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Allergen Specific Immunotherapy and the Effect on Allergy Induced Asthma

By

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Abstract

Allergies are a major public health problem affecting over 300 million people worldwide (Asamoah et. al). An allergic response can occur when a harmless substance, such as tree pollen, is inhaled into the body and mistakenly identified as a harmful substance. Antibodies then bind to the allergen causing a release of chemicals that leads to symptoms such as nasal congestion, runny nose, itchy eyes or skin reactions. For some people, this reaction can also affect the lungs and airways leading to asthma symptoms.

This review analyzes articles from PubMed, Cochran, Clinical Key and references found from UpToDate articles to assess the effect that allergens have on the upper respiratory system on a pathophysiological basis and to evaluate how immunotherapy can be used to decrease the hypersensitive reaction that occurs in people with allergy-induced asthma.

Researchers have found that immunotherapy can decrease the immune system's hypersensitivity and reduce the release of inflammatory cells. As a result, people with allergy-induced asthma were able to increase their immune system and decrease their use of medication and emergency room visits. Through these studies, the effectiveness of both subcutaneous and sublingual immunotherapies were compared in an attempt to provide a better understanding of both methods. These studies faced several challenges, including: the costs of the studies; difficulty controlling outside influences such as pollen levels; and the commitment of each patient to see the trial through to completion.

Results from these studies concluded that immunotherapy can reduce the sensitivity to those allergens that contribute to asthma symptoms in people whose medication therapy cannot

keep their symptoms under control. Although the results of these studies are encouraging, larger studies with greater sample sizes are warranted to reaffirm the knowledge gained in these studies and the positive effects of immunotherapy on people suffering from allergies and allergic asthma.

Keywords: Immunotherapy; Allergic Asthma; Hypersensitivity; Allergies; Asthma; Physiology; SCIT; SLIT.

Introduction

Seasonal allergies are a major problem around the world. Respiratory allergies were the most common type of allergy among children ages 0 to 17 between 1997-2011 with 17% of this population presenting with symptoms (Jackson, Howie, & Akinbami, 2013). Chronic nasal congestion can lead to respiratory problems, and many people treat allergies on a routine basis with over-the-counter medications. Antihistamines and leukotriene antagonists are common medications that can decrease the symptoms of select allergies; however, the use of immunotherapy is the only approach that has been shown to decrease a person's sensitivity to allergies at a cellular level.

People who suffer from allergies are at a higher risk of having asthma which can cause impaired ventilation. Children who are polysensitized early in life face a greater chance of being diagnosed with asthma and have a greater risk of hospitalization for wheezing or asthma (Yukselen & Kendirli, 2014). Immunotherapy is a process that requires a long-term commitment but has the potential to improve the overall health of the patient. A key concern when dealing with patients exhibiting chronic allergies is the progression into allergic asthma, but with

continued education and the use of immunotherapy it is possible to desensitize those patients with allergen-specific immunoglobulins.

The purpose of this scholarly project is to determine if patients exhibiting uncontrolled allergic asthma can benefit from immunotherapy to decrease their sensitivity to specific allergens and lessen their asthmatic symptoms, thus reducing their need for the use of medication and to evaluate the difference in beneficial uses between subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). This scholarly project will also address two different delivery methods of immunotherapy and compare the effectiveness of both.

Statement of the Problem

Asthma and allergic rhinitis are two of the most common chronic medical conditions across the world affecting around 300 million people (Yukselen & Kendirli, 2014). Allergic rhinitis alone has an estimated cost of more than \$2 billion dollars annually within the United States, and roughly 40% of the patients with allergic rhinitis also report coexisting asthma (Mener & Lin, 2016). There is a need for more quality research and evidence-based guidelines to further educate medical providers on the treatment options for patients when it is determined that medications are not effectively managing their allergy and asthma conditions and to demonstrate how immunotherapy can affect these conditions.

Research Questions

- 1) Can immunotherapy decrease the exacerbation of asthma symptoms in patients with allergic asthma as compared to treatment with inhaled corticosteroids?
- 2) In patients with allergic asthma, is subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) a more effective treatment plan in managing to allergic asthma?

Methodology

Research for this scholarly project was obtained by searching each of the PubMed, and Cochrane databases for articles related to immunotherapy and asthma. From this research, articles were selected that included randomized controlled studies, systematic reviews, and observational studies. Several keywords were used when researching articles in these databases including; “allergic asthma”, “hypersensitivity”, “allergies”, “asthma”, “allergy physiology”, “immunotherapy”, “allergy shots”, “SCIT”, and “SLIT”. The sources for the randomized double-blind studies came solely from the PubMed database as the other databases had little to no information regarding double-blind studies. Although there were no age or time restrictions performed during the searches, most articles found focused their research on children varying in ages from 4 to 18 years. Several articles were researched and reviewed to evaluate the physiological effects of allergic asthma to come to a full understanding of its effect on the body. The remaining articles assessed the effect of immunotherapy on medication usage and hospital visits.

The number of studies on the effects of immunotherapy on asthma were small, and a majority of those studies focused on household dust mites (HDM) specifically.

Review of Literature

Having allergies can mean something different for each person. There are some people who only have seasonal allergies, and they make do with over-the-counter medications as needed. Others have year-round symptoms but manage them with over-the-counter drugs such as loratadine or fluticasone propionate nasal spray and feel as if this is sufficient to allow them to keep going throughout the day. However, people who suffer everyday congestion and headaches without relief will go to great lengths to improve their quality of life. Most have tried multiple medications and still have problems breathing and functioning to their optimal potential. With a projected surge in the world's urban population it is estimated that by 2025 an additional 100 million people may develop asthma, and therefore asthma is set to become one of the world's most prevalent chronic diseases (Asamoah et al., 2017). Traditionally, immunotherapy has been the last resort for a lot of people, but for some it can be a life-changing experience.

Pathophysiology:

An allergic response occurs when a harmless allergen is inhaled into the body and the immune system's antibodies mistake that allergen as a harmful substance with a prevalence of allergic rhinitis occurring in 5% to 22% of people with allergies (Khan, 2014). The body binds to the allergen to protect itself causing a release of chemicals leading to one's symptoms of nasal

congestion, runny nose, itchy eyes, and skin reactions. This release of chemicals can even affect the lungs and possibly lead to asthma.

Asthma is a common disease that affects 5% to 16% of people worldwide. Although 19% to 38% of patients with allergic rhinitis have concomitant asthma, a much higher frequency of patients with asthma have concomitant allergic rhinitis (Khan, 2014). Allergy sensitization occurs within the body when an antigen-presenting cell, like a macrophage, is present in the mucosal surface of the body and it detects an allergen that has been breathed in through the nose or mouth. At this time the antigen will be taken up by the antigen-presenting cell and displayed on its surface. The antigen-presenting cell will then migrate toward the T-lymphocyte and present the allergen to it which, in turn, stimulates B-cell to produce specific antibodies to the allergen (Singh, Mehrotra, & Agarwal 1999). The antibodies that are produced are known as the IgE immunoglobulins, and they will attach themselves to high-affinity receptors on the surface of the mast cells. At this point the patient's body has become more sensitive to the specific allergen so when the patient's body encounters the same allergen again IgE will stimulate the mast cell to activate resulting in degranulation and leading to an inflammatory response. It is thought that the most crucial function of IgE in allergic diseases is its ability to sensitize mast cells to release biologically active mediators in an antigen-specific manner (Galli & Mindy 2012). This will include mostly histamine and other mediators such as leukotrienes and prostaglandins.

