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PRODUCT REVIEW

Update about Oralair® as a treatment for grass pollen allergic rhinitis

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ABSTRACT

Sublingual immunotherapy (SLIT) is a well-tolerated, safe, and effective approach to treating allergic rhinitis (AR). Oralair® is a five-grass pollen SLIT tablet containing natural pollen allergens from five of the major grass species responsible for seasonal AR due to grass pollen allergy. Recommended use is in a pre-coseasonal regimen, starting daily treatment approximately 4 months before the start of the pollen season, with treatment then continued daily throughout the season; treatment should continue for 3–5 y. Clinical efficacy and safety of Oralair® in patients with grass pollen-induced AR has been demonstrated in a comprehensive clinical development program of randomized controlled trials. Effectiveness has been substantiated in subsequent observational studies with sustained efficacy following treatment cessation and a favorable level of adherence, quality of life, benefit, and satisfaction for the patients. Supportive evidence for a benefit in reducing the risk or delaying the development of allergic asthma is emerging.

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Background

Allergic rhinitis (AR) is extremely common, affecting 10–40% of the population, with a conservative estimate of up to 500 million people affected worldwide; including over 110 million in Europe and between 30 and 60 million in the US.[1–4] Prevalence seems to be increasing in most countries, although reported prevalence rates vary in different age groups, most data indicate the highest prevalence in children and adolescents.[2,4,5] AR chiefly manifests as sneezing, rhinorrhea, with nasal congestion and pruritus; co-existing conjunctivitis —allergic rhinoconjunctivitis (ARC)—is common,4 and 10–40% of AR patients have asthma as a comorbidity.[4,6]

The principal immunological mechanism in AR is an immunoglobulin E (IgE) mediated hypersensitivity response to one or more environmental allergens.[7] Notably, the majority of patients with moderate-to-severe AR in Europe and the US are sensitized to multiple allergens.[8,9] Globally, grass, tree, and weed pollens are the major outdoor environmental triggers.[3,4] While the relative importance of different pollen allergens shows geographical, ecological, and seasonal variation, grass pollen allergy is common in most regions in Europe and in the US, and present in up to 40% of AR patients.[10–14] The importance of different grass species differs in different environments. In Europe, timothy grass (*Phleum pratense*) and sweet vernal grass (*Anthoxanthum odoratum*) are important across Northern Europe, while cocksfoot/orchard grass (*Dactylis glomerata*), perennial ryegrass (*Lolium perenne*), and meadow grass (*Poa pratensis*) have more importance in Southern Europe. All of these species, which belong to the temperate grasses (Pooidae) are relevant in broad areas of the US and Oceania as pasture grasses. In tropical and subtropical climate zones subtropical grasses (Chloridoideae and Panicoideae) with distinct major allergens play a major role.[15]

Clinical management of AR involves allergen avoidance, symptomatic relief (principally by nonspecific pharmacotherapy with intranasal corticosteroids and oral/intranasal antihistamines, including over-the-counter [OTC] medications) and allergen immunotherapy (AIT).[4,16,17] Too often, oral glucocorticosteroids, or even depot glucocorticoid injections, are prescribed, mainly by physicians not specialized in allergy. In recent years, a significant amount of data has highlighted their cumulative toxicity,[18] and their systematic use for severe symptoms should no longer be recommended.

To date, AIT remains the only disease-modifying treatment option for patients with IgE-mediated allergies such as AR with/without concomitant allergic asthma.[4–19–21] Two forms of AIT delivery are used; via sublingual administration (SLIT) in tablet or liquid forms on a daily basis and subcutaneous

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injections (SCIT), given as multiple injections at initially weekly then monthly intervals over 3 to 5 y.[4–2122–23] Both SLIT and SCIT are widely used across Europe and North America, although some differences in patterns of use and regulatory processes exist.[24] The development and introduction of effective SLIT therapies offers practical advantages, in terms of a lower risk of systemic reactions, and the capability for daily self-administration at home,[25] which negates the need for multiple physician visits over a prolonged period, a clear advantage during the COVID-19 pandemic.[26]

For grass pollen allergy two SLIT tablet formulations have full market authorizations on five continents; one using natural allergen extracts from a single grass species, (timothy grass [*Phleum pratense*]), the 1-grass tablet formulation (Grazax™/ Grastek®; ALK-Abelló, Hørsholm, Denmark/Merck, Kenilworth, NJ, USA) and a 5-grass tablet formulation, Oralair® (Stallergenes Greer, Antony, France) with a broader suite of pollen allergens, the product characteristics we describe below.

