



Perspective

Direct comparison of efficacy of sublingual immunotherapy tablets for rhinoconjunctivitis

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ARTICLE INFO

Article history:

Received for publication October 7, 2015.

Received in revised form December 3, 2015.

Accepted for publication February 15, 2016.

Introduction

For allergen immunotherapy (AIT) to be effective, it should be high dose. However, after reviewing the data on AIT dosing, one can conclude that, especially for sublingual AIT (SL-AIT), products should not only be compared on the basis of their allergen content. Clinical trial outcomes seem the best parameter. However, comparing products' performances expressed in percentages of improvement in different trials is not scientifically sustainable because of the many trial-related variables, as we review here. We conclude that some data seem to be solid and might help the physician in the product choice.

Dose-Response Relationship for Liquid SL-AIT: Importance of Factors Other Than Dosing

It has been clearly found that higher doses of subcutaneous AIT improve efficacy. With the report of a dose-efficacy relationship for several subcutaneous extracts,¹ this concept was extrapolated to SL-AIT. Liquid SL-AIT dosing in relation to efficacy was studied in Europe, where SL formulations rapidly expanded their markets. In trying to compare total allergen quantity administered in a certain timeframe, investigators were hampered by the fact that European allergen manufacturers have their own in-house standards, making comparisons with the existing data impossible. To overcome this problem, several investigators analyzed extracts from different manufacturers simultaneously in the same laboratories. All came to the same conclusion: liquid SL-AIT dosing varies widely among manufacturers of *Dermatophagoides*^{2,3} and cat and ragweed pollen.^{2,4} High-dose manufacturers administer SLIT with highly concentrated drops over the whole range of extracts analyzed, as opposed to consistently low-dose manufacturers.² However, a faultless dose-efficacy relationship could not be established. For liquid SL-AIT, only one positive dose-effect, double-blind, placebo-

controlled (DBPC) trial exists in children with respiratory allergy to tree pollen: both dosing groups improved the symptom-score compared with placebo, but medication scores only improved in the high-dose group.⁵ All other DBPC trials with liquid SL-AIT compare only one dose against placebo. Of these, high-dose trials seem to have a higher probability to show efficacy,⁶ but some positive low-dose trials exist.⁷

Possibly, the dose-effect relationship for SL-AIT is more related to the quantity of allergen that finally reaches the dendritic cells in the submucosa⁸ than to the sublingual dose. Theoretically, a low-volume, higher concentrated extract could be able to produce a higher transepithelial concentration gradient, which might result in a higher deposition of allergen and enhanced efficacy. Finally, further elements exist that might facilitate or obstruct the passage of the SL-AIT allergen into the submucosa, such as vector systems.⁹ Because all these factors play a role in SL-AIT dose finding, investigators have had difficulty in determining the optimal dose. As a result, extrapolating effective doses from one product to the other is not recommended.

Grass Pollen Tablet SL-AIT

To overcome the high variability of the liquid SL-AIT formulations, 2 of the major European allergen manufacturers decided to explore the performance of sublingual tablets, first for pollen allergy and more recently for house dust mite allergic patients. After demonstration of the safety of the products, large DBPC trials were conducted with a grass tablet that contained *Phleum pratense* grass pollen extract (Grazax/Grastek; ALK-Abelló, Copenhagen, Denmark) and with a 5-grass tablet that contained pollen from 5 cross-reacting Poaceae (Oralair; Stallergenes, Antony, France).

Variables to Be Considered in Comparing Results of Grass Pollen AIT Trials

To select the best treatment option for patients, physicians are interested in comparing efficacy reported for different treatments. However, on doing so, the reader should take into account the reported percentage of improvement compared with placebo and the magnitude of the statistically significant superiority of the

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Disclosures: Author has nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.02.008>

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products over placebo. We briefly discuss which factors should be observed in analyzing SL-AIT efficacy. For a more in-depth discussion, we refer readers to the articles by Pfaar et al¹⁰ and Larenas-Linnemann et al.¹¹

