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REVIEW

Tablet-based sublingual immunotherapy for respiratory allergy

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Abstract Allergic respiratory disease represents a significant and expanding health problem worldwide. The gold standard of therapeutic intervention is still grucocorticosteroids, although they are not effective in all patients and may cause side effects. Allergen Immunotherapy has been administrated as subcutaneous injections for treatment of allergic rhinoconjunctivitis and asthma and has been practiced for the past century. Sublingual immunotherapy (SLIT) tablets are now available for grass- or ragweed-induced rhinoconjunctivitis and will be available in Spain for house dust mite (HDM)-induced rhinoconjunctivitis and asthma in the next months. In this review, new developments in the field of tablet-based SLIT for respiratory allergy are summarized, with special emphasis on HDM-induced allergic rhinitis and asthma. SLIT tablets are the best-documented immunotherapy products on the market and represent a more patient-friendly concept because they can be self-administrated at home.

Introduction

Sublingual immunotherapy (SLIT) tablets have been developed to treat pollen-induced allergic rhinoconjunctivitis (grass pollen in Europe and ragweed pollen in USA) and house dust mite (HDM)-induced rhinoconjunctivitis and bronchial asthma. Fast dissolving SLIT-tablets have been developed by the industry in clinical programs comprising phase I tolerability studies, phase II dose-finding studies, and large phase III efficacy and safety investigations, including studies in patients with rhinoconjunctivitis as well as asthma. Due, at least in part, to the emergence of these large studies, new European Guidelines for Immunotherapy have been established by European Medicines Agency (EMA). Thus, SLIT tablets are the best-documented immunotherapy products on the market.

In Europe, three products have been developed in accordance with applicable regulatory requirements for marketing authorization. The SQ grass and HDM SLIT tablets (ALK, Horsholm, Denmark) and the 5-grass SLIT tablet (Stallergenes, Antony, France). The SQ grass SLIT tablet (Grazax®, ALK) is a fast-dissolving tablet of a freeze-dried formulation containing grass pollen extract from one grass species, Phleum pretense,[1] whereas the 5-grass SLIT tablet

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(Oralair®, Stallergenes) is a multiparticulate tablet produced by compression and containing a mixture of pollen from five homologous grass species with high IgE cross-reactivity.[2]

SLIT tablets in allergic rhinoconjunctivitis

In Europe, SLIT tablets have been developed for treatment of grass- or HDM-induced rhinoconjunctivitis. Several ''large trials'' were conducted in the past 10 years and included dose-ranging studies conducted with standardized extracts of grass and mite.

SLIT tablets for grass pollen-induced rhinoconjunctivitis

In the case of grass pollen allergy two seminal randomized, double-blinded placebo controlled trials led to the approval of grass SLIT tablets in Europe, The first, by Durham et al.[3] was a dose-finding study that compared placebo and 0.5, 5 and 15 μg of Pl p5 daily. This study found a significant reduction of symptoms and drug consumption vs placebo with the highest dose, which was subsequently accepted as the standard dose.[4,5] The other dose-finding study with grass tablets (mixture of 5 grasses) compared placebo and 8, 25 and 42 μg/ml of major allergen daily. The dose of 25 μg [300 index of reactivity (IR)] showed the best performance in efficacy and side effects[6] and was approved by the EMA.

The largest immunotherapy trial performed to date involved 1501 adults and children with grass pollen-induced allergic rhinoconjunctivitis, of whom 85% were polysensitized and 25% had asthma.[7] Use of grass pollen talets daily for 20 weeks resulted in a 20% decrease in rhinoconjunctivitis symptoms and a 23% decrease in total combined scores (symptoms plus rescue medication) compared with placebo. Additionally, specific analysis conducted in mono- and poly-sensitized patients demonstrated that, during the grass pollen season, polysensitized patients with allergic rhinoconjunctivitis benefit at least as much, if not more, from the grass pollen tablets as mono-sensitized patients.[8,9]

Concerning security, local allergic reactions were very common (oral pruritis in 46% and mouth edema in 18%) in the first 1–2 weeks of treatment, but generally disappeared when treatment was continued. Also, these reactions were less common and less severe when treatment was restarted before the next pollen season. Discontinuation due to tablet-related adverse reactions, mostly moderate-severe local reactions in the oral cavity, was very similar for both tablets[10] (close to 5%).