Characteristics of Oralair®

The active components of Oralair® comprise natural pollen allergens from five of the Pooideae major grass species throughout Europe, North America and Oceania responsible for AR due to grass pollen allergy; timothy grass (*Phleum pratense*), sweet vernal grass (*Anthoxanthum odoratum*), cocksfoot/orchard grass (*Dactylis glomerata*), perennial ryegrass (*Lolium perenne*), and meadow grass (*Poa pratensis*). Pollen allergens are incorporated in the pressed tablet as purified freeze-dried extracts, and include the principal allergens from these species, including the important group 1 allergens from timothy grass (Phl p 1), sweet vernal grass (Ant o 1), cocksfoot (Dac g 1), perennial ryegrass (Lol p 1) and meadow grass (Poa p 1) pollens. Additionally, the important group 5 pollen allergens from these grasses (Phl p 5, Dac g 5, Lol p 5 annd Poa p 5) are included as well as minor allergens.[27–29]

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Inclusion of allergens from these five different grass species provides broad coverage across different geographical regions where patient's exposure and sensitization to specific grass species may differ, and can also accommodate patient polysensitization to different grass pollen species.[27,28] The immunological rationale for including allergens from this broad group is that, while there is relatively high homology in amino acid sequence for group 1 and 5 allergens between different Pooideae species, with some degree of shared IgE and B- and *T*-cell epitopes,[29] there is also evidence of species-specific epitopes for these allergens, with minimal cross-reactivity.[30,31] A broader epitope repertoire offers a greater opportunity to induce tolerance toward multiple pollen species and allergens; recent data indicate that the allergens included in Oralair® provide a greater range of epitopes relevant to grass pollen allergy in European patients than those observed with the alternative 1-grass pollen tablet.[32]

Dosing is calibrated on the basis of index of reactivity (IR), the manufacturer's in-house reference standard for measuring total allergenic activity, used across all of its AIT products. In this system, a 100 IR/mL concentration is one which induces a wheal with a geometric mean diameter of 7 mm following skin-prick testing in 30 sensitized patients.[33,34] The licensed standard dosing of 300 IR contains approximately 20–25 µg of the timothy grass group five major allergen (Phl p 5). Using the FDA in-vitro standardized bioequivalent allergy unit (BAU) this 300 IR dose corresponds to 9,000 BAU.[33,35] This differs from the allergen content of the 1-grass pollen tablet licensed in Europe and the US constituting a single pollen allergen extract from timothy grass, which in its licensed dose of 75,000 SQ-T contains approximately 10–15 µg/mL of Phl p 5, corresponding to 2,800 BAU,[35] although some data evaluating BAU using skin-prick testing suggest greater activity (6,200 BAU).[36]

The freeze-dried allergen extracts are formulated with inactive ingredients (mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, and lactose monohydrate) to generate the final compressed tablet.[27,37] This final formulation was designed to deliver a sustained allergen release across the sublingual mucosa over 2–3 minutes, with >90% of total allergenic activity released within 2 minutes.[37] Maximal allergen absorption requires 5 minutes,[38] as earlier swallowing may reduce allergen uptake by mucosal antigen presenting cells (APCs).[37] Following swallowing, the polypeptide/peptide allergen extracts undergo proteolytic degradation in the GI tract with no significant systemic exposure; as systemic allergen absorption is limited, no formal pharmacokinetic studies have been required or performed.[27,37]

Mode of action

In general terms AIT acts by induction of immune tolerance to sensitizing allergen through a range of mechanisms, the principles of which have been comprehensively reviewed.[39–41] In brief, there are early and late phases to tolerance induction. Suppression of mast cell and basophil/eosinophil trafficking and activity, coupled with induction of regulatory T and B cells (Treg and Breg) and suppression of allergen-specific Th1/Th2 cells in peripheral blood are key early events (occurring over days/weeks).[39,41] Later effects (over months) include reduction in allergen-specific IgE levels and a concomitant increase in competitive specific IgG, and in reduction in numbers and/or activity of pro-allergic effector cells within the peripheral tissues (skin and mucosa).[39,42]

