INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

IJCMPR

Available Online at http://www.journalcmpr.com

RESEARCH ARTICLE

THE ROLE OF SLIT AS PERSONALIZED IMMUNOTHERAPY IN ALLERGEN SENSITIVE CHILDREN WITH A FOCUS TO ALLERGY IN UPPER AIRWAYS

Jabeen Fayyaz[1]., Muhammad A Hamid[2] and Qurrat ul ain Tahir[3]

[1]Clinical Fellow at the Hospital for Sick Children, Toronto
[2] Department of Paediatrics, University of Toronto; & Consultant Paediatrician, RVHS Toronto
[3]Research Assistant

ARTICLE INFO

Article History:

Received 14th July, 2016
Received in revised form 9thAugust, 2016 Accepted 27th September, 2016
Published online 28th October, 2016

Key words:

Tailored Medicine, Evidence, Review, Sublingual, Specific Immunotherapy.

ABSTRACT

Objective: The primary objective of this systematic review is to evaluate the role of personalized immunotherapy against allergy in pediatric population affected with allergy in upper airways that include conditions like allergic rhinitis, asthma, rhino-conjunctivitis, etc. This can be determined through evaluating clinical efficacy and safety of sublingual immunotherapy (SLIT) in children affected with different types of allergens.
The secondary objective is to evaluate the reduction of symptomatic medication usage and evaluate long term use of SLIT.
Methods: A systematic literature review is conducted to determine the clinical efficacy and safety behind the basic concept of administration of increasing amounts of allergen(s) in sublingual route, to allergic subjects to achieve hypo sensitization and reduction of symptoms occurring during the natural exposure to the allergen(s) itself and to review the long term use of allergen administration. The search is focused on all the randomized clinical trials of sublingual immunotherapy in children (below 18 years) with upper airway diseases associated with allergy. Identification, screening and inclusions are done from PubMed, CINAHL and Cochrane library. The research includes all studies that used personalized approach of introducing external allergens in children through sublingual route in the year 1999 to 2014. Total 30 studies with 2939children with allergic rhinitis, asthma, rhino-conjunctivitis were involved in this systematic review. The outcomes of the selected studies were evaluated.
Result: The result is evaluated for the effectiveness of the SLIT on the basis of baseline comparison, reduction of symptoms score and medication score and improvement of visual analogue scale (VAS) and clinical improvement. For safety analysis parameters were chosen based on reported adverse events and their severity. The data from 19 studies (n=2126) provided efficacy and safety evaluable data, 8 studies (n=484) provided only effective data, and 2 studies provided only safety data (n=258) and 1 study (71) found which specially focused on patient compliance. The result from 6 studies is instrumental to determine the long term efficacy of the sublingual immunotherapy.
Conclusion: This systemic review concluded that SLIT is effective through significant reduction of symptom-medication score and also well tolerated therapy for children with upper airway diseases associated with allergy.

INTRODUCTION

Allergic rhinitis is one of the most prevalent immunological disorders that represents a global health problem affecting 10%-20% of the population (ARIA Guidelines 2010). It affects the individuals who respond hypersensitivity to environmental exposures by producing allergen-specific immunoglobulin E (IgE). Epidemiological study states 6.6 million children have been diagnosed with hay fever in 2012.

Personalized therapy is the new approach in modern medical evolution that proposes the tailored or customized model for the patients. This may include any medical judgment, or the therapy (may be vaccine) for individual patient. Sometime genetic information (pharmacogenomics) can play a major role in preparing a personalized model of therapy for an individual patient. This concept is later expanded to include different customized measures targeting any individual triggering factor, symptoms or may be upon the behaviour of an individual. Allergy-**S**pecific **I**mmuno**T**herapy (SIT) is a disease modifying therapy that is effective against common allergic conditions, particularly allergic rhinitis/conjunctivitis, allergic asthma and stinging insect hypersensitivity. As per this

