Subcutaneous immunotherapy against tree pollen, grass pollen, artemisia pollen, *Alternaria alternata* and house dust mites efficiency mediators: a review

Maria Zofia LISIECKA

Department of Allergology National Medical Institute of the Ministry of the Interior and Administration 02-507, 137 Woloska Str., Warsaw, Poland.

ABSTRACT

Subcutaneous immunotherapy is a preferred desensitization technique against allergens, however generalized efficacy criteria are lacking. This research aimed to gather data on methods to determine the efficacy of subcutaneous therapy for various allergens including tree pollen, grass pollen, artemisia pollen, *Alternaria alternata* and house dust mites. Immunologic methods assessing IgE, interleukin levels, arachidonic acid metabolites, TNF-α, GM-CSF, and IFN-γ in patient plasma pre and post-treatment are best to determine efficacy as these markers directly relate to allergic reactions. In this study publications, scientific articles and research related to the effectiveness of subcutaneous immunotherapy against tree pollen (hazelnut, alder, birch), grass pollen, artemisia pollen, *Alternaria alternata* and house dust mites were used. An extensive review of the scientific literature using various scientific databases, including PubMed, Scopus, was carried out. Clinical parameters depend on reaction type. For atopic dermatitis, SCORAD and visual analog scales reflect skin damage and quality of life. For asthma, PEFR, FEV1 and FVC 25%-75% determine bronchoobstruction severity. For rhinoconjunctivitis, visual analog and RQLQ scales assess quality of life and severity. Other efficacy measures are reductions in maintenance medications, glucocorticoids, and provocation test responses.
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INTRODUCTION

A wide range of allergens exists worldwide. In Europe and North America, pollen from hazel, alder, and birch trees is a common etiological factor in respiratory allergies. Bozek and Jarzab (2013) analysed epidemiological material relating to the prevalence of bronchial asthma (BA), atopic rhinitis (AR), and atopic dermatitis (AD) among older adults. The results showed that among 7124 people surveyed, 1900 of them were found to be hypersensitive to various allergens. The proportion of women with atopy was 26.7% and that of men was 26.6%. Another study by D'Amato et al. (2007) determined that grass pollen allergy is also common in most regions of Europe and the USA and is associated with about 40% of patients suffering from allergic rhinitis. Tabynov et al. (2022) states that artemisia pollen is one of the world's top ten airborne allergens capable of causing allergic rhinitis

and Couso et al. (2021) in a study reported that *Alternaria alternata* is also a common allergen, causing 3% to 10% of allergic reactions.

Biagtan et al. (2014) indicate that dust mite allergy is a common allergy, affecting around 20 million people in the United States. House dust mites are universal and found all over the world. They are found in about 84% of households in the US. In industrialised regions, including Germany, one in four individuals is allergic to dust mites. Allergies to the pollen of different plants, grass pollen, artemisia, *Alternaria alternata*, and dust mites are thus common allergic reactions affecting a large proportion of the population in Europe, North America, and other regions of the world. Various desensitization therapies, such as subcutaneous immunotherapy (also known as specific immunotherapy or allergen-specific immunotherapy), are available to reduce allergic reactions to certain allergen types. It is based on the principle of gradually administering small doses of an allergen subcutaneously to desensitise the immune system to that substance. A meta-analysis carried out by Yepes-Nunez et al. (2023) found this technique to be highly effective, reducing the severity of AD by 50%. In another meta-analysis, Ji and Jiang (2023) noted the high efficacy of subcutaneous immunotherapy in resolving allergic rhinitis.

Clinical symptoms are one such indicator. Assessment of changes in the clinical symptoms of an allergic reaction, such as runny nose, itching, coughing or red eyes, is an important indicator of the effectiveness of subcutaneous immunotherapy (SCIT). If the intensity or frequency of symptoms decreases, this may indicate a positive treatment outcome. Another indicator is the use of medication (Azeez et al., 2019; Sirima et al., 2020). A reduction in the need for anti-allergy drugs, such as antihistamines or glucocorticosteroids, is a mediator of the effectiveness of SCIT. If a patient requires less medication to control allergic symptoms, this indicates the success of treatment. Immunological parameters are also used to assess the effectiveness of SCIT. Changes in immunological parameters such as IgE antibody levels associated with allergic

reactions and levels of cytokines including interleukin-4 (IL-4) and interleukin-10 (IL-10), which regulate the immune response, can be measured, and used to assess the progress of treatment. Finally, provocation tests are sometimes performed to assess a patient's response to an allergen before and after SCIT. If the response decreases after treatment, this may indicate that the treatment is effective (Oladipo and Illoh, 2010; Simpore et al., 2022). All these evaluation methods complement each other and help obtain a complete picture of the effectiveness of SCIT and its effect on patients' allergic reactions. It is important to remember that the evaluation of the effectiveness of SCIT must be carried out under the guidance of a qualified physician or allergist, considering the individual characteristics of each patient.