Inclusion Criteria

Major differences in outcomes can be found when the study populations differ. Patient selection is generally based on a positive skin prick test (SPT) result with the extract under investigation and an exposure-symptoms relationship in the clinical history. Because the wheal size a patient produces on being tested with a certain extract depends on the potency of the extract, a SPT with a US extract will generally generate a larger wheal than a SPT with a European extract because SPT extracts in the United States have a higher concentration of allergen than European extracts.^{12,13} As such, European AIT trials define a positive SPT result as a wheal diameter equal or greater to 3 mm without referral to the negative control, whereas US trials require patients to have a wheal diameter of 5 mm larger than the saline control. The extract used in the Timothy grass tablet European trials for this inclusion criterion was Soluprick SQ (10 HEP/mL, ALK-Abelló), whereas in the US trials of this product the highly concentrated *P pratense* (100,000 BAU/mL) American extract was used (ALK-Abelló, Round Rock, Texas).

In the 5-grass tablet US trial, the mean of 2 perpendicular wheal diameters (as opposed to major diameter) greater than 5 mm with a Timothy extract was needed for the patient to be included into the trial. Moreover, patients were required to have an erythema diameter of at least 10 mm.¹⁴ As such, the degree of SPT sensitization in patients recruited into the US and European trials is not exactly the same.

In addition, it was recently found in one group of patients that efficacy was better when adding another inclusion criterion: elevated serum allergen specific IgE.¹⁴ In some trials, this was an inclusion criterion (Timothy grass tablet trials); in others, it was not (5-grass tablet trials).

Allergic Sensitization of the Included Patients and Monopolysensitization

Another difference between the patients included in the clinical trials is their exact sensitization profile: the Timothy grass pollen trials recruited patients with SPT sensitivity to Timothy,^{15–17} whereas the 5-grass tablet trials recruited SPT-positive patients to 1 of the 5 grasses included in the tablet. As such, the Food and Drug Administration indication for the fast-dissolving Timothy grass pollen tablet (Grastek) “positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens” for pollen specific IgE antibodies for Timothy grass or cross-reactive grass pollens, whereas for the 5-grass tablet (Oralair) the indication is a positive skin test or *in vitro* test result for pollen specific IgE antibodies for any of the 5 grass species contained in this product. Investigators recently argued to what extent Northern pasture grasses completely cross-react with Timothy, after they found the presence of several grass-specific allergens (eg, for *Poa pratense* and *Lolium perenne*) that are unique to each grass species and do not cross-react.¹⁸

With respect to the efficacy of a monoallergen grass pollen tablet in polysensitized or polyallergic patients, both tablets are at least as effective in monosensitized as in polysensitized patients in reducing allergy symptoms during the pollen season.^{19,20} Evidently, this does not include efficacy of the tablets outside the pollen season.

Definition of Pollen Season and Peak Pollen Season

In pollen SL-AIT trials, the primary efficacy variable is generally the change in symptom and medication scores from preseason to in season of the active group against the placebo group. Because pollen

season severity varies year by year, demonstrable efficacy varies with it: during more severe pollen seasons, it is much easier to detect a difference between active and placebo groups.²¹ Consequently, the precise definition of what exactly is considered the start and the end of the season can make a large difference. Finally, the closer the pollen counterstation is to the patient, the more reliable the pollen counts reflect actual patient-pollen exposure. All the above hold true just as well for the peak pollen season.

Exact Definition of the Primary Efficacy Variables

Symptom and medication scores can be measured and analyzed in many different ways. Most trials use the combined symptom-medication score difference from preseason to in season. However, the symptoms score is defined in several ways: a direct 6-item (nasal and ocular), 0- to 3-point symptoms score; an adjusted symptom score in which the rescue medication taken during 2 days is added to the symptom score per day or a symptom score adjusted for the pollen count. In addition, calculation of medication scores varies. The reporting of symptom scores as mean or median is crucial. Because many patients have a low symptom score and a medication score of 0, the mean score is decreased in both groups, bringing the mean closer to one another. Additional, other variables can be used as efficacy variables, as are the visual analog scale and quality of life questionnaires.

