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Ragweed sublingual tablet immunotherapy: part I – evidence-based clinical efficacy and safety

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Sublingual tablet immunotherapy provides an attractive alternative approach to allergen immunotherapy, as the allergen is administered as a rapidly dissolving sublingual tablet. Part I of this two-part series on the ragweed sublingual tablet describes the dose-ranging clinical work, the safety studies and the clinical outcomes from the pivotal trials which provide clear evidence for statistically significant and clinically meaningful benefit in the treatment of patients suffering from ragweed-induced seasonal allergic rhinitis-conjunctivitis with or without milder asthma. The robust results observed in the clinical trials performed with the ragweed sublingual tablet are defined by the quality of their study design, their use of a standardized allergen extract, their consistent reproducibility in demonstrating therapeutic efficacy and their properly quantified and graded safety data.

First draft submitted: 12 December 2017; Accepted for publication: 21 February 2018; Published online: 10 April 2018

Keywords: allergen immunotherapy • allergic rhinitis/conjunctivitis • ragweed • ragweed pollen • ragweed subcutaneous immunotherapy • ragweed sublingual immunotherapy • ragweed sublingual tablet

Background

Ragweed (*Ambrosia artemisiifolia*; ‘common’ ragweed) (Figure 1) and its cross-reactive species are noxious weeds that thrive throughout much of North and South America. Over the past several decades, the ragweed plant (which was primarily confined to military transport bases in France and Germany post-WWII), has adapted to other parts of Europe, especially Northern Italy, Austria, Hungary and the Ukraine, and climate changes appear conducive to fostering its spread throughout Eastern Europe, the Balkans and areas abutting the Black Sea. Furthermore, international trade and travel have led to the introduction of ragweed into Asia and Australia [1–3].

Ragweed is a member of the Asteraceae/Compositae (Aster) plant family. The genus (*Ambrosia* L.) contains 25 taxa (species) (United States Department of Agriculture). Extensive clinical cross-sensitivity has been shown between members (taxa) of the *Ambrosia* genus (short ragweed, giant ragweed, western ragweed, false ragweed) [4,5].

Furthermore, *in vitro* studies (ELISA-inhibition; FAST) have also shown that ragweed demonstrates cross-reactivity with several other species of plants in related genera (e.g., *Artemisia*; *Xanthium*; *Rumex*), most relevant, mugwort (*Artemisia vulgaris*) which is a prominent airborne allergen in Europe (Immunoblots show similar IgE-binding to allergenic epitopes [Amb a 1, Art v 1]) and, as well, IgE homology with profilin, a minor but ubiquitous structural plant protein present in pollens and plant food [5–7].

The ragweed plant is an annual and its principal means of propagation is through bird droppings. It is found most prominently in drainage ditches, along the roadside, at construction sites, and wherever the soil is disturbed.

Native to North America, ragweed’s prevalence, is heaviest in the central portions of Canada and the Northern USA, moderate in the mid-east and central states and the mid-Atlantic; however, its spread is limited by the Rocky Mountains to the west and the Atlantic Ocean and Gulf of Mexico in the southeast, as the plant species are not



Figure 1. Short ragweed (*Ambrosia artemisiifolia*).
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found in Bermuda or much of the Caribbean, although it is present in Cuba, Jamaica and several countries of South America [2,5].

In the USA, the National Health and Nutrition Examination Survey (NHANES) estimated that ~25% of the population is sensitized to ragweed pollen [8], and it is recognized as the dominant seasonal aeroallergen for much of North America – causing significant clinical morbidity as manifested most commonly by allergic rhinitis with or without conjunctivitis, and/or asthma in susceptible individuals, associated disease sequelae (sinusitis, otitis, sleep disturbance) with an adverse economic burden due to medication costs, ancillary diagnostic procedures and lost work-related productivity.

Treatment approaches incorporate environmental measures to limit exposure to the plant and its pollen (air conditioning; wearing of masks when outdoors; physical barriers to nasal inhalation), appropriate use of controller medications (nasal corticosteroids; cromolyn drugs) in conjunction with relief meds (antihistamines; decongestants; leukotriene antagonists; anticholinergic sprays) and allergen immunotherapy [9–13].

