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REVIEW

How does the efficacy and safety of Oralair® compare to other products on the market?

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Abstract: Due to differences between allergen immunotherapy (AIT) trials in patient populations, trial design (including primary efficacy variables), the definition of a pollen season, data analysis, and comparisons between AIT products with existing data, is not possible nor valid. The efficacy of two grass pollen AIT tablets, Oralair® and Grazax®/Grastek®, should not be compared by looking at the percentage of score improvement in their respective trials. However, the evidence available concerning the efficacy and safety in trials can be compared by paying close attention to the scientific quality of the trials, details in the administration schedules, and safety issues. It can be concluded due to the high level of evidence available, that Oralair® is effective in a pre (2-months)-coseasonal schedule to reduce symptoms and medication use, and improve a patients' quality of life during the treatment season. For the long-term, where the quality of efficacy evidence is moderate at 2-year posttreatment due to a high dropout rate, the pre (4-months)-coseasonal schedule should be used. No clinical efficacy data exists for starting treatment in-season, but the clinical onset of action of Oralair® is detectable after only 1 month of treatment. In the pivotal trials in Europe and the USA, no tablet-related epinephrine was needed, though some rare severe local reactions have been reported. Research for Grazax®/Grastek® showed that the long-term efficacy needs a continuous 3-year administration (moderate-low quality evidence available), and in two patients, tablet-related epinephrine was given. Further details on the comparative efficacy of both tablets would only be possible if both were evaluated in the same, adequately powered trial.

Keywords: sublingual allergen immunotherapy, grass pollen, allergic rhinitis, allergic conjunctivitis, tablet allergen immunotherapy

Video abstract

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Introduction

Allergic rhinoconjunctivitis (ARC) is one of the most commonly occurring chronic respiratory conditions, which worldwide has been reported to affect between 10% and 30% of the population.[1] The most important inhalant allergen in Central Europe is Timothy grass pollen (*Phleum pratense*). On the other side of the Atlantic, in the USA it is among the top three most frequently found allergic sensitizers, while in the more Northern regions of the USA, tree pollens gain a greater importance.[2] Over 80% of the ARC patients seen by allergists come in with a moderate–severe form of the disease.[3] Consequently, although at first sight ARC does not seem to be a disorder of major significance, taken into account the severity of the disease and the frequent co-morbidities such as rhinosinusitis,[4] otitis media with effusion, and asthma, all impact on the quality of life (QoL) of the patient, it therefore, has to be considered a public health issue of importance.

As of today, allergen immunotherapy (AIT) remains the only disease-modifying treatment offered to patients with ARC and allergic asthma. After a century of subcutaneous (SC) applications, the sublingual (SL) route has been of growing importance

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in the last few years.[5] This is especially so after the "big trials"[6] and Cochrane meta-analyses[7,8] reported an affirmative effect. Positive outcomes on symptoms and medication scores in pivotal trials convinced authorities to approve SL immunotherapy, first in Europe as an SL solution, and more recently in Europe and the USA as SL tablets. As such, the SL-AIT now covers approximately half the AIT market in some European countries. This trend was clearly shown by McDonell et al who conducted a retrospective cohort study using IMS® Disease Analyzer (IMS HEALTH GmbH& Co. OHG [IMS], Frankfurt am Main, Germany) in Germany over a 7-year period (September 2005 – December 2012).[9] Data from 18,850 patients with a prescription for grass pollen AIT were analyzed. Although the majority of the patients still received SC-AIT, there was a statistically significant tendency for a rise in the SL-AIT prescription rate, from 8% during 2006/2007 to 29% during 2011/2012.[9] Also in the USA a rise in SL-AIT prescription tendency was detected, even though the absolute percentage of patients that are prescribed SL-AIT versus SC-AIT is still low[10] and can be expected to have risen after the Food and Drug Administration (FDA) approval of SLIT tablets in 2014.

Since the first trials on SL immunotherapy almost 3 decades ago, dosing of the SL-AIT solution has been a major issue that has still not been completely resolved. This could be due to the fact that with SL-AIT not only the quality and exact quantity of the administered extract determine its efficacy but also the vehicle and other factors that are involved in the local allergen uptake.[11] Due to this fact, major allergen manufacturers in Europe started researching SL tablets in order to have a product with a fixed dose and formulation. As grass pollen is one of the most prominent causes of ARC, the allergen selected for the tablet trials and posterior marketing has been the grass pollen SL tablet.

With the grass pollen SL-AIT tablets on the market, allergists now have several options for allergen-specific immunotherapy in patients with ARC (and allergic asthma) due to grass pollen. The authors focused on one of the grass pollen SL-AIT tablets on the market, Oralair®, and how data on this product compared to data on other grass pollen AIT possibilities.

Indications for Oralair®

In Europe, Oralair® is indicated for the treatment of allergic rhinitis with or without conjunctivitis induced by grass pollen in adults, adolescents, and children (>5 years of age) with clinically relevant symptoms, confirmed by a positive skin test and/or a positive specific serum immunoglobulin E (sIgE) test.

In the USA, the FDA approved Oralair® in 2014. According to the US product sheet, the indications are almost the same as those in Europe with two minor differences. The FDA specified the indication further, adding after "[…] positive specific sIgE testing for any of the five grass species contained in this product." Also, the FDA set the age limits for Oralair® between 10 and 65 years.

Composition of Oralair®, a five-grass pollen tablet

Oralair® contains the natural allergens of pollens from several cross-reacting grasses. These are all species from different tribes of the Northern pasture grasses: cock's-foot or orchard grass (*Dactylis glomerata* L.), sweet vernal grass (*Anthoxanthum odoratum* L.), rye-grass (*Lolium perenne* L.), Kentucky bluegrass or meadow-grass (*Poa pratensis* L.) and Timothy grass (*P. pratense* L.). The latter is commercially the most important perennial grass in the USA as it is widely cultivated for hay from the Northeast to South of Missouri. Pollen release starts in late spring and lasts until mid-autumn. The most important grass in the Southern regions of the USA, Bermuda grass (*Cynodon dactylon*), which has certain unique allergens different from the group of grasses mentioned earlier,[12] is not included in the tablet. As such, Oralair® is indicated to patients allergic to one or several of the Northern pasture grasses.

