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Invited Review Article

The global development and clinical efficacy of sublingual tablet immunotherapy for allergic diseases

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ABSTRACT

Allergy immunotherapy (AIT) is a treatment option for respiratory allergy that is complementary to pharmacotherapy, with a distinct mechanism of action. Alternative methods to subcutaneous administration of AIT that enable patients to safely self-administer AIT is considered an unmet clinical need.

The sublingual immunotherapy tablet (SLIT-tablet) is an orally disintegrating pharmaceutical formulation (oral lyophilisate) containing standardized allergens. SLIT-tablets have been developed for sublingual immunotherapy (SLIT) of cedar-pollen, grass-pollen, ragweed-pollen, tree-pollen, and house dust mite allergies. It is a once-daily tablet treatment to be self-administered after the first dose has been provided under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Once the first dose is adequately tolerated, subsequent doses may be self-administered. SLIT-tablets have proven efficacy for allergic rhinitis (AR) with and without conjunctivitis (C) and allergic asthma (AA) in adults, children, and poly-sensitized allergic patients. Meta-analyses indicate that SLIT-tablets have superior or similar efficacy compared with anti-allergic pharmacotherapies for seasonal AR and superior efficacy for perennial AR. SLIT-tablets have also demonstrated clinically relevant improvements of asthma, with significant reductions in the following: daily inhaled corticosteroid use, risk of asthma exacerbations, and asthma symptoms. SLIT-tablets are generally well tolerated, with a low risk of systemic allergic reactions. The most common treatment-related adverse events are mild-moderate oral reactions. Current evidence supports SLIT-tablets to be considered as an alternative or add-on treatment to pharmacotherapy for AR/C and asthma. Future SLIT developments may include early intervention to prevent the development or progression of allergic disease in children.

Introduction

Allergy immunotherapy (AIT) is a treatment option for respiratory allergy that is complementary to pharmacotherapy, with a distinct mechanism of action on the immune system. AIT is performed by repeated sublingual or subcutaneous doses of allergens to an allergic person in order to gradually induce immunological tolerance towards the allergens. AIT modulates the basic immunologic mechanism of the allergic disease and is the only known treatment option with the potential to provide long-term, post-treatment benefits and alter the natural course of allergic disease.[1] Sublingual immunotherapy (SLIT)-tablets are an alternative to subcutaneous immunotherapy that provide the benefits of AIT without the cost and inconvenience of frequent office visits or the discomfort of injections. The original idea supporting sublingual administration was to achieve a prompt systemic absorption of the allergen through the sublingual mucosa. However, biodistribution studies with radio-labeled allergens in humans have shown that the systemic absorption of the allergen through the oral mucosa was absent or negligible. Therefore, the clinical effect should be ascribed to the local interaction of the allergen with the mucosal immune system.[2,3] Although not fully understood, a possible mechanism of sublingual immunotherapy is that the oromucosal contact with allergen results in tolerance development through the interaction of dendritic cells, Langerhans cells, and T-cells within the mucosa or in the regional lymph nodes[4]

Sublingual immunotherapy tablet (SLIT-tablet) is an orally disintegrating pharmaceutical formulation (oral lyophilisate) containing standardized allergen extracts that been developed as sublingual immunotherapy (SLIT) for allergic rhinitis with and without conjunctivitis (AR/C) and allergic asthma (AA). SLIT-tablets have been developed for treatment of AR/C for cedar-pollen, grass-

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pollen, ragweed-pollen, tree-pollen (in development), and for AR/C/AA of house dust mite (*D.pteronyssinus*, *D farinae*) allergies. It is a once-daily tablet treatment to be self-administered after the first dose has been provided under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Once the first dose is adequately tolerated, subsequent doses may be administered without medical supervision.

Professional society AR/C guidelines recommend AIT for patients with seasonal or perennial AR/C and the recent 2017 GINA asthma guideline update recommends SLIT-tablet for patients for whom there is a clear relationship between asthma symptoms and exposure to HDM.[5,6] Despite these recommendations, AIT is underutilized, with only about 20% of patients with AR/C and even less patients with asthma, having ever received AIT.[7,8] The purpose of this review is to describe the current development and evidence of SLIT-tablets as an add-on or alternative treatment option to pharmacotherapy for AR/C and allergic asthma.

Treatment options for allergic asthma and rhinoconjunctivitis (AR/C)

Currently, the treatments for allergic diseases are based on allergen avoidance, allergy pharmacotherapy, and AIT.