The research aims to systematically describe the various tests and modalities that determine the effectiveness of subcutaneous immunotherapy in the context of allergic reactions to tree pollen (hazelnut, alder, birch), grass, artemisia pollen (weeds), *Alternaria alternata* and dust mites.

IMMUNOLOGICAL INDICATORS

A wide range of methods is available to assess the effectiveness of subcutaneous immunotherapy (SCI) in the treatment of allergies, to assess whether this treatment is successful in helping patients manage their allergic reactions. When it comes to subcutaneous immunotherapy (desensitisation) for the treatment of tree (hazelnut, alder, birch) pollen, grass pollen, artemisia pollen and allergies to *Alternaria alternata* (fungus) and house dust mites, mediators of effects may include the following (Figure 1).

Importance of IgE level in blood

This antibody plays a key role in the activation of the immune system and is involved in the transmission of allergic responses to various allergens. However, a decrease in IgE levels may indicate the effectiveness of desensitisation, a process aimed at reducing the body's allergic reactivity. Wang et al. (2020) conducted a study investigating the effect of SCIT on plasma IgE levels. By analysing the data, the

researchers found that SCIT led to a significant reduction in plasma IgE levels by 84%. These results suggest that subcutaneous immunotherapy may be an effective method of reducing allergic reactivity by reducing IgE levels. This reduction may reduce sensitivity to allergens and reduce allergy symptoms.

Importance of cytokines level in blood

The levels of cytokines such as IL-4, IL-10, IL-5 and IL-13 are important indicators of the immune response and may reflect changes in the type of allergic reaction and transition to a more neutral state. These cytokines play a role in mediating inflammatory and allergic processes in the body. In a meta-analysis conducted in 2021, researchers evaluated the effectiveness of SCIT by examining levels of IL-5 and IL-13 in peripheral plasma. They also used peak flowmetry data to measure exhalation velocity in patients and compared the difference in dosage of bronchodilators before and after SCIT. The results of the study showed that the use of subcutaneous immunotherapy against house dust mites led to improved peak flow measurements in patients with allergic asthma. This means that SCIT contributed to improved lung function and symptom relief in patients (Bogacz-Piaseczynska and Bozek, 2023.).

Levels of regulatory T-lymphocytes (T cells)

These cells regulate the immune response and the suppression of allergic reactions. An increase in their levels may be related to the effectiveness of desensitisation. Xian et al. (2020) studied the effect of SCIT on the levels of regulatory T-cells, IL-5 and IL-10, and immunoglobulin gamma in blood before and after immunotherapy. The results of the study showed that there was a significant increase in the levels of immunoglobulin gamma, IL-5, and IL-10 as well as the number of regulatory T-cells in the blood 1 year after subcutaneous immunotherapy in the study group. These data indicate a positive effect of SCIT on the immune system and support its role in the regulation of allergic reactions. These results provide further support for the use of SCIT in the treatment of allergic diseases and further research in this area may help to better understand the mechanisms of action of immunotherapy and optimise its use for patients.

Levels of specific markers of arachidonic acid metabolism

5-Hydroxyecosatetraenoic acid (5-HETE) is formed in the body from arachidonic acid by lipoxygenase (LOX) enzymes. Although not very active, 5-HETE can undergo oxidation and be converted to 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE). 5-oxo-ETE is a strong attractant for eosinophils and neutrophils and is the main product of arachidonic acid oxidation in the body. Importantly, 5-oxo-ETE plays an important role in the development of asthma and is a potential treatment target for eosinophilic diseases such as allergic rhinitis and asthma. Reddy et al. (2017) studied the change in the level of arachidonic acid metabolites after subcutaneous immunotherapy against dust mite allergens, there was a significant decrease in their plasma levels after desensitizing therapy.

CLINICAL INDICATORS

Reduction of allergy symptoms

This includes a reduction in rhinitis (runny nose), conjunctivitis (eye inflammation), skin symptoms (redness, itching) and other related allergy symptoms. Valovirta et al. (2006) assessed the effectiveness by evaluating the reduction of rhinoconjunctivitis symptoms in the study group, the reduction of which was the evidence of the effectiveness of this type of treatment, and the dosage of medication needed to treat the clinical symptoms was also assessed, where a reduction in dosage was also considered a positive sign. Vogelberg et al. (2020) compared the efficacy of subcutaneous and sublingual immunotherapy on relapse-free time and improvement in asthma presentation and adherence, where subcutaneous immunotherapy showed the highest efficacy.