The mast cells activated by IgE and specific antigens produce mediators that drive early phase reactions and contribute to late phase reactions, but these mast cells also secrete diverse cytokines, chemokines and growth factors that have the potential to influence airway remodeling (Galli & Mindy 2012).

The leukotrienes increase microvascular permeability that results in edema and narrowing of the airways and stimulate the secretion of mucus in the lower respiratory tract. This damage contributes to the chronic changes seen in patients, such as airway remodeling and associated airway hyperresponsiveness.

Allergen-specific immunotherapy (SIT) can modify the course of allergic disease by preventing exacerbation, reducing the risk of new allergic sensitizations, and deterring the development of clinical asthma in children treated for allergic rhinitis. Furthermore, one of the main goals of SIT is to achieve sustained clinical effects in post-treatment follow-up over a recommended period of three to four years (Karakoc-Aydiner et al., 2015).

Allergen Specific Immunotherapy (ASI) is administered by giving small predetermined doses of allergens to patients over a period (usually several years) and tapered to promote immune tolerance, while bettering allergic symptoms (Akdis, 2017). SIT is the only treatment that may change the natural course of allergy sensitivities from transforming into allergic asthma and reduce the risk of acute respiratory exacerbations (Akdis, 2017). Traditional medication with inhalant corticosteroids may help alleviate the symptoms associated with allergic asthma, but only ASI has the potential to change the natural course of allergic asthma by reducing the risk of respiratory exacerbations and symptoms.

While the mechanism of action of SCIT is not fully understood, it is based on the principle that repeated allergen exposures in allergic individuals results in immune tolerance by reducing the sensitivity to the allergen (James & Till, 2016). An initial early step in SCIT may be the H2-dependent suppression of a high affinity IgE-receptor that is expressed on the surface of the mast cells.

Examination of the T cell response demonstrated that both Th2 (IL-4, IL-5 and IL-13) and Th1 (IFN- γ) cytokine production was decreased while IL-10 levels were increased. These IL-10 producing T cells were able to suppress allergen-specific T cell proliferation and activation and are now recognized as regulatory T (TReg). While the appearance of the IL-10 producing TReg is rapid, within seven days of starting bee venom SCIT, full tolerance if it is going to occur requires three to five years of treatment (Steinke & Lawrence, 2014).

Theme 1 - In patients with allergic asthma, can immunotherapy decrease the exacerbations of asthma symptoms compared to inhaled corticosteroids?

Blumberga, Groes, Haugaard, & Dahl (2006) performed a randomized, double-blind, placebo-controlled trial with household dust mites (HDM) allergic individuals with asthma to examine the steroid-sparing effects with the use of SCIT. Those accepted into the trial were chosen from the outpatient clinic of the Aarhus Kommune hospital, from general practitioners in the Aarhus area. Criteria for those included into the trial were: 18-60 years of age, allergy to HDM (*Dermatophagoides pteronyssinus*, *D. pter*), shown to have a positive skin prick test greater than 3 mm and allergen-specific IgE serum, perennial asthma with regular symptoms requiring long-term treatment with inhaled corticosteroids, and a case history of allergy to HDM as the cause of the asthma symptoms. Subjects were omitted from the trial if they exhibited: a positive skin prick test to cat or dog and had daily contact with a pet; positive skin prick test to the fungus *Cladosporium herbarum* or *Alternaria alternate*; previous HDM immunotherapy; use of inhaled long acting beta agonist during the study; or treatment with beta-blockers. Once chosen for the trial, patients were randomized into the SCIT to receive injection of *D. pter* or a

placebo group that would receive injections containing histamine dihydrochloride. During the trial there was a baseline period that was followed by three years of immunotherapy treatment. During the baseline period, inhaled corticosteroid (ICS) were adjusted with a stepwise approach to define the lowest dose needed to maintain asthma control. This was performed by treating all patients with inhaled fluticasone propionate (FP). The daily dose of ICS was stepwise reduced every three weeks until their asthma was no longer controlled. Lack of control was determined when two or more of the following criteria were fulfilled: increase in total symptom scores over seven days by ≥ 7 or a daily symptom score by ≥ 3 over two consecutive days; increase in total number of salbutamol inhalations over seven days by ≥ 7 ; or morning peak expiratory flow $\leq 90\%$ of baseline for a minimum of four days of the seven. When the criteria were met, treatment was continued with dosage one step higher for the trial. During the treatment phase, this stepwise reduction was repeated after the 1st, 2nd, and 3rd year of therapy. Dose adjustments were not allowed at any other time during the trial. The immunotherapy process was performed with an up-dosing performed during an eight-week period with two to three injections received weekly followed by maintenance treatment for the next three years. Patients were asked to complete daily diaries during the month of January before starting their immunotherapy and after treatment for the remaining three years. Asthma symptoms were to be recorded for showing signs of breathlessness, coughing, wheezing, and chest-tightness. Then asthma symptoms were further broken down by daytime and nighttime asthma symptoms on a six-point scale (0-5, with zero indicating no symptoms and five indicating severe symptoms). The use of the medication (salbutamol) was also recorded in the diaries. Exposure to HDM allergens were evaluated each January by mattress dust sampling, but no measures were taken to reduce HDM. An analysis of the difference in treatment between SCIT and the placebo was performed by using the Wilcoxon

Rank Sum Test on a 5% significance level. A total of 112 patients were willing and eligible for screening and 54 of those 112 patients were randomized into the study. After the second year of treatment, a secondary analysis showed that the modification between the two groups was statistically significant ($p = 0.03$), with a median reduction of 50% in the ICS dose for the active group and 25% in the ICS dose for the placebo group. In addition, after three years of treatment the median ICS dose reduction was 82% in the active group and 42% in the placebo group ($p = 0.17$). This corresponds to a median ICS dose of 1000 μg FP daily at baseline to a median ICS dose of 250 μg FP daily after three years of active SCIT. For the placebo group, the median ICS dose decreased from 750 μg FP daily at baseline to a median ICS dose of 500 μg FP daily. In conclusion, it was found that inhaled corticosteroid sparing effects were evident in the patients with moderate persistent asthma.

This study was limited by its pool of subjects because it only accepted patients from the outpatient clinic of Aarhus Kommune hospital and from general practitioners in the Aarhus area. Broadening the search area for potential patients would have provided the study with a more diverse group and potentially more accurate statistics.

