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A REVIEW ON SUBLINGUAL IMMUNOTHERAPY FOR THE TREATMENT OF ASTHMA, ALLERGIC RHINITIS AND CONJUNCTIVITIS

M. Pramod Kumar*, D. Prathibha[1], G. Ravi Teja[1], K. Keerthana[1] and S. K. Mymoonissa[1]

Department of Pharmacy Practice
*Assistant Professor Pulla Reddy Institute of Pharmacy.
[1]5th Year Pharm.D Pulla Reddy Institute of Pharmacy.

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***Corresponding Author**
M. Pramod Kumar
Assistant Professor Pulla Reddy Institute of Pharmacy, Department of Pharmacy Practice.

ABSTRACT

Allergen specific immunotherapy is aimed at modifying the natural history of allergy by inducing tolerance to the causative allergen. Sub-cutaneous immunotherapy has a major flow in side effect, especially in possible anaphylactic reaction, and this prompted the search for safe ways of administration of allergen extracts. SLIT has met such need while maintaining a clinical efficacy comparable to SLIT. The systematic revision of the available literature was substantially free from serious systemic reaction. A number of Meta analysis clearly showed that SLIT is effective in allergic rhinitis by significantly reducing the clinical symptoms and the use of anti-allergic drugs. Beside the efficacy on symptoms, the preventive activity and the cost effectiveness are important outcomes of SLIT in asthma. The need to meet included more data on the efficacy in the house dust mist might asthma optimal techniques of Administration and as previously done with SLIT introduction of adjuvants able to enhance the immunological response and use of Recombinant allergens.

KEYWORDS: Asthma, Allergic Rhinitis and Conjunctivitis.

Methods used for locating selecting extracting and synthesizing data

Articles on the clinical and immunological effects of SLIT on allergic asthma were located in PubMed and embase by using the keyword “sublingual immunotherapy”, “allergic asthma”,

"meta-analysis", "efficacy", "MOA" and "cost effectiveness" 7meta analysis evaluating SLIT efficacy in asthma were retrieved systematic literature review was conducted search was focused on all the double blind studies.

Search strategy:- Medline, embase, cochrane controlled trial register, Abstract of cochrance Airways group, hand search and archives of some SLIT produces. All the selected studies word assessed and evaluated for quality in a standardized independent way.

INTRODUCTION

Mechanism of Action

The pivotal action is the anti inflammatory effect of the immunotherapy, including SLIT, based on ability to modify the phenotype of T cells, Which in allergic subject is characterized by a prevalence of the two types, with production of lL4,IL5,IL13,IL17,IL32 cytokines. The immunotherapy induced changes results in a Th-1 type response related to An increased in IFN gamma, and IL 2 to production or by a Th2 reduced activity through a mechanism Of energy or tolerance increase cell tolerance is characterized by the generation of allergen specific increase regulatory cells, which produce cytokines such as IL10 and TGF-beta with immunosuppressant immuno regulatory activity. A prominent role in SLIT is played by dendritic cells in the oral mucosa which are of critical importance in Inducing tolerance to antigen the tolerance a patterns that are promoted by dendritic cells and derived by increased account for the suppressed or reduced activity of inflammatory cells and for the is of typic switch of antibody synthesis from IgE to IgG and especially to IgG 4.[1]

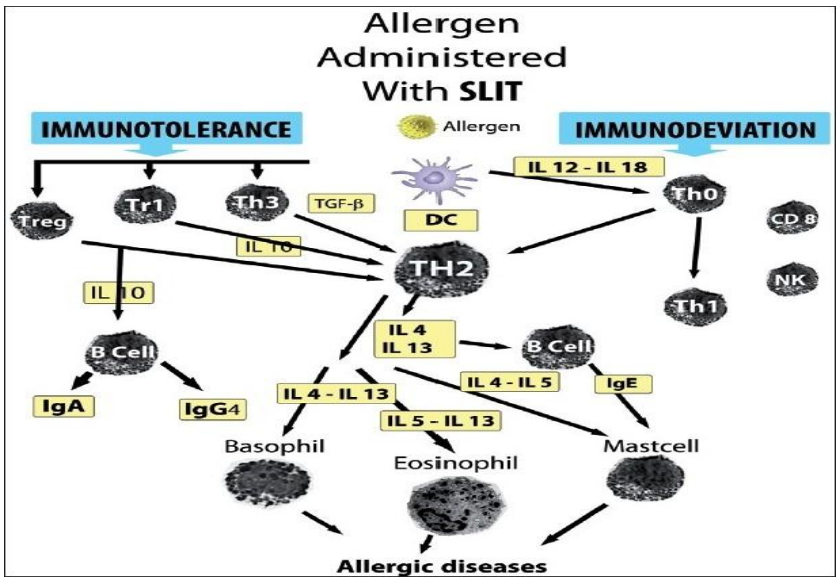

Figure 1: Mechanism of action.