In SLIT therapy with Oralair®, following sublingual application, allergen extract uptake and capture by oral mucosal dendritic cells (Langerhans cells [LC]) is rapid (15–30 minutes) which allows antigen processing with minimal proteolytic degradation and preservation of T and B cell epitope repertoires.[41] Subsequent LC migration to the regional lymph nodes occurs over the following 12–24 hours. There, interaction with naive CD4+ T cells leads to Treg/Breg induction and allergen-specific Th1/Th2 cell suppression, and subsequently the later responses described above.[41,42]

Efficacy and safety of Oralair® in allergic rhinitis

The clinical efficacy and safety of Oralair® in AR has been extensively evaluated in a comprehensive clinical development programme, comprising phase I–III studies in adults and children in Europe and North America, followed by subsequent longitudinal observational studies, and studies utilizing real-world data (RWE) from specific patient populations and registries to evaluate benefit in routine clinical use (Table 1).

Phase I–III studies

The phase I–III studies involved a total of 2,512 patients, of which 1,514 received Oralair®.[28–43–48–6263–65] In these studies, the majority of subjects (approximately 60%) were polysensitized, and 15–20% had co-existing mild asthma. Most studies evaluated a pre-coseasonal regimen where treatment was initiated 2–4 months before the estimated start of the pollen season, then continued throughout the season (for a minimum period of 1 month). The primary outcome measures were principally those of reduction in ARC symptom scores, using a mean or Average Rhinoconjunctivitis Total Symptom Score (ARTSS), a daily Combined Score (CS) assessing both symptom reduction and use of rescue medications, or an Average Adjusted Symptom Score (AAdSS), which also combines symptoms and medication use. Safety and tolerability were extensively evaluated.[27,63] Most studies were conducted for a single season, although one long-term study in Europe/Canada evaluated discontinuous treatment over three consecutive seasons and with subsequent 2-y follow-up.[46–48]In the single-season European studies, treatment was initially started at a 100 IR dose with gradual up-titration by 100 IR increments to the allocated treatment dose;[28] no up-titration was performed in the US study,[45] or in the European long-term sustained efficacy study,[46] where treatment started with the 300 IR dose on day 1.

The key dose-ranging study in adults aged 18–45 y enrolled 628 subjects with moderate-to-severe grass pollen-related ARC for ≥2 y, with or without mild asthma across 10 European countries.[28] Three doses were evaluated; 100 IR, 300 IIR,and 500 IR doses, each given in a pre-coseasonal regimen.[28] For the primary study outcome, treatment with the 300 IR dose significantly reduced the mean RTSS compared with placebo (3.58 ± 3.0 vs 4.93 ± 3.2; $p = .0001$); with a 37% improvement in median symptom scores.[28] No significant benefit over placebo was seen with the 100 IR regimen, while outcomes with the 500 IR regimen were comparable to that seen with the 300 IR formulation, with a risk-benefit analysis thereby favoring the 300 IR dose.[28] The benefit of 300 IR in symptom reduction was seen across all patients regardless of symptom severity, sensitization status and presence of concomitant mild asthma.[66] In a subsequent *post hoc* analysis, evaluating benefit in terms of a symptom reduction and lower use of rescue medications, the least squares (LS) mean daily CS was 29.6% lower in the 300 IR treatment group compared with placebo ($p < .0001$).[67] This study established the 300 IR dosing strategy for further studies and subsequent clinical use. Data from a phase I randomized study show this dose has a rapid onset of action; patients were challenged using an allergen-exposure chamber, before and during treatment with the 300 IR dose.[43] Incremental reductions in ARTSS were seen as early as week 1, with a significant benefit compared with placebo after 1 month, and maintained over 2 and 4 months of treatment, where a 33.3% median reduction in ARTSS versus placebo was found.[43]

The principal European pre-licensure pediatric study enrolled 278 children and adolescents with moderate-to-severe grass pollen-related ARC for ≥2 years (where allergy was confirmed by a positive skin prick test response), with or without mild asthma.[44] Treatment with the 300 IR dose led to a reduction in the ARTSS, with a median improvement of 39.3% compared with placebo. Reductions in ARTSS were seen in younger (5–11 y) and older (12–17 y) children, and in all patients, regardless of sensitization or asthma status.[44] The LS mean daily CS was 30.0% lower in the 300 IR treatment group compared with placebo ($p = .0005$).[67]

