

Oralair®, Ragwitek®, and Grastek®: Novel Approaches to Treating Pollen-Induced Allergic Rhinitis

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Allergic rhinitis is an inflammatory disorder affecting 400 million people worldwide with the highest prevalence in industrialized countries.¹ In the United States, roughly 10% to 30% of children and adults suffer from this condition.² Allergic rhinitis is characterized by symptoms including sneezing, rhinorrhea, nasal congestion, pruritus affecting the conjunctiva and nasopharynx, and lacrimation; it is classified by pattern (seasonal, perennial, and episodic) and severity (mild, moderate, or severe).³ Previous research has shown that allergic rhinitis is associated with reduced performance at school and work, and frequent clinician visits.⁴ As a result, allergic rhinitis imposes a significant economic burden: a 1996 study estimated that direct medical costs for allergic rhinitis/acute conjunctivitis were \$5.9 billion and that medications accounted for ~25% (\$1.5 billion) of those expenditures.⁵

Current treatment options for allergic rhinitis include pharmacotherapy and immunotherapy. Common pharmacotherapy options include intranasal corticosteroids, H₁ antihistamines (oral and intranasal), nasal decongestants, montelukast, intranasal anticholinergics, and nasal saline.⁶ These therapies, although effective, are limited because they only provide symptomatic relief rather than affecting underlying disease processes, and these agents have to be used frequently. For example, on average, patients need intranasal corticosteroids for 61% of days per pollen season and daily use of intranasal corticosteroids is often needed to help effectively manage seasonal allergies.⁷

Immunotherapy, also referred to as de-sensitization or hypo-sensitization, is effective for patients who have specific IgE antibodies to relevant allergens. In contrast to the aforementioned pharmacotherapy options, immunotherapy targets the underlying pathophysiology of allergic rhinitis for an individual patient, thus potentially reducing the use of symptom-targeted rescue medications.⁸ Subcutaneous immunotherapy is not ideal due to higher

frequency of local and systemic anaphylaxis compared to sublingual immunotherapy.⁹ Sublingual immunotherapy offers potential advantages over subcutaneous administration because it is cheaper, easier to administer, and more comfortable and convenient for patients. Furthermore, immunotherapy may offer sustained symptom relief even years after discontinuation of therapy.¹⁰

Three sublingual immunotherapies have recently received FDA-approved indications for the treatment of pollen-induced allergic rhinitis, with or without conjunctivitis. Oralair®, manufactured by Greer®, is a five allergen extract containing sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass mixed pollens. Ragwitek® (Merck & Co, Inc.) contains short ragweed pollen allergen extract and Grastek® (Merck & Co, Inc.) contains timothy grass pollen allergen extract. The purpose of this article is to review the pharmacology, dosing and administration, clinical trial efficacy, and safety data of these three new sublingual immunotherapy (SLIT) medications for the treatment of pollen-induced allergic rhinitis.

PHARMACOLOGY

The precise mechanism of action of allergen immunotherapies is not known. The response to immunotherapies, whether administered sublingually or subcutaneously, likely is associated with inducing immunologic tolerance, including a relatively long-lived decrease in allergen-specific T cell responsiveness and cytokine production, against the allergen for which the patient is being treated.¹¹ Repeated administration of the allergen elucidates humoral and cellular immunologic changes, resulting in decreased early and late allergic response of conjunctiva, nasal mucosa, bronchi, and cutaneous tissue.¹² Additionally, allergen-induced eosinophils and basophils are reduced, and mast cell infiltration is minimized. The final outcome is a blunting of mucosal secretions and reduction of nonspecific bronchial sensitivity to histamine.¹¹

The majority of the allergens present in immunotherapy are a mixture of proteins and glycoproteins. The allergen extract is expected to be broken down to amino acids and small polypeptides in the gastrointestinal tract leading to no detectable amount of intact allergens in the blood. Therefore, no pharmacokinetic studies in animals or in humans have been conducted to investigate the pharmacokinetic profile of any of the SLIT medications.¹³⁻¹⁵

DOSING AND ADMINISTRATION

Prior to the initiation of SLIT, clinical sensitivity to the standardized pollen extract should be established by careful evaluation of the patient's history, with confirmation by diagnostic skin testing and IgE titers. Oralair® is available as 100 index of reactivity (IR) and 300 IR tablets, Ragwitek® is available as a 12 AntigenE Unit (amb a1-U) tablet, and Grastek® is available as a 2800 bioequivalent allergy unit (BAU) tablet. The recommended dosing and timing schedules of Oralair®, Ragwitek®, and Grastek® are sum-