Comparative efficacy

Although it has been more than a decade since the first Cochrane meta-analysis on SL-AIT[7] convinced the medication community on the clinical efficacy of SL-AIT, the value of analyzing several trials with SL-AIT products grouped together in meta-analyzes is progressively being questioned of late. This is especially so after a group of experts made an in-depth analysis of the outcome variables used in different trials,[13] which led them to conclude that the heterogeneity between trials is large, especially between trials conducted by different allergen manufacturers. Previously, world leaders in the field had already made recommendations for trials with AIT in an effort to harmonize the design of AIT trials.[14]

As both symptoms and medication use are two linked variables, a combined symptom–medication score is the preferred primary efficacy variable. However, some trials use only the symptom score as their main outcome. Even among the trials using a combined symptom–medication score, these are not constructed in the same manner: some investigators use the 6-item total symptom score–in which nasal and ocular symptoms all are scored 0–3 adding up to a maximum total of 18 points, to which then the value of

the medication score (0–3 per day) is added. This approach results in a sub-valuation of the medication score, as there is a top daily symptom score of 18, whereas the top daily medication score can only reach 3. This is why other researchers use the same rhinoconjunctivitis symptom score, but calculate a balanced symptom–medication score as follows:

$$\frac{\left[\frac{\text{Total Rhino-ocular score}}{18}+\frac{\text{Med score}}{3}\right]}{2(\text{score result between 0 and 1})} \quad (1)$$

Investigators from Stallergenes constructed an adjusted symptom score, in which the daily symptoms were adjusted according to medication intake from the previous 2 days.[15] However, as no other company used this method, scientists were asked by the authorities to recalculate the results of the 5-year pivotal trial of Oralair® with the more conventional symptom–medication score and these results were published in 2015.[16] Two papers on the same data-set have now been published for the long-term efficacy of Oralair®.[15,16]

Another variable that is different between trials is the definition of the pollen season. Some investigators defined the start of the pollen season in their trial as the presence of 3 consecutive days with a pollen count of 10 grains/m^3 or more, while others defined the start of the season with a higher pollen count (see Table 2 for details of specific trials). This is important for the outcome of the trial and directly affects the symptom score difference between active and placebo treatments. Investigators from the Imperial College in London showed that the higher the pollen count, the greater the difference in symptom scores between the patients in the placebo and the AIT group.[17,18]

The last variation related to outcome variables we mention here is the expression of the results of the symptom and medication scores. In AIT trials, it is quite common for a remarkable group of subjects to not take any rescue medication at all. This holds true for both the active and the placebo groups. As such, the mean values for rescue medication use for placebo and active treatment arms do not differ too much, skewed by a high rate of zero scores. Presenting the data as median values is much less sensitive to several zero values and normally shows a larger difference between active and placebo. Thus, if symptom reduction is expressed as the difference between active pre-posttreatment and placebo pre-posttreatment median values, the percentage of gain is generally higher than that expressed as the percentage of difference between mean values pre-posttreatment of the AIT versus the placebo group. When reviewing a paper and the percentage gain is presented, the reader needs to check if the authors are showing the percentage gain in median or in mean score values.

Making such an in-depth analysis leads to the conclusion that the efficacy from one product to the other by comparing the percentage of improvement in scores between product A, as observed in trial A, versus product B in trial B, should not be compared. Only products evaluated in trials with the same methodology, patient population, and with the same analysis and presentation of the data can be directly compared in their efficacy. Such trials, until now, have not been published for the AIT grass tablets.

What can be concluded concerning AIT efficacy from the published trials

What can be concluded from the trials conducted with grass pollen AIT and specifically, with the five-grass tablet Oralair®, is the level of evidence to support the efficacy of the products in certain situations. The level of evidence is directly related to the quality of the trials published. Conventionally, double-blind, placebo-controlled, randomized trials have been considered as the highest level of evidence; however, specific flaws in the design and presentation of a double-blind, placebo-controlled, randomized trial can reduce its quality of evidence, eg, underpowered trials, trials with indirect outcome measures, or trials with selective presentation of the data. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the evaluation of the quality of published data takes all of these variables into account and assigns quality of evidence on a four-step scale, from very low to high.

In the "Grass pollen subcutaneous AIT" and "Grass pollen sublingual AIT" sections, the quality of evidence that exists in the published literature up until now is reviewed. This focuses on the efficacy of grass pollen AIT with specific administration schedules and in specific patient groups, focusing on SL-AIT with liquid and tablet formulations. To put the results in a broader context, the evidence existing for grass pollen SC-AIT will also be reviewed.

Grass pollen subcutaneous AIT

A Cochrane meta-analysis from 2007 showed that SC-AIT for seasonal allergic rhinitis was effective with a reduction in the symptoms score (standard mean difference [SMD] −0.73) and in the medication score (SMD −0.57).[3] Fifty-one double-blind, placebo-controlled (DBPC) trials were included, but of those only 15 were suitable to add to the symptom score analysis (Table 1). Moreover, most trials

Table 1 Number and quality according to GRADE of the double-blind, placebo-controlled, randomized trials of SC-AIT in patients with SAR included in the Cochrane meta-analysis 2007

Author	Year	Country	ITx	Plac	Quality score**
Alvarez-Cuesta	2005	Spain	25	28	3, moderate
Ariano	1999	Italy	13	12	2, low
Armentia-Medina	1989	Spain	19	11	
Arvidsson	2002	Sweden	24	25	3, moderate
Balda*	1998	Germany	51	60	2, low
Bodtger*	2002	Denmark	17	18	3–4, moderate–high
Bousquet	1987a	Germany/France	15	19	
Bousquet	1987b	France	39	20	
Bousquet	1988	Germany/France	15	10	
Bousquet	1989	Germany/France	13/15/18	14	
Bousquet*	1990	France	20/19	18	
Bousquet	1991	Germany/France	18/17	18	
Brewxzynski*	1999	Germany	10	10	
Brunet	1992	Canada	13	14	
Corrigan*	2005	UK/Germany	77	77	2–3, low–moderate
Dolz	**1996**	**Spain**	**18**	**10**	**3, moderate**
Drachenberg*	2001	German/Austria	74	50	4, high
Drachenberg	2002	Germany	54	27	Not scored
Ferrer*	2005	Spain	28	29	3, moderate
Fling	1989	USA	12	7	
Frew*	**2006**	**UK**	**203**	**103**	**4+, high**
Grammer	1982	USA	21	19	
Grammer	1983	USA	13	13	
Grammer	1984	USA	21	21	
Grammer	1984	USA	19	31	
Grammer	1986	USA	15, 4, 1	20	
Grammer	1987	USA	36	37	
Iliopoulos	1991	USA	21	20	
Jutel*	2005	Poland/Germany	29	28	2, low
Karmaker	1994	India	86	19	
Lee	1982	USA	48	28	
Leynadier	**2001**	**France**	**16**	**13**	**3, moderate**
Litwin	1991	USA	20	19	
Meriney*	1986	USA	10	10	
Metzger	1981	USA/England	50	50	
Mirone	2004	Italy	16	16	1–2, very low
Norman	1982	USA	10	10	
Ortolani*	1984	Italy/USA	8	7	
Ortolani*	1994	Italy	18	17	
Paraskevopoulos	2005	UK	12	6	
Pastorello	1992	Italy/Germany	10	9	
Tari	1997	Italy/Germany	20	20	2, low
Varney*	1991	UK	21	19	
Walker*	**2001**	**UK**	**22**	**22**	**4, high**
Zenner*	1997	Germany	45	42	4, high

Notes: *Studies used for the symptom score of Cochrane meta-analysis 2007.[1] **GRADE score is the scoring of quality of evidence according to GRADE as reported in online documents;[2] only publications from 1995 onward were scored. Data in bold indicate studies used for the dosing recommendation of grass-pollen SC-AIT in the practice parameters on immunotherapy, third update.[3]

Abbreviations: AIT, allergen immunotherapy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SAR, seasonal allergic rhinitis; SC-AIT, subcutaneous allergen immunotherapy; ITx, immunotherapy; Plac, placebo.

were small, with between ten and 25 subjects in the active group. Among the trials that fulfilled the inclusion criteria, there was only one large trial with over a 100 subjects in the active group. This was a GRADE high-quality of evidence trial (Table 2), in which two doses of standardized alum-adsorbed Timothy grass pollen were tested against a placebo.[39]

Although both doses, 10,000 and 100,000 SQ-U (standard quality units), every 6 weeks were effective in reducing symptoms and medication scores, the higher dose was more

so. Interestingly, treatment was started on average 38 weeks preseasonally and thus patients received SC-AIT for almost a year, even though the schedule was officially called a pre-coseasonal schedule (Table 3).