The pivotal US study evaluated efficacy and safety of a pre-coseasonal 300 IR treatment schedule in 473 adults aged 18–65 y with grass pollen-related ARC for ≥2 y, with or without mild asthma.[45] A significant reduction in the LS means of the daily CS scores was seen with Oralair® compared with placebo (0.32 vs 0.45; $p < .001$); corresponding to a 28.2% difference. Again, the benefit was seen irrespective of sensitization status or comorbid asthma.[45]

In a long-term study in 633 adults aged 18–50 y, patients in the treatment arm received the 300 IR dose in either a 2-or 4-month discontinuous pre-coseasonal scheme over three consecutive seasons (with a treatment-free period after the end of the pollen season, until restarting treatment 2–4-months prior to the following pollen season).[46] For the third season of active treatment, treatment with both the 2- and 4-month pre-coseasonal schedule significantly reduced the mean AAdSS by 36.0% and 34.5%, respectively, compared with placebo ($p < .0001$ for both).[46] Reductions in ARTSS and improvement in QoL were also seen.[46] Follow-up over the subsequent 2 y

Table 1. Overview of key selected studies with Oralair®.

	Population (n)[a]	Summary
Phase I–III		
VO56.07A (NCT00619827) Horak et al.[43]	Adults (18–50 y) with moderate-severe ARC (*n*=45)	Phase I: Demonstrated rapid onset of action of the 300 IR dose with reductions in symptom scores seen as early as week 1.
VO34.04 (NCT00367640). Didier et al.[28]	Adults (18–45 y) with moderate-severe ARC ± mild asthma (*n*=472)	Phase IIb/III: Pivotal dose-ranging study in Europe. Demonstrated efficacy of the 300 IR dose in reducing ARC symptoms and use of rescue medications for symptomatic relief. Favorable safety and tolerability. Outcomes were consistent, regardless of sensitization status or presence of comorbid asthma.
VO52.06 (NCT00409409) Wahn et al.[44]	Children (5–17 y) with moderate-severe ARC ± mild asthma (*n*=139)	Phase III: Pivotal European pediatric study, which demonstrated efficacy in reducing ARC symptoms and use of rescue medications with good safety and tolerability profile. Outcomes were consistent, regardless of sensitization or asthma status.
VO61.08 (NCT00955825) Cox et al.[45]	Adults (18–65 y) with moderate-severe ARC ± mild asthma (n=133)	Phase III: Pivotal US study. Demonstrated efficacy of the 300 IR dose in reducing daily symptoms and medication use. Favorable safety and tolerability. Outcomes were consistent, regardless of sensitization status or presence of comorbid asthma.
VO53.06 (NCT00418379) Didier et al.[46–48]	Adults (18–50 y) with moderate-severe ARC ± mild asthma (n=414)	Phase III: Demonstrated benefit of 300IR dose when given across 3 consecutive seasons, with sustained efficacy seen for up to 2 y after treatment cessation. Outcomes were consistent, regardless of sensitization or asthma status.
Post-licensure studies		
Post-approval safety studies (PASS) Pfaar et al.; Eberle et al.; Gerstlauer et al.[49–51]	Children and adults (5–65 y) with moderate-severe ARC ± mild asthma (n=1,911)	Confirmed safety of the 300 IR dose. Most ADRs were local, associated with sublingual administration in early treatment phase. Treatment discontinuation due to ADRs ranged from 5–9%. No anaphylaxis events were reported.
French 1-y, prospective, open-label, observational study Blin et al.[52]	Children and adults (>5 y) with moderate-severe ARC ± mild asthma (n=483)	Reduction in frequency and severity of symptom in children and adults.
German 2-y, prospective, open-label, observational study Shah-Hosseini et al.[53,54]	Children and adults (4–75 y) with moderate-severe ARC ± mild asthma (n=1,482)	Demonstrated sustained efficacy over 2 consecutive years of treatment, with reduction in symptom scores compared with pre-treatment scores and reduction in symptomatic medication use in both children and adult patients.
Spanish 2-y, prospective, open-label, observational study Antolin-Amerigo et al.[55]	Children and adults (≥6 y) with moderate-severe ARC ± mild asthma (n=591)	Reduction in frequency and severity of symptoms; reduction in medication use; high rate of treatment satisfaction.
German 1-y prospective, open-label, observational study Schafer et al.[56]	Adults (≥18 y) with moderate-severe ARC ± mild asthma (n=327)	Significant improvements in ARC symptoms and reduction in medication use; improved QoL and treatment satisfaction.
Netherlands prospective, open-label, observational study over 1 season Ras et al.[57]	Children and adults (≥5 years) with moderate-severe ARC ± mild asthma (n=196)	Reduction in frequency and severity of ARC symptoms; high persistence with treatment (70%) and intention to continue the following season (80%).
Italian prospective, open-label, observational study over 1 season Pastorello et al.[58]	Children and adults (12–45 y) with mild/moderate-severe ARC ± mild asthma (n=47)	Reduction in symptom severity and medication use.
German 1-y prospective, open-label, observational study Klein et al.[59]	Children and adults (≥5 y) with moderate-severe ARC ± mild asthma (n=883)	90% of subjects (children, adolescents and adults) reported benefit (as measured using the 'Patient Benefit Index—Allergic Rhinitis (PBI-AR) score'. Benefits were similar in mono- and polyallergic children but higher in polyallergic adolescents and adults.
Longitudinal claims database studies (France/Germany) Devillier et al.; Zielen et al.[60,61]	Adults with moderate-severe ARC ± mild asthma (n=3,950)[b]	Demonstrated reduction in symptomatic medication use in patients receiving SLIT over 2 y (Oralair® or Grazax™) compared to controls; benefit was evident for up to 6 y after cessation of SLIT. Use of SLIT was associated with a reduction in prescriptions for new asthma cases, and if asthma did develop, onset was later with SLIT compared with controls; patients with asthma also required fewer asthma medications following SLIT treatment.