Effects of SLIT on Asthmatic symptoms and drug consumption

The first Meta analysis on SLIT is asthma was conducted by Olaguibd et.al and included 7 randomised control studies on children aged up to 14 years. By using the cochrance method based on calculation of the SMD between actively and placebo treated patients the author found that SLIT was significantly effective on asthma symptoms (SMD-1.42, P=0.01) and on drug consumption (SMD-1.01, P=0.06).

Another meta-analysis considering a study on pediatrics patients with a total number of patients corresponding to 441 and 232 actively treated and 209 placebo treat reported a significant reduction in both symptoms scores (SMD -1.14, P=0.02) and drug consumption (SMD=1.63, P=0.007).

In 2006, a meta-analysis on the efficacy of SLIT in asthma included 25 studies with an overall number of 1706 patients calculating the SMD, the reduction of asthamatic symptoms did not reach the statistical significance but using the intention to treat methods for outcome measures, significant decrease of asthma symptoms and drug consumption and significance decrease of asthma symptoms and drug consumption and significant improvement of lungs function and biochemical hyperactivity were detected.

NNT-3.7, That is in the range of those reports for the injective SLIT in asthmatic and Rhinitis patients.

Preventive capacity of SLIT

Confirmation was offered by a study on 216 children's with allergic rhinitis, who were randomised to receive drugs alone or drugs with SLIT for 3 years. the clinical score was assessed yearly during allergens exposure. Pulmonary function testing and Meta choline challenge were performed at the beginning and end of the studies. 144 children received SLIT and 72 receive drugs only new Sensitisation appeared in 34.8% of controls and in 3.1% of SLIT patient (Odd ratio 16.85).

Mild persistent asthma was less frequently in SLIT patient the number of children's with a positive meta choline challenge result decreased significant after 3 years only in SLIT groups.

In a survey over a mean follow up of 11.6. Months after the end of treatment, 80.8 percent of patient still maintains the previous achieved benefits.

The long lasting effects of SLIT were further demonstration in a prospective study on patients with allergic asthma due to, who were divided into two match groups: 35 underwent a 4-5 years cover of SLIT with standardized extract and 25 received only drug therapy the patients were evaluated at three times.(Baseline, end of SLIT and 4-5 years after SLIT discontinued). Regarding presence of asthma and anti asthma drugs.

The SLIT group showed a significant difference versus baseline the presence of the asthma ($p=0.001$) the use of asthma medications ($p=0.01$) number difference was observed in controlled group. This demonstrated that the clinical efficacy for 4-5 years after discontinuation.[1]

Cost effectiveness

The maximum cost effectiveness is achieved when I sell it after 3 to 5 years of treatment is discontinued but the clinical efficacy is maintained over time.[1]

Objectives

The primary objective of this systemic review was to review the clinical efficacy and safety of sublingual immunotherapy.[4]

Methods

Type of studies

Randomised controlled trials were included in adding two double blind status open studies also reviewed double-blind placebo-controlled study.

Type of interventions:- The intervention investigated was immunotherapy delivered by sublingual route with or without subsequent swelling all type of allergens all doses and all length of treatments were considered.

Type of outcome measurements

Asthmatic symptoms by mean of a symptom score enter on a diary card with subsequent totaling and average. The following arithmetic symptoms were generally quantified daily dyspnea, cough wheeze and chest tightness.

Asthmatic medications requirement by means of a score entered on a diary card to evaluate the reduction in the need for medications with subsequent totaling and averaging. This generally involved quantification of the use of corticoids and bronchodilators in particular.

Respiratory function test including peak expiratory flow rate (PEFR) forced expiratory volume in 1S (FEV1) and forced expiratory flow between 25% and 75% of vital capacity.[1]

* Non specific bronchial provocation
* Adverse effect
* Quality of life
*cost effectiveness
*preventive capacity
* Symptoms of rhinitis and conjunctivitis
* patient compliance

Search strategy

* Medline, Embase, LILACS and cochrane controlled trials registers were researched using the terms 1: asthma or wheeze; 2.1 immunotherapy or hyposen or desen and sublingual.

Data analysis

Majority of the studies presented continuous outcomes and there were analysed as standard mean difference SMD with calculating of 95% confidence intervals the SMD was used because many studies have measured the same outcomes on different scales.

Category outcomes were analysed as risk difference(RD) and relative risk(RR) both with calculation of the 95% of CI the number needed to treat or number needed to harm were also estimated.

For categorical outcomes, the analysis was performed according to the intervention to treat methods and for continuous outcomes the results were analysed only in relation to the participants who complete the trials.