As for safety, in the high-dose group there were nine subjects (4.4%) with a grade 3 systemic adverse reaction, while in the low-dose group there was none.[4]

The long-term data for grass-pollen SC-AIT was reported from a trial conducted at the end of the previous millennium in which symptom and medication scores maintained the improvement accomplished after 3 years of continuous SC-AIT, when in a double-blind randomized study extension patients were continued for another 2 years on SC-AIT or on a placebo.[41]

With these robust data supporting the efficacy and long-term effects of grass pollen SC-AIT with a high-dose standardized extract started long before the pollen season, there have been few new trials with conventional SC-AIT in grass pollen-allergic patients over the past years.[49] This is probably due to the fact that in the field of SC-AIT the focus of investigators has changed over time, from documenting efficacy to shortening the buildup phase[50,51] and enhancing the safety, using hypoallergenic formulations or recombinant molecules.

Grass pollen SL-AIT in adult and pediatric patients: efficacy for one season

Precoseasonal schedule in adult and pediatric patients

Didier et al conducted the pivotal "big trial" that showed a dose–response efficacy for precoseasonally administered Oralair® in 628 patients.[19] After a short buildup phase incrementing the daily dose with 100 index of reactivity (IR) 4 months before season-start, patients then continued onto the dose pertaining to their randomized group. No clinical benefit was found in the 100IR group, while the 300IR and 500IR groups showed similar results in favor of the AIT over placebo. As a result, the 300IR dose (25 µg of group 5 grass pollen major allergen) was selected as the optimal dose for commercialization.[19] The same investigational team went on to define the optimal duration of the preseasonal phase in another long-term study. Both 2- and 4-month preseasonal treatments with Oralair® were equally effective in reducing symptoms during the subsequent pollen season.[20]

Two years later, Wahn et al confirmed the efficacy and safety of the five-grass tablet in children.[21] The study design recruited children ≥4 years of age and showed improved symptom and medication scores, both during the pollen season[21] and during the peak pollen season.[22]

In a US trial of 438 patients,[5] similar results were found to those by Didier et al.[19] There were however, several minor differences between both trial setups. In the US trial, the patients received directly the 300IR dose without up-dosing, the pollen season definition was homogenized with another grass-tablet sublingual immunotherapy (SLIT) trial, and authorities asked the investigators to change the primary efficacy parameter to a daily combined symptom–medication score (DCS). DCS and the adjusted symptom score all statistically improved significantly in the active group. As opposed to other trials, patients in the placebo group had free access to the rescue medication and their rescue medication score was higher than that of the active group. Even so, the patient-rated overall improvement during the trial worked out positively for the active group.

In the intention-to-treat data, the DCS reached a 28% improvement over placebo, which is more than the World Allergy Organization (WAO) recommended 20% cutoff defined as a clinically relevant outcome. Also, in this US trial, specific sIgE was not an inclusion criterion. An interesting observation in this trial became clear in a post hoc analysis grouping those patients with Timothy pollen sIgE as either <0.1 or ≥0.1 kU/L. In the group with sIgE <0.1 kU/L, no treatment effect could be detected.[45]

During the same time Cox et al's[45] trial was conducted, another grass pollen tablet was researched: the fast dissolving Timothy grass pollen tablet, Grazax®/Grastek®. There are three main differences between this formulation and Oralair®. First, Oralair® is composed of the pollens of five cross-reactive grasses, while Grazax®/Grastek® only includes Grazax® timothy grass pollen. Second, the quantity of group 5 major allergen in Oralair® is stated to be approximately 25 µg, while that of Grazax®/Grastek® is 15 µg; and third, the excipient of Grazax®/Grastek® contains fish gelatingelatin, which allows for very fast dissolving of the tablet once put under the tongue; the dissolving of Oralair® takes somewhat longer.

Putting these details aside, the most important point is the clinical performance of the product. In this sense, Grazax®/Grastek® has also shown to be effective in a one-season preseasonal (8-week)-coseasonal schedule. In Europe, large DBPC trials, both in adults[24] and in children ≥4 years of age[52] found that Grazax®/Grastek® reduced symptom and medication scores and improved QoL, as tested with the validated, disease-specific, rhinoconjunctivity QoL questionnaire.

Table 2 Quality of evidence (according to the GRADE approach) of SLIT studies on Oralair®, and several pivotal trials with other grass pollen formulations

Author, year study details	Design (starting score)	Large effect**	Confound annulated*	Dose–response gradient	Total (+)
Oralair® for allergic rhinoconjunctivitis trials					
Didier et al,[19] 2007 SAR (10% mild asthma) 157 100IR/d, 155 300IR/d, 160 500IR/d, 156 placebo Pre (4 m) + coseason, 300IR =25 µg group 5 daily	DBPC (4)	X	X	Yes	+1
Didier et al,[20] 2011 SAR (13.7% mild asthma) SLIT preseason (2 m) + coseason: 207 recruited, 147 FAS SLIT preseason (4 m) + coseason: 207 recruited, 149 FAS Placebo 219 recruited, 165 FAS 25 µg group 5-grass tablet/day	DBPC (4)	X	Novel adjusted symptom score previously validated	Trend to more improvement compared to placebo year by year (NS)	+1.5
Didier et al,[15] 2013 **Continuation of Didier et al 2011[20]** +1 yr SAR (13.7% mild asthma) After 3 yrs SLIT and 1 yr observation: SLIT preseason (2 m) + coseason: 137 SLIT preseason (4 m) + coseason: 143 Placebo 155	DBPC (4)	X	X	X	0
Didier et al,[16] 2015 **Continuation of Didier 2011[20]** +2 yrs SAR (12.7% mild asthma) After 3 yrs SLIT and 2 yrs observation: SLIT preseason (2 m) + coseason: 117 SLIT preseason (4 m) + coseason: 127 Placebo 133	DBPC (4)	X	Large symptom reduction in placebo (more severe pts withdrew), even so statistically significant improvement in SLIT grps	X	+1
Wahn et al,[21] 2009 SAR (21% mild asthma) 131 SLIT, 135 placebo; 4–17 yrs of age precoseason, 25 µg group 5-grass tablet/d	DBPC (4)	X	X	X	0
Halken et al,[22,*] 2010 Moderate-severe AR (intermit asthma) SLIT 131, placebo 135, 5–17 yrs of age 25 µg group 5 daily, precoseason 6 m	DBPC (4)	+1	X	X	+1
Horak et al,[23] 2009 Onset of action: allergen challenge chamber ARC, 18–49 yrs of age SLIT 45, placebo 44 25 µg group 5-daily for 4 m; out of season	DBPC (4)	4 m: +1	X	Trend for dose–effect over time	+1
Cox et al,[5] 2012 ARC (20% mild asthma) SLIT 210, placebo 228 precoseason, 25 µg group 5-grass tablet/d	DBPC (4)	X	X	X	0
Other grass pollen sublingual tablet immunotherapy trials					
Durham et al,[24] 2006 AR (and mild persist asthma), 18–65 yrs of age Pre-(8-week) coseasonal for one season SLIT 2500SQ-T 144, 25000SQ-T 148, 75000SQ-T 321, placebo 307 0.5, 5, or 15 µg Phl p 5 daily	DBPC (4)	X	X	Yes	+1

