained over nearly a century in injection-type allergen-specific immunotherapy have motivated the development of newer, alternative routes [22]. There are different forms of local immunotherapies, involving oral, sublingual and nasal routes of allergen administration [35]. The sublingual route was extensively studied and, recently, validated [25, 36, 37]. The safer sublingual route of allergen administration is attracting interest and different allergen forms may be optimal for inducing tolerance by this route [31]. SLIT can be considered a milestone in the history of SIT, since it is expected to change the clinical practice. There are a lot of studies devoted to the advantageous features of sublingual immunotherapy [25]. Pharmacokinetic studies showed that, differently from nasal mucosa, allergen extracts administered by SLIT are not immediately adsorbed but are long retained before being drained to local lymph nodes. This difference may be responsible of the absence of severe side effects and instead of short-lasting local symptoms. Studies by biopsies of the oral mucosa should greatly help in defining the presence and the role of cells involved in the mechanisms of oral tolerance [38].

Adverse events and safety concerns, efficacy and ease of application seem to be the stimulating factors for the development of a sublingual form of this treatment modality, wherein the principal factor is the capture of the antigen (allergen) by dendritic cells, in the location where oral tolerance arises. Due to the presence of high numbers of tolerogenic dendritic cell subsets in this region, programming of the immune system towards a regulatory state with unresponsiveness to specific allergens occurs. Induction of peripheral tolerance through the generation of regulatory T cells is the key event, with several functional modulations in the allergic immune response [39]. Anti-inflammatory mechanisms ob-

served during sublingual immunotherapy (SLIT) with high allergen doses proved to be similar compared to subcutaneous immunotherapy. Recent data obtained in biopsies clearly indicate that the pathophysiology of the oral mucosa, and in particular mucosal dendritic cells, plays a pivotal role in inducing tolerance to the administered allergen [20].

Evidence suggests that oral dendritic cells play a key role in inducing tolerance especially when allergen is taken up via Fc receptor bound IgE. This suggests that although both would target allergen-specific T cells, allergen formulations may differ with respect to IgE epitopes for optimal SLIT compared with subcutaneous immunotherapy (SCIT) [22].

Sublingual application of allergen extracts in specific immunotherapy is a modern approach aimed at improving patient treatment acceptance through reduced serious side effects. This therapeutic approach has proven to be efficacious and safe for the treatment of allergies caused by airborne allergens: 1) studies have shown a rapid onset of action, as early as seven days after beginning treatment; 2) a strong effect during treatment, superior to most forms of symptomatic treatment; 3) a lasting effect after cessation; 4) a preventive effect against new sensitizations and new-onset asthma; and 5) an unprecedented safety profile compared to the subcutaneous route. SLIT is an established treatment option for moderate to severe allergic rhinoconjunctivitis with or without asthma, which can be given to adults as well as to children above five [40]. Sublingual specific immunotherapy (SLIT) can be suggested for use in children with allergic rhino-conjunctivitis, and seasonal asthma, especially if they are mono-sensitive, for a duration of no less than three years. The earlier treatment begins, the better is the outcome [41].

SLIT has been shown to be an effective treatment of allergic rhinitis and asthma in both children and adults. The therapy is well tolerated with mainly minor gastrointestinal side effects that subside in few weeks. The ideal treatment length and dosage still require further verification. Additional studies evaluating long-term efficacy and the immune response of SLIT still need to be performed, and additional standardized antigens still need to be developed [33].

Several aspects of the immunopathological response modified by sublingual immunotherapy have been investigated. Immunotherapy modifies the immune response by decreasing the specific IgE levels and Th2-type inflammation in the mucosa when allergen exposure occurs, shifting this toward a Th1-type response [33]. More recently, a crucial role for a subpopulation of T cells has been evidenced: T regulatory cells (Treg). Allergic patients have a defect of Tregs, and SLIT should be able to induce a specific Treg response. This issue is very relevant as the Treg-dependent cytokines, namely IL-10 and TGF-beta, are involved in the regulation of IgG and IgA antibodies production. Recent evidence shows that SLIT is also able of inducing a Treg response as detected by IL-10 production. IFNgamma is a typical Th1-dependent cytokine. SLIT may induce a significantly increased production of this cytokine and it may be considered as an early marker of SLIT response. Therefore, also SLIT is able of exerting the effects on immune response as well as the subcutaneous route [42].

So, immunotherapy whether by subcutaneous injection of allergen extract or by oral/sublingual routes modifies peripheral and mucosal TH2 responses in favour of TH1 responses and augments IL-10 synthesis by TRegs both locally and by peripheral T cells. Recent researches into the cellular and molecular basis of allergic reactions have advanced our understanding of the mechanisms involved in allergic diseases. They have also helped the development of innovative approaches that are likely to further improve the control of allergic responses in the future. Novel approaches to immunotherapy that are currently being explored include the use of peptide-based allergen preparations, which do not bind IgE and therefore do not activate mast cells, but reduce both Th1 and Th2-cytokine synthesis, while increasing levels of IL-10. Alternative strategies include the use of adjuvants, such as nucleotide immunostimulatory sequences derived from bacteria CpG or monophosphoryl lipid A that potentiate Th1 responses. Blocking the effects of IgE using anti-IgE such as omalizumab, a recombinant humanized monoclonal antibody that selectively binds to IgE, has been shown to be a useful strategy in the treatment of allergic asthma and rhinitis. The combination of anti-IgE-monoclonal antibody omalizumab with allergen immunotherapy has proved beneficial for the treatment of allergic diseases, offering improved efficacy, limited adverse effects, and potential immune-modifying effects [19, 43]. This combination may also accelerate the rapidity by which immunotherapy induces TReg cells. If allergic diseases are due to a lack of allergen-specific TReg cells, then effective therapies should target the induction and the development of TReg cells producing cytokines such as IL-10 [43].