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TABLE 1 | Approved dosing and timing schedules of sublingual immunotherapies.⁹

Medication	Age (years)	Dose & Titration	Timing
Oralair®	10 to 17	Day 1: 100 IR once daily Day 2: 100 IR twice daily Day 3: 300 IR once daily Maintenance: 300 IR once daily	Begin treatment 4 months prior to grass pollen season and maintain dosing throughout pollen season
	18 to 65	300 IR once daily	
Ragwitek®	18 to 50	12 amb a 1-U once daily	Begin treatment 12 weeks prior to ragweed season and maintain dosing throughout ragweed season
Grastek®	5 to 50	2800 BAU once daily	Begin treatment 8 weeks prior to grass pollen season and maintain dosing throughout pollen season

IR = index of reactivity; amb a1-U = AntigenE unit; BAU = bioequivalent unit.

marized in **TABLE 1**. The tablet must be placed under the tongue until completely dissolved. Patients should be instructed to avoid swallowing for 1 minute after placing the tablet under the tongue. Oralair®, Ragwitek®, and Grastek® should not be administered with food or beverage and patients should be instructed to wait at least 5 minutes after the tablet has dissolved to eat or drink anything. Drug interactions with Oralair®, Grastek®, and Ragwitek® have not been evaluated.¹³⁻¹⁵

CLINICAL TRIALS

Five major multicenter, double-blind, placebo-controlled, randomized clinical trials have been published comparing Oralair®, Ragwitek®, or Grastek® to placebo. **TABLE 2** summarizes these trials.

Oralair®

Two phase 3 studies of Oralair® have been published. The first included 278 children (male and female) aged 5 to 17 years with moderate-to-severe allergic rhinoconjunctivitis for at least 2 years confirmed by positive skin prick test.¹⁶ Eligible patients also had a score of at least 12 on the rhinoconjunctivitis total symptom score (RTSS), determined on the basis of the most severe symptoms during the previous grass pollen season. Major exclusion criteria included allergic rhinitis cause by sensitization to allergens other than grass pollen, asthma requiring treatment other than β_2 -agonists, any previous desensitization therapy for grass pollen, and any contraindications for immunotherapy. Of the 278 enrolled patients, 139 were randomly assigned to receive once daily Oralair® 300 IR four months prior to grass pollen season and 139 were randomly assigned to receive matching placebo. In both study arms, treatment was continued for the duration of the pollen season. The primary outcome was the mean daily RTSS an 18-point scale, which assess for the 6 most common allergic rhinitis symptoms, over the entire pollen season. A higher RTSS is associated with worse or added symptoms (Clark) and a change of 1 point in the RTSS is deemed clinically meaningful.¹⁷ Additionally, The FDA has proposed that a clinically meaningful effect of immunotherapy is a point estimate of at least minus 15 percent, with an upper limit of at least minus 10 for the 95 percent confidence interval.¹⁸ Over the course of one allergy season, the Oralair® group had a 1.26 lower mean RTSS relative to the placebo group, representing a clinically-meaningful 28% improvement.¹⁶

The second study enrolled men and women aged 18 to 50 years with seasonal grass pollen-induced allergic rhinoconjunctivitis for at least the 2 previous pollens seasons, as determined by

skin prick testing.¹⁹ Of the 633 enrolled patients, 207 were randomly assigned to treatment with Oralair® 300 IR starting 2 months before pollen season, and 207 were randomly assigned to Oralair® 300 IR starting 4 months before pollen season; 219 patients were randomly assigned to placebo treatment. Treatment continued for the duration of the pollen season and was repeated for 2 additional seasons for a total study length of 3 pollen seasons. Antihistamine, nasal corticosteroid, and oral corticosteroid use was allowed as rescue medication. The primary endpoint was the average adjusted daily symptom score (AAdSS) after the third pollen season. The AAdSS is an 18-point subjective scoring system, similar to the RTSS, which assesses 6 rhinoconjunctivitis symptoms; a higher AAdSS is indicative of more frequent and worse symptoms. The AAdSS also accounts for rescue medication use.²⁰ At study year 3, 465 patients entered the treatment period. At the end of the 3rd season of treatment, the absolute differences in AAdSS for each treatment group compared with placebo were: -1.96 (37.7% reduction compared to placebo) for the 2-month treatment group and -1.81 (34.8% reduction compared to placebo) for the 4-month group.¹⁹