Limitations in design/execution	Inconsistency of results		Indirectness of evidence	Imprecision of results	Publication bias	Total (–)	Quality of evidence
Symptom score alone is the primary outcome variable	X		X	X	X	–1	4, high
ITT but data of 59 pts not apt for inclusion, –1	X		No medication score (primary outcome = novel symptom score adjusted for medication intake)	X	X	–1	3–4, moderate–high
Dropout rate >15%	Reduction in days with rescue med in 300IR but not in 500IR		X	X	X	–1	3, moderate
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
X	X		X	X	X	0	4, high
No description of dropouts	X		X	Large CI	X	–2	3, moderate
Blinding and randomization technique not explained	No change in nasal airflow and nasal secretion weight		X	X	X	–2	3, moderate
X	X		X	X	X	0	4, high
X (GOOD: ITT analysis)		X	X	Differences vs placebo and trends calculated, not between dosing grps	X	–1	4, high

(*Continued*)

Table 2 (*Continued*)

Author, year study details	Design (starting score)	Large effect**	Confound annulated*	Dose–response gradient	Total (+)
Dahl et al,[25] 2008 AR (and mild persist asthma), 18–65 yrs of age Continuous, 22 m Second year: SLIT 189, placebo 162 15 µg Phl p 5 daily	DBPC (4)	X	X	X	0
Durham et al,[17] 2012 AR (and mild persist asthma), 18–65 yrs of age Continuous, 34 m Fifth year: SLIT 135, placebo 103 15 µg Phl p 5 daily	DBPC (4)	X	X	X	0
Nieminen et al,[26] 2010 (mechanistic study) Respiratory allergy, 5–15 yrs of age SLIT low dose 10, high 10, placebo 10 Low: 24.000 SQ-U, high 200.000 SQ-U/week, 2 yrs	DBPC (4)	X	X	Yes	+1
Bufe et al,[27] 2009 SAR (42% mild asthma) 114 SLIT, 120 placebo; 5–16 yrs of age Precoseason, 15 µg Phl p 5 tablet/d	DBPC (4) Rhinitis DBPC (4) Asthma	X X	X X	X X	0 0
Blaiss et al,[28] 2011 AR (and mild persist asthma), 5–17 yrs of age Precoseasonal for one season SLIT 175, placebo 169 15 µg Phl p 5 daily	DBPC (4)	X	X	X	0
Nelson et al,[29] 2011 ARC (24% mild asthma), 18–65 yrs of age SLIT 184, placebo 207 15 µg Phl p 5 daily, 6 m precoseason	DBPC (4)	X	X	X	0
Maloney et al,[30] 2014 ARC (25% mild asthma), 5–65 yrs of age SLIT 750, placebo 751 Precoseason, 15 µg Phl p 5 tablet/d	DBPC (4)	X	X	X	0
Some of the most recent grass pollen sublingual liquid immunotherapy trials					
Bozek et al,[31] 2014 SAR, 60–70 yrs of age SLIT 41, placebo 37 20 µg group 5 (240IR) drops 5 days/wk 4 m preseasonal for 3 years	DBPC (4)	X	X	X	0
Swamy et al,[32] 2012 AR (mild/moderate persist asthma), 6–57 yrs of age (55% of SLIT grp are children) Dual SLIT 20, placebo 10 15 µg Phl p 1 (sic) and 20 µg Der f 1+2, daily for 12 months. Post-Tx evaluations 12+6 and 12+12 m	DBPC (4)	X	Small grps and even so statistically significant difference	X	+1

Limitations in design/execution	Inconsistency of results	Indirectness of evidence	Imprecision of results	Publication bias	Total (–)	Quality of evidence
Originally planned as 1 yr trial. Only 60%/51% of original AIT/ placebo continued. NS difference in symptom–medication scores between continuing/stop: –0.5	X	X	X	X	–0.5	3–4, moderate–high
Same as earlier: –0.5 + dropout rate since study extension: 18.6% AIT and 36% placebo: –1	X	X	X	X	–1.5	2–3, low–moderate
X	X	X	Small grps	X	–1	4, high
X	X	X	X	X	0	4, high
X	X	Only symptom + medication	Very small numbers (9 vs 3 days)	X	–2	2, low
X (GOOD: ITT analysis)	X	X	X	X	0	4, high
X	X	X	X	X	0	4, high
X (GOOD: ITT analysis)	X	X	X	X	0	4, high
No clear description randomization –0.5	X	X	Non-validated VAS scoring for symptoms	Medication scores 1st and 2nd year not stated	–2.5	1–2, (very) low
Randomization method not described, –1	X	X	Small grps	X	–2	3, moderate

(*Continued*)

Table 2 (*Continued*)

Author, year study details	Design (starting score)	Large effect**	Confound annulated*	Dose–response gradient	Total (+)
Wahn et al,[33] 2012 ARC (and GINA gr I-II asthma), 4–12 yrs of age Precoseasonal SLIT, placebo 40 μg group 5 drops daily, 8 m	DBPC (4)	X	X	X	0
Stelmach et al,[34] 2012 Rhinitis (20 also asthma), 6–18 yrs of age Precoseasonal 20 pts, continuous 20 pts, placebo 20 pts, for 2 yrs 10 μg group 5-grass drops daily	DBPC (4)	X	X	X	0
Panzner et al,[35] 2011 (24 m open continuation of 12 m DBPC[36]) AR, mean age 17.6 yrs (±10 yrs), nr of children unknown 3 yrs study continuation after 1 yrs DBPC SLIT 26, supralingual 25 pts 11.2 μg group 5 (six-grass pollen extract) 3/week for 3 yrs	Randomized, noncontrolled (4)	X	X	Year-by-year improvement in symptons and medi-cations, +1	+1
Ott[15] 2009 Persistent seasonal AR, 8–65 yrs of age SLIT 99, placebo 46 five-grass, 25 μg group 5-grass drops daily (300IR) coseasonal ×3 yrs	DBPC (4)	X	X	X	0
Agostinis et al,[37] 2009 AR (60% mild asthma), 4–16 yrs of age SLIT 20, control 20 precoseasonal for 2 yrs 1,000 AU drops five × week	Randomized controlled (4)	X	Small grps, even so statistically significant	X	+1
Ahmadiafshar et al,[38] 2012 ARC, 5–18 yrs of age SLIT 12, placebo 12 pts 900IR Lolium drops, 3 times/wk, 6 m	Randomized controlled (4)	X	X	X	0
Pivotal grass pollen subcutaneous immunotherapy trials					
Frew et al,[39] 2006	DBPC	X	X	+1	+1
Walker et al,[40] 2001	DBPC	X	X	X	0
Durham et al,[41] 1999	DBPC	X	X	X	0
Dolz et al,[42] 1996	DBPC	X	X	+1, progressive improvement over the 3 yrs	+1
Leynadier et al,[43] 2001	DBPC	X	X	X	0