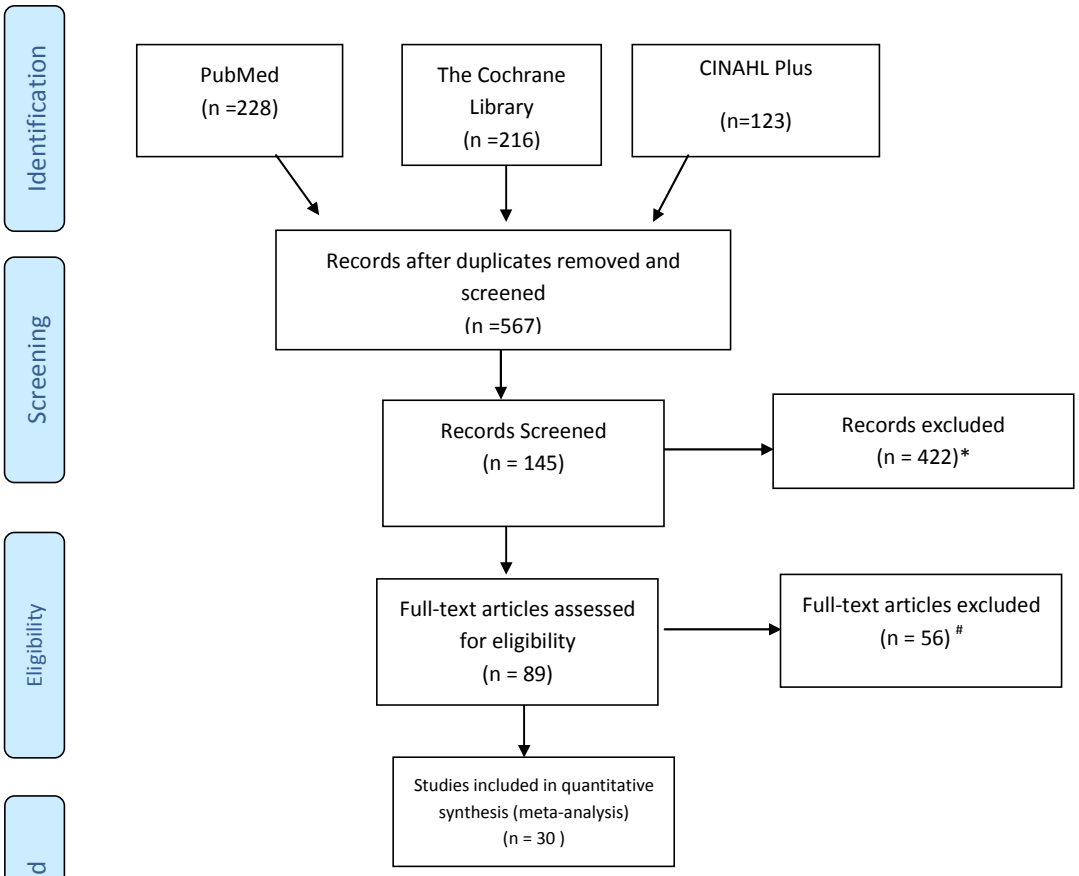
therapy, administration of an increased amount of patient's relevant or detected allergens are done till the dose reaches to the threshold to induce immunologic tolerance to those identifies/detected allergens. Thus, this process of introduction of ***patient's relevant*** allergens can be encompassed under the personalized therapy. Subcutaneous Immunotherapy (SCIT) and Sublingual immunotherapy (SLIT) are the types of SIT. As the concept has come from vaccination so the first development of dose administration route was SCIT which occurred in the first years of the twentieth century. Ease of use and compliance for dosing, alternative way of non-parenteral, non-painful routes are always preferable. The sub lingual route of such personalized administration of allergens got the most attention in last 2-3 decades. The first randomized controlled trial with the sublingual route (SLIT) was published in the year 1986. The published study results have taken place in EAACI and WHO Position Papers.Both the position papers states that allergic diseases due to parietaria, mites and grass can be well controlled through SLIT without risking the safety parameters in adults. The tolerability of SLIT in adults is also backed through evidence of post marketing surveillance conducted in more than five hundred adult patients making it one of a large study of its kind. The studies are even done in mixed population (adult and children both).

There's a high regulation and restriction to conduct trials including children, as they are vulnerable subjects. This review includes 30 studies that only have children as participants between 0-18 years of age. As an alternative for allergic rhinitis to SCIT, SLIT has gained more popularity in European countries than in United States. Currently, FDA has only given approval for one SLIT preparation and maximum of the SLIT preparation are not authorized to be marketed in USA, though European Medicine Association (EMEA) has well accepted SLIT as an effective and safe customized therapy for allergic diseases.

The primary aim of this study is to determine the effect of personalized way of administering SLIT in symptom reduction, frequency of using drugs in case of naturally occurring allergic reactions or altering immunological markers in blood. This review can also help to determine the safety of SLIT and the immunological markers and the allergen sensitivity in nose, eye and skin (the targeted organs). The secondary aim is to evaluate long term immunological effect of SLIT.