Hui et al. (2014) executed a three-year randomized, double-blind, placebo-controlled trial studying the effects of SCIT on allergic asthma. The study focused on the allergen of house dust mites and a sample of children ranging in ages 5-14 years of age with asthma symptoms. The patients were separated into two groups: the treatment group ($n=45$; males, 24 and females, 21); and the control group ($n=45$; males, 22 and females, 23). With regards to the baseline parameters there were no statistical differences between the two groups, such as age, gender, duration of asthma, and dose of inhaled corticosteroids (ICS). Those within the treatment group received weekly injections of house dust mite serum starting at 20 U/ml with increased

concentration weekly. The patients in the control group were treated with a desensitization vaccine. Patients in each group were also treated with ICS according to a pediatric asthma control trial. The ICS treatment was revised every one to three months throughout the trial. Once a patient's symptoms of asthma had been under control for three months the dose of ICS was decreased. If the patient had been observed as asthma free for six months, then a complete withdrawal from ICS was issued. Over the three-year period of the study, ICS doses were shown to gradually decrease within both the treatment group and the control group; however, the treatment group showed a significantly greater drop in the use of ICS than did the control group. The discontinuation rate of ICS in the treatment group was (28.9%) as compared to the control group's discontinuation rate of (20.0%). Asthma symptoms were recorded during daytime and nighttime throughout the trial. The asthma symptom scores of the treatment group compared to those of the control group declined from baseline during the trial just as the ICS dose decreased. This data demonstrates that asthma symptoms were significantly lower each year of the trial group as compared to those of the control group ($p < 0.05$), indicating that SCIT is effective and safe for the treatment of children with allergic asthma to alleviate asthma symptoms and reduce the doses of ICS that are required.

This study was limited by type of allergen because it only tested the subjects against household dust mites. Since multiple allergies typically affect people, more tests should be performed with a larger group of allergens.

Karakoc-Aydiner et al. (2015) performed a three year analysis of the use of SCIT for children with a longstanding history of allergies who experienced little or no symptomatic relief by using pharmacotherapy. Forty-eight individuals with mild to moderate persistent asthma and/or rhinitis were selected for participation according to the Global Initiative for Asthma

guidelines (GINA) who were sensitive to house mites and who had been seeking treatment at a facility for a minimum of two years using corticosteroid therapy without improvement. The qualified patients were given subcutaneous immunotherapy and their symptoms were checked at baseline, one year, and three years of treatment by using a four-point scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe symptoms). A total medication score was also obtained by having patients score their use of medications as follows: beta-2 agonists, 1 point; inhaled/intranasal corticosteroids, 2 points; and 1 corticosteroid tablet, 3 points. During the trial asthma symptoms significantly improved 3 years after treatment in the SCIT group when compared with baseline ($p = .03$). The total asthma symptom score (cough, wheezing, breathlessness, dyspnea) for those receiving SCIT at baseline was 1.1 (0.8) and by year three was 0.14 (0.26). Showing an 86% improvement in score throughout the trial. The SCIT group showed a reduction in total medication score at the end of three years when compared to baseline ($p = .01$) with the control group. Baseline numbers for SCIT were 2.5 (1.2) and at three years 0.3 (0.7) for an 82% improvement. When looking at the lung function there was not a statistical difference to show any benefit to the use of SCIT. While using SCIT there was a significant increase in the number of specific IgG4 levels at both the one year and three year checks as compared to baseline, but no specific changes in the IgE levels. Karakoc-Aydiner et al. (2015) continued to discuss the unknown function of IgG4 in the reaction of allergies but speculated that it was the quality and not the quantity of pollen-specific IgG4 that correlated with the clinical response after SCIT, suggesting that serum inhibitory antibodies might be useful immunological markers for monitoring SCIT response. The conclusion at the end of the trial was that by adding SCIT, patients' symptoms showed a significant improvement in the four-point scale, and their

asthma symptoms were in the frequency of daily symptoms and medication use with SCIT as compare to using only corticosteroids therapy.

This study was limited by its method since it was not a double-blind or a placebo-controlled trial. Because of this, the statistical figures obtained are subject to debate.

Maestrelli, Zanolla, Pozzan, and Fabbri (2004) used a randomized, double-blind, placebo-controlled trial of 72 individuals ranging in ages 8 to 43 (32.6% < 18 years old) discussing the possible benefits in the use of immunotherapy to individuals who have an allergen to house dust mites and suffer from asthma. Each subject was carefully selected based on their severity of mild to moderate asthma, sensitivity to dust mites upon a skin test, and the presence of serum-specific IgE (\geq class 3). Patients were rejected from the trial if any of the following presentations were found during the screening process: respiratory diseases other than asthma; cardiovascular or immunologic diseases or other severe illnesses; active smoking status; FEV₁ persistently less than 70% of predicted value; previous immunotherapy with household dust mites (HDM) within three years from the start of the study; recurrent asthma exacerbations or more than two emergency hospitalizations for an asthmatic attack in the previous year; or work-related symptoms of asthma or occupational asthma. Patients were recruited for the study over a five-month period and, if accepted into the trial, studied for four years. First, a one-year observation period was conducted in order to stabilize patients' symptoms. After the observation period, an investigator independent from the treatment team randomized each patient to receive SCIT or a placebo injection for three years. Each patient's asthma was monitored for sensitivity during the trial, and drug treatment guidelines were specified according to the recommendations of GINA. Salbutamol (metered-dose inhaler (MDI), 100 μ g) was used as a bronchodilator. Beclomethasone dipropionate (MDI, 250 μ g per actuation) was chosen as the anti-inflammatory

agent used during the trial. For the duration of the trial no other anti-inflammatory drugs were allowed, except antihistamine tablets for rhinitis. Throughout the trial a clinical assessment was performed each year in February or March (visit 1), May (visit 2), September or October (visit 3), and December (visit 4). Upon each visit, spirometry measurements were performed and, if needed, drug treatment was modified depending on the severity and clinical presentation of asthma. Twenty-three of the initial 95 subjects withdrew from the trial before its conclusion (15 within the placebo group and eight within the active treatment group). At the end of the three-year trial, the proportion of subjects that did not use bronchodilators was reviewed. For subjects within the control group, in the observational year 26.4% of patients did not use a bronchodilator, in year 1 it was 24.2%, in year 2 it was 24.2%, and in year 3 25.3% did not use a bronchodilator with a difference from the observational year of -1.1%. In contrast, subjects within the treatment group began the observational year with 22.1% not using a bronchodilator, year 1 it was 25.3%, year 2 it was 24.1%, and by year 3 the number increased to 28.5% of the subjects not using a bronchodilator. This results in a difference of +6.4% with a $p < .01$ which is a significant reduction in the use of a bronchodilator for the treatment group and suggests a positive response to immunotherapy treatment for those with allergic asthma.

This study was limited by the low number of participants that were involved. A larger number of patients would provide more accurate statistics when compared to the population as a whole.