Ragwitek®

Ragwitek® was studied in a phase 3 randomized, double-blind, placebo-controlled trial that enrolled men and women aged 18 to 50 years, with a diagnosis of ragweed pollen-induced allergic rhinitis who had received treatment during the previous ragweed pollen season.²¹ Other inclusion criteria were positive skin test for ragweed pollen allergic reaction and FEV₁ \geq 70% of the predicted value. Patients were excluded if they required regular medication for symptomatic relief of allergic rhinitis, if they were treated previously with immunotherapy, or if they had asthma requiring treatment with inhaled corticosteroids. Of the 473 patients enrolled, 150 received 6 Antigen E Unit treatment, 159 received 12 Antigen E Unit treatment, and 164 were randomly assigned to placebo. All patients were treated for a total of 52 weeks. The primary endpoint was mean total combined score (TCS), which is the sum of daily symptom score (DSS) and daily medication score (DMS), during peak pollen season. The DSS is an 18-point scale assessing for frequency and severity of allergic rhinitis symptoms and is similar to the RTSS. The DMS is a 36-point scale that awards points based on rescue medication use. A higher TCS is associated with more severe and frequent symptoms and increased rescue medication use.²² During the peak pollen season, 6 Antigen E Unit and 12 Antigen E Unit treatment groups had a 1.76 (21% lower than placebo) and 2.24 (27% lower than placebo) lower mean TCS score respectively compared to placebo.²¹

Grastek®

Grastek® was studied in men and women aged 5 to 65 years with a history of diagnosed grass pollen induced allergic rhinitis with or without asthma who had received treatment for allergic rhinitis the previous pollen season.²³ Participants were included if they had had positive skin prick test and FEV₁ ≥70% predicted. Major exclusion criteria were immunosuppressive treatment within the past 3 months, previous immunotherapy with grass pollen allergen for longer than 1 month within the last 5 years, and asthma and allergic rhinitis requiring medications. A total of 1301 patients were enrolled, of which 629 were randomly assigned to once daily Grastek® 2800 BAU, and 672 patients were randomly assigned to matching placebo, both starting 12 weeks prior to the grass pollen season and continuing for the duration of the grass pollen season. The primary endpoint was the TCS averaged over the entire grass pollen season. Grastek® treatment yielded a 0.98 lower TCS score compared to placebo, representing a 23% lower TCS score with active treatment.²³

Sustained Efficacy

An important question with immunotherapy is its ability to provide sustained efficacy following a treatment regimen. Unfortunately, data supporting any sustained efficacy of sublingual immunotherapy after terminating therapy are limited. Specifically, data on long-term sustained efficacy of Oralair® and Ragwitek® are currently unavailable, although one such trial assessing benefits two years after treatment cessation is ongoing for Oralair®.¹⁹ One published trial has compared Grastek® to placebo treatment for three years and analyzed data for the subsequent two years where both groups received placebo.²⁴ This study found that the

Grastek® treatment group had fewer allergic rhinitis symptoms the first year after treatment cessation. However, two years after treatment cessation, no difference was observed in symptoms comparing the group that originally received Grastek® (for 3 years) and the group that received placebo initially. These data suggest that sustained efficacy with these agents may require continued use of SLIT.

ADVERSE EVENTS

Short- and long-term adverse event data were established for Oralair®, Ragwitek®, and Grastek® in five clinical trials.^{16,19,21,23,25} The most common reported adverse events of Oralair®, Ragwitek®, and Grastek® are listed in TABLE 3. Sublingual immunotherapy should be used cautiously in patients with conditions that reduce the ability to survive serious allergic reactions or which increase risk of adverse reactions with epinephrine administration (i.e., concomitant immunotherapy, recent MI, arrhythmias, unstable angina, β-blocker use). Additionally, immunotherapies may rarely cause eosinophilic esophagitis, acute asthma exacerbations, and life threatening anaphylactic reactions. Oralair®, Ragwitek®, and Grastek® are contraindicated in patients with history of eosinophilic esophagitis, history of severe allergic reaction to immunotherapy, hypersensitivity to any medication component, and severe, unstable, or uncontrolled asthma.

COST

Cost data for a typical 1-month supply of Oralair®, Ragwitek®, and Grastek® are summarized in TABLE 4.