METHOD

A systematic literature review is conducted to determine the clinical efficacy and safety behind the tailored model of



*Reasons for exclusion:

- Only Clinical Trials are included
- Only SLIT and SCIT
- Age out of study range

Reasons for exclusion in full text assessment:

- Less than 15 days data excluded
- Type of extract used not specified
- Safety and effectiveness not evaluable under the review scope

administration of increasing amounts of allergen(s) by sublingual route, to allergic subjects to achieve hypo sensitization and reduction of symptoms occurring during the natural exposure to the allergen(s) itself and to review the long term use of allergen administration. The search is focused on all the randomized clinical trials of sublingual immunotherapy in children (below 18 years). Identification, screening and inclusions are done from PubMed, CINAHL and Cochrane library. The RCTs conducted in 1999 to 2014 are all considered during the selection process. Total 30 clinical trials with 2939 children with one or more association of allergic rhinitis, asthma and rhino-conjunctivitis; were involved in this systematic review. The outcomes of the selected studies are then evaluated.

Flowchart for literature search procedure

RESULTS

The studies included in this review can be classified as: studies that included only grass pollen,[1,4,10,11,19,23,27-29] few studies that included only house dust mites (HDM)[2,3,6,7,9,15,17,20,24,26, 30,32,33] and there is one study that include both HDM and grass pollen extracts[14.]

This review is not only limited to these two allergens but also include other types like olive pollen, parietaria[5,12], cypress pollen and tree pollen[16,19]. There is also evidence of a study that considered the patient who were mono-sensitized/ poly-sensitized with respiratory allergies[31].

The efficacy is evaluated on the basis of reduction of symptom score (SS), medication score (MS), symptom- medication score (SMS), improvement of visual analogue score and clinical improvement. The safety of SLIT is evaluated on the basis of reporting of adverse events, severity of adverse events and evidences of Serious Adverse Events (SAE).

The review includes follow up of immunotherapy for allergen sensitive paediatric population starting from 18 days to 3 years covering paediatric age from 1 year to 18 years.

The data from 19 studies (n=2126) provided efficacy and safety evaluable data, 8 studies (n=484) provided only effective data, and 2 studies provided only safety data (n=258) and 1 study (71) found which specially focused on patient compliance.

Table Data from 31 studies to determine the use of SLIT in pediatric population from 1999-2014

Trial Acronym/ Author(s)	Year	n	Age (years)	Sensitivity	SLIT Type	Control Group	Duration	Adverse Event(s)	SLIT Effectiveness
Di Rienzo V, Puccinelli P *et al*	1999	48	5-12	grass pollen	Grass pollen allergenic extract *(Phleumpratense, Loliumperenne, Dactylisglomerata, Poapratensis, Festucapratensis)*	systemic antiallergic drugs	1 year	Two cases of a cutaneous erythematous reaction in the submandibular area, slight edema of the eyelids and worsening of the oculorhinitis symptoms.	Significantly less in SMS for SLIT in comparison to the control group were found ($p < 0.0001$).
Bahçeciler NN, Işik U *et al*	2001	15	11.7 +/- 3.3	HDM	Dermatophagoidespteronys sinus (D. pteronyssinus) + Dermatophagoidesfarinea (D. farinea) 50/50 extract.	Placebo	6 months	None reported	SLIT group was found to have less SS than the placebo group ($P = 0.007$).
Pajno GB, Morabito L *et al*	2000	24	8-15	HDM	Aqueous mite extract of D. pteronyssinus	Placebo	2 years	Tiredness, swelling of the mouth, lips, and face (at 2 h) and one case of itching of the mouth (at 3 h), resolved spontaneously without drugs, and were reported during the induction phase with the first administrations of the most diluted vial.	Decrease SS ($P=0.0001$) and MS ($P=0.0001$). The VAS on overall asthma symptoms improved in the SLIT group ($P=0.0001$).
Bufe A1, Ziegler-Kirbach E *et al*	2004	161	8. 97 - 9.6	grass pollen	Grass pollen extract	Placebo	3 years	None reported	A significant improvement of clinical symptoms after 3 years.
Pajno GB, Vita D, Parmiani S *et al*	2003	38	8 -14	Parietaria pollen	Parietaria pollen + inhaled fluticasone	Placebo + inhaled fluticasone	13 months	Not mentioned	SMS and VASs were significantly better (P between <0.001 and 0.043) with decreased early skin response in the active SLIT+fluticasone ($P<0.001$).
Marcucci F, Sensi L *et al*	2003	24	4-16	HDM	4 μg of the major mite allergen Group 1 and 2 μg of the major mite allergen Group 2	Placebo	1 year	Not mentioned	SS improved [Nasal tryptase and nasal IgE in basal conditions were significantly increased in untreated children ($P = 0.0156$ and $P = 0.0313$, respectively)].
Niu CK, Chen WY *et al*	2006	97	6-12	HDM	Dermatophagoidespteronys sinus (D.p.) and Dermatophagoidesfarinae (D.f.).	Placebo	24 weeks	None reported	Significant improvement in SS [FVC, FEV1 and PEF as compared to baseline ($P=0.042$, $P=0.048$, and $P=0.001$, respectively)].