The modality of allergen immunotherapy, as contrasted to pharmacotherapy, offers a form of treatment capable of inducing regulatory pathways that result in suppression of the underlying inflammatory process that otherwise underpins the untoward allergic diathesis, restoring a state of immune tolerance and providing long-term clinical remission of the disease entity, as defined by attenuation, if not complete suppression, of the symptoms manifested by the patient suffering from the aforementioned allergic respiratory conditions [14–16].

This paper will review the clinical efficacy and safety of ragweed sublingual immunotherapy (SLIT) based on the evidence-based literature and safety data of immunization with a sublingual ragweed extract tablet for the treatment of ragweed-induced respiratory allergies.

Table 1. Selected studies of ragweed sublingual immunotherapy.

Study	Date	Study design	Tx Grps	Findings	Ref.
Johnstone	1957	SBPC	RWIT (4 dosing regimens); PL	High dose and moderate dose regimens showed significant benefit for SAR ($p < 0.01$) and in preventing the development of asthma ($p = 0.01$)	[17]
Lowell	1963	DBPC pre-seasonal	RW; PL	↓ Sxs in peak season vs PL group ($p = 0.05$)	[18]
Lowell	1965	DBPC Pre-seasonal	Multiple allergen IT	In 2nd season, symptomatic pts randomized to IT with/without RW	[19]
Norman	1968	DBPC x 4 Yr pre-seasonal	Whole RW; purified AgE; PL	Sx improvement: whole RW grp: 44% vs PL ($p = 0.004$); AgE grp: 31% vs PL ($p = 0.03$)	[20]
Lichtenstein	1971	DBPC x 1 Yr pre-seasonal	Whole RW; purified AgE	~40% reduction in cx symptoms in each tx group ($p < 0.01$); ↓ in BHR; ↑ in IgG blocking antibody (correlated w/ dose)	[21]
Norman	1971	RDBPC perennial	Whole RW; RW AgE	Improvement in mean daily symptom index scores in whole RW and AgE-treated groups versus PL ($p < 0.01$)	[22]
Norman	1978	RDBPC 3-Yr	RW + GR-allergic pts tx w/ RW or PL	RWIT group reported sx improvement in in fall RW season; GRIT group had no improvement in fall	[23]
Van Meter	1980	RDBPC 1-Yr seasonal study	Rinkle (RIT: 0.006 mcg Amb a 1) vs PL	RIT group's symptom-medication diary scored were NS compared with PL	[24]
Van Meter	1980	RDBPC in SAR	RW SIT versus RIT	RW SIT group reported 50% reduction in sx scores vs RIT ($p < 0.01$); RW SIT superior to PL ($p < 0.01$); RIT NS vs PL ($p = 0.3$)	[25]
Creticos	1996	RDBPC in asthma	RW SIT versus PL	RW SIT group reported improvement in asthma symptoms + medication scores + PEF ($p = 0.009$; Yr 1) and RW bronchial challenge ($p = 0.03$)	[26]

AgE: Antigen E; BHR: Basophilhistamine release; cx: Clinical; DBPC: Double-blind placebo-controlled; GRIT: Grass immunotherapy; IT: Immunotherapy; NS: Not significant; PEF: Peak expiratory flow; PL: Placebo; pt: Patient; RDBPC: Randomized single-blind placebo-controlled; RIT: Rinkle immunotherapy; RW: Ragweed; RWIT: Ragweed immunotherapy; SAR: Seasonal allergic rhinitis; SBPC: Single-blind placebo-controlled; SIT: Standard immunotherapy; sxs: Symptom; tx: Treatment; Yr: Year.

As a framework for this therapeutic approach, it is prudent to begin with an overview of ragweed immunotherapy through its traditional subcutaneous method of administration for the treatment of ragweed-induced allergic respiratory disease.

Overview: subcutaneous immunotherapy with standardized ragweed extract

Subcutaneous injection of extract with standardized ragweed has been the accepted method of administering ragweed immunotherapy in the USA for decades. Early studies in Boston and subsequent studies carried out by the group at Johns Hopkins clearly defined target dose, immunologic mechanisms, clinical efficacy and safety [17–27]. Selected evidence-based clinical trials that highlight the potential clinical benefits of SCIT are compiled in **Table 1**.