Mathur and Viswanathan (2014) reviewed studies pertaining to allergic asthma in both children and adults. One study of 639 adults demonstrated no correlation between the increased sensitivity of a skin prick test to asthma symptoms, quality of life, emergency room visits, hospitalizations, lung function or response to treatment. Therefore, while atopy has the potential

to be present in those with asthma, it is not clear whether atopy is a predictor of the severity of asthma. In contrast, with children, there is evidence showing that the presence of atopy in early childhood is a risk factor for the subsequent development of asthma. One of the studies conducted with 147 children ranging from birth to 10 years of age showed that there was a relative risk of 17.14 of the subjects having asthma at 10 years of age as well as the presence of atopy at the same age. The study found that controlling the airway is an important step in controlling the subjects' symptoms. Using corticosteroids to lower the eosinophils or mepolizumab to neutralize monoclonal antibody to IL-5 to reduce eosinophils has shown to decrease the number of exacerbations in adults with eosinophilic or steroid-dependent asthma.

This analysis was limited because it was not a double-blind or placebo-controlled trial. Instead, it was a review of other studies that have been performed and this review does not give any reasonable explanation as to how the numbers were obtained; therefore, they are not as reliable.

Mener and Lin (2016) performed a comprehensive literature review of articles dated as recently as 2016 to conclude that immunotherapy can help to reduce the symptoms of asthma for those suffering with allergies. They analyzed the function of T-helper 1 (Th1) and T-helper 2 (Th2) cells to show how the body reacts to an allergic reaction and why allergen specific immunotherapy can be effective in a reduction in corticosteroid use as well as inhalers. There were 34 randomized control trials that were used as the basis for these results. The subjects of the trials consisted of 920 children ranging in ages from four to 18 with allergic asthma or rhinoconjunctivitis with dust mites being the most highly sensitive allergen. The trials found that in children with at least mild asthma undergoing three years of SCIT to *D. pteronyssinus* and *D. farinae*, nearly 70% may have a clinically significant response. Another systematic review of 61

studies with subjects in ages ranging from seven to 71 that evaluated single-allergen immunotherapy regimens showed high-grade evidence that SCIT improved asthma symptoms. However, there was low strength of evidence that SCIT improved areas of lung function despite many the studies showing improvement of bronchial hyper-reactivity compared to those in the placebo group.

This review was limited because it was a meta-analysis and not a double-blind or placebo-controlled study. Reviewing many studies does provide valuable information, but a review does not explain how the underlying statistics were obtained. Because of this, the numbers are subject to debate.

Theme 2 - Is subcutaneous immunotherapy a more effective treatment plan sublingual immunotherapy in response to allergic asthma?

Asamoah et al. (2017) performed a meta-analysis on multiple studies searching nine electronic databases from inception to October 31, 2015. Systematic reviews were independently screened by two reviewers against pre-defined eligibility criteria and critically appraised using the Critical Appraisal Skills Programmed quality assessment tool for systematic reviews. Data was descriptively and thematically synthesized. These studies focused on deliveries of allergen immunotherapy (AIT) through the following routes: subcutaneous (SCIT; n = 3); sublingual (SLIT; n = 4); and both SCIT and SLIT (n = 2). The evidence found that allergen immunotherapy delivered by SCIT and SLIT can improve medication and symptom scores and measures of bronchial hyperreactivity. Eighty-eight different articles were analyzed up to 2015 studying the effects of immunotherapy with allergic asthma. The articles mostly focused on children, but a few articles involved adults as well. The studies assessed the overall

health, amount of medication usage, quality of life, lung function, and overall safety while having the SCIT administered. Examples from 10 different studies with 668 people showed that 90% of those tested had improved outcomes for both SCIT and SLIT. Another trial pooled together information from 21 different studies and found allergen immunotherapy resulted in a significant reduction in medication compared to the placebo group.

The most promising evidence for SCIT-focused review of asthma symptom reduction was given by the meta-analysis which included 88 randomized controlled trials of moderate quality randomizing a total of 3,459 asthma patients. Meta-analysis revealed that 35 trials demonstrated significant reductions in asthma symptom scores based upon: the estimated standardized mean difference (SMD) for all allergens combined was -0.59 (95% CI -0.83 to -0.35) for immunotherapy versus placebo, but there was high diversity between studies ($I^2 = 73\%$). The authors concluded that it would have been necessary to treat three patients (NNT = 3; 95% CI 3–5) to avoid one patient's asthma symptoms deteriorating. Patients' asthma symptoms showed the most improvement with AIT on: pollen (NNT = 3; 95% CI 2.0–16.0); animal dander (NNT = 3; 95% CI 2–18); and additional allergens such as molds, chemically modified allergoids or antigen–antibody complexes (NNT = 3; 95% CI 3–4). A smaller improvement was observed following HDM's immunotherapy where six patients would need to be treated to avoid one deteriorating (NNT = 6; 95% CI 4–16).

Eight studies reported on medication scores, all eight used single allergen immunotherapy. The studies included 592 patients. Five out of eight of the studies demonstrated a greater reduction in medication use in the SCIT group as compared to the comparator arm, and two of the studies did not report the direction of change.

A systematic review which included nine double-blind placebo-controlled trials found a statistically significant decrease in allergy symptom scores: SMD -0.95 (95% CI -1.74 to -0.15) in SLIT administration when compared to the placebo group there was high diversity ($I^2 = 92\%$). Furthermore, seven studies enrolling 220 patients analyzing dust mite allergen presented a significant ($p = 0.02$) decrease in rescue medication use: SMD -1.48 (95% CI -2.70 to -0.26) but significant diverse ($I^2 = 96\%$). Subgroup analysis according to age showed a significant reduction in children (SMD -1.86 ; 95% CI -3.34 to -0.38) but not in adults (SMD 0.23 ; 95% CI -0.33 to 0.78).

Finally, a comparison between SCIT and SLIT was performed in the review, which was comprised of four trials of asthma patients with the use of HDM immunotherapy. The information gathered upon completion of the review established a superior reduction in asthma symptoms in three studies with SCIT compared to SLIT, although one study showed greater reduction in symptoms with SLIT. All studies were judged to be of moderate quality. Research of three studies comparing the safety of administration showed that SLIT and SCIT each reported three local reactions. While SLIT never showed any systemic reactions SCIT reported four, including one anaphylaxis event (defined as flushing, wheezing and dyspnea requiring adrenaline) all with positive outcomes. In the end, these studies determined that the overall data obtained demonstrated substantial evidence based on investigation of the effectiveness and safety of immunotherapy for the improvement of asthma with the potential to improve medication usage. There was also evidence to support the theory that the use of SCIT was slightly more effective in treatment compared to SLIT, but the safety aspect to SLIT was superior to SCIT.

This study was limited because it was not a double-blind or a placebo-controlled trial. It was a meta-analysis that provided a lot of valuable information, but it did little to give strong

statistics and demonstrate how those statistics were obtained in order to stand up against criticism.