Fiocchi A, Pajno G *et al*	2005	65	3-7	HDM, grass pollen, olive pollen, parietaria pollen and cypress pollen	House dust mites, grass pollen, olive pollen, parietaria pollen and cypress pollen	No treatment	18 days	Reported in 11 children, none of them severe enough to require discontinuation of immunotherapy. Six reactions occurred in the 60 months or younger age group and 7 in the older than 60 months age group, with no differences between these 2 groups.	Safety study
Marcucci F, Sensi L *et al*	2005	24	4-16	HDM	mite allergen	Placebo	3 years	Not mentioned	SS decreases at 2nd years for rhinitis and asthma (p = 0.0009 and 0.0019, respectively) at 3rd year MS for rhinitis, asthma (p = 0.0105, 0.0048, and 0.02, respectively).
Rolinck-Werninghaus C, Wolf H *et al*	2004	97	3-14	grass pollen	Pangramin SLIT	Placebo	32 months	49% events reported in SLIT	The multiple SMS reduced by SLIT (P=0.0498). The MS improved significantly (P=0.0025).
Novembre E, Galli E *et al*	2004	113	5 - 14	grass pollen	Mixed grass pollens (Dactylisglomerata, Loliumperenne, Festucapratensis, Phleumpratense, and Poapratensis)	SIT	3 years	0.44/1000 during the build-up phase and approximately 0.083/1000 during the maintenance phase	At 2nd year lower SS (*P* = .03) and MS (*P* = .009) and SMS (*P* = .001). 3rd year lower MS (*P* = .02). Subjective symptom evaluation scores were significant in both the second (*P* = .0004) and third years of follow-up (*P* < .0001)
Pajno GB, Passalacqua G *et al*	2004	30	8–14	Parietaria pollen	allergen Par j 1	Placebo	2 years	Not Mentioned	SS decreases (P =.005). SLIT abrogates the seasonal bronchial hyperreactivity in children with asthma due to Parietaria.
Passalacqua G, Musarra A *et al*	2007	71	2–13	HDM and grass pollen	allergen mites, grasses and grass + olive mixture	No treatment	6 months	Certainty of side effect not confirmed. 1.4% probability.	At 3 months 85% and at 6 months 84% of subjects had a compliance rate >75%.
Pham-Thi N, Scheinmann P *et al*	2007	111	5-15	HDM	SLIT with tablets of HDM extract	Placebo	18 months	SLIT was well tolerated with mild/moderate local adverse events. No severe systemic reactions were reported.	QoL was significantly improved, reduction of SS [skin sensitivity to HDM (p < 0.01)] and a significant increase in HDM-specific IgE and IgG(4) antibodies (p < 0.001)
Valovirta E, Jacobsen L *et al*	2006	88	5-15	tree pollen	Glycerinated mixture of Betulaverrucosa, Corylusavellana and Alnusglutinosa	Placebo	18 months	None reported	Significant reduction of MS (P = 0.04) and SS (P = 0.03).
Lue KH, Lin YH *et al*	2006	20	6-12	HDM	Dermatophagoidespteronys sinus (D.p.)/D. farinae (D.f.) 50/50 extract.	Placebo	6 months	No SAE reported	There was a significant difference in night time asthma SS, specific IgG4 (p < 0.05), daytime symptom and MS, total IgE, eosinophil count, FEV1, and mean evening PEF rate significantly improved (p < 0.05).
Wahn U, Tabar A *et al*	2009	278	5-17	grass pollen	5-grass-pollen sublingual immunotherapy (SLIT) tablets	Placebo	4 months	No SAE reported with mild to moderate ARs	Significant decrease of rescue MS and proportion of days using rescue medication during the pollen season (P = .0064 and P = .0146, respectively).
Ozdemir C, Yazi D *et al*	2007	90	4–16	HDM	SLIT + pharmacotherapy	pharmacotherapy	3 years	Not mentioned	MS decrease, 52.4% of subjects in the SLIT + pharmacotherapy group were able to discontinue ICS treatment for at least 6 months, which was only 9.1% for the pharmacotherapy group.