If one of the main advantages, supposedly attributable to AIT, is the immune modulation and as a consequence the long-term efficacy after AIT discontinuation, symptom and medication scores in the years after stopping AIT should be considered an important efficacy variable. Unfortunately, solid long-term data are very hard to obtain, and only those groups with high expertise in motivating patients to adhere to the filling in of diaries and the attending of clinic visits have been able to generate reliable results. Well-conducted, properly powered, prospective long-term efficacy trials in AIT are practically nonexistent. For both grass tablets, one long-term trial has been published. In both these trials, even though the high drop-out rate in the placebo group might have led to a positive selection bias and thus might have masked a positive outcome for the active group, a statistically significant improvement could be shown for SL-AIT over placebo (moderate-high quality of evidence).

Finally, immunologic markers of ongoing allergic inflammation vs biomarkers of allergen-specific tolerance and immune regulation are strong indicators of efficacy. In this field, experts have been looking for ideal biomarkers, which until now have been hard to find. Allergen specific IgG4 levels clearly increase with AIT, both subcutaneous and sublingual, but they cannot be linked to efficacy. The functional fraction of the of the total pool of IgG4 is probably more important (functional antibody blocking assay). However, this is still not an ideal biomarker. Topical biomarkers after allergen challenge and novel biomarkers of basophil histamine release²² seem to be promising options.

Dropout Rate

In trials with a higher dropout rate, finding a statistically significant difference between the active and the placebo group might become challenging in 2 senses. With 1-season trials, the study might become underpowered. As such, a group of investigators recently analyzed the dropout rate in SL-AIT DBPC trials. The authors conclude that an overall dropout rate of approximately 15% does not seem to be a factor of importance. How this compares to the dropout rates in SC-AIT trials is not known.

On the other hand, a high dropout rate in long-term trials might skew the results. Patients who do not fare well with the AIT are more likely to leave the study or turn down the invitation to participate in a study extension than patient who experienced relief during the first-season treatment. As such, the risk is imminent that

Table 1

Quality of Evidence According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Tool²⁸ of SLIT Studies on Grazax/Grastek and Oralair and Several Pivotal Trials With Related Sublingual and Subcutaneous Grass Pollen Formulations

Source	Design (Starting Score)	Large Effect ^a	Confound Annulated ^b	Dose-Response Gradient	Total Positive	Limitations in Design and Execution	Inconsistency of Results	Indirectness of Evidence	Imprecision of Results	Publication Bias	Total Negative	Quality of Evidence
Grazax/Grastek for Allergic Rhinoconjunctivitis Trials												
Durham et al, 2006 ¹⁵ ; AR and mild persistent asthma; 18–65 years old; pre-seasonal (8 weeks) for 1 season; SLIT; 2,500 SQ-T, 144 patients; 25,000 SQ-T, 148 patients; 75,000 SQ-T, 321 patients; placebo, 307 patients; 0.5 or 5 or 15 µg/d of Phl p 5	DBPC (4)	x	x		+1	x (good: ITT analysis)	x	x	Differences vs placebo and trends calculated, not between dosing groups	x	–1	4, high
Dahl et al, 2008 ²⁹ ; AR (and mild persistent asthma); 18–65 years old; continuous, 22 m; second year: SLIT, 189; placebo, 162; 15 µg/d of Phl p 5	DBPC (4)	x	x	x	0	Originally planned as 1-year trial. Only 60/51% of original AIT/placebo group continued. NS difference in symptom-medication scores between continuing and stopping: –1	x	x	x	x	–1	moderate
Durham et al, 2012 ³⁰ ; AR (and mild persistent asthma); 18–65 years old; continuous; 34 m; fifth year: SLIT, 135 patients; placebo, 103 patients; 15 µg/d of Phl p 5	DBPC (4)	x	x	x	+1	Same as above: –1 + dropout rate since study extension: 18.6% AIT and 36% placebo: –1	x	x	x	x	–2	moderate

