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Background

Atopy refers to the genetic tendency to develop allergic diseases such as allergic rhinitis, asthma and atopic dermatitis (eczema). Atopy is typically associated with heightened immune responses to common allergens, especially inhaled allergens and food allergens. Allergen immunotherapy (AIT) is a treatment involving the administration of increasing doses of clinically relevant allergens to patients who have allergic disease. It consists of several routes of administration such as subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), and the demand for SLIT is increasing rapidly. Allergen-specific sublingual and subcutaneous immunotherapy is thought to work primarily by inducing T-cell tolerance and promoting regulatory T-cells, which secrete the suppressive cytokines interleukin (IL)-10 and transforming growth factor (TGF)- beta. This in turn leads to production of the non-inflammatory immunoglobulins IgG4 and IgA, thus directing the immune response away from the inflammatory, atopic IgE response. Among the allergens, house dust mite (HDM) allergy was shown to be common in Malaysia. Conventional treatment for allergic rhinitis includes oral or topical antihistamines and intranasal corticosteroids with the goal of treatment being symptomatic relief. With advanced technology and recent updates, AIT offers an option therapy to provide relief which subsequently will reduce the symptoms of atopy. Hence, this review was conducted upon request by our senior otolaryngologist from Hospital Sultanah Bahiyah, Alor Setar to review the best current scientific evidence SLIT on treatment of atopy.

Objective

To review the best current scientific evidence on effectiveness/efficacy, safety, cost/cost-effectiveness and organisational issues related to SLIT for the treatment of atopy (allergic rhinitis, eczema and asthma).

Methods

A systematic review was conducted. Review protocol and search strategy was developed by the main author and *Information Specialist*. Electronic databases were searched through the Ovid interface; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to March 31, 2022. Searches were also run in PubMed, INAHTA and Cochrane Library. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on March 31, 2022.

Results and conclusions

From a total of 722 titles identified through the Ovid and PubMed interfaces, nine studies were included in this review which consisted of seven systematic review of RCTs which three are from Cochrane Library, and two economic studies. The included articles were published between 2013 and 2021. Most studies were conducted in United States of America, European countries, United Kingdom, Japan and Korea.

Allergic Rhinitis (AR):

There was sufficient good level of evidence retrieved on SLIT for allergic rhinitis. In term of effectiveness (reducing symptoms and medication scores), evidence demonstrated that there was significant reduction in symptoms for SLIT therapy when compared with placebo. Sublingual immunotherapy showed a significant benefit in term of reducing symptoms and medications used, but inconclusive results

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when comparing between subcutaneous (SCIT) and SLIT in treating patients with AR. Adverse events were common with both SCIT and SLIT and majority were local reactions at the point of administration and resolved spontaneously without treatment.

Asthma:
Based on retrievable evidence, there was sufficient good level of evidence retrieved on SLIT for asthma in term of controlling event of exacerbations requiring an emergency department (ED) or hospital visit. The pooled estimate from these studies suggests SLIT may reduce exacerbations compared with placebo or usual care, but the evidence is very uncertain (OR 0.35, 95% (CI) 0.10 to 1.20) due to very low-certainty evidence. In term of asthma symptom and medication scores SLIT showed a trend of SLIT benefit over placebo or usual care. SLIT likely does not increase severe adverse events (SAEs) compared with placebo or usual care and SLIT may be a safe option for people with well-controlled mild-to-moderate asthma and rhinitis who are likely to be at low risk of serious harm.

Atopic Dermatitis (Eczema):
Based on retrievable evidence, there was sufficient good level of evidence retrieved on SLIT for AE in term of participant- or parent-reported global assessment of disease severity at the end of treatment, and the results showed inconclusive (10 trials of house dust mite (HDM). Meanwhile, for participant- or parent-reported specific symptoms of eczema, by subjective measures which includes two trials (n= 184) did not find that the specific immunotherapy (either SCIT or SLIT) improved SCORAD or sleep disturbance when compared to placebo. Therefore, for patients with AE the findings showed inconclusive results to suggest the use of SLIT as an option treatment. There is no retrieved evidence on safety SLIT for AE.

Cost/Cost-effectiveness
A HTA report in 2013 by Meadow A which includes of 14 economic evaluations (EEs) and two reviews of EEs resulted that both SCIT and SLIT were more beneficial than symptomatic treatment (ST), and in some cases also become less costly than ST over time. From this review, there were studies expressed results as incremental cost-effectiveness ratios (ICERs), both SCIT and SLIT were found to be cost-effective at thresholds of £20,000 per quality-adjusted life-year (QALY).

Another economic evaluations paper by Hardin FM in 2021 showed that when compared to SCIT, SLIT is economically favourable and should be considered the financially conscious option for patients with 40% adherence to therapy. By assuming an 80% compliance rate with allergen immunotherapy (AITs) and an estimated efficacy (assumed to be clinically significant improvement in symptoms) of 70% for SLIT and 80% for SCIT, at the 12-month mark, the baseline total cost to the payer of SLIT per successful treatment outcome is USD $1196 while the charge of SCIT per successful treatment outcome is USD $2691.

Economic Implication
In our own calculation, based on the cost calculation, the estimated annual cost of allergy immunotherapy HDM SLIT tablet per patient is between MYR 4,823.00 to MYR 5,918.00. To achieve the disease modification, a recommended treatment of three years will incur an estimated cost between MYR13,729.00 to MYR 17,014.00 per patient.

Since the recommended indication of this tablet is for those who are not adequately controlled with standard pharmacotherapy, the expected total expenditure will be based on the prevalence of this population.

Organisational:
There was no guideline retrieved which specifically addressed the use of allergen immunotherapy. However, the chronology of SLIT begins in 1998 when WHO recognised that SLIT was a promising alternate mode of immunotherapy and encouraged continued clinical investigation into this form of treatment. Subsequently, in 2001 the ARIA guidelines have documented on SLIT, and have consistently supported the effectiveness and safety of SLIT throughout subsequent updates. Following that in 2009) by their position paper - World Allergy Organization (WAO) published their opinion that the cumulative evidence showed SLIT represented a viable alternative to SCIT and also encouraged continued clinical investigation to characterise optimal techniques.