In addition, provocation studies have defined the inflammatory pathways inciting the disease process [28–30], the role of the humoral limb in the body's protective immune response [31–33] and cell regulatory pathways that are capable of harnessing the untoward allergic diathesis [14–16,34].

Furthermore, provocation studies of the skin, nose and lungs [26,35–37] and environmental exposure chambers [38,39] have provided an *in vivo* method of characterizing the therapeutic response to allergen immunotherapy which support the clinical outcomes from natural exposure field clinical trials.

However, subcutaneous immunotherapy is saddled with an inconvenient injection regimen that requires regular physician visits over multiple years, is uncomfortable and painful to many patients, especially children, and can be associated with adverse systemic reactions that can be severe, including anaphylaxis [10,11,40,41].

One alternative to injection therapy is that of sublingual administration of the allergen. Oral application of the allergen has been in use for several decades in Europe [42]. The more recent application of SLIT through the administration of the allergen extract in a tablet form has gained wide acceptance in Europe, North America and Asia for grass, ragweed, and house dust mite based on its ease of application, a simple sublingually administered route, its robust clinical data supporting efficacy and its favorable cumulative safety profile [10,42–45].

Table 2. Primary efficacy data supporting US FDA approval.

Study	# Subjects	TCS RW-tablet	TCS placebo	Point estimate (% diff)	95% CI	p-value	Ref.
Creticos	784	6.41	8.46	-24.2	-36.5; -11.3	0.0015	[50]
Nolte	565	6.22	8.46	-26.5	-38.3; -14.6	0.0002	[51]

#: Number; diff: Difference; RW: Ragweed; TCS: Total combined score.

This article will review the clinical efficacy and cumulative safety that has been generated in the double-blinded placebo-controlled clinical trials that have been performed with a standardized sublingual ragweed extract tablet for the treatment of ragweed-induced respiratory allergies.

SLIT with standardized ragweed extract administered as an SLIT-tablet
Overview

A rapidly dissolving, once daily, 12 mcg Amb a 1 Unit ragweed SLIT-tablet (Ragwitek®; ALK) received US FDA and Canadian (HPFB) approval in 2014 for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, in patients 18–65 years of age, who have a clinical history of disease and who have positive skin test sensitivity or *in vitro* testing to pollen-specific IgE antibody to ragweed pollen [46]. As of this publication, the product has not received European regulatory approval.

As there is extensive cross-reactivity among the taxa of the *Ambrosia* genus, it would be expected that the short ragweed extract would also provide efficacy against giant, western, and false ragweed in the USA; however, data for European short and giant ragweed are conflicting [4–7]. It is recommended that the sublingual therapy be initiated 12 weeks prior to the anticipated start of the ragweed season and continued on a daily basis through the ragweed season. For safety reasons, the FDA has mandated that the patient should receive the first dose at a supervised medical facility, be instructed in the signs and symptoms associated with allergic reactions to immunotherapy, and be trained in the proper use of epinephrine and provided with a prescription for this drug [46]. (The latter requirement has not been espoused by the European regulatory authorities with respect to sublingual immunotherapies).

The treatment should not be prescribed to patients with severe, unstable or uncontrolled asthma. And in this context, it behooves the physician to carefully assess the immunized patient during the initiation phase and through the course of the ragweed season and develop an action plan to recognize, treat and decide if therapy should continue in a patient that experiences new onset or worsening of asthma.

Furthermore, the occurrence of gastroesophageal symptoms (e.g., reflux, gastritis) should lead to a careful clinical evaluation to rule-out the development of eosinophilic esophagitis which may necessitate discontinuation of treatment.

Clinical studies with ragweed sublingual tablet immunotherapy
Criteria for efficacy data supporting regulatory approval

The results for the primary outcome for both pivotal trials met the new criteria established by the FDA for an immunotherapy agent to be considered for approval by the agency. (Table 2) The new guidance requires that a drug must meet both of the following two efficacy criteria: the total combined score (TCS) must demonstrate an average relative difference of 15% compared with placebo, and [2] the upper bound of the 95% CI must be ≤ -10% [47].

Furthermore, the results meet the guidance set forth by the World Allergy Organization (WAO) in 2012, which proposed that a 20% mean reduction in the (TCS) compared with placebo be considered the minimum change that corresponds to a clinically meaningful benefit [48]. This is also espoused in the current German, Austrian and Swiss guideline on allergen immunotherapy [11].