Nieminen et al, 2010 ³¹ (mechanistic study): respiratory allergy; 5–15 years; SLIT: low dose, 10 patients; high dose, 10 patients; placebo, 10 patients; low, 24,000 SQ-U; high, 200,000 SQ-U/wk; 2 years	DBPC (4)	x	x	Yes	+1	x	x	x	Small groups	x	–1	4, high
Bufe et al, 2009 ³² ; SAR (42% mild asthma); 114 patients; placebo, 120 patients; 5–16 years; pre-season; 15- μ g/d Phl p 5 tablet	DBPC (4) Rhinitis DBPC (4) Asthma	x	x	x	0	x	x	x	x	x	0	4, High
		x	x	x	0	x	x	Only symptom and medication	Very small numbers (9 vs 3 days)	x	–2	2, low
Blaiss et al, 2011 ³³ ; AR and mild persistent asthma; 5–17 years; pre-season for 1 season; SLIT, 175; p placebo, 169; 15 μ g/d of Phl p 5	DBPC (4)	x	x	x	0	x (good: ITT analysis)	x	x	x	x	0	4, high
Nelson et al, 2011 ¹⁷ ; ARC (24% mild asthma); 18–65 years; SLIT, 184 patients; placebo, 207 patients; 15 μ g/d of Phl p 5; 6 m; pre-season.	DBPC (4)	x	x	x	0	x	x	x	x	x	0	4, high
Maloney et al, 2014 ³⁴ ; ARC (25% mild asthma), 5–65 years; SLIT, 750	DBPC (4)	x	x	x	0	x (good: ITT analysis)	x	x	x	x	0	4, high

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Table 1 (continued)

Source	Design (Starting Score)	Large Effect ^a	Confound Annulated ^b	Dose-Response Gradient	Total Positive	Limitations in Design and Execution	Inconsistency of Results	Indirectness of Evidence	Imprecision of Results	Publication Bias	Total Negative	Quality of Evidence
patients; placebo, 751 patients; precoseason; 15- μ g/d Phl p 5 tablet												
Oralair for Allergic Rhinoconjunctivitis Trials												
Didier et al, 2007 ³⁵ ; SAR (10% mild asthma); 100 IR/d, 157 patients; 300 IR/d, 155 patients; 500 IR/d, 160 patients; placebo, 156 patients; precoseason (4 mo); 300IR = 25 μ g/d of 5- grass tablet	DBPC (4)	x	x	Yes	+1	Symptom score alone is the primary outcome variable	x	x	x	x	–1	4, high
Didier et al, 2011 ¹⁹ ; SAR (13.7% mild asthma); SLIT preseason (2 mo) and coseason; 207 recruited, 147 FAS; SLIT preseason (4 mo) and coseason; 207 recruited, 149 FAS, placebo, 219 recruited, 165 FAS; 25 μ g/d of 5-grass tablet	DBPC (4)	x	Novel adjusted sympt score previously validated.	Trend to more improvement compared to placebo year by year (NS).	+1.5	Even though stated ITT analysis, 59 patients were excluded	x	No medication score (primary outcome = novel symptom score adjusted for medication intake)	x	x	–1	3–4, moderate- high
Didier et al, 2013 ³⁶ ; continuation of 2011 study by Didier et al plus 1 years; SAR (13.7% mild asthma); after 3-year SLIT and 1-year observation: SLIT preseason (2 mo) and coseason, 137	DBPC (4)	x	x	x	0	Dropout rate >15%	Reduction in days with rescue medication in 300 IR but not in 500 IR	x	x	x	–1	3 moderate