TABLE 2 | Summary of data from major phase 3 trials of Oralair®, Ragwitek®, and Grastek®.^{16,19,21,23}

Study	Major Inclusion Criteria	Treatment Arms	Primary Endpoint	Results
Wahn ¹⁶ Oralair®	<ul style="list-style-type: none"> Age 5-17 years RTSS ≥12 Asthma requiring only β₂-agonists AR due to covered allergens 	<ul style="list-style-type: none"> Placebo (n=135) 300 IR x 4 months prior to and during GPS (n=131) 	<ul style="list-style-type: none"> Daily RTSS (18 point scale) averaged during entire GPS 	<u>RTSS score, mean ± SD:</u> <ul style="list-style-type: none"> Placebo: 4.51 ± 2.93 300 IR: 3.25 ± 2.86
Didier ¹⁹ Oralair®	<ul style="list-style-type: none"> Age 18-51 years Seasonal grass pollen induced AR 	<ul style="list-style-type: none"> Placebo (n=165) 300 IR x 2 months prior to and during GPS (n=147) 300 IR x 4 months prior to and during GPS (n=149) 	<ul style="list-style-type: none"> AAdSS during the 3rd GPS (18 point scale) 	<u>AAdSS score, mean ± SD:</u> <ul style="list-style-type: none"> Placebo: 5.28 ± 3.94 300 IR (2 months): 3.38 ± 3.21 300 IR (4 months): 3.46 ± 3.63
Nolte ²¹ Ragwitek®	<ul style="list-style-type: none"> Age 18-50 years FEV₁ ≥70% predicted Ragweed-induced AR 	<ul style="list-style-type: none"> Placebo (n=164) 6 Amb a 1-U x 52 weeks (n=150) 12 Amb a 1-U x 52 weeks (n=159) 	<ul style="list-style-type: none"> TCS^a (56 point scale) averaged during peak RPS 	<u>TCS score, mean:</u> <ul style="list-style-type: none"> Placebo: 8.46 6 Amb: 6.70 12Amb: 6.22
Maloney ²³ Grastek®	<ul style="list-style-type: none"> Age 5-65 years FEV₁ ≥ 70% predicted Grass pollen-induced AR 	<ul style="list-style-type: none"> Placebo (n=672) 2800 BAU x 12 prior to and during GPS (n=629) 	<ul style="list-style-type: none"> TCS^a (56 point scale) averaged during entire GPS 	<u>TCS score, median:</u> <ul style="list-style-type: none"> Placebo: 4.22 2800 BAU: 3.24

^aTotal Combined Score (TCS) = daily symptom scale + daily medication scale; TCS has a 56 point scale with higher values indicating worse allergic rhinitis symptoms and more frequent rescue medication use.

IR = index of reactivity; GPS = grass pollen season; AAdSS = average adjusted symptom score; RTSS = rhinoconjunctivitis total symptom score; BAU = bioequivalent allergy unit, TCS = total combined score; Amb a 1 U = FDA reference units (1 Amb a 1-U = 1 mcg of A artemisiifolia); RPS = ragweed pollen season; AR = allergic rhinitis.

TABLE 3 | Adverse event data from trials of Oralair®, Ragwitek®, and Grastek®.

Adverse Event	Placebo	Oralair® 300 IR	Ragwitek® 12 amb a 1-U	Grastek® 2800 BAU
Any Adverse Event	8.6% – 46.4%	54.7% – 62.9%	39.4% – 68.4%	58.6 %
Oral pruritus	0% – 3.2%	22% – 32.4%	7.1% – 19.4%	18.5%
Mouth edema	0% – 3.2%	5% – 12.9%	0.5% – 16.9%	13 %
Throat irritation	1.5% – 5.4%	7.9% – 15%	7.7% – 29%	23.2%

Data represent percent of patients experiencing the adverse event in phase 3 clinical trials.

CONCLUSION

Four hundred million people suffer from allergic rhinitis and current treatment options only provide symptomatic relief. Oralair®, Ragwitek®, and Grastek® are novel sublingual immunotherapies which are effective for reducing the severity and frequency of allergic rhinitis symptoms and are associated with modest side effects. Immunotherapy is unique because the mechanism of action is hypothesized to treat the underlying disease process and sublingual is preferred over subcutaneous immunotherapy due to cheaper cost, easier administration, and patient convenience. Despite the theoretical benefit of Oralair®, Ragwitek®, and Grastek®, data are lacking to support sustained efficacy of these agents. Sublingual immunotherapies are expensive which makes them unfavorable compared to much cheaper current treatment options. As a result, further long-term efficacy data is warranted to determine the future role of sublingual immunotherapies in therapy.