The improvement in the quality of life of patients using this technique is also a good indicator of the effect. For example, Nevot-Falco et al. (2020) assessed outcomes by using the visual analogue scale (VAS) to assess the dynamics of clinical manifestations with

therapy, and the mini–rhinitis quality of life questionnaire (miniRQLQ) to examine improvements in patient's quality of life concerning treatment. The results of the study showed that SCIT significantly improves the quality of life in patients with allergic rhinitis. Patients reported a reduction in the intensity of their symptoms and an improvement in their general condition. This demonstrates the positive effect of subcutaneous immunotherapy on patients' living conditions. Thus, evaluating the effect of SCIT on patients' quality of life using various tools, such as VAS and miniRQLQ, allows a more complete and objective study of the treatment outcomes of allergic rhinitis and determines the effectiveness of this therapy.

Reduced medication use is an important indicator of the effectiveness of SCIT in the treatment of allergic reactions. A reduction in the need for anti-allergy drugs, such as antihistamines and glucocorticosteroids, may indicate positive desensitisation results. Contoli et al. (2023) studied the effectiveness of subcutaneous immunotherapy in the treatment of allergic rhinitis caused by house dust mites and tree pollen. The study assessed the need for continued administration of vasoconstrictors, which are commonly used to relieve the symptoms of allergic rhinitis. They noted that subcutaneous immunotherapy can significantly reduce the need for continuous vasoconstrictor medication in patients. This demonstrates the positive effect of desensitisation on the symptoms of allergic rhinitis and the long-term benefits of this treatment. Moreover, reducing medication use can have a positive effect on patients' overall health and improve their quality of life.

REACTION TO PROVOCATION

Provocation tests are useful in medicine for assessing allergic reactions by giving the patient a controlled dose of an allergen. These tests allow to observe changes in the strength or lack of response to provocation, which may indicate progress in desensitisation, a process aimed at reducing the body's allergic sensitivity. One study published in 2011 investigated the effectiveness of SCIT using provocation tests for birch pollen allergens. In this study, the researchers studied the response to provocation in patients and came to important conclusions. They found that SCIT promotes desensitisation to the allergen and requires a higher dose of the allergen to trigger an allergic response in patients with BA. This indicates a positive effect of SCIT on allergy sensitivity levels and treatment progress. It is interesting to note that some patients have achieved complete tolerance to this type of allergen as a result of subcutaneous immunotherapy. This means that their body has become completely insensitive to the allergen, and they do not require additional treatment to prevent allergic reactions (Mauro et al., 2017).

The combined methods used in meta-analyses and randomised clinical trials include a wide range of indicators focusing on the quality-of-life measures, improvements in clinical presentation and functional tests, as well as the safety of subcutaneous immunotherapy and provocative test results. In a meta-analysis by Dhami et al. (2017), the efficacy of BA control after SCIT was studied by evaluating the required medication dosage, improvement in quality of life, and improvement in pulmonary function parameters: peak expiratory flow rate (PEFR), FEV1 and forced expiratory flow at 25-75% of FVC 25-75%), and the effect of therapy on bronchial hyperresponsiveness to specific allergens such as artemisia pollen and *Alternaria alternata* was also studied. These criteria showed different aspects of the effectiveness of SCIT and provided maximum information on the efficacy, safety, and tolerability of this treatment. Another meta-analysis by Tie et al. (2022) evaluated the clinical manifestations of rhinitis before and after treatment, the need for medication and an assessment of the required dosage to control the clinical manifestations of allergy, as well as an assessment of the quality of life through the specified rhinoconjunctivitis quality of life questionnaire (RQLQ). In a randomised controlled trial by Bogacz-Piaseczynska and Bozek (2022), the eczema area and severity index (EASI), the percentage of affected skin to body area, plasma IgE scores, improvement

in quality of life and the need for drug therapy for AD before and after SCIT served as performance mediators. Valero et al. (2022) meta-analysis used a VAS to assess clinical efficacy, a quality-of-life questionnaire and an assessment of the reduction in vasoconstrictor dosage in allergic rhinitis patients who received SCIT therapy.