The FDA approval for the ragweed SLIT-tablet was based on five studies that included a Phase I dose-ranging study, two Phase II/III pivotal trials and two safety studies [49–52].

Dose-ranging study

The dose-ranging study by Nayak [49] was a dose-escalation, double-blind, randomized, placebo-controlled study that evaluated 53 adult ragweed 55 allergic patients over a 28-day treatment period. The 40 subjects that received ‘active’ therapy were randomized to ragweed tablet formulations of 3–50 mcg of Amb a 1 U tablets. The findings from this study provided the basis for the subsequent clinical trials that evaluated a 1.5, 6.0 and/or 12 mcg Amb a 1 U tablet strengths.

Pivotal Trial #1

Creticos *et al.* [50]. performed a multinational clinical trial (USA, Canada, Hungary, Ukraine and Russia) that evaluated 784 adults with short ragweed-induced allergic rhinitis/conjunctivitis with or without mild asthma (GINA I/GINA II). Study patients were randomized in a DBPC fashion to receive 52 weeks of daily treatment with 1.5, 6 or 12 units of the major allergenic moiety of short ragweed (*Ambrosia artemisiifolia*) (Amb a 1) or placebo.

Subjects recorded daily symptoms and medication usage on an electronic diary, and adverse event diaries were maintained through the entire duration of the study to monitor safety.

The primary efficacy end point was the TCS during the peak of the ragweed season (this score is the combination of the daily symptom score + the daily rescue medication score and was calculated for each patient on each day: analysis used adjusted linear models and tests included least square means and 95% CI for the between-treatment differences).

Secondary outcomes included the TCS for the entire season, the daily rhinoconjunctivitis symptom score (DSS) and the daily medication score (DMS) for the entire and peak periods of the ragweed season.

The DSS was comprised of four nasal symptoms (sneezing, runny nose, stuffy nose, itchy nose) + 2 ocular scores (gritty/itchy eyes, watery eyes) and was graded on a standard 4-point scale (0 [none] to 3 [severe]).

The daily rescue medication score based on an ordinal score for which patients administered relief medications in a stepwise manner based on symptom severity (patients were provided with an oral antihistamine [loratadine], an ocular antihistamine [olopatadine], a nasal steroid [mometasone] and oral prednisone).

The statistical results for the primary efficacy end point (TCS; during peak ragweed season) showed a stepwise improvement in clinical symptoms according to ragweed treatment regimen (1.5 Amb a 1 U: 9% [$p = 0.22$]; 6 Amb a 1 U: 19% [$p = 0.01$]; 12 Amb a 1 U: 24% [$p = 0.002$] vs placebo). Similar clinical benefit was demonstrated for analysis of TCS for the entire ragweed season with the 6 and 12 Amb a 1 U tablets (18% [$p = 0.01$]; 27% [$p < 0.001$], respectively).

The 95% CI for the respective doses for the primary end point (TCS; peak season) provided strong evidence that the data were robust [6 Amb a 1 unit dose (treatment diff vs placebo): -1.58 (95% CI: -2.8 to [0.36; $p = 0.01$]; 12 Amb a 1 unit dose: -2.04 [95% CI: -3.03 to -0.79; $p = 0.002$]]; thereby, providing confidence that the point estimate data were clinically meaningful.

Statistically significant improvements were also observed for several of the study's secondary outcomes including the DSS vs placebo for the 12 Amb a 1 dose (peak season: 18% [$p = 0.01$] and entire season: 21% [$p = 0.002$]), and the DMS vs placebo (peak season: 6 Amb a 1 U dose: 35% [$p = 0.005$]; 12 Amb a 1 U dose: 36% [$p = 0.003$]/entire season: 6 Amb a 1 U dose: 35% [$p = 0.004$]; 12 Amb a 1 U dose: 38% [$p = 0.003$]). The Visual Analog Scale (VAS) also reflected a significant score for the 12 Amb a 1 U dose vs placebo for the peak season: 21% ($p = 0.04$) and entire season: 22% ($p = 0.02$) evaluations.

Consistent with successful studies of immunotherapy, the treatment induced a rise in ragweed-specific IgG4 antibody ($p < 0.001$) in the active treatment groups as contrasted to the placebo group, and this tracked with symptom reduction in the treated groups.