patients; SLIT preseason (4 mo) and coseason, 143 patients; placebo, 155 patients													
Didier et al, 2015 ²⁵ : continuation of the 2011 study by Didier et al plus 2 years; SAR (12.7% mild asthma); after 3-year SLIT and 2-year observation: SLIT preseason (2 mo) plus coseason, 117 patients; SLIT preseason (4 mo) plus coseason, 127 patients; placebo, 133 patients	DBPC (4)	x		Large sympt reduction in placebo (more severe patients withdrew), even so statistically significant improvement in SLIT group versus placebo	x	+1	Post hoc calculation of combined symptom- medication score but enough power to do so; dropout since start of study: AIT, 41%; placebo, 39%	x	x	x	x	–2	3, moderate
Wahn et al, 2009 ³⁷ : SAR (21% mild asthma); SLIT, 131 patients; placebo, 135 patients; 4–17 years; precoseason, 25- μ g/d 5- grass tablet	DBPC (4)	x	x		x	0	x	x	x	x	x	0	4, High
Halken et al, 2010 ³⁸ : moderate- sever AR (intermittent asthma); SLIT, 131 patients; placebo, 135 patients; 5–17 years; 25- μ g/ d 5-grass tablet; precoseason (6 mo)	DBPC (4)	+1	x		x	+1	No description of dropouts	x	x	Large CI	x	–2	3, moderate
Horak et al, 2009 ³⁹ : onset of action: allergen challenge chamber; ARC; SLIT, 45	DBPC (4)	4 mo: +1	x		Trend for dose- effect over time	+1	Masking and randomization technique not explained.	No change in nasal airflow and nasal secretion weight	x	x	x	–2	3, moderate

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Table 1 (continued)

Source	Design (Starting Score)	Large Effect ^a	Confound Annulated ^b	Dose-Response Gradient	Total Positive	Limitations in Design and Execution	Inconsistency of Results	Indirectness of Evidence	Imprecision of Results	Publication Bias	Total Negative	Quality of Evidence
patients; placebo, 44 patients; 25- μg/d 5-grass tablet for 4 mo; out of season Cox et al, 2012 ¹⁴ ; DBPC (4)		x	x	x	0	x	x	x	x	x	0	4, high
ARC (20% mild asthma); SLIT, 210 patients; placebo, 228 patients; precoseason; 25-μg/d 5- grass tablet Some of the Most Recent Grass Pollen SLIT Trials (2009–2015)												
Bozek et al, 2014 ⁴⁰ ; SAR; SLIT, 41 patients; placebo, 37 patients; 20 μg of 5-grass pollen (240 IR) drops 5 d/wk; 4 mo preseasonal for 3 years	DBPC (4)	x	x	x	0	No clear description randomization, –0.5	x	x	Nonvalidated VAS scoring for symptoms	Medication scores first and second years not stated	–2.5	1–2, (very) Low
Swamy et al, 2012 ⁴¹ ; AR (mild/ moderate persistent asthma); 6–57 years (55% of SLIT group are children); dual SLIT, 20 patients; placebo, 10 patients; 15 μg of Phl p 1 and 20 μg of Der f 1+2, daily for 12 months; posttreatment evaluations 12 ± 6 and 12 ± 12 mo	DBPC (4)	x	Small groups and even so statistically significant difference	x	+1	Randomization method not described, –1	x	x	Small groups	x	–2	3, moderate
Wahn et al, 2012 ⁴² ; ARC (and GINA group I–II asthma); 4–12 years;	DBPC (4)	x	x	x	0	No ITT mentioned, –1; 16.5% dropout in active group, <20%	x	x	Change in lung symptoms not reported	x	–1 (for RCT)	3 (for RCT)

