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EDITORIAL

Subcutaneous versus sublingual immunotherapy

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1. Introduction

The first description of hay fever was by John Bostock in 1819. Since then, allergen IgE sensitization is recognized as playing a major role in allergic rhinoconjunctivitis (ARC), asthma, Hymenoptera sensitivity, drug allergy, atopic eczema and other diseases. A variety of treatments are available for allergic diseases among which is allergen immunotherapy (AIT). It is the only therapy known to modify the underlying immunologic abnormalities which cause these diseases [1].

The first attempt to utilize subcutaneous immunotherapy (SCIT) was in 1911 when Leonard Noon used grass pollen extract to treat grass-pollen-induced 'hay fever' or ARC [2]. Sublingual immunotherapy (SLIT) was introduced by French K. Hansel 25 years later in 1936. However, double-blind controlled studies indicated that SLIT was not effective because of the suboptimal doses of allergen extracts used for therapy.

Today, SLIT formulations with optimal allergen doses are proven to be efficacious. For example, the US FDA approved Grastek® (Merck Sharp & Dohme Corp. Whitehouse Station, NJ, USA) and Oralair® (Stallergenes, Antony, France) for select grass-pollen- and Ragwitek™ (Merck Sharp & Dohme Corp. Whitehouse Station, NJ, USA) for ragweed-pollen-induced ARC in 2014. Other SLIT formulations are approved for use throughout different parts of the world, particularly Europe. Dust mite and cat allergen SLIT are under development in the United States.

SLIT and SCIT are the most common routes used today for AIT to treat ARC. Regional variation in preference exists throughout the world. SCIT is used primarily in clinical practice in the United States, while SLIT and SCIT are equally used depending on the region in Europe [3].

Which one, SCIT or SLIT, should be utilized for ARC? Patient characteristics to be considered include: seasonality of the symptoms, whether he/she is mono- or poly-allergic, socio-economic factors, patient preference, and anticipated patient adherence for the treatment regimen. Regulatory approval is also an important consideration. Other considerations include: safety, the availability of standardized versus non-standardized extracts, long-term clinical benefit, and ability to afford and utilize epinephrine (in the USA) or appropriately supervise SLIT

administration at home for any age, but particularly for a minor [4]. This editorial focuses on how to choose between SCIT and SLIT in clinical practice.

2. Clinical benefit

The appropriate use of SCIT and SLIT results in sustained clinical benefit. A double-blind randomized trial by Durham et al. shows that grass SCIT for ARC for 3 years had a statistically clinical effect for another 3 years following cessation of therapy. Grastek® and Oralair® SLIT trials indicate that 3 years of treatment for ARC is followed by 2 years of clinical efficacy [5,6]. However, the FDA package insert for Grastek® indicates continued efficacy for only 1 year and for Oralair® no continued efficacy beyond treatment as mandated by the FDA. Similarly, there are no data to indicate that Ragwitek™ has sustained efficacy beyond treatment.

SLIT formulations include tablets and drops, both of which are clinically effective; however, there are no head-to-head controlled studies directly comparing the same allergen extract administered as a SLIT tablet versus drops [7].

Which is more effective, SLIT or SCIT? There are no appropriately powered, well-designed, head-to-head controlled studies comparing SCIT and SLIT. One meta-analysis by Nelson et al. demonstrates superior efficacy with SCIT versus SLIT [8]. However, a 2015 meta-analysis of 37 studies measuring symptom scores and 31 measuring medication scores report similar efficacy between SCIT and SLIT tablets versus placebo for grass-pollen-induced ARC. However, no clinically significant differences for grass SLIT drops versus placebo were found [9]. Both SCIT and SLIT induce immune tolerance via regulatory T-cells and suppression of the type-2 cellular immune response [4].

3. Mono versus polyallergic patients

A key factor to determine which form of therapy, SCIT versus SLIT, is appropriate for a given patient for ARC is determined by a detailed history and appropriate skin or *in vitro* tests to confirm sensitivity. For poly-allergic patients, i.e. those with

perennial symptoms and seasonal exacerbations caused by multiple allergens, SCIT seems to be more appropriate simply because of the number of allergens necessary for treatment. At this time, it is impractical to give optimal doses of many allergens by SLIT because of the limited number of regulatory-approved SLIT products and the difficulty of using multiple doses each day. In contrast, monoallergic individuals, who have symptoms only during the grass and/or ragweed seasons, may be more appropriately treated with SLIT, because of the convenience of administering one or two allergens by this route at home. Similarly, it may be more convenient to treat with SLIT for patients allergic to dust mites or cat dander for perennial symptoms.

Of importance, studies show variable results with multi-allergen SLIT administered in a mixture versus separately [10,11]. The most robust data for SLIT indicates that there is a significant reduction in symptoms in monoallergic patients using SLIT compared to placebo. Therefore, additional information is necessary regarding the use of multiple allergens for this form of therapy. Likewise, there are some data to show that mono- and multi-allergen SCIT is efficacious; however, more confirmatory data for poly-sensitization SCIT efficacy is necessary [12]. Poly-allergic subjects in the USA are usually treated with SCIT whereas in Europe, one or several allergens are utilized to treat either by SCIT or SLIT.

Current recommendations indicate that if more than one SLIT tablet is administered, it should be spaced at least 30 min apart to theoretically allow appropriate absorption of one allergen at a time and to identify potential side effects from one versus the other SLIT product being utilized [13]. SLIT tablets versus 'allergy drops' may provide the optimal way to deliver the allergen to the oral mucosal membranes. Some physicians use SLIT 'allergy drops', employing the same extracts utilized for SCIT. This is an FDA 'off-label' use of this form of therapy.