Notes: *All plausible confounding variables may be working to reduce the demonstrated effect, or increase the effect if no effect was observed. **RR = relative risk. Large effect RR <0.5, very large effect RR <0.2. RR has been calculated from the data given in the articles. ¥Same study as Wahn 2009.[16]

Abbreviations: A, active; P, placebo; PAR, perennial allergic rhinitis; pt, patient; SAR, seasonal allergic rhinitis; SLIT, sublingual immunotherapy; DBPC, double-blind, placebo-controlled; SPT, skin prick test; yrs, years; m, months; FAS, full analysis set; vs, versus; GRADE, Grading of Recommendations Assessment, Development and Evaluation; AIT, allergen immunotherapy; NS, not significant; ITT, intention to treat; Med, medication; AR, allergic rhinitis; CI, confidence interval; ARC, allergi rhinoconjunctivitis; SQ-T, standard quality tablets; VAS, visual analog scale; Post-Tx, post treatment; GINA, Global Initiative on Asthma; RC, rhinoconjunctivitis; Nr, number; SD, standard deviation; SQ-U' standard quality unit; Grp, group; WAO, world allergy organization.

Limitations in design/execution	Inconsistency of results	Indirectness of evidence	Imprecision of results	Publication bias	Total (–)	Quality of evidence
No ITT mentioned, –1. 16.5% dropout in active grp, =<20%	X	X	(change in lung symptoms not reported)	X	–1 (for RC)	3 (for RC)
(preestablished adjusted to 1,000 pollen grains/m^3 of symptom and medication scores: no reduction)	X	X	Small grps, underpowered	X	–1	3, moderate
No control grp, small grps: only statistically significant difference pre-post Tx, not between both active grps; no description dropout per grp	X	Post hoc fusion of grps to improve stats, but does not seem to affect outcomes; –0.5	X	Incorrect conclusion: medication score in supra-lingual not improved	SLIT –2.5; supra-lingual –3.5	SLIT: 2.5 supra-lingual 1.5
Methods of randomization nor blinding described: –1 Statistically significant difference grps at baseline: –1	X	X	Median scores not mean	X	–3	1, very low
No medication score	X	VAS "well-being" only once a year: –2	X	X	–3	2, low
Very small grps. No comparison of symptom–medication reduction SLIT vs placebo	Much more adverse effects in placebo grp	Incomplete nasal symptom score (no congestion measured)	No SD nor CI given for symptom nor medication	X	–4	0, very low
X	X	X	X	X	0	4+, high
X	X	X	X	X	0	4, high
X	X	X	X	X	0	4, high
–1, no clear primary end-point, no comparison A vs P	X	X	–1, *P*-values: not clear if over time or comparison A vs P	X	–2	3, moderate
–1, small grps	X	X	X	X	–1	3, moderate

Table 3 Clinical efficacy of SLIT: focus on five-grass tablet Oralair®

Author, year	Q score*	Age (yr)	Active/placebo or control	Dropout	Allergen, drop/tablet	Duration	Dose (μg/dose and dosing frequency)
Oralair®							
Didier et al[19] 2007	4	18–45	157-155-160/156	18-22-19/10	5-grass, tablet	4–6 m	100, 300 and 500IR daily (300IR =25 μg Phl p 5)
Didier et al[20] 2011	3–4	18–50	2 m preseason 207/4 m preseason 207/ placebo 219	60/58/54	5-grass, tablet	4–6 m ×3 yrs	25 μg Phl p 5 daily (300IR)
Didier et al[15] 2013	2–3			At 4 yrs: 70/65/64			
Didier et al[16] 2015	3			At 5 yrs: 90/80/86			
Wahn et al[21] 2009	4	4–17	139/139	8/4	5-grass, tablet	8 m	25 μg Phl p 5 daily (300IR)
Halken et al[22] 2010 (additional data to Wahn et al[21] 2009)	3					6–8 m	25 μg Phl p 5 daily (300IR)
Horak et al[23] 2009	3	18–50	45/44	3/3	5-grass, tablet	4 m	25 μg Phl p 5 daily (300IR)
Cox et al[45] 2012	4	18–65	210/228		5-grass, tablet	6 m	25 μg Phl p 5 daily (300IR)
Other grass pollen SL-AIT							
Maloney et al[30] 2014	4	5–65	750/751			6 m	15 μg Phl p 5 daily
Blaiss et al[28] 2011	4	5–17	175/169	33/29	Phleum pratense, tablet	6 m	15 μg Phl p 5 daily
Bufe et al[27] 2009	4	5–16	126/127	12/7	Phleum pratense, tablet	6 m	15 μg Phl p 5 daily
Durham et al[24] 2006	4	18–65	75k: 321 25k: 148 2.5k: 144 plac: 307	75k: 27 25k: 9 2.5k: 8 plac: 21	Phleum pratense, tablet	4 m	15 μg Phl p 5 daily
Durham et al[17] 2012	2–3	18–65	316/318	5 years: 181/215	Phleum pratense, tablet	34 m	15 μg Phl p 5 daily

Dose vs SCIT	Disease	Manufacturer	Statistically significant differences found in the following comparisons	No statistically significant differences in following comparisons
30	R(mA)	Stal	SLIT vs placebo: ↓ Total rhinoconjunctivitis symptom score, days without symptoms in 300IR and 500IR groups. ↓ Days with rescue medication use in 300IR group. ↑ QoL dose-dependent increase in sIgG4	SLIT vs placebo: NS differences 100IR in any variable NS days with rescue medication use in 500IR group vs placebo
30	R(mA)	Stal	SLIT vs placebo: ↓ Average adjusted sympt score in 2 m and 4 m preseasonal groups, and ↓ Daily combined and medication score	X
			SLIT vs placebo: ↓ Average adjusted symptom score in 2 m and 4 m preseasonal groups. ↓ Daily combined and medication score	X
			SLIT vs placebo: after 3 yrs SLIT: ↓ Daily combined score in 2 m and 4 m preseasonal group. After 2 yrs post-SLIT: ↓ Daily combined score in 4 m preseasonal group	2 yrs after treatment: in 2 m preseasonal: daily combined score, daily rhinitis and daily med score In 4 m preseasonal: daily rhinitis score
30	R(mA)	Stal	SLIT vs placebo: improved total and individual rhinitis sympt (P=0.01) and medication (P=0.0064) scores. Less days with medication intake (P=0.015)	X
30	R(mA)	Stal	SLIT-placebo: total symptom score reduced at whole and peak pollen season. Nasal and ocular sympt reduced. Less rescue medication during whole and peak pollen season	X
30	RC(mA)		SLIT vs placebo: allergen challenge chamber (ACC) symptom reduction at 1, 2, and 4 months	SLIT vs placebo: ACC symptom reduction at 1 week; ACC nasal airflow and weight of nasal secretions and SPT reactivity at 1, 2, and 4 months
30	ARC	Stal	SLIT-placebo: whole pollen season daily combined (= sympt + med), sympt, medication and adjusted symptom scores all reduced in SLIT. RQLQ and patient rating of treatment efficacy better in SLIT	SLIT-placebo: nasal itching
NS	RC(A)	ALK	SLIT-placebo: whole pollen season daily total combined (TCS = sympt+ med), sympt and medication scores all reduced in SLIT. Peak pollen TCS and RQLQ better in SLIT	X
NS	RC(A)	ALK	Active vs placebo: daily symptom (25%), daily med (81%), total score (26%) and QoL improved 18% ($P<0.04$)	SLIT-placebo: asthma symptom score
30	R(mA)	ALK	Active vs placebo: sign reduction in RC symptoms score (−24%), asthma score (−64%), RC meds (−34%), well days (+28%). All $P<0.03$	X
30	RC(mA)	ALK	Active 75,000 SQ-T vs placebo: ↓ Medication score entire season, sympt and med score peak pollen season and subgroup with ≥2 m pre-seasonal SLIT. ↑ QoL and well days	75.000 SQ-T vs placebo: sympt score over entire season 2.500 and 25.000 SQ-T NS in any variable
30	RC(mA)	ALK	Active vs placebo: ↓ Medication score entire season, sympt and med score peak pollen season and subgroup with ≥2 m preseasonal SLIT. ↑ QoL and well days	

