Allergology International xxx (2018) 1–11

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited Review Article

The efficacy of sublingual immunotherapy for allergic diseases in Asia

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ARTICLE INFO

Article history:
Received 22 January 2018
Received in revised form
5 February 2018
Accepted 14 February 2018
Available online xxx

Keywords:
Asia
Disparity
Efficacy
Randomized controlled trial
Sublingual immunotherapy

ABSTRACT

Sublingual immunotherapy (SLIT) has been proven to be safe and effective from an abundance of Western literature, but data from Asia is less complete. This review aims to examine the basic science, safety and efficacy of SLIT in Asian patients, and to determine future research needs in Asia. We performed a literature search on PUBMED, Scopus, and Cochrane Library database for articles on SLIT originating from Asian countries through Nov 2017. There were 18 randomized, double-blind, placebo-controlled trials, of which 9 involved solely paediatric subjects. Overall, sublingual immunotherapy is safe and is efficacious in Asian populations in allergic rhinitis (AR) and asthma. House dust-mite SLIT is effective in both mono- and polysensitized AR patients. Efficacy of SLIT is comparable to subcutaneous immunotherapy. Data on long term efficacy is lacking. A disproportionate majority of research originates from China and Japan, reflecting an asymmetry of access to SLIT within Asia. Significant disparities exist in the development of the allergy speciality, prescription patterns of SLIT, and pharmacological potencies of different SLIT products within and between Asian nations. We conclude that current available evidence suggests SLIT is efficacious in Asians but data quality of evidence is hampered by non-placebo controlled studies with methodological limitations. More data is needed in South and Southeast Asian populations. Future efforts may be directed towards improving access to SLIT in developing countries, standardization of SLIT dosage, and evaluating long term clinical outcomes.

Introduction

In the last two decades, sublingual immunotherapy (SLIT) earned a reputation as a safe and effective therapeutic modality for allergic diseases, particularly allergic rhinitis (AR) and asthma.[1] It is a treatment with disease-modifying properties having the potential to cure allergies, and does not have the systemic complication profile and invasiveness of subcutaneous immunotherapy (SCIT). Pooled data from extensive well-conducted randomized, double-blind, placebo-controlled trials in the West have shown that SLIT is safe and effective.[2] Data from Asia is less complete. As such, it is timely and important to review existing literature from Asia on the basic science, safety and efficacy of SLIT in Asian patients, and to determine future research needs in Asia.

Asia is an expansive continent supporting nearly 60% of the world's population, and is home to China and India, two of the world's fastest growing economies.[3] It is ethnically and culturally diverse, but more importantly, there exist huge disparities among Asian countries in economic development. One would therefore expect research into allergy and its management in Asia is to be inevitably confounded by the complex interplay of genetic, cultural, environmental and socioeconomic influences. In this review, we will focus primarily on the evidence for efficacy and safety of interventional studies on SLIT conducted in Asia. Secondarily, we will also explore some of the unique contextual details surrounding SLIT in Asia.

Literature search

Search strategy

A literature search was conducted using the search term “sublingual immunotherapy” on Pubmed, Scopus, and Cochrane Library.

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Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2018.02.007

Inclusion and exclusion criteria

We included articles originating from Asian countries, with a focus on East Asia. We excluded studies on non-human subjects and articles not directly relevant to sublingual immunotherapy in Asia, i.e. review articles on allergy management in general or on sublingual immunotherapy globally. Language of article was not an exclusion criterion.

Prioritization and analysis of studies

We identified and included for analysis all randomized, double-blind, placebo-controlled trials. Other interventional studies were evaluated on a case-by-case basis. While these trials inherently lack methodological strength, we acknowledge that relevant and useful clinical information that are otherwise not available (e.g. long term efficacy data) may be obtained, and are cited appropriately.

Characteristics of published work

The search yielded 5123 citations on sublingual immunotherapy, of which 441 were of potential interest. After excluding duplicates and applying our inclusion and exclusion criteria, we shortlisted 135 articles (Fig. 1). There were 18 randomized, double-blind, placebo-controlled trials, of which 9 involved solely paediatric subjects. The characteristics and salient results are summarized in Table 1.

Publications originated from 6 countries in Asia, chief among which are China and Japan, contributing to 51.9% and 29.6% of studies respectively. Together, these two countries are accountable for 81.4% of all articles and 83.3% of randomized, double-blind, placebo-controlled trials on SLIT from Asia (Fig. 2). South Asian (e.g. India, Sri Lanka) and Southeast Asian (e.g. Vietnam, Malaysia, Indonesia) countries are severely under-represented, even though these regions collectively make up more than 50% of Asia's population.[3]

The chronological distribution of research articles on SLIT in Asia, by year of publication, is presented in Figure 3. The rapid rise of interest in SLIT in Asia can be seen to parallel the rest of the world.