The effectiveness of desensitisation, or subcutaneous immunotherapy, can vary considerably for each patient. This is caused by various factors that can affect the results of treatment. One key factor is the type of allergy, as different allergens can cause different immune responses in patients. The duration and intensity of treatment are also important. Subcutaneous immunotherapy is usually administered over several years, with the dose of allergen gradually increasing. This allows the body to gradually adapt to the allergen and develop a tolerance to it. However, the optimal duration and intensity of treatment can vary from patient to patient and must be determined by the physician based on individual characteristics and needs. Evaluation of the effectiveness of desensitisation requires a comprehensive approach and should be carried out by an experienced medical professional. Clinical and laboratory data, such as allergy symptoms, provocation test results, IgE antibody levels and cytokines, play an important role in assessing the effectiveness of treatment. This approach makes it possible to determine the progress of desensitisation more accurately and to make appropriate adjustments to treatment protocols to achieve maximum results in each patient.
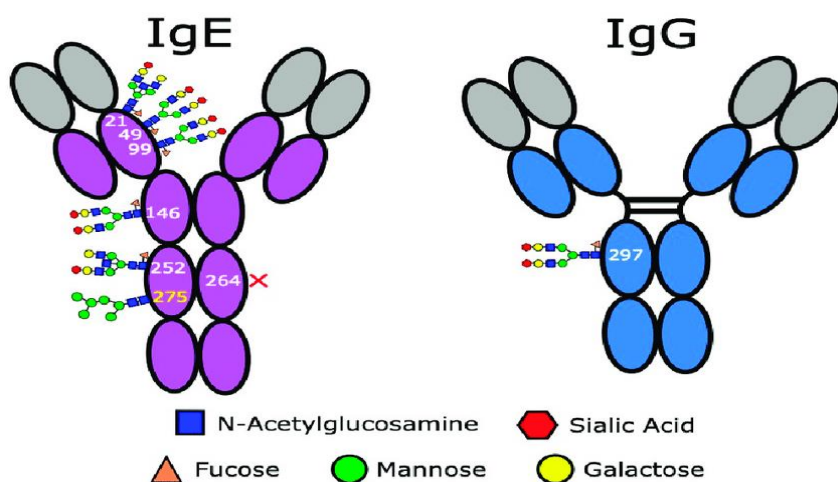

Figure 1: Differences between immunoglobulin E (IgE) and G.
Source: Chauhan et al. (2020).

Conclusion

Based on an analysis of the available literature on subcutaneous immunotherapy (desensitisation) therapy against tree pollen (hazel, birch alder), cereal pollen, artemisia pollen, *Alternaria alternata* and house dust mites efficiency mediators, the following conclusions can be made. Levels of cytokines such as IL-4, IL-5, IL-13, TNF-α are important indicators of the immune response and can be used to assess the effectiveness of subcutaneous immunotherapy. Changes in the levels of these cytokines after immunotherapy indicate a decrease in allergic reactivity and desensitisation. Arachidonic acid metabolites, including 5(S)-HETE, 8(S)-HETE, 11(S)-

HETE, 15(S)-HETE and 11-hydro TXB2, may also mediate the effectiveness of subcutaneous immunotherapy. Changes in their levels after therapy reflect the inflammatory and immune regulatory processes associated with allergic reactions. Clinical parameters, including patients' quality of life, duration of a positive outcome, reduction in the need for continuous medication or reduction in doses required for attack control, FVC, FEV1 and symptoms of allergic rhinitis and dermatitis are also important mediators of the effectiveness of subcutaneous immunotherapy. An improvement in these parameters after immunotherapy indicates a reduction in symptoms and an improvement in the patient's quality of life.

The effectiveness of SCIT is optimally assessed using integrated approaches that encompass both clinical and immunological criteria, allowing for a comprehensive evaluation of a patient's response to treatment. Clinical criteria analyze symptoms, diagnostic results, and overall therapeutic response, while immunological criteria assess the immune system's state and its influence on treatment outcomes. Tailoring these criteria to individual needs enhances diagnosis and treatment effectiveness, providing precise and personalized patient care.

In the long term, developing a standardized SCIT performance assessment protocol would enable more objective and systematic evaluations across various clinical trials. This protocol might include clinical indicators such as symptom measurement, reaction severity, and medication effectiveness; immunological parameters like specific antibodies and cytokines; and quality of life assessments through patient questionnaires. Additionally, tracking the duration of SCIT's effects is crucial for a comprehensive effectiveness assessment. The creation and implementation of such a protocol would require extensive research and collaboration across clinics to ensure it accommodates diverse patient characteristics and provides reliable, unified criteria for evaluating SCIT's efficacy.

COMPETING INTERESTS

The author declares that she has no competing interests.

AUTHORS' CONTRIBUTIONS

MZL designed the study, conducted the experiments and performed data analysis, wrote the first draft.

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