n = number of subjects receiving Oralair®.
n = number of subjects receiving Oralair® or Grazax™.

without treatment indicates sustained benefit; in those patients receiving the 4-monthly treatment schedule, compared to placebo significant, clinically meaningful relative differences in the LS means of the daily CS scores in the first and second post-treatment years were observed (25.3% [p = .0103] and 28.1% [p = .0478], respectively).[47,48] Efficacy was independent of sensitization or asthma status.[47,48]

Across these studies, Oralair® showed a favorable safety profile, apparent in both adult and pediatric subjects, and in patients with or without mild asthma.[27,63] While adverse reactions (ADRs) were reported in more than 10% of patients, the majority were mild or moderate local reactions; chiefly oral pruritus (25%) or throat irritation (21%).[63] Most occurred during the first week of treatment and the frequency decreased with subsequent use. Treatment discontinuation was low (<2.5% of subjects, all due to local reactions) and in the long-term study was lower in each successive season of active treatment, with none in the third year.[27,63] Systemic ADRs were uncommon, with no reported anaphylaxis; no patients receiving Oralair® in these studies required use of adrenaline/epinephrine.[27,63]

These studies supported approval and licensure, initially in Europe in 2008, Australia in 2011 and Canada in 2012 (for use in patients aged 5–65 y of age), and the US in 2014 (where while initial approval was for use in patients aged from 10 to 65 y, a subsequent license extension for use in children ≥5 y was granted in November 2018). Oralair® is currently authorized in more than 30 countries.

It should be recognized that no direct head-to-head randomized studies evaluating effectiveness of Oralair® in comparison with the alternative grass pollen SLIT tablet have been performed. Furthermore, substantial heterogeneity in study design and study outcomes exists, which makes drawing conclusions from meta-analysis studies problematic.[68]

Post-Licensure studies

Data from subsequent studies provides further evidence of effectiveness and safety of Oralair® in real-world use. A large 2-y, prospective, open-label, observational study in Germany involving 1,482 patients aged 4–75 y demonstrated sustained effectiveness over 2 consecutive y of treatment,[53,54] with a 65.5% reduction in the mean rhinoconjunctivitis score in the overall population compared with mean pre-treatment scores; the percentage of patients taking symptomatic medication decreased from 83.8% to 42.7%.[54] Results were broadly comparable in both adult and pediatric patients, and in both polyallergic and monoallergic patients.[54] A French prospective observational cohort study evaluated Oralair® real-world use in 280 adults and 203 children with AR and a positive pollen allergy test across a single pollen season, with treatment started at least 3 months prior to the start of the 2015 season.[52] The mean treatment duration was 5.2 and 5.6 months in adults and children, respectively. About two-thirds of patients improved from persistent to intermittent symptoms and from moderate-severe to mild disease compared to the previous pollen season (75.0% of adults and 85.7% of children) and >50% the patients reported the absence of the most frequent symptoms of rhinitis during treatment with Oralair®.[52]