(*Continued*)

Table 3 (*Continued*)

Author, year	Q score*	Age (yr)	Active/placebo or control	Dropout	Allergen, drop/tablet	Duration	Dose (µg/dose and dosing frequency)
Bozek et al[31] 2014	2	60–70	41/37	3/3	5-grass, liquid	4 m for 3 yrs	20 µg group 5 5 days/week
Stelmach et al[34] 2012	4 3	6–18	Cont 20 Pre-co 20 Pla 20	1/3/2	Grass, drops	2 yrs	10 µg group 5 daily cont: for 2 yrs Pre-co: 2×6 mo
Swamy et al[32] 2012	3	5–58	20/10	0/0	DUAL = grass and HDM, drops	12 m	15 µg Phl p 1
Wahn et al[33] 2012	3	4–12	158/plac 49	26/2	6-grass, drops	8 m	40 µg group 5 daily
Pajno et al[46] 2011	3	8–16	Continuous 40/ coseasonal 40	3/5	Grass, drops	CONT 3 yrs COS: 3×4 m	8 µg group 5, 5 times/week
Panzner et al[35] 2011 open extension of previous DBPC 12 m trial (Panzner et al[36] 2008)	2.5	Mean 17.6	SLIT 26, supra-lingual 25	8	6-grass, drops	12 m (+24 m open)	11.2 µg group 5, 3 times/ week
Ott et al[44] 2009	1	8–68	142/67	43/21	5-grass, drops	3 m ×3 yrs	25 µg Phl p 5 daily (300IR)
Agostinis et al[37] 2009		4–16	SLIT 20, control 20	0/0	Grass, tablet	pre-co for 2 yrs	1000 AU drops 5× week
Ahmadiafshar et al[38] 2012	0	5–18	SLIT 12, Plac 12	2/2	Lolium, drops	6 m	900IR 3/week
Stelmach et al[47] 2009	2	6–17	SLIT 20, plac 15	5/10	Grass, drops	pre-co for 2 yrs	10 µg group 5 grass drops daily
Trials with only safety data							
Seidenberg et al[48] 2009	1	5–17	SLIT 193	10 (+50 <4 m treatment)	Grass and/or tree, drops	4 m	Started with ultra-rush up-dosing: 30-90-150-300IR each 30 minutes (µg?)

Notes: *Q score = quality assessment according to GRADE. Ref for effect size calculation: Thalheimer W, & Cook S. (2002, August). *How to calculate effect sizes from published research articles: A simplified methodology*. Retrieved November 16, 2012 from http://work-learning.com/effect_sizes.htm. X values represent trials where there were no parameters of importance to report in the corresponding column. Reproduced from *Annals Allergy Asthma Immunol*. Epub 2016. Larenas-Linnemann D, Why direct efficacy comparison of SLIT tablets for rhino-conjunctivitis, based on existing data, is non-valid. Copyright © 2016 with permission from Elsevier.[61]

Abbreviations: A, asthma; mA, mild asthma; AUC, area under the curve; B2, beta2-agonist; CET, cetirizine; DBPC, double-blind placebo-controlled; GI, gastrointestinal; HDM, house dust mite; ICS, inhaled corticosteroid; Med score, medication scores; MEF25, mid expiratory flow at 25% pulmonary capacity; NS, not stated or not applicable; OIT-low/high, oral immunotherapy low dose/high dose; PFT, pulmonary function testing; QoL, quality of life; R, rhinitis; RC, rhinoconjunctivitis; SAE, serious adverse event; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; CONT SLIT, continuous year round schedule of SLIT; yrs, years; m, months; SMS, symptom and medication score; Stal, Stallergens; Tx, treatment.

Dose vs SCIT	Disease	Manufacturer	Statistically significant differences found in the following comparisons	No statistically significant differences in following comparisons
NS	RC	Stal	Active vs placebo: sign. ↓ total nasal symptom score in active 1st, 2nd, and 3rd season (3rd yrs: 64 vs 7%). ↓ Med score 3rd year 51% more than placebo. No SAE, only transient local AE in active group. Less NPT nasal flow reduction	Active vs placebo: non-nasal symptoms, PEF, NPT symptom score, sIgE [Medication scores 1st and 2nd year?]
NS	RC(mA)	Stal	Both active groups vs placebo: sign improvement Med + Symp score, sympt score Pre-co group vs placebo: sign reduction Med score	X
			X	Medication score continuous group. Asthma symptoms
1–2.8× each dose	RC	Greer	Active-placebo: Rhinoconjunctivitis symptom score, medication score and combined score reduced at 12 m and at 24 m (12 m after treatment discontinuation) ($P<0.001$)	X
NS	RC(A)	All pharm	SLIT vs placebo: change in pre-posttreatment higher for Symp-Med, Symp, Med scores. SLIT higher rate of positive response (=>40% decrease of the AUC of the SMS)	SLIT vs placebo: Mean nr. of well days
NS	RA	Stal	Continous vs coseasonal: 1st year: sympt + med, symp, chest sympt and Med scores improved more in CONT SLIT	3rd year: no difference in clinical outcomes between continuous vs co-seasonal SLIT
Total: 20×	R	Sevapharma	Pre-posttreatment Supra and SLIT: sympt, medication and combined score reduced year by year	SLIT vs Supra: trend for more sympt and med reduction in SLIT (NS)
30	R	Stal	SLIT vs placebo improvement vs baseline year: ↓ combined symptom-med score progressively over 3 treatment years (P=0.043–0.0019)	SLIT vs placebo compared to baseline year: SLIT higher medication score (!) 1y post-Tx: combined sympt-med score NS
NS	R(A)	Lofarma	SLIT vs control: VAS improved after 1st and 2nd year (both: $P<0.05$). SLIT pre-post Tx: reduction in sympt ($P<0.05$)	Control pre-post Tx: no reduction in sympt
100?	RC	Stal	SLIT pre-post Tx: reduction in sympt ($P<0.05$) and medication score ($P<0.05$)	SLIT vs placebo: not reported
NS	A	Stal	SLIT vs Pl: asthma symptoms ($P<0.002$), nasal sympt ($P<0.04$), nasal + asthma sympt, asthma medication and nasal + asthma + med score. (both $P<0.001$)	SLIT vs Pl: ocular symptoms, total asthma + nose + eye sympt
Final dose approx 30× SCIT dose	RC(A)	Stal	During updosing: 60 pts (31%) reported 117 predominantly mild and local AE, which resolved within 150 minutes During maintenance: 562 AE; most frequent local AE were oral pruritus, burning sensation, lip or tongue swelling, and GI symptoms; the most frequent systemic AE were RC and A. One clinically significant asthma event in an 11-year old male asthmatic: SLIT was resumed after 4 days	