The treatment was well-tolerated with no life-threatening events, deaths, or anaphylaxis observed in the study. Furthermore, no treatment-related serious AEs, systemic allergic reactions or asthma exacerbations were observed in the study. Asthma patients comprised 16–19% of the patient groups and, although not significant, reported symptom improvements of 26–39% versus placebo.

The majority of treatment-related adverse events (TRAEs) were mild or moderate in severity and the most common TRAEs (active treatment groups vs placebo) were throat irritation (12–21% vs 4%), oral pruritus (5–14% vs 1%), ear pruritus (7–13% vs 1%) and tongue edema (4–8% vs 1%). Study discontinuation due to TRAEs were infrequent (5; 8; 5%, respectively vs 3% in placebo), albeit tongue edema was the most frequent adverse event leading to discontinuation from the study.

In summary, this Phase II/III pivotal trial demonstrated clinically meaningful benefit for the ragweed therapeutic agent at an optimal dose of 12 Amb a 1 U (units) that was safely self-administered in a daily regimen that was well tolerated.

Pivotal trial #2

Parallel to this study, Nolte *et al.* [51]. performed a second Phase II/III pivotal trial that studied the 6 and 12 Amb a 1 U dose regimen vs placebo. In this randomized single-blind placebo-controlled clinical trial, 565 adults

Table 3. All treatment-related adverse events occurring in at least 5% of subjects in any treatment group for each trial.

Subjects reporting AE, n (%)	28-d trials Trial 1 (P06081) [†]				52-wk trials Trial 3 (P05233) [‡]				Trial 4 (P05234)			
	Placebo MK-3641 6 Amb		MK-3641 12 Amb		Placebo MK-3641 6 Amb		MK-3641 12 Amb		Placebo MK-3641 1.5 Amb		MK-3641 6 Amb	
	(n 1/4 65) [†] 1-U (n 1/4 66)	1-U (n 1/4 65)	(n 1/4 65) [†] 1-U (n 1/4 66)	1-U (n 1/4 65)	(n 1/4 186) [†] 1-U (n 1/4 188)	1-U (n 1/4 186)	(n 1/4 186) [†] 1-U (n 1/4 188)	1-U (n 1/4 186)	(n 1/4 196) [†] 1-U (n 1/4 196)	1-U (n 1/4 196)	(n 1/4 196) [†] 1-U (n 1/4 196)	1-U (n 1/4 196)
Any	13 (20.0)	24 (36.4)	27 (41.5)	64 (21.1)	27 (14.5)	99 (52.7)	115 (61.8)	17 (8.6)	55 (28.1)	78 (40.0)	86 (44.3)	86 (44.3)
Ear pruritus	0	4 (6.1)	5 (7.7)	2 (0.7)	4 (2.2)	30 (16.0)	30 (16.1)	2 (1.0)	14 (7.1)	26 (13.3)	24 (12.4)	24 (12.4)
Eye pruritus	4 (6.2)	2 (3.0)	3 (4.6)	5 (1.6)	7 (1.1)	1 (0.5)	8 (4.3)	3 (1.5)	3 (1.5)	3 (1.5)	3 (1.5)	3 (1.5)
Dry mouth	1 (1.5)	0	4 (6.2)	1 (0.3)	2 (1.1)	3 (1.6)	0	1 (0.5)	0	2 (1.0)	2 (1.0)	2 (1.0)
Oral hypoesthesia	0	1 (1.5)	4 (6.2)	2 (0.7)	1 (0.5)	2 (1.1)	2 (1.1)	0	2 (1.0)	6 (3.1)	4 (2.1)	4 (2.1)
Mouth edema	0	1 (1.5)	0	1 (0.3)	0	2 (1.1)	1 (0.5)	0	0	3 (1.5)	2 (1.0)	2 (1.0)
Oral pruritus	1 (1.5)	11 (16.7)	11 (16.9)	5 (1.6)	43 (7.1)	35 (18.6)	36 (19.4)	2 (1.0)	10 (5.1)	28 (14.4)	16 (8.2)	16 (8.2)
Oral paresthesia	3 (4.6)	3 (4.5)	4 (6.2)	16 (5.3)	4 (2.2)	14 (7.4)	20 (10.8)	5 (2.5)	10 (5.1)	15 (7.7)	9 (4.6)	9 (4.6)
Throat irritation	1 (1.5)	8 (12.1)	5 (7.7)	9 (3.0)	10 (5.4)	48 (25.5)	54 (29.0)	7 (3.5)	24 (12.2)	41 (21.0)	41 (21.1)	41 (21.1)
Swollen tongue	1 (1.5)	3 (4.5)	3 (4.6)	0	6 (3.2)	22 (11.7)	36 (19.4)	1 (0.5)	11 (5.6)	11 (5.6)	13 (6.7)	13 (6.7)
Pruritus	2 (3.1)	1 (1.5)	1 (1.5)	6 (2.0)	0	12 (6.4)	9 (4.8)	4 (2.0)	3 (1.5)	7 (3.6)	4 (2.1)	4 (2.1)