Evidence of sustained effectiveness during and after treatment has been shown in retrospective analyses of longitudinal prescription claims databases in France and Germany.[60,61] In the French study, prescription use for symptomatic AR medications was identified for patients who had received at least 2 successive seasonal treatment cycles with grass pollen tablets (either Oralair® or Grazax™) (n = 1,099) and compared with that used in a control group of patients (n = 27,475) who had received only symptomatic AR medications.[69] For patients receiving grass pollen tablets, medication use was analyzed for the period at least 1 y after the last dispensed prescription of tablets. This study reported that patients receiving grass pollen tablet therapy had a 50% reduction in symptomatic medication use, while patients without SLIT therapy had a 20% increase in use.[60] An extensive retrospective longitudinal analysis of a German prescription database compared outcomes in AR patients who had received treatment with grass pollen tablets (either Oralair® or Grazax™) over at least 2 successive seasons (n = 2,851) and compared outcomes with 71,275 matched controls (patients with seasonal AR prescribed nasal corticosteroids but no AIT).[61] This study followed patients for up to 6 y after cessation of SLIT grass pollen tablet treatments. Over the follow-up period, symptomatic medication use in patients receiving grass pollen tablet therapy was significantly lower than that seen in the control group (by 18.8%; p < .001).[61]

Studies from Spain, Germany, the Netherlands, and Italy have shown high levels of treatment compliance and adherence across the grass pollen season and patient-reported treatment satisfaction.[53–55–58] In Spain, treatment adherence over two seasons was estimated at 96.8%,[55] and in general, both patients and specialists exhibited a positive attitude toward the five-grass pollen tablet (with patients rating satisfaction as 7.5 on a 0–10 scale).[55] Treatment compliance in the 2-y German study described earlier was high,[53] with compliance rated as 'always' or 'predominantly yes' by 97.0% of subjects at the end of the first season of treatment.[53] Another German study reported that compliance rated highly over 1 y,[56] while in the Netherlands, persistence with treatment was 85% after 1 month and 70% after 7 months.[57] Most recently a large German multicentre observational study evaluated Oralair® use over one season in 883 children, adolescents, and adults with AR, many of whom were polyallergic; outcomes were measured using a validated 'Patient Benefit Index—Allergic Rhinitis (PBI-AR) score. Clinically relevant benefit was reported in 89–95% of subjects in all age-groups; in adolescents and adults, higher benefit was reported in polyallergic subjects than in monoallergic subjects.[59] Some data indicate benefit in patients sensitized to both temperate and subtropical grasses. A small observational study evaluated the impact of Oralair® over three consecutive pollen seasons in Australian patients (n = 63); of which 93.2% had ryegrass pollen allergy. In total, 74.6% were polysensitized to subtropical and temperate grass pollen, and 23.8% monoallergic to temperate grass pollen.[70] Improvements in total symptom scores were observed in both monoallergic and polysensitized patients in the first pollen season, with these improvements sustained over the second and third pollen seasons.[70]

Safety has been specifically evaluated in post-approval safety studies (PASS), in adults (n = 808),[49] children and adolescents (n = 796),[50] and younger children (5 to 9 y) (n = 307).[51] These confirm the majority of ADRs to be local, chiefly oral pruritus or edema of mild–moderate severity associated with sublingual administration; most of these were associated with the first day of treatment (supporting the recommendation that the initial dose should be administered under physician supervision). Treatment discontinuation due to ADRs ranged from 5% to 9%. No reports of anaphylaxis were evident, and no patients required use of adrenaline/epinephrine.[49–51]

Benefit in patients with allergic rhinitis with or without concomitant allergic asthma