DaVeiga et al. (2017) discussed the risk of SCIT and the possibility of systemic reactions occurring due to the injections. DaVeiga et al. (2017) stated that over the last 20 years the possibility of a systemic reaction is around 0.25 to 0.51% per individual injection, and patients with exquisite sensitivity to individual allergens may be at an elevated risk for a fatal reaction from SCIT. They continue by stating that it has been theorized that individuals with increased wheal-flares at the time of allergic testing were more highly allergic and have an increased risk of a systemic anaphylactic reaction to SCIT. In their study, they followed patients from 2001 through 2007 while 16,375 SCIT injections were administered. During this time there were a total of 46 systemic reactions that occurred in 20 patients. A rate of a systemic reaction occurred in 0.28% of patients per injection visit with a mean age of 36 with 65% being female, 90% white, and 35% with asthma. It was also concluded that 63% of the systemic reactions occurred in patients with prior systemic reactions, and 83% of reactions occurred within the buildup to maintenance phase. It was also shown that 50% of the reactions occurred within 30 minutes of receiving the injection, 39% occurred within 30 to 60 minutes of the injection, and 11% occurred after 60 minutes of the injection. If a severe reaction did occur, it was within the first 30 minutes after injection, and 28% of those required the use of an epinephrine pen for treatment. All patients made a full recovery. After looking at their research of each patient they were able to conclude that those who had experienced a severe reaction to their allergy skin testing with larger wheals obtained were six times more likely to experience a systemic reaction compared to those where were not highly allergic (OR = 5.83; 95% CI:1.23-27.59, $p = 0.026$). They also

determined that the estimated odds of experiencing a systemic reaction increased by 17% for each additional four plus skin test results.

This study was limited because it was not a double-blind or a placebo-controlled trial and it lacked sufficient controls. While the authors did conduct their own research, questions regarding the accuracy of the results could be posed because of the study's lack of controls.

Khinchi, Poulsen, Carat, Andre', Hansen, and Malling (2003) performed a randomized, placebo-controlled, double-blind, double-dummy study comparing sublingual and subcutaneous immunotherapy in people allergic to birch pollen. They began with 89 patients with a mean age of 30, having at least two years of seasonal birch pollen rhinoconjunctivitis. The birch pollen allergy was confirmed by a positive skin-prick test and a positive conjunctival provocation test using a standardized extract and the presence of specific IgE using the CAP system (a new solid-phase immunoassay, fully automated, used for the titration of specific IgE antibodies). Patients with mild seasonal birch pollen induced asthma were admitted into the trial. Subjects were excluded based on having perennial allergies, chronic, nonallergic rhinitis or sinusitis, previous immunotherapy with birch pollen within the past five years, and treatment with beta blockers. Based on this criteria, 71 patients were assigned into three groups: SLIT-group: which received sublingual drops and placebo injections; SCIT-group: which received subcutaneous injections and placebo sublingual drops; and Placebo-group: which received placebo sublingual drops and placebo subcutaneous injections. The placebo arrangements were conducted with caramelized sugar for the sublingual and histamine dihydrochloride 0.01, 0.1, and 0.5 mg/ml for injections to give the same appearance of those receiving the actual birch serums. Treatment during this trial took place from September 1997 to September 1999, and the sublingual treatments were self-administered at home while the injections were done in the office. Rhinoconjunctivitis

symptoms were required to be logged in daily diaries during the birch pollen season (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). Each patient was also administered acrivastine, levocabastine 0.5 mg/ml eye drops for self-medication. If a patient's symptoms were uncontrolled by acrivastine 24 mg, levocabastine 6 eye drops and nasal spray levocabastine 6 puffs, then 5 mg prednisolone tablets were administered. Scoring of the medication was as follows: 8 mg acrivastine (4 points); 2 eye drops of levocabastine (1 point); 2 puffs of levocabastine nasal spray (1 point); one tablet prednisolone (6 points). Following each birch pollen season, the patients were asked to assess their quality of life using the Danish version of the SF-36 Health Status Questionnaire. Calculations of the immunotherapy-induced treatments were performed in two different ways. First, by subtracting the pretreatment values for each patient from the data obtained during the treatment seasons. The first treatment season showed an improvement of the median rhinoconjunctivitis symptom score by 0.36 score points (on a 0-3 scale) in the SLIT-group (95% CI 0.18-0.86), by 0.75 score points in the SCIT group (0.02-1.31) and deterioration by 0.2 score points in the Placebo-group (-1.05-0.22). The median medication scores showed an increase in scores as well with 0.29 in the SLIT-group (-2.57-0.82), no change in the SCIT-group (-1.52-2.65) and an increase by 1.35 score points in the Placebo-group (-4.04-0.12). These numbers infer a statistically significant difference of changes with rhinoconjunctivitis scores ($p < 0.002$) and medication scores ($p < 0.02$) comparing the SLIT-group to the Placebo-group. The SCIT-group was also shown to be statistically significant when compared to the Placebo-group ($p < 0.002$ and $P < 0.002$, respectively). However, there was no statistical difference seen when comparing the SLIT-group and the SCIT-group to each other. The second method used for calculations evaluated the first treatment season, in 1998, relative to the pretreatment season. The exposure of pollen during the first treatment season was 2.29 times

higher when compared to the pretreatment season. As a result, the placebo-treated patients symptoms scores decreased by a factor of 1.45 (0.87-2.09) and their medication score increased by a factor of 2.01 (1.02-3.56). The SLIT-group improved in symptoms by a factor 0.78 (0.6-1.06) and decreased medications score by a factor 1.03 (0.77-1.75) ($p < 0.01$ and $p < 0.05$) resulting in the disease severity being only half of what the Placebo-group was. The SCIT-group's symptoms increased by a factor 0.48 (0.28-1.02) and reduced medications score by 0.78 (0.3-2.0) showing a disease severity of one-third of the Placebo-group ($p < 0.001$ and $p < 0.02$). As with the first method though, there were no significant differences found between the SLIT-group as compared to the SCIT-group.

This trial was limited because it did not contain a large enough number of participants in order to provide a good representation of the general population. The trial was performed with a high quality as compared to others, but a larger number of participants are needed in order to gain a full understanding of the potential effects of immunotherapy on the general population.