The current variation in clinical trials hampers the formulation of clear-cut recommendations on how to perform sublingual immunotherapy (SLIT) in terms of doses, doses schemes, target populations, allergens and specific products from manufacturers [27, 30, 44, 45].

The inability of the protein to survive gastrointestinal physiological barriers is a generally encountered problem in oral administration of protein drugs. In order to overcome the problems of low allergen bioavailability and absorptivity, during oral immunotherapy, several stabilization strategies have been outlined in the recent years. Hexose monosaccharide, ethyl alcohol and water vehicles, oxygen-containing metal salt based preparations, particles with enteric coating, and poly (lactic-co-glycolic) acid microspheres are among of that interventions. Regarding the enormous potential of oral responsiveness and/or oral tolerance, research that focuses on new and improved carriers or vehicles for safe allergen oral delivery has great potential in treating allergic diseases [35].

Studying of antibody levels against diphtheria induced by different schemes of immunization using oral diphtheria toxoid administration achieved availability of those ones for routine revaccination and additional booster doses [46, 47].

BALB/c-mice were vaccinated intracutaneously with a combination of diphtheria and tetanus toxoids or a combination of diphtheria and tetanus toxoids with a whole cell vaccine of B. pertussis (three times, days -21 to -7) prior to systemic sensitization (days 1-14) and repeated airway challenges (days 28-30) with ovalbumin [48]. Compared with negative controls, systemic sensitization and airway allergen challenges induced high serum levels of allergen-specific IgE, predominant Th2-type cytokine

production, airway inflammation and development of in vivo airway hyperreactivity. Vaccination with diphtheria and tetanus toxoids prior to sensitization suppressed IgE formation and development of eosinophilic airway inflammation. Co-vaccination with a whole cell pertussis vaccine inhibited allergen sensitization, airway inflammation and development of in vivo airway hyperreactivity. Prevention was due to an allergen-specific and general shift from a predominant Th2 towards a predominant Th1 immune response. Vaccination with diphtheria and tetanus toxoids alone or in combination with whole cell pertussis vaccine prior to allergen sensitization prevented allergen-induced Th2 immune responses. Vaccine antigens may down-regulate allergic responses to a range of common allergens [48].

The data obtained provide evidence that SLIT is associated to economic advantages and/or monetary savings, specifically in terms of reduction of economic burden of the disease. Although the number of studies is still limited, the available data support a SLIT effect on sparing costs for respiratory allergy [21].

It'll be to have been perspective to join desensitizing effect of non-injection modes of immunotherapy and natural route and booster effect of oral vaccine administration on humoral DTP immunity for achievement safe and effective immunization of allergic children and adults.

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ADVERSE REACTIONS TO VACCINES AND WAYS OF ITS PREVENTION

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The overview concerns allergic reaction on vaccines and possible ways of increasing safety of immunization on basis of use of local specific immunotherapies (SIT) experience, particularly the sublingual route. The use of chemically altered allergens, allergoids; alternative routes of administration, particularly the sublingual route; use of novel adjuvants, such as CpG oligonucleotides and mycobacterial vaccines; other approaches, such as allergenic peptides, relevant T-cell epitope peptide immunotherapy; DNA vaccination, recombinant and engineered allergens, chimeric molecules and combined therapy are all approaches that have yielded positive results to increase safety of SIT and improve its efficacy.

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ПОБОЧНЫЕ РЕАКЦИИ НА ВАКЦИНЫ И ПУТИ ИХ ПРЕДОТВРАЩЕНИЯ

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Обзор посвящен побочным реакциям на вакцины и возможным путям повышения безопасности иммунизации на основе опыта применения локальной специфической иммунотерапии (СИТ), особенно ее сублингвального применения. Использование химически измененных аллергенов, аллергоидов; альтернативные пути введения, особенно сублингвальный; использование новых адъювантов, таких как CpG олигонуклеотиды и микобактериальные вакцины; другие подходы, такие как применение аллергенных пептидов, релевантной Т-клеточной епитоп пептидной иммунотерапии; ДНК вакцинации, рекомбинантных и сконструированных аллергенов, химерических молекул и комбинированной терапии – все это подходы, которые дали положительные результаты для улучшения безопасности и эффективности СИТ.

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ПОБІЧНА ДІЯ ВАКЦИН ТА ШЛЯХИ ЇЇ ПОПЕРЕДЖЕННЯ

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Обзор присвячений побічній дії вакцин і можливим шляхам підвищення безпеки імунізації на основі досвіду застосування локальної специфічної імунотерапії (СІТ), особливо її сублінгвального застосування. Використання хімічно змінених алергенів, алергоїдів; альтернативні шляхи введення, особливо сублінгвальний; використання нових ад'ювантів, таких як CpG олігонуклеотиди і мікобактеріальні вакцини; інші підходи, такі як застосування алергенних пептидів, релевантної Т-клітинної епітоп пептидної імунотерапії; ДНК вакцинації, рекомбінантних і сконструйованих алергенів, химеричних молекул і комбінованої терапії – все це підходи, які дали позитивні результати для покращення безпеки та ефективності СІТ.