In general, the optimal dose for a given allergen is administered daily for SLIT whereas for SCIT, once maintenance is reached, it is administered monthly. Studies suggest that the monthly dose of SCIT required to induce allergen tolerance is equal to the daily dose required for SLIT [14].

4. Safety

AIT is tolerated for the vast majority of patients on such therapy. Side effects for SCIT include common local reactions at the site of the injection and, more rarely, systemic allergic reactions. Systemic allergic reactions can be serious, even fatal. To the contrary, SLIT is safer than SCIT. Reactions usually are local and limited to the mouth. Occasionally, system allergic reactions occur; however, life-threatening anaphylaxis is extremely rare. For example, 0.1–3.5% of injections result in a systemic allergic reaction for SCIT, whereas there is a 0.056% of systemic allergic reactions per SLIT dose. Fatalities have been reported with SCIT but not SLIT [15,16]. Guidelines, depending on the SLIT product, indicate that the first one or more SLIT doses be administered in a physician-supervised setting and thereafter, at home [17]. However, even though SLIT is generally safe, the FDA requires that patients be prescribed epinephrine for self-administration because of the

remote chance of a systemic allergic reaction. This is not a requirement for SLIT prescribed in Europe.

5. Cost and adherence

Multiple studies indicate that SCIT and SLIT are cost-effective [18]. An analysis of SCIT in a USA Medicaid population found a 12% reduction in direct costs following such therapy. SLIT similarly decreases health-care expenditures [19]. While both are economically advantageous, when appropriately utilized, adherence to both types of therapy is similar with equal percentages of patients remaining on therapy for a similar duration. A total of 11–77% of patients prematurely discontinued SCIT, whereas 22–93% do the same with SLIT [20]. These studies highlight the importance of involving the patient in the decision to use AIT and which form of therapy to be utilized.

6. Conclusions

Both forms of AIT are accepted and proven methods to treat ARC. SCIT is currently used to treat ARC, asthma, Hymenoptera hypersensitivity, and atopic dermatitis, whereas SLIT is primarily used to treat ARC. Studies are ongoing to determine whether SLIT too is an efficacious treatment modality for other diseases. Patients polyallergic to many allergens in the United States are more commonly treated with SCIT versus SLIT, whereas in Europe, polyallergic patients, because of a limited number of aeroallergens which cause allergic diseases in Europe versus USA, are treated with either SLIT or SCIT. Those sensitive to one, two, or even three allergens could be treated with SLIT or SCIT. SLIT is safer than SCIT, even though the former is utilized at home. SCIT should be administered in a medical clinic with a physician present with knowledge of how to treat a systemic allergic reaction during injection therapy. Likewise, the patient should wait at least a half-hour in the medical facility after their injection. Even though systemic allergic reactions are extremely rare with SLIT, appropriate instructions for the use of epinephrine, when required by regulatory agencies, are necessary. Education as to how such therapy works and the reasons for its use is of absolute importance for adequate adherence by the patient for either form of therapy. Other forms of immunotherapy, for example, the use of modified allergens or recombinant allergens and epicutaneous therapy may be forthcoming, and the physician and the patient may even have more choices for the form of AIT utilized in the future.

Declaration of interest

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References

1. Jongejan L, Van Ree R. Modified allergens and their potential to treat allergic disease. *Curr Allergy Asthma Rep.* 2014;14(12):478.

2. Calderón M, Cardona V, Demoly P. One hundred years of allergen immunotherapy European academy of allergy and clinical immunology celebration: review of unanswered questions. *Allergy*. 2012;67(4):462–476.
3. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy*. 2007;62:317–324.
4. Durham SR, Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis?. *J Allergy Clin Immunol*. 2016;137(2):339–349.e10.
5. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129(3):717–725.e5.
6. Didier A, Malling H-J, Worm M, et al. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clin Transl Allergy*. 2015;5:12.
7. Radulovic S, Wilson D, Calderon M, et al. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy*. 2011;66(6):740–752.
8. Nelson HS. Subcutaneous immunotherapy versus sublingual immunotherapy: which is more effective?. *J Allergy Clin Immunol Pract*. 2014;2(2):144–149.
9. Nelson H, Cartier S, Allen-ramey F, et al. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. *J Allergy Clin Immunol Pract*. 2015;3(2):256–266.e3.
10. Amar SM, Harbeck RJ, Sills M, et al. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol*. 2009;124(1):150–155.
11. Swamy RS, Reshamwala N, Hunter T, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *J Allergy Clin Immunol*. 2012;130(1):215–24.e7.
12. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. *J Allergy Clin Immunol*. 2009;123(4):763–769.
13. Tabatabaian F, Casale TB. Selection of patients for sublingual immunotherapy (SLIT) versus subcutaneous immunotherapy (SCIT). *Allergy Asthma Proc*. 2015;36(2):100–104.
14. Cox L. Sublingual immunotherapy for aeroallergens: status in the United States. *Allergy Asthma Proc*. 2014;35(1):34–42.
15. Epstein TG, Liss GM, Murphy-Berendts K, et al. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008–2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract*. 2014;2:161–167.
16. Cox LS, Larenas Linnemann D, Nolte H, et al. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol*. 2006;117(5):1021–1035.
17. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. 2014;7(1):6.
18. Jutel M, Agache I, Bonini S, et al. International consensus on allergen immunotherapy II: mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol*. 2016;137(2):358–368.
19. Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol*. 2008;121(1):227–232.
20. Cox LS, Hankin C, Lockey R. Allergy immunotherapy adherence and delivery route: location does not matter. *J Allergy Clin Immunol Pract*. 2014;2(2):156–160.