A real strength of the two prescription claims database studies described above was their indirect analysis of asthma onset and progression in AR patients.[60,61] In the French prescription claims database study, new asthma treatments dispensed were also evaluated during follow-up, with new treatments dispensed in 1.8% of subjects who received grass pollen tablet therapy and in 5.3% receiving only symptomatic medications.[60] This corresponds to a 63.7% relative risk reduction in prescriptions for new asthma in patients receiving grass pollen tablets compared with control (p = .0018). Prior SLIT was also associated with a slower progression of asthma medication dispensing during the follow-up period.[60] In the German study, of those patients without asthma at the beginning of the study index period, development of asthma was less frequent with SLIT compared with the control group; both during active treatment (odds ratio [OR]: 0.71;p = .013) and over the follow-up period (OR: 0.57; p = .013).[61] Furthermore, time to new asthma onset was significantly longer in patients who had received prior SLIT compared with the control group, while following grass therapy cessation, asthma medication dispensed (a proxy for asthma progression) fell by an additional 16.7% relative to the pre-treatment period.[61]

These data provide indirect supportive evidence for a potential preventive effect on disease progression of grass pollen allergy tablets, during treatment and prolonged for up to 6 y after treatment cessation, where treatment is associated with a lower frequency of new onset of asthma medication dispensed, delayed onset of asthma medication dispensed when asthma does develop, and slower disease progression. Further supportive evidence is needed, and may be taken from an interesting observational study evaluating the development of acute asthma attacks immediately following a thunderstorm; 'epidemic thunderstorm asthma' (ETA).[71,72] In Australia, the major allergenic trigger is exposure to ryegrass (*Lolium perenne*) pollen, and a catastrophic ETA event occurred in November 2016 in Melbourne.[73] In this study, which evaluated asthma exacerbations in patients exposed during this ETA event, of 17 subjects who had received treatment with Oralair® for seasonal AR, none developed an acute asthma exacerbation. In contrast, 7/17 subjects (41%) in a control group of AR patients who had not received any AIT therapy developed an acute asthma exacerbation during this ETA event.[72] Furthermore, detailed analysis of a subgroup of the Melbourne ETA cohort indicated that the degree of sensitization to ryegrass pollen, and in particular the group 5 allergen Lol p 5, had discriminatory value between sensitized patients who experienced ETA and those who experienced no asthma.[74] The fact that Lol p 5 is a dominant Group 5 allergen within Oralair® is consistent with the strong protective effect observed following SLIT.[29]

Although ETA may be considered a rare weather event, data suggest that the risks associated with exposure to Group 5 allergens are not confined to such events and extreme levels of pollen exposure; milder conditions (e.g. increased humidity) may exacerbate exposure and even very low levels of pollen exposure (10 grains/m3) are associated with increased rates of asthma hospitalization, particularly in children.[75,76] Asthma-related hospitalizations are consistently elevated across a large region of eastern Australia during the peak in springtime exposure to temperate grass (e.g. ryegrass) pollen, with evidence that children are particularly at risk.[77,78] Consequently, while current evidence-based guidelines such as the 2019 ARIA Care Pathways for AIT highlight that the outcomes reported for the Melbourne ETA cohort described above already support the prioritization of grass pollen AIT for patients at risk of thunderstorm asthma,[79] they also indicate that AIT should also be considered in patients living in geographically at-risk regions (for rye grass pollen exposure) who have had asthma exacerbations during the pollen season and also those with more limited disease such as moderate AR.[79]

Economic aspects

Treatment costs for Oralair®, given in a pre-coseasonal regimen, varies depending upon region. In Germany, agent costs when given over a 3-y treatment period (given once daily over 7 months in a pre-seasonal and co-seasonal schedule) have been estimated at €2,100.[80] 3-y Oralair® SLIT cost estimates have also been reported for Austria (€2,813), Spain (€1,523), and Switzerland (€ 2,805).[81] In contrast, estimated annual symptomatic medication costs of €183 have been reported in a recent Swedish economic analysis.[82] However, these medication cost differentials are offset by substantial direct and indirect cost benefits achieved with SLIT.[83,84]

From a formal health economic perspective, numerous studies have evaluated the cost-effectiveness of AIT in the treatment of AR Studies specifically evaluating the cost-effectiveness of Oralair® have reported favorable economic outcomes in comparison to SCIT and alternative SLIT formulations.[80,85,86] In one German study (from 2012), using a Markov model that included 3-y of treatment with outcomes measured over a 9-y time horizon, treatment with Oralair® was associated with a predicted cost-utility ratio of €14,728 per quality of life year (QALY) gained versus treatment with symptomatic medication alone; well below a willingness-to-pay threshold of € 20,000 often used to determine favorable cost-effectiveness.[86] In this study, Oralair® use would also lead to greater cost savings (€1,142) than treatment with an alternative 1-grass tablet.[86] In a second German study (from 2015) using a similar model, the authors reported that Oralair® use was more cost-effective than treatment with a commercial mix of