Because of significant heterogenetic when SMDS were used the random effects model was utilized to obtain some statics for the overall efficacy of sublingual immunotherapy. The chi-square test were performed to assess the heterogenetic between the studies taking P value of < 0.1 to indicate a significant difference between the studies sensitivity analysis was performed.

RESULTS

*Eight randomised double-blind placebo-controlled studies of SLIT were selected five subjects were Run with house dust mite one with olive pollen grains another with pellitory

pollen Another with grass pollen also clinically relevant results were shown, independently from statistical significance, in the use of SLIT for the respiratory allergens due to several allegens (Olive, wall pellitory and grass Pollen) and on the whole for rhino conjugate is due to HDM in childrens for mild to moderate persistent asthma due to HDM, statistical significance and low to moderate relevant clinical effects were observed.[6]

*There is a strong evidence that States sublingual immunotherapy improve asthma symptoms, with 8 of 13 studies reporting greater than 40% improvement versus the comparators "moderate evidence support that sublingual immunotherapy use decreased rhinitis or rhino conjugate" symptoms with 9 of 36 studies demonstrated greater than 90% improvement was the comparator medications used for asthma and allergy and decreased by more than 40% in 16 of 14th studies of sublingual immunotherapy with moderate great evidence. moderate evidence supported that sublingual immunotherapy improves conjuctivites is symptoms 13 studies combined Symptoms and medications scores(20 studies) and disease specific quality of life (8studies) evidence was similar in strength to support the use of SLIT in the children less than 18 years of age for allergic rhinitis and asthma.[5]

*Analysis of SLIT for respiratory allergic in children's found a non significant reduction in nasal symptoms scores and medication score in that meta-analysis 7 trails were included 232 patients for nasal symptoms and 146 for medical scores of which two were not available for the cochrane review, although it should be noted that their inclusion only added an additional 22 actively treated patients, the SMD in rhinitis symptoms scores was - 0.44(95% CI – 1.22 to 0.35 p=0.27) and for medical scores -1.01(95% CI -0.06 to 0.04, p= 0.06).

In the second response to the lack of significant noted in the cochrance review a meta-analysis of more recent trials of allergic rhinitis and a paediatric patients and including twice as many status 484 patients for the symptom score and 279 patient for the medicals scores was conducted in that analysis the SMD for nasal symptoms scores was 0.56(95% CI -1.01 to -0.10, p=0.02) and for medications score - 0.76(95% CI -1.46 to –o.o6, p=0.03).

In the cochrance review the corresponding values for changing and symptoms and medications scores compared to the placebo were -0.42(95% CI -0.06 -0.150 and 0.43(95% CI -0.06 to 0.23) respectively.

A double blinded randomised trials involved use of an ALK – A bello grass Pollen SLIT preparations among 114 adults patient suffering from the rhinitis and Asthma treatment with grass Pollen tablets pre season and during the pollen season was associated with a significant 37% reduction in the rhinoconjuctivitis score and a 41% reduction in the medication score during the season. The end of the third symptoms score were 2.1(1.7) and 3.3(2.2) and meditation score were 2.4(3.9) and 4.2(4.1) for SLIT and placebo, respectively these results are clearly in line with the findings of cochrane reports.

The impetus for SLIT and other alternative routes of immunotherapy were associated of SLIT with severe adverse reaction in a limited number of cases; therefore particular allention has been paid to satisfy in studies of SLIT. The occurrence of symptomatic reactions with SLIT ranges between 0.8% and 40.7% while after 15 years of SLIT; the corresponding rate is much lowering with estimated of 13 to 18%. As noted throughout this report the favourable safety. Profile of SLIT has been confirmed in recent trials, with low rate of systematic events being reported.

A meta-analysis sought to investigate a potential relationship between dose of allergens administrations by SLIT and ADE. After reviewing 25 studies various SLIT preparations it was concluded that the overall rate of ADE associated with the use of SLIT was very low at 1.8 to 4.9 events for 1000 SLIT doses.

Result of 8 control trials 1472 adults and 218 children's using various SLIT preparations from a single manufacturers were analyse the for reporting adverse events. The conclusions from the review were that treatment with SLIT was not associated with any serious adverse event although mild gastrointestinal and buccal cavity associated events for more frequently with SLIT.

In total 268 children receiving SLIT for respiratory allergens were followed for up to 3 years and during that time 8 side effects were reported yielding an event rate of 0.083/1000 doses no serious adverse events were reported.[5]

*Rhinitis or rhinoconjuctivis symptoms School were reported in 36 placebo controlled studies involving 2985 participant. The most frequency studied allergens were grass mix (10 studies; 28%) and dust mite (8studies, 22%) The majority of the studies(94%) demonstrated

greater improvement in the SLIT versus placebo. The magnitude of incidence was moderate to strong in the 14 studies (39%).