[†] Does not include information from seven subjects removed from analysis owing to significant departure from Good Clinical Practice by the study site.[‡] Does not include information from five subjects removed from analysis owing to significant departure from Good Clinical Practice by the study site.

AE: Adverse event.

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Table 4. Ragweed sublingual immunotherapy tablet (ragwitek [ALK]).

Therapeutic agent	Short ragweed pollen extract formulated as a 12 Amb a 1 Unit dissolvable tablet
Indication	Allergic rhinitis with or without conjunctivitis in adult patients sensitive to short ragweed pollen
Identification of appropriate patients for treatment	Evidence of IgE-mediated sensitivity to short ragweed as confirmed by positive skin test to an extract of the allergen or by <i>in vitro</i> testing for pollen-specific IgE antibody to short ragweed pollen
Application method	Administer single tablet sublingually (under the tongue); tablet dissolution should occur within 15–30 s (do not drink/swallow for at least 1 min)
Initiation of treatment	Initiate treatment at least 12 weeks before the onset of the ragweed pollen season and continue treatment, as tolerated, on a daily basis throughout the season
Handling of missed doses	Treatment interruptions of up to 7 days acceptable without physician follow-up
Pregnancy	Consult physician for guidance
Contraindications	Severe, unstable, or uncontrolled asthma; history of eosinophilic esophagitis; history of any severe systemic allergic reaction to allergen immunotherapy; history of severe local reaction after having received SLIT; hypersensitivity to inactive ingredients in the product (gelatin [fish source]; mannitol; sodium hydroxide)
Epinephrine	US FDA has required patients to be prescribed auto-injectable epinephrine and to be instructed in its appropriate use for the treatment of a severe allergic reaction to the ragweed tablet

SLIT: Sublingual immunotherapy.

Adapted with permission from Creticos PS. Sublingual immunotherapy for allergic rhinoconjunctivitis and asthma. In: UpToDate, Post TW (Ed.), UpToDate, Waltham, MA. (Accessed on 14 Feb 2018.) Copyright © 2018 UpToDate, Inc. For more information visit www.uptodate.com [12].

with short ragweed-induced allergic rhinitis/conjunctivitis with or without mild asthma (GINA I/GINA II) were enrolled in a 1:1:1 design to receive daily SLIT-tablet (6 or 12 Amb a 1 units) or placebo. This too was designed as a 52-week trial in order to obtain longer exposure safety data. The same study methodology and clinical outcomes were performed.

The ragweed SLIT-treated patients reported significant improvement in their TCS for both the peak and entire ragweed season for both the 6 Amb a 1 unit ragweed tablet (peak season: 21% [$p = 0.004$]; entire season: 16% [$p = 0.03$]) and the 12 Amb a 1 unit ragweed tablet (peak season: 27% [$p < 0.001$]; entire season: 26% [$p < 0.001$]) regimens versus placebo.

The 95% CI for the respective doses for the primary end point (TCS; peak season) again provided strong evidence that the data were robust (6 Amb a 1 unit dose [treatment diff vs placebo]: -1.76 [-2.95 to -0.57]; 12 Amb a 1 unit dose: -2.24 [-3.41 to -1.07]).