Similar results were obtained in the US trials in adults,[30,53] adolescents,[30] and in children aged ≥5 years.[28,30] In a post hoc analysis of pooled evidence from several trials with the fast-dissolving tablet it became clear that the best results were obtained in patients with a 4-month preseasonal period, compared to those with a shorter preseasonal treatment phase.[54]

All the aforementioned trials were GRADE 4, high-quality trials (Table 2). Thus, high-quality evidence exists to state that both grass pollen tablets are effective in a 2-month precoseasonal schedule in adults and children with ARC in Europe and in the USA. For Grazax®/Grastek®, 4-month preseasonal is best.

Preseasonal schedules

Until now there have been no publications on the grass tablet SL-AIT in a merely preseasonal schedule. The only recent preseasonal study with grass pollen SL-AIT was conducted by Bozek et al[6] with a five-grass liquid formulation, delivering 240IR sublingually 5 days per week in elderly allergic rhinitis patients. A marked reduction in symptom and medication scores was documented during the 3rd year's pollen season after 4-month preseasonal administration over 3 consecutive years.[31] The GRADE quality of this trial was 1–2, (very) low. In conclusion, there exists no evidence for efficacy of preseasonal only administration of the grass tablets.

Coseasonal schedules with in-season starting

As many patients visit their physicians when they are already presenting symptoms, it is often not possible to start AIT preseasonally. This is why the possibility of in-seasonal starting of AIT was explored. The first point in analyzing this option is the safety issue, with SL-AIT tablets being highly concentrated it might therefore not be safe to start them in-season. For Grazax®/Grastek®, there is some evidence with respect to the safety of such management; however, no clinical outcomes of efficacy were reported.[55]

In conclusion, there is no evidence on the clinical efficacy of coseasonal administration of the grass pollen tablets. There is limited, favorable evidence existing on the safety of Grazax®/Grastek® started in-season.

Mono- and polysensitized subjects

In all of the previously described trials, more than half of the patients were polysensitized. Especially in the US trials, polysensitization rates of over 80% were reported.[28,45] In the 3-year Oralair® trial, analysis were conducted on this subgroup of patients, reporting the same efficacy as in the mono-sensitized patient group.[20] Also, in an analysis of pooled data from several trials with Grazax®/Grastek®, Calderon et al concluded that polysensitized patients benefit as much, if not more, from AIT as monosensitized patients.[56] Great care should be taken in interpreting these statements, as investigators are only referring to the benefit of the grass pollen AIT tablets for the ARC patient during the 2 months' pollen season.

In conclusion, during the grass pollen season, polysensitized ARC patients benefit at least as much, if not more, from the grass pollen tablets as monosensitized patients.

Grass pollen SL-AIT in adult patients: efficacy over subsequent seasons

Administering Oralair® over 3 consecutive years in a precoseasonal schedule demonstrated sustained efficacy in the reduction of symptom and medication scores year after year, both with a 2-month and with a 4-month preseasonal start.[20] Dahl et al[25] and Durham et al[57] also documented the sustained efficacy of Grazax®/Grastek®. However, the administration of the latter was in a continuous year-round daily schedule, as opposed to the 6-months-per-year, precoseasonal schedule of Oralair® (Table 3). Both these trials delivered moderate–high quality of evidence, GRADE 3–4 (Table 2).

In conclusion, both grass pollen tablets have sustained clinical efficacy when administered year after year, for Oralair® in a precoaseasonal schedule and for Grazax®/Grastek® during continuous administration.

Grass pollen SL-AIT in adult patients: long-term efficacy posttreatment

The aforementioned 3-year trials of Oralair® and Grazax®/Grastek® went on into respective extension phases of 2 years posttreatment, during which the patients continued to score seasonal symptoms and rescue medication use, but without any further SL-AIT. Three years treatment of preseasonal (4-month)-coseasonal Oralair® resulted in a statistically significant reduction in the combined symptom and medication scores, even after 2 years off-treatment. However, if the preseaonal phase was reduced to only 2 months, a trend toward long-term efficacy was registered without reaching statistical significance. Because of the high dropout rate in such long trials, the quality of evidence is moderate, GRADE 3 (Table 2).

For Grazax®/Grastek®, 3 years of continuous administration also led to a 2 years posttreatment clinical efficacy,

as expressed by the combined symptom–medication score. As this trial was originally planned for only 1 year, during the extension phase to 3 treatment years plus, in the post-AIT years more than 60% of the patients were lost, resulting in the quality of evidence being low–moderate, GRADE 2–3.

Thus, long-term efficacy of a 3-year course of SL-AIT after 2 years off-treatment was shown for Oralair® with a pre (4-month)-coseasonal dosing schedule, and for Grazax®/Grastek® with a continuous daily dosing schedule. The quality of evidence for these results is moderate and low-moderate respectively.

Grass pollen SL-AIT in adult patients: onset of action

Almost all trials focused on the efficacy of the grass pollen AIT during the course of the whole pollen season. Until now, there has been only one trial that directly investigated the onset of action.[23] This was done between the 2007 and 2008 grass pollen seasons by Horak et al in the Vienna Allergen Chamber, the first allergen challenge chamber (ACC) in function. The ACC allows a controlled pollen exposure to a group of grass pollen-allergic patients simultaneously under standard conditions. After a pre-randomization challenge to select patients with a certain minimum rhinoconjunctivitis symptom score in order to assure the inclusion of moderate–severe allergic patients, 89 subjects were randomized to 4-month treatment with Oralair® (n=45) or placebo (n=44). After the baseline challenge and the start of the AIT, subjects were rechallenged in the ACC during 4 hours sessions at 1 week, 1, 2, and 4 months. The symptom score in the Oralair® group was lower during each test-session in comparison with the placebo, even at 1 week, but the difference reached statistical significance by the 1-month challenge. At months 2 and 4, the difference in symptoms score improvement during challenge between active and placebo steadily grew until a relative mean improvement compared with the placebo of 29.3%. As the sample size was not calculated to power the study for the secondary endpoints of nasal airflow, nasal secretion weight, and skin prick test reactivity, no statistically significant differences could be detected between active and placebo groups in these parameters, although tendencies were toward improvement in the active group. The investigators concluded that Oralair® shows a symptom reduction on pollen-exposure from ≥1 month of treatment.[23]

In conclusion, after 1 month of treatment with Oralair®, the symptom exacerbation due to pollen exposure in an ACC, is reduced, compared to the placebo.