precoseason SLIT, placebo; 6-grass aqueous extract, 40 μ g of 5-grass pollen daily in drops, 8 mo													
Stelmach et al, 2012 ⁴³ ; rhinitis (20 also had asthma), 6–18 years; pr- coseasonal, 20 patients; continuous, 20 patients; placebo, 20 patients; 2 years; 10 μ g/ d of 5 grass drops	DBPC (4)	x	x	x	0	Preestablished adjusted to 1000 pollen grains/m ³ of symptom and medication scores: no reduction	x	x	Small groups, underpowered	x	–1	3, moderate	
Panzner et al, 2011 ⁴⁴ 24-mo open continuation of 12-mo DBPC ⁴⁵ ; AR; mean (SD) age, 17.6 (10) years; number of children unknown; SLIT, 26; supralingual, 25 patients; 11.2 μ g/wk of 5-grass pollen (6-grass pollen extract) 3 times per week for 3 years	Randomized, non- controlled (4)	x	x	Year by year improvement in symptom and medication scores, +1	+1	No control group, x small groups: only statistically significant difference pre- post treatment, not between both active groups; no description dropout per group	x	Post hoc fusion of groups to improve stats, but does not seem to affect outcomes: –0.5	x Incorrect conclusion: medication score in supralingual not improved	SLIT, –2.5; supralingual, –3.5	SLIT, 2.5; supralingual, 1.5		
Ott et al, 2009 ⁴⁶ ; persistent seasonal AR, 8– 65 years; SLIT, 99; placebo, 46; 5-grass, 25 μ g/d of 5-grass drops daily (300 IR); coseasonal for 3 years	DBPC (4)	x	x	x	0	Methods of randomization or masking described: –1; statistically significant difference groups at baseline: –1	x	x	Median scores not means	x	–3	1, very low	
Agostinis et al, 2009 ⁴⁷ ; AR (60% mild asthma); 4–16 years; SLIT, 20 patients; control, 20 patients;	Randomized controlled (4)	x	Small groups, even so stat sign	x	+1	No medication score	x	VAS well-being only once a year: –2	x	x	–3	2, low	

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Table 1 (continued)

Source	Design (Starting Score)	Large Effect ^a	Confound Annulated ^b	Dose-Response Gradient	Total Positive	Limitations in Design and Execution	Inconsistency of Results	Indirectness of Evidence	Imprecision of Results	Publication Bias	Total Negative	Quality of Evidence
preseasonal for 2 years; 1000-AU drops 5 times per week Ahmadiashar et al, 2012⁴⁸: ARC; 5–18 years; SLIT, 12 patients; placebo, 12 patients; 900- IR <i>Lolium</i> drops, 3 times per week; 6 mo	Randomized controlled (4)	x	x	x	0	Very small groups; no comparison of symptom and medication score reduction SLIT vs placebo	Many more adverse effects in placebo group	Incomplete nasal sympt score (no congestion measured)	No SD or CI given for symptoms or medication	x	–4	0, very low
Pivotal Grass Pollen Subcutaneous Immunotherapy Trials (Basis for SCIT Dosing Recommendations)												
Frew et al, 2006⁴⁹: SAR, 18–60 years; SLIT; 100,000 SQ-U, 203 patients; 10,000 SQ-U, 104 patients; placebo, 103 patients; 20 µg of Phl p 5 monthly for ≥10 mo	DBPC	x	x	+1	+1	x	x	x	x	x	0	4+, high
Walker et al, 2001⁵⁰: SAR and asthma; 22 –64 years; SCIT, 22 patients; placebo, 22 patients; 100,000 SQ-U (20 µg of Phl p 5) every 4 weeks during 2 years	DBPC	x	x	x	0	x	x	x	x	x	0	4, high
Durham et al, 1999⁵¹: SAR; 26–50 years; first year: SCIT, 20 patients; placebo, 20 patients; then 3 years all SCIT (N = 37); 32 continued for 3 years: SCIT, 16 patients;	DBPC	x	x	x	0	Small groups, no power calculation, 5- year dropout rate, 20%	x	x	x	x	–1	3, moderate

placebo, 16 patients (+15 new controls); SCIT = 100,000 SQ-U (20 µg of Phl p 5) every 4 weeks													
Dolz et al, 1996 ⁵² ; asthma and/or AR; 15–35 years; <i>Phleum-Dactylus-Lolium</i> extract of 100,000 USQ/mL, 1 mL every 4 weeks during 3 years	DBPC	x	x	+1, progressive improvement during the 3 years	+1	–1, no clear primary end point, no comparison active vs placebo	x	x	–1, <i>P</i> values: not clear if over time or comparison active vs placebo	x	–2	3, moderate	
Leynadier et al, 2001 ⁵³ ; SAR; adults; SLIT, 16 patients; placebo, 13 patients; 5-grass calcium phosphate-adsorbed, 30 IR (0.6 mL of 50 IR/mL = 2.1 µg of Phl p 5) monthly for 12 months	DBPC	x	Small groups, even so statistically significant	x	+1	Small groups, no randomization or masking method described	x	x	x	x	–2	3, moderate	