Seidenberg J, Pajno GB *et al*	2009	193	5 - 17	grass or tree pollens	Standardized mixtures of grass pollen (cocksfoot, meadow grass, rye grass, sweet vernal grass, and timothy) and tree pollen (birch, alder, and hazel)	None	7 months	There was 1 clinically significant asthma event in an 11-year old boy with known asthma in whom SLIT was resumed after an interval of 4 days.	Safety study
Acquistapace F, Agostinis F *et al*	2009	171	6–18	Different allergens	Previously treated with specific SLIT with the related allergen extracts (SLITone ALK-Abellò)	New cases	2 years	Not mentioned	Lower SS (p = 0.0001) and MS (p = 0.0001) with active group.
Stelmach I, Kaczmarek-Woźniak J *et al*	2008	50	6- 17	grass pollen	Five grass pollen with ultra-rush induction.	Placebo	2 years	59% of subjects in the first year of treatment and in 35% in the second.	Improved asthma SS (41% vs. placebo group), reduced nasal symptoms (25% vs. placebo group) and the use of rescue MS (10% vs. placebo group), improved forced expiratory volume in 1 sec.
Keles S1, Karakoc-Aydiner E	2011	51	<18	HDM	SCIT plus SLIT	SCIT vs SLIT vs Pharmacotherapy	18 months	Not mentioned	The improvement in VAS for rhinitis was significant only in the SCIT plus SLIT group.
Yonekura S, Okamoto Y *et al*	2010	31	7 - 15	HDM	House dust	Placebo	40 weeks	One patient in the active group reported a bitter taste	Symptoms score improved [nasal (p = 0.0183) and ocular (p < 0.0001) symptoms]. MS was statistically lower (both p < 0.05)
Wahn U, Klimek L *et al*	2012	207	4 - 12	grass pollen	High-dose grass pollen SLIT	Placebo	1 year	None reported	SMS for the active group imvoved (P = .0040). Rhinoconjunctivitis SMS (P = .0020). separated symptom and medication scores were also statistically different between active and placebo groups (P = .0121 and P = .0226, respectively).
Halken S, Agertoft L *et al*	2010	278	5-17	grass pollen	Five-grass pollen tablet (SLIT)	Placebo	1 year	None reported	SS significantly decreases. (nasal (p = 0.0183) and ocular (p < 0.0001) symptoms)
Ahmadiafshar A, Maarefvand M *et al*	2012	24	5-18	Rye grass-pollen	Rye grass pollen antigen	Placebo	21 weeks	None reported	Significant reduction of SS in intervention group (p<0.05). MS were also reduced (p<0.05).
Yukselen A, Kendirli SG,	2013	30	11.5 - 11.8	HDM	D. pteronyssinus and D. farinae (50/50) mite extract for sublingual use	SCIT	2 years	Not mentioned	The reduction of CI with SLIT was more evident after 2 years of treatment
De Castro G, Zicari AM *et al*	2013	140	6-14	monosensitized/ polysensitized patients having respiratory allergies.	Monomeric allergoid tablets	only symptomatic drugs	3 years	7.2% had worsening of symptoms (1st year), 5.7% oral burning or itching, 2.9% urticaria and 14% gastrointestinal effects (stomachache, nausea)	SLIT benefit obtained in the long-term in the study, the CI showed an improvement of about 50% vs baseline values.
Lin Z, Zhou L *et al*	2013	116	<18	HDM	House-dust mite (HDM) extract	No treatment	6 months	Not mentioned	SS (nasal symptom score and total nasal symptom scores) were significantly decreased(p < 0.01). Clinical improvement (mRNA levels of TIM-1 and IL-5 decreased and IL-10 mRNA level increased) in well-controlled children (p < 0.05).
Shao J, Cui YX *et al*	2014	264	3-13	HDM	Dermatophagoidesfarinae	Without SLIT	12 months	None reported	SLIT showed lower SS, VAS scores (all, p < 0.01), and asthma medication consumption decreased (p < 0.01) throughout the period. The specific IgG4 was significantly increased after SLIT treatment.

We also found that 6 studies (n=468) with a maximum duration of 3 years and minimum age of 4 year to maximum of 17 year children were also providing the evidence of long term efficacy of the sublingual immunotherapy.

The research populations included in this review mostly had respiratory allergic symptoms[1-12, 14-24 and 26-31] which included allergic rhinitis with or without asthma, rhino-conjunctivitis, and mild to moderate asthma.

