

Current Standards and Improvements in the Use of SLIT Tablets for Allergen Immunotherapy

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Opinion statement

The clinical use of sublingual allergen immunotherapy (SLIT) can be traced back several decades. Ever since that first use, scientists have sought to develop new ways of application for immunotherapy. SLIT with aqueous formulations was mainly used but has a number of practical limitations, such as the need for refrigeration, poor dosing accuracy, and allergen spreading from the sublingual zone to other enoral and pharyngeal regions. Solid pharmaceutical formulations of allergen extracts in the form of freeze-dried sublingual tablets have been first clinically studied in the 1990s and were followed by

DBPC prospective studies from 2006 onwards. Today, there are numerous different products of fast dissolving SLIT tablets for several allergens. Their clinical use and scientific background and evidence are discussed.

The clinical use of sublingual allergen immunotherapy (SLIT) in the treatment of respiratory allergies can be traced back to the first reliable report on a successful oral or sublingual aqueous formulations of pollen allergen extracts by J. Harvey Black in 1927. SLIT with aqueous formulations has been examined in randomized double-blind, placebo-controlled clinical trials since the 1980s. However, aqueous (drop) SLIT formulations have a number of practical limitations, such as (i) the need for cooling the solutions, (ii) sometimes poor dosing accuracy, with the need for multiple actuations of pump-type dispensing devices, and (iii) spreading from the sublingual zone in which allergen absorption is thought to be optimal.

Solid pharmaceutical formulations of allergen extracts—typically as fast-dissolving, freeze-dried sublingual tablets—are one way to overcome those restrictions. The following summarizes products' characteristics and clinical data of examples of SLIT-tablets from three companies for the treatment of allergic rhinoconjunctivitis with/without concomitant asthma. The first clinical trial of SLIT tablets has been performed in the 1990s using the monomeric allergoid Lais®. This allergoid is obtained by a chemical modification (carbamylation) of the native extract, resulting in a substitution of ϵ -amino groups of allergen lysine residues. It is claimed that this reaction does not induce polymerization and does not affect the immunological properties. Today, the company Lofarma (Milan, Italy) produces a range of Lais® SLIT tablet formulations for allergen immunotherapy, including extracts of a three-grass-pollen mixture (*Holcus lanatus*/*Phleum pratense*/*Poa pratensis*, 33:33:33), pellitory pollen (*Parietaria judaica* and *Parietaria officinalis*, 50:50), ragweed pollen (*Ambrosia artemisiifolia*), olive pollen (*Olea europea*), alder/birch pollen (*Alnus incana*/*Betula pendula* 50:50), mugwort pollen (*Artemisia vulgaris*), house dust mites (*Dermatophagoides pteronyssinus*/*Dermatophagoides farinae* 50:50), and cat dander (*Felis domesticus*). Three hundred and 1000 AU tablets are available. In practical terms, a four-day induction phase builds up from one 300 AU tablets per day to four 300 AU tablet per day. The maintenance phase comprises a 1000 AU tablet taken two to five times a week. The monomeric allergoid tablet Lais® from Lofarma is approved by several regulatory agencies for use as a named patient preparation but not as an authorized product.

Two other extensive clinical development programmes in SLIT tablet immunotherapy concern two grass pollen SLIT tablets (GRAZAX® / GRASTEK® from ALK-Abelló (Hørsholm, Denmark) and Oralair® from Stallergenes Greer (London, UK), both of which have received marketing authorization for the treatment of seasonal allergic rhinitis in children and adults in several countries and regions around the world (including the USA and the European Union). These two competing products differ in terms of allergen source and content as following: GRASTEK® / GRAZAX® is a tablet-formulated allergen extract indicated as immunotherapy for SLIT in patients with grass pollen-induced allergic rhinitis from timothy (*Phleum pratense*) or other cross-reacting grass pollens. A

GRASTEK® / GRAZAX® tablet contains 75,000 standardized quality tablet (SQ-T) units or 2800 bioequivalent allergy units (BAU corresponding to around 15 µg of major allergen (Phleum p 5). The GRASTEK® / GRAZAX® formulation presents as a round, white-to-off-white sublingual tablet with a debossed, round detail on one side, packaged in blister units. The inactive ingredients are gelatin (from a fish source), mannitol, and sodium hydroxide. In contrast to drop formulations, GRASTEK® / GRAZAX® does not require cooling and storage at 20 °C to 25 °C is recommended. The once-daily tablet is placed under the tongue and left to dissolve there for at least 1 min before the patient may swallow. In the USA (but not in all countries), the first dose of GRASTEK® must be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases, and the requirement for prescription of self-injectable epinephrine and instruction in the proper use of this emergency treatment in the event of an anaphylactic reaction are given.