A conjunctivitis outcome was reported in 13 studies involving 1074 patients. All but one study demonstrated an improvement compared with the placebo group. The evidence was of moderate strength.

Medications scores were reported in 41 studies involving 2162 patients grass mix (100 studies, 24%) and dust mite(9 studies 22%) were the most commonly studies allergens 38 studies(93%) demonstrated greater improvement in the symptoms of the SLIT group was comparator with 16 studies demonstrating a strong magnitude of association.

Disease specific quality of life was reporting in 8 studies involving 819 patients half of these study showed statistical is significant grain in QOL after treatment SLIT the compared with placebo the evidence was moderate in the support of SLIT.

The studies did not uniformly or consistently reporting safety info although 47 studies 75% mentioned safety the lack of standard grading system and heterogeneous reporting system used by the different studies that safely outcomes can be presented descriptively.

Local reactions work more frequently in patients receiving SLIT (ranging 0.2% -97%) then in the comparator group (Range 3% -38.5%) There were no reporting episodes of anaphylaxis, life threatening reaction or death in any treated person across the studies.

For 20 studies with 1501 patients, no severe reactions were observed but rather only mind adverse effects like local reactions, generally in the mouth, such as pruritis, erythema and edema These usually occurred within 30 minutes following the vaccine used and generally resolved spontaneously the risk found were relative risk is 1.83 with 95% CI: 1.40 -2.40 and RD- 0.07 with 95% CI 0.04- 0.10 and the NNH using SLIT was 14.28 patients in order to cause an Adverse effect in one patient.

In 9 studies with 303 patients the asthmatic symptoms were analysed separately from other allergic symptoms such as rhinitis and conjuctivitis the combined SMD for the symptoms scores following SLIT was 0.38 with 95% CI 0.79 to 0.083 the CI included zero, does indicating a non significant reduction in the in asthmatic symptoms there was significantly heterogenetic between the studies (X^2= 2 2.17, P= 0.005, I^2= 63.9%).

10 studies with 360 patient generally analysis of asthmatic symptoms together with other allergic symptoms(rhinitis conjugated and latex allergy) the combined SMD following SLIT was- 1.18 with 95% CI -1.93 to -0.43 thus indicating a significant reduction in allergic symptoms there was a significant heterogenetic between the studies(x^2=84.71, p<o.oooo1, I^2 =89.4%).

Composite symptoms plus medications scores were available in 7 studies however these two outcomes for allergies in general asthma together with rhinitis and conjuctivitis and the combined SMD following SLIT was - 0.79 with 95% CI -1.342 to - 0.24 thus demonstrated significance.

In 10 studies there was a significant reduction in the use of medications for asthma together with rhinitis and conservatives (SMD -0.82 with 95% CI -1.25 to -0.39) however in 6 studies with 254 patients there was no sign reduction in the need for medication for asthma alone.

(SMD - 0.91 95% CI 1.94 to 0.12) there was also a significant heterogenetic and this two outcomes (respectively x^2= 40.53 p< 0.00001, I^2= 77.8% and x^2 =60. 74 p<0.00001 I2=9 1.8%) Among the respiratory function test evaluated (FEV, FEV1%, PEF and FEF 25-75%), FEV 1% showed a sign improvement (SMD 1.48, 95% CI 0.13 2.85) among 144 patients in 4 studies and among 42 patients into studies. These results of the studies which are greater than zero indicated that treatment by SLIT was improved flavoured other evolution including the bronchial provocation test, did not show any significant improvement flavouring treatment by SLIT.[4]

Khinchi et al conducted a double blinded, double dummy placebo control studies of high dose SLIT and SCIT compared with placebo in patients with Birch-pollen associated ARC. reduction and symptoms and medication score was significantly for SLIT(P<0.002 and p< 0.02) and SCIT (P<0.002) and p<0.002) compared with placebo difference were numerically greater for SLIT but not significantly so compared with SLIT Although the status was in adequately powered to detect such difference, five grade 3 systematic reductions and 1 grade 4 systematic reactions were observed in SCIT group, 1 grade 3 systematic reactions was observed in the Placebo group, no grade 3 or 4 reactions were seen in the SLIT group. Thus both were effective and serious systematic reactions only occured after SLIT.[7]

CONCLUSION

The overall evidence provides a moderate grade level of evidence to support the effectiveness of SLIT for treatment of asthma, allergic rhinitis and conjuctivities but high quality of studies are still needed to answer regarding optional dosing strategy. There were limitations in the standardization of adverse events reporting, but no life threating adverse events were noted in the review. The review provide an evidence of reduction in symptoms of asthma, allergic rhinitis and conjunctivitis by using SLIT.

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