SCIT allergoids (with incremental cost savings of €458) and more cost-effective than symptomatic treatment alone (with incremental cost savings of €1,385).[80] A Canadian study (from 2013) found that use of Oralair® was associated with substantial cost savings in the first year of treatment compared with SCIT ($2,471) and 1-grass tablet SLIT therapy ($1168).[85] The cost savings over SCIT were principally due to SCIT having higher physician costs and indirect patient costs associated with work lost due to the need to attend for regular specialist appointments; cost savings over the 1-grass pollen tablet were driven chiefly by lower medication costs associated with Oralair® due to the pre-coseasonal regimen rather than the perennial regimen used with the 1-grass pollen tablet.[85]

License

In Europe, Oralair® is indicated for the treatment of AR with or without conjunctivitis induced by grass pollen in adults, adolescents, and children (above 5 y of age) with clinically relevant symptoms, confirmed by a positive skin test and/or a positive specific IgE test.[87] In the US, while initial approval was for use in patients aged from 10 to 65 y, a subsequent license extension for use in children ≥5 y was granted in November 2018.[88] For all patients in the EU, and for those aged 5–17 y in the US, Oralair® should be administered as a 100 IR dose on day 1, a 200 IR dose on day 2 and then a 300 IR/day dose for the duration of treatment.[87,88] In the US, up-titration is not necessary for patients aged 18–65 y, who can start treatment with the 300 IR tablet on day 1.88. The first dose should be administered under physician supervision; patients should be monitored for at least 30 minutes.[87,88] In the US, as part of the prescribing information, all patients must be prescribed an adrenaline/epinephrine autoinjector to be used in the case of anaphylactic reactions.[88]

In the EU and US, Oralair® is contraindicated in patients with severe, unstable and/or uncontrolled asthma, and/or hypersensitivity to any inactive ingredient in the product.[87,88] Additional contraindications or relative contraindications include history of eosinophilic esophagitis, concomitant use of beta-blockers, and the presence of severe immunodeficiency, autoimmune disease or malignant disease.[87,88]

Perspective on use in clinical practice

The disease-modifying action of AIT makes it an attractive, and currently underutilized, clinical intervention for many patients with moderate to severe seasonal AR. Patient selection requires a convincing clinical history of seasonal AR due to grass pollen allergy with confirmation of sensitization by positive skin prick test or measurement of serum allergen-specific IgE. Patients with mild AR may respond adequately to symptomatic pharmacotherapy, but even with mild AR patient preference may recommend SLIT with Oralair® in order to avoid the need for chronic medication and to lessen the risk of ETA in geographic areas with substantial perennial ryegrass pasturelands.[71,72]

With Oralair®, treatment regimens typically commence 4 months pre-seasonally with either pre-seasonal or pre-coseasonal regimens of 4 to 6 months annually for 3 or 4 y. Patient education optimizes safety and the likelihood of adherence and benefit. The first dose should be administered under direct physician observation with subsequent dosing in the home. Although not part of formal preregistration trials, and not necessary for the mechanism of action, it is noteworthy that, in clinical practice, coadministration of a non-sedating antihistamine for the first week or two of initiation decreases local ADRs. This does not interfere with clinical efficacy or tolerance induction, and may encourage adherence as local pruritus and swelling are typically short term but annoying issues for some patients.

Polysensitization is not inherently a contraindication to SLIT if patients experience a clear seasonal exacerbation with relevant sensitization. Indeed, for those patients polysensitized to two or more allergen sources e.g., grass pollen and HDM and/or tree pollens such as birch or olive, and/or ragweed pollen, some may benefit from use of more than one SLIT therapy targeting different allergen types.[89] Oralair® can favorably be combined with other forms of AIT such as sublingual drops or tablets. Sequential initiation of therapy, staggered at a 4-weeks interval between commencing the different AIT treatments, has led to the best results in terms of tolerability and adherence.[89] Thereafter both forms of AIT can be administered concurrently, usually one in the morning, then the other at night time to reduce any potential interference.

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