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TABLE 4 | Average retail cost for Oralair®, Ragwitek®, and Grastek®.

Medication	Cost (1-month supply) ^a
Oralair® 300 IR	\$363.99
Ragwitek® 12 amb a 1-U	\$297.99
Grastek® 2800 BAU	\$299.99

^aAverage pricing represents cash price (i.e., without insurance) from Walgreens, CVS, and Publix stores in the Gainesville, FL area on 12/16/2014.

PERSONALIZED MEDICINE CORNER

Tramadol: Is toxicity risk affected by genotype?

Numerous case reports and studies detail how genotype for cytochrome P450 2D6 (*CYP2D6*) can affect response to codeine and some other opioids. In the March 2015 issue of *Pediatrics*, Orliaguet and colleagues published a new report of a child with the ultrarapid *CYP2D6* genotype who developed severe respiratory depression after a single dose of tramadol.¹ This report adds to the existing evidence of risks with codeine and tramadol in *CYP2D6* ultrarapid metabolizers.

Tramadol is a weak analgesic with low affinity for the μ -opioid receptor. Most of the drug's analgesic effects stem from *CYP2D6*-mediated activation to O-desmethytramadol, which is 200 times more potent than tramadol. Approximately 5% of people are *CYP2D6* ultrarapid metabolizers who quickly convert tramadol to O-desmethytramadol, potentially leading to toxicity. Conversely, about 5% to 10% of individuals are poor metabolizers with no *CYP2D6* activity. These patients do not convert tramadol to O-desmethytramadol and therefore have insufficient pain relief.

The recent case describes a 5-year-old boy with obstructive sleep apnea syndrome who underwent adenotonsillectomy under general anesthesia.¹ His post-operative stay was uneventful, and he was discharged 6 hours after surgery with a prescription for tramadol 20 mg. His parents gave him a dose of tramadol at 11 pm. The next morning, he was found lethargic and brought to the emergency department, where he had a Pediatric Glasgow Coma Scale score of 8, respiratory depression, and signs of opioid overdose. He recovered within minutes after receiving IV naloxone. Workup revealed elevated O-desmethytramadol concentrations in his urine and the ultrarapid *CYP2D6* metabolizer genotype.

Although this is the first report of tramadol toxicity in a child with the ultrarapid *CYP2D6* genotype, numerous reports exist of children with the ultrarapid genotype who developed respiratory depression, toxicity, or died after exposure to codeine.² In 2013, a boxed warning was added to codeine labeling warning of deaths related to ultrarapid metabolism in children following tonsillectomy or adenoidectomy, and codeine is now contraindicated in this setting. However, no such warning exists for tramadol, and limited genetic information is provided in its FDA-approved labeling.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) consists of experts in pharmacogenetics and laboratory medicine who provide guidelines on **how** to translate genotype results into prescribing decisions.³ The guidelines do not address **when** to order a genotype test, leaving that up to the clinician. CPIC guidelines advise against using codeine or tramadol in *CYP2D6* ultrarapid or poor metabolizers because of increased risk for toxicity or reduced efficacy, respectively.⁴ Oxycodone and hydrocodone are also metabolized to more active compounds by *CYP2D6* and are not good alternatives. Acetaminophen or an NSAID is preferred for treating mild pain in *CYP2D6* ultrarapid or poor metabolizers; morphine or other opioids that are not affected by *CYP2D6* variability are preferred for moderate-to-severe pain.

When to think about *CYP2D6* genetic testing:

- Prior to prescribing tramadol or codeine to a child
- Prior to tonsillectomy or adenoidectomy if opioids may be used post-operatively
- Prior to prescribing tramadol or codeine to an adult, especially if other risk factors for respiratory depression are present (e.g. obstructive sleep apnea)
- In a child or adult without pain relief or with signs of toxicity from tramadol or codeine
- In a child or adult not responding as expected to oxycodone or hydrocodone, as these drugs are also metabolized by *CYP2D6* to more active compounds

Get more information on ordering and reimbursement for *CYP2D6* testing from the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu). You can also request our *CYP2D6-Opioids Clinical Summary* for a short review of the most relevant studies in this area.

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