In respiratory and cutaneous allergic symptoms, the decrease of symptoms score was checked by reduction of asthmatic symptoms, nasal symptoms, ocular symptoms and skin response. Nasal symptom measured by Nasal IgE, the value was obtained by allergen specific nasal challenge test or nasal provocation tests. Chest symptoms checked by FVC, FEV1 and PEF. Cutaneous symptoms were observed through pollen season vs. baseline skin sensitivity test. Other than these, tests like IgE, IgG(4), T(H)[1] cytokinase tests were conducted. Significant differences were reached in patient treated with SLIT. Clinical improvementsare also related to symptoms score. For medicine score, reduction of medication used during therapy was mainly considered. The considerable medications which included in studies were systemic antihistamines and/or corticosteroids, inhaled corticoids, inhaled beta agonists and other symptomatic drugs on need. In symptoms-medication score, both the parameters (symptoms + medication) were considered.

House Dust Mites: HDM sensitivity was reviewed in 1033 children between 2-18 years of age. House dust mites are the commonly identified allergens causing hypersensitivity in children. The 15 studies included in this review were in 2000 to 2014 with study duration ranging from 18 days to 3 years. In a study done in 24 children in 2000 showed tiredness, swelling of the mouth, lips, and face (at 2 h) and one case of itching of the mouth (at 3 h) that resolved spontaneously without drugs, and were reported during the induction phase with the first administrations of the most diluted vial.[3] No Serious events are reported in this classification.

Grass Pollen: This is the second large sub group testing hypersensitivity of grass pollen extracts (including rye grass extract) through 12 studies conducted from 1999 to 2012. 1424 children between 2-18 years participated in total to determine the safety and effectiveness of grass pollen extracts through these twelve studies across geographic boundary. Five mixed grass pollens: *dactylis glomerata, lolium perenne, festuca pratensis, phleum pratense* and *poa pratensis* are the commonly identified pollens to trigger allergic reactions in children. Three long durational studies spanning from 2 years to 3 years[10, 11, 23] are conducted in 260 children to which determined less medication in the second and third years of therapy, and their symptom scores tended to be lower. From the second year of immunotherapy, subjective evaluation of overall allergy symptoms was favourable in the actively treated children.[11] A significantly improved asthma symptom scores (41% vs. placebo group), reduced nasal symptoms (25% vs. placebo group) and the use of rescue medications (10% vs. placebo group), improved forced expiratory volume in 1 s.[23] The significant reduction in multiple symptom medication and improvement in medication score.[10]

Among 12 studies, one study mentioned of two cases of a cutaneous erythematous reaction in the submandibular area, slight oedema of the eyelids and worsening of the oculo-rhinitis symptoms.[1] Another study on 193 children shown 1 clinically significant asthma event in an 11-year old boy with known asthma in whom SLIT was resumed after an interval of 4 days.[21] No SAE reported in any of the cases.

Parietaria and Tree Pollen: Two studies of parietaria pollen are conducted between age group of 8-14 years that included in total 68 children in the year 2003[5] and 2004[12]with a duration from 1to 2 years. No safety issue is reported in either study and provided evidence to believe that SLIT abrogates the seasonal bronchial hyper reactivity in children with asthma due to Parietaria.[12] and decreased early skin response when administered with fluticasone inhalation providing better result for chest and nose symptoms, drug scores, eye symptoms and VAS.[5] A significant reduction of symptoms observed in 88 children treated with tree pollen including medication and symptom reduction scores.[16]

In 2009, '*different allergen*' sensitivity study was conducted on 121 children. It is a comparison study on new cases to the children previously treated with SLIT. At the end of the two years long observation period asthma symptoms were present in 14 subjects in the case group (15%) and in 20 children (24%) in the control group (p = 0.13). No safety related issues are reported.[22]

For safety evaluation total 24 studies[1-4, 7,8,10-19, 21, 23,25-31](n=2267) are included to obtain safety data. Among them 2 studies [8&21]are primarily focussed on safety data and one study[14] highlighted the evidence on improved compliance rate. In total ten studies reported no adverse events with 2studies[17 &19] specifically accounted no serious adverse event reporting. 13 studies [1, 3, 8, 10, 11, 14-15,21,23,25, 26&31] mentioned local mild to moderate eventsthat include cutaneous erythematous reaction, worsening of the oculorhinitis[1], tiredness, swelling of the mouth, lips, face and one case of itching in mouth[4].Mild to moderate allergic rhinitis[19], asthma event[21], local oropharyngeal itching[25] and bitter taste[26] are other reported events observed in this review. The worsening of symptoms, 5.7% oral burning or itching, 2.9% urticaria and 14% gastrointestinal effects (stomach ache, nausea)[31] mainly occurred in build-up phase and rarely occurred in maintenance phase. No SAE and uncommonly required treatment is reported.