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; CI, confidence interval; DBPC, double-blind, placebo controlled; FAS, full analysis set; GINA, Global Initiative for Asthma; HDM, house dust mite; ITT, intent to treat; NS, nonsignificant; OCT, open controlled trial; OIT, oral immunotherapy; OR, odds ratio; PAR, perennial allergic rhinitis; RCT, randomized clinical trial; RR, relative risk; SAR, seasonal allergic rhinitis; SLIT, sublingual immunotherapy; SPT, skin prick test.

^aLarge effect relative risk, less than 0.5; very large effect RR, less than 0.2. The relative risk has been calculated from the data given in the articles.

^bAll plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed.

Table 2
Some of the Large DBPC Trials Conducted With Grass Pollen Immunotherapy in Patients With Rhinoconjunctivitis Using Grazax or Oralair or Sublingual or Subcutaneous Products Related to Them

Product	Dosing	Reduction in Symptom-Medication Score			Comment
		First Season	Third Season	1–2 Years After Treatment	
SC-AIT	100,000 SQ-U = 20 µg of 5-grass pollen every 6 weeks	Yes, Frew et al, 2006 ⁴⁹	Yes, Durham et al, 1999 ⁵¹	Yes, Durham et al, 1999 ⁵¹	A 3-year course was just as effective for 4–5 years as a continuous 5-y course
SL-AIT liquid 300 IR	Coseasonal 25 µg of 5-grass pollen daily	Yes, Ott et al, 2009 ⁴⁶	Yes, Ott et al, 2009 ⁴⁶	1 Year after: no, Ott et al, 2009 ⁴⁶	1 Year after treatment combined score nonsignificant; symptom $P = .02$; definition of pollen season restrictive (high pollen count) ^a
SL-AIT liquid 120 IR	Precoseasonal (2 mo) vs continuous 10 µg/d	Yes, both, Stelmach et al, 2012 ⁴³	Second season: yes, both, Stelmach et al, 2012 ⁴³	Not done	Pediatric trial; the precoseasonal group received SLIT for 6 mo for 2 years
Grazax/Grastek tablet, fast dissolving	Precoseasonal (8 wk) 15 µg/d of 5-grass pollen	Yes, Durham et al, 2006 ¹⁵	Not done	Not done	Dose-finding trial; 15 µg (75,000 SQ-T) daily effective
	Continuous 15 µg/d of 5-grass pollen	Yes, Dahl et al, 2006 ¹⁶	Second season: yes, Dahl et al, 2008 ²⁹	Yes, Durham et al, 2012 ³⁰	First year start 4 mo preseasonally; after first season a study extension was added: only 60% AIT/51% placebo continued to year 2
Oralair tablet	Precoseasonal (2 mo) 25 µg/d of 5-grass pollen	Yes, Didier et al, 2015 ²⁵	Yes, Didier et al, 2011 ¹⁹	Yes at 1 year, Didier et al, 2013, ³⁶ ; no at 2 years, Didier et al, 2015 ²⁵	Only precoseasonal (4 mo) effective in the long term; quite marked reduction placebo group years 4 and 5
Oralair tablet	Precoseasonal (4 mo) 25 µg/d of 5-grass pollen	Yes, ^b Didier et al, 2007 ³⁵	Yes, Didier et al, 2013 ³⁶	Yes, Didier et al, 2013, ^{25,36}	

Abbreviations: Pre(4m), preseasonal administration starting 4 months before the season is expected to start; SC-AIT, subcutaneous immunotherapy.

^aThe higher the pollen count, the easier it is to find efficacy.³⁰

^bNo combined score given; symptom and medication scores analyzed separately.

the improvement observed in the active group over subsequent seasons is in part due to positive patient selection: only those patients who feel better continue. In this case, no strong conclusions can be drawn, unless the first-season symptom-medication scores of the active group dropouts are compared with the first-year symptoms of the patients in the final analysis set.