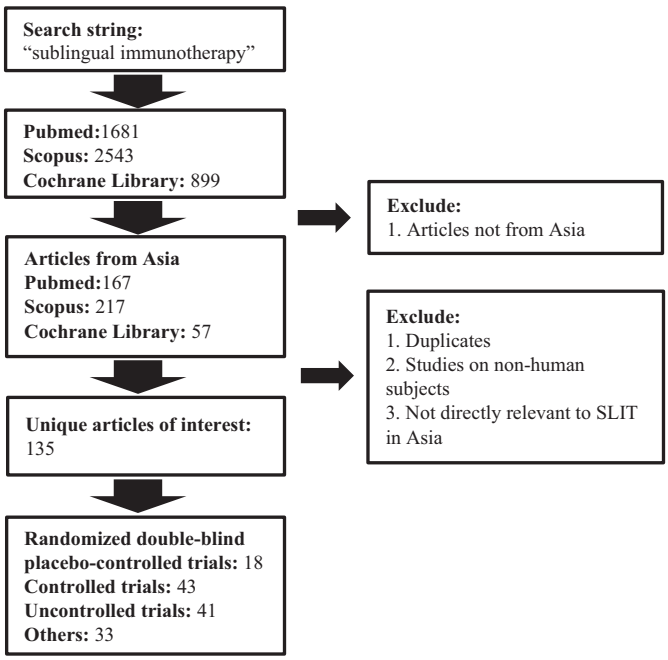

Fig. 1. Flowchart of results of literature search strategy.

Efficacy of SLIT in Asia

Overall clinical efficacy

In randomized, controlled trials (RCT) in Asia, SLIT is consistently shown to produce clinical improvement in allergy control, in AR[4–15] as well as asthma,[16–20] in all except one study[21] (Table 1). Additionally, it has been shown to produce objective improvements in lung function tests in asthmatic subjects.[16–18] Improvement in symptoms begin from 8 to 12 weeks of therapy and is sustained throughout course of treatment,[14,15,19] although it has been reported in two separate controlled trials on house dust mite (HDM)-induced AR to begin as early as 4 weeks.[22,23]

In a 6-month RCT, one Taiwan study failed to show statistically significant improvement in symptom and medication scores compared to placebo. The authors postulated possible reasons to be insufficient duration of therapy, dosage, and time in contact with oral cavity.[21] Fujimura *et al.* found SLIT to be not significantly different with placebo in ameliorating symptoms of Japanese cedar (JC) pollinosis after 1 year of treatment, although significant efficacy was found in the subsequent years of follow up.[6]

While demonstrating clear overall benefit over placebo comparing pooled inter-group data, it is recognized that SLIT does not work effectively for all users. Wang *et al.* reported achievement of well-controlled asthma in 80.5% with SLIT,[20] while Fujimura *et al.* reported clinical response in only 55%.[6] In a single-arm, uncontrolled trial of 6-month HDM SLIT in children, Lin *et al.* reported the rates for well-controlled, partly controlled and uncontrolled AR to be 43.1%, 32.8% and 24.1%, respectively.[24]

Monosensitized versus polysensitized patients

Polysensitization is a highly prevalent and clinically-significant phenomenon. In a large cross-sectional multi-centre study in China, more than 90% of atopic patients are sensitized to two or more allergens and 83.7% had concomitant sensitization to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*.[25] The results of numerous trials are consistent in demonstrating that HDM SLIT is equally effective in controlling symptoms and reducing medication usage in polysensitized AR patients, in both adult and paediatric populations.[22,26–29] In one study, the authors found clinical symptom scores to show improvement earlier in the monosensitized group at 6 months and 1 year compared to the polysensitized group, but no difference at 1.5–2 years.[30] There are no studies directly comparing the clinical efficacy of single mite allergen SLIT against dual mite allergen preparations (e.g. SLIT containing *Der p and Der f* in 1:1 ratio).

It is speculated that the single HDM extract induces immune tolerance by activating inducible regulatory T cells which exert a partially nonspecific immunologic regulatory effect on immune responses even to unrelated antigens.[22,31] This biological phenomenon is termed "bystander effect". However, an important caveat is that existing data is only limited to HDM-induced AR in China. More studies are required to understand the treatment response profiles using different allergens, on different populations, and on asthma. A comparative trial on single-allergen versus multi-allergen SLIT may shed more light on the clinical significance of the bystander effect, and thus inform clinicians on the management of polysensitized patients.

Please cite this article in press as: Liu X, et al., The efficacy of sublingual immunotherapy for allergic diseases in Asia, Allergology International (2018), https://doi.org/10.1016/j.alit.2018.02.007