This review includes six studies to give the evidence of long term efficacy and safety parameters. From these studies it had been observed that clinical improvement was significantly improved after two to three years of the therapy [4,9,11,20,23,30]. Two studies[11&23](n=163) mentioned that in first year or in build-up phase the reported adverse events are more than the maintenance phase.

DISCUSSION

SLIT reduces rhinitis and asthma expressions. The studies conducted by different researcher supports that SLIT drops containing known quantities of major allergens is one of the major step towards qualitative improvement of allergen immunotherapy. Effective maintenance through SLIT can provide symptoms relief and less dependent on rescue medication within the first season. In respiratory allergic symptoms, the decrease of symptoms score was checked by reduction of asthmatic symptoms, nasal symptoms and ocular. The use of SLIT showed lower SS and VAS scores. A significant long term benefit can be seen by the use of personalized therapy through SLIT. The effect of SLIT is

evident after 2 years of treatment. Both the nasal and ocular score improvement is significant. The use of SLIT has shown no serious adverse events with few cases of local side effects and worsening of existing symptoms. This gives an impact of a very safe profile for pediatric use.

CONCLUSION

This review of use of sublingual immunotherapy will open the window for the future use of personalized approach of immunotherapy in paediatric populations with an expectation to get more personalized therapy registered for paediatric use which can further retard off-label and unregistered use of SLIT. This evidence based review also shows that the tailored approach is considerably safe with no serious event found considering all the indicators to determine effectiveness and compliance towards the treatment.

The studies included in this review has only one compliance study (n= 71, duration= 6 month) in the children age group 2-13 years[14]. There is an emergent need to conduct more studies focussing on therapy compliance in children with a subset of school attendance percentage in asthmatic children, night time vs morning symptom under personalized allergy therapy. There is also a scope to find the role of sublingual therapy in comparison to other conventional route in terms of compliance as study endpoint determination.

The review highlights further scope of studies to determine the cost burden to the parents through comparative approach in terms of therapy duration, cost incurred during build up and maintenance phase, number of clinic/hospital visit, self-administration and concomitant and rescue medication.

Abbreviation

AR- Allergic rhinitis
CI – Clinical improvement
FVS – Forced vital capacity
FEV1- Forced expiratory volume capacity in 1 sec
ICS – Inhaled corticosteroids
MS- Medicine score
PEF – Peak expiratory flow
SAE – Serious adverse event
SCIT- Sub cutaneous immunotherapy
SLIT – Sub lingual immunotherapy
SMS – Symptoms – Medicines- Score
SS- Symptoms score
VAS – Visual Analogue score

References

1. Di Rienzo V, Puccinelli P, Frati F, Parmiani S.; Grass pollen specific sublingual/swallow immunotherapy in children: open-controlled comparison among different treatment protocols; Allergol Immunopathol (Madr).1999 May-Jun; 27(3):145-51.
2. Bahçeciler NN, Işik U, Barlan IB, Başaran MM; Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study; Pediatr Pulmonol. 2001 Jul;32(1):49-55.
3. Pajno GB, Morabito L, Barberio G, Parmiani S; Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study; Allergy.2000 Sep;55(9):842-9.
4. Bufe A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P etal; Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study; Allergy.2004 May;59(5):498-504.
5. Pajno GB, Vita D, Parmiani S, Caminiti L *et al*; Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate; Clin Exp Allergy. 2003 Dec; 33(12):1641-7.
6. Marcucci F, Sensi L, Frati F *et al*, Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites; Allergy.2003 Jul;58(7):657-62.
7. Niu CK, Chen WY, Huang JL, Lue KH, Wang JY, Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan; Respir Med.2006 Aug;100(8):1374-83. Epub 2006 Jan 5.
8. Fiocchi A, Pajno G, La Grutta S *et al*; Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years; Ann Allergy Asthma Immunol.2005 Sep;95(3):254-8.
9. Marcucci F, Sensi L, Di Cara G. *et al*; Three-year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing sub-lingual immunotherapy; Pediatr Allergy Immunol. 2005 Sep;16(6):519-26.
10. Rolinck-Werninghaus C, Wolf H, Liebke C, *et al*; A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen;Allergy.2004 Dec;59(12):1285-93.
11. Novembre E, Galli E, Landi F, *et al*; Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis; *J Allergy Clin Immunol.* 2004 Oct;114(4):851-7.
12. Pajno GB, Passalacqua G, Vita D, *et al*; Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial; Allergy, 2004 Aug;59(8):883-7.
13. Passalacqua G, Musarra A, Pecora S, *et al*; Quantitative assessment of the compliance with once-daily sublingual immunotherapy in children (EASY project: evaluation of a novel SLIT formulation during a year); Pediatr Allergy Immunol.2007 Feb;18(1):58-62.
14. Pham-Thi N, Scheinmann P, Fadel R, *et al*; Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures; Pediatr Allergy Immunol.2007 Feb;18(1):47-57.
15. Valovirta E, Jacobsen L, Ljørring C, *et al*; Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children; Allergy.2006 Oct;61(10):1177-83.
16. Lue KH, Lin YH, Sun HL, *et al*; Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study; Pediatr Allergy Immunol, 2006 Sep;17(6):408-15.