Pokladnikova, Krcmova, and Vlcek (2008) conducted an open-label randomized clinical trial that was carried out from January 1, 2002 to January 1, 2006, examining the effectiveness of SLIT vs SCIT over a three-year period to determine which is more effective not only with individual symptoms but with costs as well. A total of 64 patients were randomly selected to take part in three study groups: SLIT, SCIT, and control. Those in the SCIT group were administered treatment within the clinic, while the SLIT group self-administered at home. All patients were at least 18 years of age and had a history of seasonal allergic rhinoconjunctivitis (SARC) for at least two years that was uncontrolled by symptomatic treatment, and moderate persistent rhinitis (according to the classification of seasonal allergic rhinitis severity based on Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations, 2001). Each year of the

trial, patients were asked to evaluate the severity of rhinoconjunctivitis symptoms during the peak of pollen season before and after immunotherapy treatment. The evaluation was measured using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) to obtain its data. The study compared the proportion of clinically improved patients in the third year of SLIT to the first year of immunotherapy. For each of the groups reviewed, a clinically significant difference was observed if the calculated score was at least greater than 0.5 points. After a decrease in the medication usage related to SARC, it was calculated as mean defined daily dose (DDD) per anatomical therapeutic class (ATC) using the ATC/DDD methodology. Data was then categorized among the groups and examined using the χ^2 test or Fisher exact test (2-tailed). Kruskal-Wallis, Wilcoxon tests, analysis of variance, and paired t test were used for variables, with normal distribution, $p < 0.05$ considered as statistically significant. Of the 64 people within the study, 19 received SLIT (SLIT, $n = 19$), 23 received SCIT (SCIT, $n = 23$), and 22 were in the control group (Control, $n = 22$). Four of the patients who began in the SLIT and control groups were withdrawn from the trial before the final results were obtained. No statistically significant differences in characteristics were found between the groups within the baseline. By the end of the trial the number of clinically improved patients measured by the RQLQ did not significantly differ between the SLIT and SCIT groups (RQLQ for the SLIT vs SCIT group: 41% vs. 48%, $p \geq 0.75$). During each year of the trial there was a clear decrease in the need for symptomatic medication for the SLIT and SCIT groups, but no significant decrease was indicated for the control group (SLIT group -56DDD, SCIT group -70DDD; control group 6DDD; $p = 0.002$). The study found a significant decrease in symptomatic medication was reached within the first and second year of immunotherapy treatment, and SCIT patients showed a marginally increased clinical outcome. As for the cost to the patient, SLIT was received at a slightly lower cost when

compared to SCIT therapy (\$206 vs \$299, $p = .34$). Copayments for the allergen extracts (\$84 for SLIT vs. \$65 for SCIT; $p < .001$) and loss of income were the main factors when considering the overall costs. If the cost of SCIT itself was considered as a fixed cost, then SCIT was approximately one third less expensive when compared to SLIT (27%, \$88 vs. \$69; $p < .001$). While there was a higher dropout rate in this study, Pokladnikova et al. (2008) does state that recent studies show noncompliance rates of up to 50% of patients starting SCIT because of the inconvenience of weekly shots in the clinic and travel time.

In order to evaluate costs, the study considered the following factors: direct medical costs, including costs of medication and health care services; costs arising from adverse effects of treatment (medication, emergency department visit, hospitalization); and health care service costs, including specialist visits (consultations, laboratory tests, diagnostic tests, nurse services), emergency department visits, and hospitalizations. The health care services costs were calculated by multiplying the number of units per service and the unit price. The medication costs were determined from the number of DDDs and the cost per DDD. Travel costs were computed by multiplying the number of specialist visits and travel costs per specialist visit.

This study was limited because it was not a double-blind or a placebo-controlled trial and it was based on foreign costs and currency. It also lacked the number of participants needed to represent the population with good statistical numbers. This study was performed overseas and although the currency was converted into U.S. dollars for the purposes of the cost analysis, the costs do not exactly represent the types and amounts of costs that patients located in the United States would experience when undergoing the same type of treatment.

Saporta (2012) performed a retrospective, consecutive chart review of allergy patients to determine the effectiveness of SCIT vs. SLIT. A total of 93 patients were selected that met the criteria of any age with nasal allergies with or without asthma that has been treated with immunotherapy for the past six months and has also had two evaluations. The evaluation implies symptom scoring, evaluation of medication usage, and determination of the peak flow meter (PFM) value. Evaluations were performed during the trial every three to six months to assess patients progress. Scoring systems used were based off the scoring of symptoms from none to severe, presence of asthma, and a recording of allergic activities. Pre-treatments were evaluated and the amount of medications the patient was taking at the time reflected severity without the use of immunotherapy treatment. Then the patients were established with a SCIT or SLIT form of immunotherapy based on consideration of each patient's distance from trail, age, allergen severity, and needle phobias with 50 patients receiving SCIT and 43 patients receiving SLIT. The study was managed so that there were no statistical differences between the two groups, therefore the patients' reactivity to allergens in both groups can also be considered the same. As a result of the trial it was concluded that wheezing and coughing seemed to respond to either SCIT or SLIT with coughing slightly better with SCIT ($p = 0.37$) and wheezing better with SLIT ($p = 0.024$), and improvement of asthmatic symptoms as well as decreases in short-acting beta agonist (SABA) use was significant at $p < 0.05$. The study resulted in findings that validate the theory that SLIT can be as effective as SCIT to regulate the symptoms of nasal allergies of patients with or without asthma as well as decrease medication usage. However, considering the increased risk and difficulty in treating younger children it can be suggested that SLIT should be considered the main treatment plan for these patients and that SCIT only be used in times of SLIT failure.

This study was limited in that it was a retrospective chart review and not double-blind or a placebo-controlled trial.

Yukselen and Kendirli (2014) performed a meta-analysis from several studies to evaluate the effectiveness of both SCIT and SLIT in patients with allergic asthma. While analyzing studies of SCIT, 24 prospective, randomized, studies involving 962 asthmatic patients was performed and showed a significant improvement in symptoms and drug intake related with asthma as compared to the placebo group. Concluding immunotherapy was beneficial in 17 (71%) studies, inefficacious in four (17%) studies, and equivocal in three (12%) studies. With each study being done it was determined that significant steroid-sparing effect of immunotherapy was shown in moderate persistent asthmatic patients included in those studies. In another study looking at the effect of SLIT, 452 patients were treated and a marked improvement in symptoms and a drop-in medication usage was seen regarding asthma. As with SCIT, the steroid sparing effect of SLIT was observed with the trial. Additional studies were conducted comparing SCIT and SLIT to determine if there was a difference in the outcome of treatment. The study elected to treat patients with asthma and rhinitis with SCIT, SLIT, or a placebo for one year to determine the outcome. The study found that one year of SCIT improved symptom scores of both rhinitis and asthma while SLIT had benefits only on symptoms of rhinitis. However, medication usage of both rhinitis and asthma showed a significant decline in both treatment groups. Another group performing a randomized control trial found similar results stating they observed that the effect of SLIT on asthma symptoms and drug intake was less eminent than SCIT in the first year; however, the effect of SLIT was more noticeable in the second year. This group concluded that both clinical and immunologic improvement begins earlier with SCIT when compared to SLIT in mite-allergic children with rhinitis and asthma. Yukselen goes on to discuss the safety aspect of

immunotherapy. He found that SCIT has a risk for both local and systemic adverse reactions; however, if detected and treated early the symptoms are reversible. It was also found that asthma could be a risk factor for the systemic reactions of SCIT so those with uncontrolled asthma should delay SCIT until their symptoms are better controlled. SLIT was investigated specifically with grass pollen in patients with asthma. Evaluations of side effects potentially related to asthma, such as cough and wheezing, were observed and no difference was found in the numbers of such effects between the SLIT and placebo group, and no asthma exacerbations were reported in relation to SLIT. In conclusion, SCIT and SLIT have both been shown to be effective in response to allergic asthma. However, SCIT has been slightly more effective with a quicker response time within the first year of treatment. SLIT could be a reasonable alternative for those concerned about the potential side effects of immunotherapy, but if choosing SLIT one must do so with the understanding that it has a slower response time when compared to SCIT.