Safety

The initial trials with Oralair® were cautiously started with a short buildup phase of 5 days up-dosing.[19] In this first dose-finding trial, mild treatment-emergent adverse events (TEAEs) were frequent and found in >60% of the subjects in each of the dosing groups. However, there was a dose–response relationship for discontinuation due to TEAEs of 3.8%, 5.2%, and 6.9% in the 100IR, 300IR, 500IR dosing groups, respectively, and 0% in the placebo group. Yet, there were no serious study treatment-related AEs.[19] Thus, since the product did not seem to cause any major systemic AEs, subsequent trials started directly with the 300IR tablet, with the indication to take the first tablet under strict medical supervision. As such, in the 3-year European trial by Didier et al[20] and in the US trial by Cox et al,[45] the study-subjects took the 300IR tablet from day 1 onward. The AE profile of Oralair® maintains more or less stable between the various subsequent trials: mild–moderate oral symptoms at study start are seen in more than half of the patients, but very rarely lead to discontinuation. Moreover, the discontinuation rate due to TEAEs progressively declines season after season: from 6% in the 1st year, to 0.6% and 0% in years 2 and 3, respectively.[20] Also, two serious drug-related TEAEs only occurred during the first year: one severe local allergic reaction and one because of angioedema, both leading to permanent discontinuation from the study.

Although none of the large European trials used epinephrine, in the US trials of the grass tablets, patients were instructed to carry an epinephrine autoinjectorautoinjector. In the USA, during the Oralair® study there were no serious TEAEs. During the European trials, 11/228 (4.8%) in the active group withdrew because of TEAEs.[45]

In the ACC trial by Horak et al[7] conducted out of season, all patients in the active group were given the 300IR tablet from the start, and no patient withdrew because of an AE. Sixty percent of the patients in the active group experienced a TEAE versus 31.8% of the placebo patients, but these were mild local events, (oral pruritus and throat irritation) lasting normally <2 weeks.

Observational, "real-life" studies can be useful complements to the results of randomized controlled trials. An observational, real-life safety study of a five-grass pollen SL tablet was conducted in children and adolescents (5–17 years old) to evaluate the safety and AEs with Oralair®. Of the 796 fully documented patients, 27.4% experienced at least one adverse drug reaction during the study, 11.8% on the 1st day of dosing. Seventy-five percent of those were of mild–moderate severity and no adrenaline was used. Seventy-six (9.2%) of the subjects discontinued the SL-AIT because of an AE.[58]

In the fast-dissolving grass tablet trials, Durham et al[24] reported that more than half of the patients had mild local reactions, oral sensations, that had a median duration of 4 and 10.5 days in both of the highest dosing groups of this trial (15 µg Phl p five daily). In these groups, 5.1% of subjects withdrew because of an AE. One serious drug-related AE was reported in the middle-dosing group (5 µg Phl p five daily): one patient had uvula edema, which resolved without medication and the patient continued in the study.[24] In the Grastek® US trial, 82% experienced an AE (77% in placebo group). Most of them were local mild–moderate reactions that resolved in a mean of 1–7 days. There were 5.2% discontinuations due to AE. Two subjects were administered epinephrine, one of them being in the SLIT group who developed dysphagia, uvular edema, and pharyngeal edema at the application site, along with a macular rash and chest discomfort (WAO grade 1 systemic reaction[59]). After treatment with antihistamine, epinephrine, and prednisone, the event was controlled within an hour, without any further repercussions.[53] In the pediatric trial, two Grastek® patients received epinephrine, but only one was due to a reaction to the tablet, with this child developing lip angioedema, slight dysphagia, and intermittent cough immediately after the first dose (day 1) of grass AIT. After the investigator administered epinephrine the symptoms resolved. The event was graded as of moderate severity by the investigator.[28]

In the US trials, at least two subjects administered erroneously epinephrine, misinterpreting symptoms as if they were due to an allergic reaction.[28,29]

In conclusion, local allergic reactions were very common in the first 1–2 weeks of treatment. Neither of the grass pollen tablets caused anaphylactic shock or fatalities in trials, although some grade 1–3 systemic AE (WAO Grading system[59]) have been seen, and in the US trial, epinephrine autoinjector prescription is warranted. Several systemic reactions have been treated at the office, as most have been after the first dose. In two Grastek® US trials, an epinephrine autoinjector was used, because of a tablet-related reaction (one patient each).[28,29] Discontinuation because of AE ranged between 5% and 9%.

Conclusion

Currently two SL tablets exist on the market for the treatment of grass pollen–induced ARC, one being a five-grass pollen tablet, Oralair®, the other being the fast-dissolving Timothy grass pollen tablet, Grazax®/Grastek®. Comparing the efficacy of these two tablets with existing data is not possible as both have been tested in different clinical trials. As discussed in this paper and also observed previously,[60] the definition of combined symptom–medication scores and single symptom or medication scores varies between trials, as do the study design, study population, and other variables. This is one of the flaws of meta-analysis and makes comparing efficacy indirectly in meta-analysis doubtful.

However, what can be stated based on the existing evidence is the efficacy and safety of the tablets in specific dosing schedules, patient groups, and situation. Moreover, depending on trial details, a level of evidence can be assigned to each of these situations. As such, we have a high degree of evidence for the efficacy of Oralair® in a pre (2-month)-coseasonal schedule for individual pollen seasons and subsequent pollen seasons.[8–10] However, the long-term posttreatment effect is best accomplished with the pre (4-month)-coseasonal schedule,[10] be it that here the level of evidence is moderate due to a dropout rate after 5 years of approximately 40%. Similar efficacy and safety have been found for pediatric and polysensitized patient groups, be it only for variables recorded during the pollen seasons. Obviously, efficacy of the grass pollen AIT in polysensitized patients with symptoms outside the grass-pollen season cannot be expected.

For Grazax®/Grastek®, very similar results are published on efficacy, with the difference that the 4-month preseasonal schedule gave the best results in an analysis of pooled data from three DBPC trials,[11] and the long-term efficacy has only been documented after a continuous, all-year-round administration schedule for 3 years, with low–moderate quality of evidence available.[12]

Concerning safety, local, mild–moderate adverse reactions are very common the first 1–2 weeks of the treatment, but generally disappear when treatment is continued. Also, they are less common and less severe when treatment is restarted before the next pollen season, with precoseasonal Oralair®.[9] In the Oralair® trials, no use of epinephrine has been documented. In trials with Grazax®/Grastek®, an epinephrine autoinjector was used in two patients because of adverse reactions, judged to be probably tablet-related.[13,14] Discontinuation due to tablet-related adverse reactions, mostly moderate–severe local reactions in the oral cavity, is very similar in the DBPC trials, ranging ~5% for both tablets. In a post-marketing Oralair® trial it was 9%.

For patients (Europe ≥5 years of age, USA ≥10 years of age) with grass pollen–induced allergic rhinitis with or without conjunctivitis, confirmed by the presence of sIgE to Northern Pasture grass pollens, the pre (4-month)-coseasonal administration of Oralair® for 3 subsequent years is an

effective and safe management strategy with long-term efficacy for at least 2 years posttreatment. Administration for only 6 months of the year, as opposed to the continuous administration needed for long-term effects of Grazax®/Grastek®, is favorable from a pharmacoeconomic point of view. Even though the safety profile for Oralair® is clean for anaphylactic shock and WAO grade 4–5 systemic reactions, and no epinephrine was used in the pivotal trials with this tablet, in the USA, an epinephrine autoinjector has to be prescribed together with either of the tablets.

Disclosure

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