17. Bernardini R, Campodonico P, Burastero S, *et al*; Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study; Curr Med Res Opin. 2006 Aug; 22(8):1515-22.
18. Ozdemir C, Yazi D, Gocmen I, Yesil O, *et al*; Efficacy of long-term sublingual immunotherapy as an adjunct to pharmacotherapy in house dust mite-allergic children with asthma; Pediatr Allergy Immunol. 2007 Sep;18(6):508-15.
19. Seidenberg J, Pajno GB, Bauer CP, *et al*; Safety and tolerability of seasonal ultra-rush, high-dose sublingual-swallow immunotherapy in allergic rhinitis to grass and tree pollens: an observational study in 193 children and adolescents; *J Investig Allergol Clin Immunol.* 2009;19(2):125-31.
20. Acquistapace F, Agostinis F, Castella V, Efficacy of sublingual specific immunotherapy in intermittent and persistent allergic rhinitis in children: an observational case-control study on 171 patients. The EFESO-children multicenter trial;Pediatr Allergy Immunol. 2009 Nov;20(7):660-4. doi: 10.1111/j.1399-3038.2009.00860.x. Epub 2009 Mar 23.
21. Stelmach I, Kaczmarek-Woźniak J, Majak P, *et al*; Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen; Clin Exp Allergy. 2009 Mar;39(3):401-8. doi: 10.1111/j.1365-2222.2008.03159.x. Epub 2008 Dec 23.
22. Keles S, Karakoc-Aydiner E, *et al*; A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes; *J Allergy Clin Immunol.*2011 Oct;128(4):808-815.e7. doi: 10.1016/j.jaci.2011.04.033. Epub 2011 Jun 8.
23. Kim EH, Bird JA, Kulis M, *et al*; Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization; *J Allergy Clin Immunol.* 2011 Mar; 127(3):640-6.e1. doi: 10.1016/j.jaci.2010.12.1083. Epub 2011 Feb 1.
24. Yonekura S, Okamoto Y, Sakurai D, *et al*; Sublingual immunotherapy with house dust extract for house dust-mite allergic rhinitis in children; Allergol Int. 2010 Dec;59(4):381-8. doi: 10.2332/allergolint.10-OA-0200. Epub 2010 Sep 25.
25. Wahn U, Klimek L, Ploszczuk A, *et al*; High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study; *J Allergy Clin Immunol.* 2012 Oct;130(4):886-93.e5. doi: 10.1016/j.jaci.2012.06.047. Epub 2012 Aug 29.
26. Ahmadiafshar A, Maarefvand M, Taymourzade B, *et al*; Efficacy of sublingual swallow immunotherapy in children with rye grass pollen allergic rhinitis: a double-blind placebo-controlled study; *Iran J Allergy Asthma Immunol.* 2012 Jun; 11(2):175-81. doi: 011.02/ijaai.175181.
27. Yukselen A, Kendirli SG, Yilmaz M, *et al*; Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy; *Asian Pac J Allergy Immunol*. 2013 Sep;31(3):233-41. doi: 10.12932/AP0276.31.3.2013.
28. De Castro G, Zicari AM, Indinnimeo L, *et al*; Efficacy of sublingual specific immunotherapy on allergic asthma and rhinitis in children's real life; Eur Rev Med Pharmacol Sci. 2013 Aug;17(16):2225-31.
29. Lin Z, Zhou L, Luo X, *et al*; Suppression of TIM-1 predicates clinical efficacy of sublingual immunotherapy for allergic rhinitis in children; *Int J Pediatr Otorhinolaryngol.* 2013 Aug;77(8):1345-9. doi: 10.1016/j.ijporl.2013.05.032. Epub 2013 Jun 22.
30. Shao J, Cui YX, Zheng YF, *et al*; Efficacy and safety of sublingual immunotherapy in children aged 3-13 years with allergic rhinitis; *Am J Rhinol Allergy*. 2014 Mar-Apr;28(2):131-9. doi: 10.2500/ajra.2014.28.4006.