This analysis was limited because it was a meta-analysis of other studies that have been performed. Due to this, the methods used to determine the statistics that are presented are not thoroughly explained and the numbers become open for debate regarding their accuracy.

Yukselen, Kendirli, Yilmaz, Altintas, and Karakoc (2011) performed a randomized, double-blind, placebo-controlled, double-dummy study over a one-year immunotherapy period. Focusing the study on SLIT and SCIT in terms of their efficacy in children with rhinitis and asthma monosensitized by household dust mites (HDM). To have accurate numbers it was necessary to study each patient's asthma symptoms and establish a baseline level of medication scores. To achieve this, patients were asked to participate in follow-up visits for one year before beginning immunotherapy. Those patients considered for the trial were required to have a clinical history of at least one year of rhinitis and asthma related to HDM with no history of

earlier immunotherapy. Fulfillment of the criteria for asthma was done according to the GINA guidelines, and the diagnosis of persistent allergic rhinitis was based on criteria in the World Health Organization consensus statement on allergic rhinitis and its impact on asthma. A positive skin-prick test, with a wheal of 13 mm or greater was used for HDM, and the presence of specific immunoglobulin E using the CAP system for both *D. pteronyssinus* (D.pt.) and *D. farinae* (D.f.). During the first year of the trial patients had follow-up visits to assess their baseline symptom scores so that their medication scores could be adjusted in relation to their asthma and rhinitis. For patients exhibiting a need, budesonide inhalers (100-800 g/day) and salbutamol were recommended for controlling their asthma. Rhinitis symptoms were alleviated with intranasal mometasone and antihistamines. No patient was treated with oral corticosteroids or leukotriene antagonists. All participants were instructed to take anti-mite measures, for instance cleaning of bedrooms and carpets and regular washing of teddy bears. In the beginning of the second year, the immunotherapy period, the patients were randomly placed into three groups by a computer-generated method, with no significant difference between the three groups in terms of age ($p = 0.51$) and gender ($p = 0.99$). The SCIT group (10 patients) received active SCIT and placebo sublingual drops, the SLIT group (11 patients) received active SLIT and placebo subcutaneous injections, and the placebo group (10 patients) received placebo sublingual drops and subcutaneous injections. SLIT was self-administered at home and drops were taken each day before meals and held under the tongue for two minutes before swallowing. When beginning SLIT, one drop of 10 TU/ml was placed and held under the tongue for two minutes before swallowing. This method was increased by one drop each day for 28 days, then 28 drops three times per week was considered maintenance. SCIT was also administered in a titration method with weekly injections starting at 0.2-0.8 ml of 50 TU/ml (weeks 1-3), 0.2-0.8 ml of 500

TU/ml (weeks 4-8) and 0.2-0.8 ml of 5,000 TU/ml (weeks 9-12). At the end of 12 weeks, the patient was considered to be on a maintenance dose, which was repeated every fourth week. Throughout the year patients completed a self-assessment diary each day, scoring the symptoms of rhinitis (rhinorrhea, sneezing, nasal itching and blocked nose) and asthma (coughing, wheezing, dyspnea and chest tightness). The rating system used was: 0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe. Then, a calculation of both the rhinitis and asthma scores was performed to produce a total symptom score. The scores were calculated as monthly median values once obtained during the immunotherapy year. The calculations showed a statistically significant difference in symptoms associated with rhinitis and asthma with both SCIT ($p = 0.005$ for both) and SLIT ($p = 0.008$ and $p = 0.012$) when compared to the baseline year. When compared to the placebo group, the decrease in symptom scores regarding rhinitis was found to be significant in the SCIT group ($p = 0.03$). The SLIT group's rhinitis symptoms were significantly reduced when compared to the baseline year ($p = 0.008$), but when compared to the placebo group it was not found to be statistically significant. With regards to asthma symptoms, SCIT showed significantly reduced ailments ($p = 0.01$), while SLIT exhibited no statistically significant effect ($P = 0.48$) when compared to the placebo group. While looking at the medication usage for both rhinitis and asthma SCIT significantly decreased usage for patients ($p = 0.05$ for both) when compared to the placebo group and the baseline year ($P = 0.005$ and $P = 0.02$). With SLIT there was a significant decrease in medication scores regarding rhinitis ($p = 0.03$) and a tendency for a decrease ($p = 0.18$) in medication for asthma while compared to the baseline year. But, even with the reduction in medication scores it was not statistically significant ($p = 0.18$ for rhinitis and $p = 0.16$ for asthma). After the total mediation analysis was

scored, it was determined that the use of both SCIT and SLIT reduced medication usage when compared to the baseline year ($p = 0.005$ and $p = 0.002$).

The limitation of this trial was the brief timeline of one year. Even though a baseline was obtained before the study began, more than one year is needed to obtain accurate statistical numbers showing how both SCIT and SLIT react within each patient.

Discussion

With allergic asthma affecting over 300 million people worldwide today (Asamoah et al., 2017), and the amount of office visits that it brings, there is a significant need for good evidenced-based studies showing the effects that immunotherapy has for those patients with uncontrolled asthma. While conducting this review it became clear there are few studies that have been done comparing SCIT to those taking corticosteroids. A total of six articles were broken down to compare asthma symptoms with the use of SCIT vs. corticosteroids. Three of the articles are randomized, placebo-controlled, double-blind trials with good statistical analysis. The remaining three reviews are meta-analysis added due to lack of additional trials found and should be reviewed with caution.

Seven articles were reviewed comparing the efficacy of SCIT to SLIT. The use of SLIT is a newer concept compared to SCIT and there are few studies comparing the two forms of treatment as well. Two of the articles were performed with randomized, placebo-controlled, double-blind trials with statistical data, but the number of patients within the study was low. The other articles were a mix of systemic review, open-label randomized reviews, and chart review from medical providers but are open for debate without strong statistical values.

Can immunotherapy decrease the exacerbation of asthma symptoms in patients with allergic asthma as compared to treatment with inhaled corticosteroids?

An analysis that was provided from 21 studies showed that allergen specific immunotherapy significantly decreased medication usage with all allergens combined versus a placebo of -0.53 (95% CI -0.80 to -0.27) with moderate between study heterogeneity ($I^2 = 67\%$). Additional evidence from a study of 50 patients with a moderate risk of bias showed significant improvement in the patients' quality of life. Data was also shown that was inconclusive regarding the impact immunotherapy had on lung function when compared to placebo. Findings demonstrated that the standardized mean difference for peak expiratory flow was 0.14% (95% CI -0.33 to 0.61) and forced expiratory volume in one second (FEV1) was -0.32 (95% CI -0.96 to 0.31) (Asamoah et al., 2017). Additional studies were also done comparing the use of immunotherapy and the use of inhaled corticosteroids on patients suffering from allergic asthma on a sample size of 90 children ranging in ages 5 to 14 with allergies to HDM specifically. A treatment therapy of immunotherapy and inhaled corticosteroids as needed was used for half of the group, while the other half of the group was only given treatments of inhaled corticosteroids as needed. Over the first year, it was shown that those in the treatment group significantly reduced the amount of inhaled corticosteroids needed as compared to the control group. The ICS discontinuation rate in the treatment group (28.9%) was significantly higher than that in the control group (20.0%) ($Z=-2.327$, $p=0.020$) (Hui et al., 2014).