On the other hand, it has been demonstrated that clinical benefit of grass pollen SLIT-tablet identified during the treatment period, is maintained for a long-time period; thus, SLIT tablets have a disease-modifying effect. The results of two studies of grass pollen allergen tablet immunotherapy administered daily either preseasonally[11] or continuously[12] for 3 years were remarkably similar. In both studies, there was an approximate 30–40% reduction in symptoms and rescue medication use during the 3 years period of therapy. Furthermore, the beneficial effect of immunotherapy was maintained for at least 2 years after stopping treatment.

SLIT tablets for HDM-induced rhinoconjunctivitis

Recent studies have also demonstrated the efficacy and safety of SLIT tablet in subjects with perennial allergic rhinitis sensitized to HDM. In a randomized, double blind, single-site trial,[13] 124 adults with HDM-induced allergic rhinitis with or without conjunctivitis and with or without asthma received 12 Developmental Units (DU) of HDM SLIT-tablet (ALK), 6 DU of HDM SLIT-tablet or placebo daily for 24 weeks. Subjects underwent 6-h exposure challenges in an environmental exposure chamber (the Vienna Challenge Chamber) at screening and weeks 8, 16 and 24. The results demonstrated dose- and time-dependent improvements with HDM SLIT-tablet versus placebo. At the end of treatment period, the mean total nasal symptom score (TNSS) improvement relative to placebo was 48.6% with 12 DU and 26.6% with 6 DU. The HDM SLIT-tablet was well tolerated and no investigator-assessed anaphylactic allergic reactions or reactions requiring adrenalin were observed. Therefore, it was suggested that the dose of 12 DU was appropriate for further evaluation to determine the magnitude of effect in a natural allergen exposure environment.

The results of an study published more recently using a different HDM SLIT-tablet (Stallergenes) were consistent with those of the study previously reported.[13] Roux and coworkers[14] sought to assess the efficacy and safety of 3 doses of HDM SLIT-tablet in an environmental exposure chamber. Adults with HDM-induced allergic rhinitis were given a daily sublingual tablet containing placebo or HDM allergen extract at a dose of 500 IR, 300 IR, or 100 IR for 6 months. Participants registered their rhinitis symptoms during 4-hour HDM environmental exposure chamber challenges at randomization and after 1, 2, 4, and 6 months of treatment. The mean differences from placebo in the area under the curve of the rhinitis total symptom score for the 500 IR, 300 IR and 100 IR groups indicated a dose-dependent effect, with reduction in symptom scores of 33%, 29% and 20%, respectively. The more frequent adverse events were throat irritation and oral pruritus. There were no reports of anaphylaxis, but adverse events leading to premature discontinuation were more common in the 500 IR group. Therefore, the dose of 300 IR was selected for further development of this treatment.

A phase II trial[15] with the HDM SLIT-tablet (ALK) showed a beneficial effect on combined rhinitis symptom and medication scores in a subgroup of asthmatic patients with symptomatic allergic rhinitis at inclusion.

The results of two-phase III studies with the HDM SLIT-tablet (ALK) were recently published. In a randomized, double-blind, placebo-controlled trial conducted in 12 European countries,[16] a total of 992 adults with moderate-to-severe HDM-induced allergic rhinitis despite treatment with pharmacotherapy received a daily sublingual tablet containing placebo, 6 SQ-HDM or 12 SQ-HDM for approximately 12 months. The results demonstrated absolute reductions in total combined rhinitis score of 1.18 ($P = 0.002$) and 1.22 ($P = 0.001$) compared with placebo for 6 SQ-HDM and 12 SQ-HDM, respectively. The statistically significant