Population Analyzed

Many AIT publications report only on those patients who closely followed the treatment protocol in a per protocol analysis. This is, however, not a complete analysis because it only selects those patients who are following the prescription. According to the CONSORT criteria for clinical trial reporting, the correct way to present the data is as an intent-to-treat (ITT) analysis.²³ In those trials that report analyses based on all randomized participants who had at least 1 posttreatment diary data entry available for analysis (ie, the ITT population), the results are generally less favorable because there are usually several individuals who received hardly any medication and yet are still counted in the end results; however, ITT results are more realistic.^{15,17,24,25} As such, results of a per-protocol analysis in one article should not be compared with ITT results in another. The latest publications on both grass pollen tablets correctly report ITT.

Duration of the Administration of SL-AIT

SL-AIT has been given in different administration schedules: as continuous administration, as a precoseasonal schedule, and as a coseasonal schedule. The duration of administration has a direct effect on costs and adherence. However, too short a preseasonal administration interval might not be as effective.^{25,26}

Comparative Efficacy of AIT in Grass Pollen Allergic Individuals

In conclusion, it is now clear that products cannot be compared based on the reported results in the different trials. Moreover, trial heterogeneity restrains analysis of pooled data and is one of the well-known shortcomings of meta-analysis.²⁷ Comparative efficacy analysis of products would only be valid in an adequately powered head-to-head, double-dummy, DBPC trial. For now, the best approach is analyzing the clinical assays one by one on content and quality to determine whether a certain product is effective in the population studied.

With the published information as of September 2015, we present the quality of evidence for efficacy, product per product (Table 1), and briefly discuss this below. Table 2 summarizes the available information of large trials conducted with products related to both grass pollen tablets. SC-AIT with *P pratense*, 20 µg of the major allergen Phl p 5 administered every 4 weeks, is effective (high quality of evidence). Efficacy lasting for at least 3 years after such a 3-year SC-AIT course had been shown reported.⁵¹

A small DBPC trial, dating back to 2002, revealed efficacy of the *P pratense* grass pollen extract (30 µg of Phl p 5 daily) in 56 patients with severe allergic rhinoconjunctivitis⁵⁴ (high quality of evidence). Coseasonal, sublingual, high-dose, 5-grass pollen drops vs placebo was effective in reducing rhinitis and ocular symptoms but not medication scores in the next season and the posttreatment year. Moreover, the pollen season definition was more restricted than in most trials, which might have helped the efficacy variables²¹ (very low quality of evidence).⁴⁶ There are several other positive grass pollen liquid SL-AIT trials of varying qualities of evidence (Table 1) with products unrelated to the tablets.

Both grass pollen tablets were effective from the first pollen season onward in children and adults and for 3 seasons (high quality of evidence in adults) and even 2 years after administration was discontinued (moderate quality of evidence). Of note, for Grazax/Grastek the administration schedule was continuous; for Oralair a pre-seasonal (2 or 4 months) schedule was indicated.⁵⁵ During the 5-year time span of both trials, 40% to 50% of the patients were lost, reducing the long-term strength of evidence.

As for the optimal duration of the pre-seasonal phase, a long-term effect for Oralair was only accomplished in the pre-seasonal group (4 months),²⁵ confirming data from a post hoc analysis by Calderon et al.²⁶ A 3-year, pre-seasonally conducted, observational, real-life trial reported the safety of Grazax in pre-seasonal administration, but no clinical efficacy data were described.⁵⁶

Concerning in-season use of tablets in an allergen challenge chamber trial, the onset of action for Oralair was documented at 1 month.³⁹ For Grazax no severe systemic reactions were observed, and the 3% dropout rate caused by adverse events (mostly local) was similar as in other trials, but the only efficacy variable was immunologic.⁵⁷

In conclusion, although no direct comparison between the efficacy of each grass tablet can be made (eg, comparing percentages of improvement), clear differences or possible distinctions can be detected related to the quality of evidence reported here.

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