Considering the large population that allergies and allergic asthma affect, few studies have been done to understand it. Double-blinded trials by Blumberga, Groes, Haugaard, & Dahl (2006); as well as Maestrelli, Zanolla, Pozzan, & Fabbri (2004); and Hui et al. (2014) showed the most valuable statistics in concerns of subcutaneous immunotherapy and its effectiveness to

decrease the use of medications. Other studies by Karakoc-Aydiner et al. (2015) and Mathur & Lin (2016) also show benefits with immunotherapy but are less specific in how their studies were performed. Using smaller sample sizes and without the use of double-blind studies makes for a debate on the accuracy of the numbers. Now, more randomized, double-blind, placebo-controlled studies need to be conducted with larger sample sizes. The better the studies the more confident we can be in telling patients just how effective immunotherapy can be when compared to inhaled corticosteroids and other antihistamines used to fight off allergies and allergic asthma.

In patients with allergic asthma, is subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) a more effective treatment plan in managing to allergic asthma?

Regardless of the form of treatment, the safety of the patient is always a concern when patients are given anything to help alleviate their symptoms. When injecting a patient with an allergen that is known to cause a reaction there is a concern of a systemic anaphylactic reaction that could compromise airflow, as well as the fact that not all patients want to put themselves through a weekly injection. While no single case of mortality has ever been reported with SLIT, this is not the case with SCIT (Saporta, 2012). This is just one reason why an individual might not want to start on subcutaneous immunotherapy. The alternative to a subcutaneous injection could be SLIT, but just how much safer or effective is SLIT compared to a subcutaneous injection? Studies have shown that with SLIT asthma medication usage can decrease over a years' time, but only SCIT was able to improve the symptoms of both rhinitis and asthma while SLIT had benefits only on the symptoms of rhinitis (Yukselen & Kendirli, 2014). Each of SLIT and SCIT will regulate the number of T cells that are involved with an allergic response by

suppressing Th1 and Th2 causing a reduction to the responses of a specific allergen. In trials, SCIT was shown to have a much quicker response than SLIT within the first year, and it was shown that some lower dosed treatments of SLIT might not become effective until the second year of treatment (Nelson, 2014). However, while SCIT has been shown to be more effective in the symptomatic benefits seen there are additional risks when compared to SLIT. SCIT has been shown to have the risks of both a local and a systemic adverse reaction, such as an anaphylactic response, but if caught early these reactions can be reversed with proper treatment to reverse the effects. SLIT is only known to have local side effects of mild itching or swelling associated with it, and no anaphylactic reactions have been linked to it. Therefore, SLIT could be considered as an initial course of treatment, instead of SCIT, when dealing with aspects in practice such as a younger child, phobias of needles, or long drives to the clinic.

The use of SLIT is a newer concept compared to SCIT and studies are just now really starting to come out comparing the two therapies. Khinchi, Poulsen, Carat, Andre', Hansen, and Malling, as well as Yukselen, Kendirli, Yilmaz, Altintas, and Karakoc all performed trials comparing the differences between SCIT and SLIT. Both used randomized, double-blind, placebo-controlled groups so as to obtain more accurate unbiased statistical numbers. Other studies that were found include meta-analysis papers that discussed and compared findings with other trials conducted. The studies were not as detailed in their findings and while statistics were given, they are not as supported medically as the randomized, double-blind trials. Data found did show a slightly more beneficial usage with SCIT, but SLIT was shown to be a comparable substitute if needed. As discussed above, the safety of SCIT and SLIT must be considered when choosing a form of treatment. It is important for medical providers to have knowledge in order to give patients a full understanding of the treatment options that are being presented and the

potential side effects of SCIT and SLIT. Therefore, more research needs to be done comparing both SCIT and SLIT with larger sample sizes and randomized, controlled groups involved in order to provide more accurate and reliable information for medical providers and patients.

In conclusion, the literature supports the statement that immunotherapy can help patients with allergies and allergic asthma to reduce the amount of inhaled corticosteroids that are needed to lessen the severity of their symptoms that lead to acute exacerbations and require hospital visits. Although there were not a great number of quality studies found, there was enough literature supporting positive findings associated with SCIT and SLIT to warrant further research and studies. Based on the studies reviewed, SCIT has been shown to be a slightly more effective treatment than SLIT. However, SLIT can be utilized as an alternative to SCIT. More research is needed on these topics with larger sample sizes in order to fully understand the pathophysiology behind immunotherapy. This additional research is necessary in order to help medical providers better educate themselves and their patients about the benefits associated with immunotherapy, and to better determine the effectiveness of both SCIT and SLIT.

Application to Clinical Practice

It is almost inevitable that those who work as a primary care provider will treat numerous patients with allergies. Allergies is a world-wide condition that causes a cough, nasal congestion, runny nose, itchy eyes, and even sleeping difficulties. If these symptoms are not controlled at an early age there is chance of acquiring allergic asthma as well.

During the first stage of allergies over-the-counter medications such as Loratadine, cetirizine hydrochloride, Fexofenadine, and diphenhydramine are commonly used

antihistamines. For some patients, this is enough to keep their allergies under control and not interfere with their active daily living, but for others the symptoms can progress causing reactions that can potentially react with one's lungs leading to asthma conditions. If this occurs, then a combination treatment of antihistamines with inhaled corticosteroids is needed to keep the symptoms under control. If the condition continues to progress, and the symptoms persist on a daily basis, then immunotherapy should be considered by the provider and the patient should be referred for allergy testing.

If a patient has been on a long-acting beta agonist and corticosteroids and their asthma is still not under control, a medical provider should discuss immunotherapy with them. The medical provider should explain the process of immunotherapy and how treatment can gradually reduce a patient's immune-system response to certain allergy triggers. While testing for allergen-specific immunoglobulins is not normally performed within a primary care facility, the weekly injections that are administered can be provided by the patient's primary care provider if this arrangement is more convenient for the patient. By the end of the treatment, the patient's immune system builds up a tolerance to the allergens over time and the patient's allergic reactions diminish. In turn, the patient's asthma symptoms should decrease as well.

Throughout the course of receiving immunotherapy it is important to educate the patient regarding what triggers their symptoms and ways that they can avoid encountering them. Certain medications might be needed in the beginning until the patient's immune system can adjust to what is happening within the body. But, over time, daily usage should decrease resulting in fewer exacerbations and better active daily living.

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