Treatment should be initiated at least 12 weeks before the expected start of the grass pollen season and should be continued throughout the season. With a view to sustained effectiveness, ALK-Abelló recommends that GRASTEK® / GRAZAX® should be taken daily for three consecutive years (including the intervals between the grass pollen seasons).

GRASTEK® / GRAZAX®'s efficacy was assessed on the basis of double-blind, placebo-controlled, randomized, parallel group, multicenter clinical trials conducted over a single season or over five successive seasons.

The sustained efficacy of GRASTEK® / GRAZAX® was evidenced in a 5-year study.

The possible preventive effect of treatment with GRASTEK® / GRAZAX® on asthma development in pediatric patients (aged 5 to 12) with grass pollen-induced allergic rhinoconjunctivitis has been investigated in the GRAZAX® Asthma Prevention (GAP) trial.

Oralair® is a freeze-dried, tableted extract of pollen from sweet vernal grass (*Anthoxanthum odoratum*), cocksfoot/orchard grass (*Dactylis glomerata*), perennial rye grass (*Lolium perenne*), meadow grass (*Poa pratensis*), and timothy grass (*Phleum pratense*). Oralair® is indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis. In most countries, Oralair® is approved for children (aged ≥5 in the European Union and ≥10 in the USA) and adults. The manufacturer states the potency of the maintenance dose as 300 index of reactivity (IR), which is equivalent to around 25 µg of the group five major allergens or 9000 BAU. An up dosing phase is recommended in children; the five grass pollen tablet is administered as a 100 IR dose on day 1, a 2 × 100 IR dose on day 2, and then a 300 IR/day dose on day 3 and thereafter. Adults may initiate treatment with the maintenance treatment (300 IR) directly).

Oralair® was approved based upon trials in adults and children with grass pollen-induced allergic rhinitis in the European Union and in North America. A post-treatment effect was observed and a good safety profile has been confirmed in DBPC and post-marketing studies.

RAGWITEK® is a SLIT tablet formulation of short ragweed pollen extract that has been launched in North America.

ALK-Abelló is also developing a birch pollen SLIT tablet and has tested the dose-response profile in an environmental exposure chamber.

Stallergenes Greer has also developed a birch pollen SLIT tablet containing recombinant Bet v 1 allergen that has been studied in a DBPC multicentre phase II trial.

ALK-Abelló and Stallergenes Greer are also working with their respective local partners to develop sublingual cedar pollen SLIT tablets for the Japanese market.

ALK-Abelló, Stallergenes Greer, and Lofarma have developed SLIT tablet formulations of house dust mite (HDM) extracts. The preparations contain allergens from bodies and feces of two house dust mite species, i.e. *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.

ACARIZAX® is approved for the treatment in HDM-induced allergic rhinitis and asthma in adolescent and adult patients in 14 European countries, Australia, Japan (as MITICURE™ in the latter country), and for allergic rhinitis in the USA.

Actair® (STG320) is a HDM SLIT tablet developed by Stallergenes Greer in partnership with Shionogi & Co. Ltd. in Japan and was approved in Japan and in Australia being indicated for the treatment of HDM-induced allergic rhinitis.

For both preparations, a rapid onset of action with significant efficacy compared to placebo within 2 months after start of treatment has been shown for rhinitis and asthma, a sustained duration of effect of at least 1 year after end of a 6–12-month treatment period was proven in rhinitis and asthma patients. As demonstrated with ACARIZAX®, especially patients with more severe asthmatic disease under moderate to high ICS may benefit.

The Global Strategy for Asthma Management and Prevention (GINA) report (<http://ginasthma.org/>) now recommends AIT as a treatment option for allergic asthma for the first time: “Consider adding SLIT (sublingual allergy immunotherapy) in adult HDM sensitive patients with allergic rhinitis who have exacerbations despite ICS (inhaled corticosteroids), provided FEV1 is > 70% of predicted lung function”.

Novel strategies may be developed for the routine treatment of asthmatic patients—not only with HDM allergy.

Future perspectives of SLIT include the use of recombinant modified variants of common allergens such as grass, birch or ragweed pollen, HDM, or cat allergens as basis for SLIT tablets. The combination of a SLIT tablet with an adjuvant either as immune-potentiator or cell targeting vector may also be a very promising future development.