The purpose of allergen avoidance is to decrease exposure to allergens. For patients allergic to widespread inhalant allergens such as grass and tree pollen, allergen avoidance which creates a low-exposure allergen environment (such as, the patient's home) is not a practical treatment option. For perennial allergens, such as house dust mite, this implies extensive sanitation and environmental control measures, e.g., mattress/pillow covers, frequent washing of bed clothing, focus on ventilation and decreasing humidity, increased frequency of vacuuming. Even if allergen levels are reduced in the home, other locations such as schools and day cares, are important sources for continuing exposure. Evidence suggests that mite allergen avoidance is not sufficient to relieve patients' symptoms; therefore, international treatment guidelines question whether the effect justifies the cost and effort.[5,9]

Pharmacotherapy for respiratory allergy most commonly includes antihistamines (oral or topical), local corticosteroids (nasal and/or inhaled), leukotriene antagonists, and inhaled β2-agonists, depending on the clinical manifestation and severity. Despite availability of these medications, rhinitis patients note that they are dissatisfied with treatments due to incomplete relief, slow onset of action, relief that lasts for <24 h, and decreased effects with continued use.[10] In addition, asthma exacerbations remain a significant problem in many patients despite conventional treatment (e.g., inhaled corticosteroids [ICS] or ICS/long-acting beta agonists (LABA) combination). Newer biologic therapies, such as anti-IgE, have demonstrated efficacy with respect to reduction in asthma exacerbations, but are generally reserved for the most severe patients, and are associated with significant costs. Common to all approved forms of allergy pharmacotherapy treatments is that they do not provide long-term, post-treatment benefits or alter the natural course of the allergic disease.

AIT is another treatment option for respiratory allergies and is delivered either subcutaneously (SCIT) or sublingually (SLIT). SCIT is generally administered weekly or biweekly under medical supervision in a physician's office, whereas SLIT is generally administered daily at home via drop or tablet formulations. In some parts of the world, SLIT drops are an off-label use of extracts intended for SCIT.[6,11] Such off-label use is concerning, as there is little evidence to support the efficacy of such practice, the allergen extracts are not adequately standardized, and a safe and effective dose has not been established through rigorous clinical trials. Additionally, when utilizing SLIT drops, multiple allergens may be mixed together which augments the dosing variability of this treatment. In contrast, SLIT-tablets are well-characterized, standardized oral formulations that have been evaluated in large clinical trials and have been recently approved by regulatory agencies in the marketed countries. Furthermore, the Timothy SLIT-tablet has been shown to provide preventive and long-term benefits, including sustained improvement and persistent efficacy beyond the treatment period both in adults and children.[12,13]

Key development goals of sublingual immunotherapy tablets for AR/C and asthma

The three key development goals for SLIT-tablets include: (1) Prevention of allergic symptoms: Efficacy in the first pollen season after start of specific immunotherapy and some months of treatment; (2) Sustained clinical effect: Maintenance of significant and clinically relevant efficacy during 2–3 treatment years of continuing daily treatment; and (3) Disease-modifying effect: Sustained significant and clinically relevant efficacy in post-treatment years.[14–16] Table 1 provides an overview of the different SLIT-tablets and their current development status in adults and children.

Many pivotal clinical trials conducted in countries worldwide have demonstrated efficacy of SLIT-tablets for AR/C, for asthma and for the prevention of disease progression.[17–36] Two SLIT-tablets are currently approved in Australia, Europe, the United States, and Canada for grass AR/C. These tablets are the timothy grass SLIT-tablet (GRASTEK®/GRAZAX®, ALK, Hørsholm, Denmark) for patients aged 5 + years, and the 5-grass (sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass) SLIT-tablet (ORALAIR®, Stallergenes, Antony, France/Greer Laboratories, Lenoir, NC, USA) for patients aged 10 + years in the US and 5 years and older in other countries.[37,38] One SLIT-tablet is approved in the United States,[39] Canada and Europe for ragweed AR/C (RAGWITEK®, RAGWIZAX®, ALK, Hørsholm) for patients aged 18 + years. Two SLIT-tablets for HDM (ODACTRA®/ACARIZAX®/MITICURE®, USA/ALK/Torii Pharmaceutical, Tokyo, Japan and ACTAIR® (Stallergenes/Greer) are approved in Europe (not ACTAIR®), Australia, and Japan for treatment of AR, and also for allergic asthma (ACARIZAX® only) in Europe and Australia. The HDM (ODACTRA®/ACARIZAX®/MITICURE®) SLIT-tablet is approved for patients 18 + years in North America,[40] 12 + years in Europe and Australia, and recently for 5 + years in Japan. Two tablets (Torii Pharmaceutical, Tokyo, Japan and Stallergenes/Greer) are approved for Cedar pollen AR in Japan. A tree tablet (ALK-Abello) containing birch pollen extract is in Phase III development.

The key learnings from multiple SLIT-tablet trials are that the magnitude of efficacy is dose-dependent. Dose dependent efficacy may be most notable in an EEC design (chamber trial), where the variability of allergen exposure, which is inherent in any in-field trial, is removed. The onset of effect on allergic symptoms occurs approximately 4–8 weeks (earliest assessment in EEC) after treatment initiation.[41,42] Onset of effect occurs slightly later in field trials (12–16 weeks) with a treatment effect that was maintained throughout the year/season with continued treatment.[36] The overall treatment effect is consistent regardless of age group, gender, race, asthma status, or allergen sensitization profile (monosensitized/polysensitized).[43] Fig. 1.[44]

Other key findings from numerous SLIT-tablet trials are that the magnitude of the observed treatment effects range from approximately 16%–40% in relative reduction in symptom and medication scores. The variation is related to allergen exposure during the season and year of the trial.[45] When allergen exposure during the trial year is high the greatest treatment effects are observed. In lower pollen exposure years, the treatment effect is less pronounced. The treatment effect appears to be similar in patients

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