Both treatment doses also showed efficacy for the DSS and DMS secondary outcomes as compared with placebo in the peak season (14 and 17%, respectively [$p < 0.05$]); whereas, for the entire season, only the 12 Amb a 1 unit dose showed significance for the DSS (17% [$p = 0.01$]), and the Visual Analog Scale score (24% ($p = 0.009$)) versus placebo.

As would be expected with an immunotherapeutic regimen that was administered at an appropriate dose, and similar to the observations in the other Phase II/III clinical trial, the treatment regimens induced ragweed-specific IgG4 antibody vs placebo ($p < 0.001$).

The ragweed SLIT-tablet was well tolerated with no life-threatening events, deaths or systemic allergic reactions observed in the study. Furthermore, the majority of treatment-related AEs were mild oral mucosal reactions, although one study patient (in the 6 Amb a 1 group) received adrenaline for perceived pharyngeal edema.

The most frequently reported TRAEs (active treatment groups vs placebo) were throat irritation (25; 29 vs 5%), oral pruritus (18; 19 vs 3%), tongue pruritus (17; 14 vs 2%) ear pruritus (16; 16 vs 2%) and swollen tongue (12; 19 vs 3%).

Four hundred twenty three randomized patients completed the study (75%). The primary reason for study withdrawal were reasons unrelated to study drug assignment (10%) and adverse events (6.5%). It was noted by the authors that 'no patients discontinued the trial because of treatment failure'.

In summary, this second Phase II/III pivotal trial likewise demonstrated that ragweed extract could be administered safely at a dose that provided effective clinical relief for ragweed-induced seasonal allergic rhinitis and conjunctivitis.

Canadian subgroup analysis

Kim *et al.* [53], published the findings of the 337 Canadian patients randomized in the two pivotal trials (reviewed above) and reported that the 6- and 12-Unit Amb a 1 tablets significantly reduced TCS during the peak ragweed season by 26% ($p = 0.0009$) and 40% ($p < 0.0001$), respectively. Similar findings were observed for the entire pollen season. Safety data showed that adverse events were generally mild to moderate, transient, and occurred early in treatment. These observations demonstrated that the sublingual tablet had a favorable risk profile in a geographic region of North America that is exposed to high ragweed pollen counts.

Safety studies

Pooled safety data from two 28 day safety studies and the above-cited 52-week pivotal trials have been reported with the ragweed sublingual tablet [52]. In all four studies, the first dose of study medication was administered in the medical setting with subsequent dosing self-administered at home by the study subject.

The data from these four randomized clinical trials ($n: 757/198/454/ 1058$ study subjects) provided solid evidence for the tolerability of the ragweed tablet over the dosing range of 1.5 to 12 Amb a 1 units as compared with placebo (Table 3).

These data showed that although TRAEs were more frequent in the 6- and 12-unit treatment groups, these were primarily local application-site reactions with the local oral-mucosal adverse events self-limited in nature – typically lasting 15–30 min post dose and tapering with each respective dose over the course of the first week of treatment. The median time to onset of local oral-mucosal adverse events (e.g., oral discomfort, oral pruritus, oral paresthesia, throat irritation, oropharyngeal swelling, lip swelling) was 1–4 days. No dose-response was seen in relation to onset.

As shown in Table 3, the manifestation of mouth edema was reported by 1.1–5.6% of study subjects receiving active drug in the four clinical trials ($n = 1699$ of 2466 study subjects); however, this untoward adverse event did not result in either airway obstruction or respiratory compromise in any of these study patients. Although the treatment-emergent and treatment-related adverse events were slightly higher in the asthmatic subpopulation, the symptomatology and severity were similar to the subpopulation without asthma.

Needless to say, the potential for the occurrence of oropharyngeal swelling leads to the importance of carefully instructing patients on the recognition of those oropharyngeal symptoms/signs that either progress or persist, as this may be an indicator for administration of epinephrine or discontinuation of treatment.

Reassuringly, there were no treatment-associated asthma exacerbations or deterioration in asthma control associated with the ragweed sublingual tablet use.

Furthermore, no treatment-related anaphylactic shock, life-threatening adverse events, or serious adverse events (SAEs) related to active drug treatment were observed in any of these four clinical studies.

Among the four studies, epinephrine was administered nine times in eight subjects (four injections were for ragweed SLIT-tablet related adverse events: systemic allergic reaction [1]; local mouth and/or pharyngeal-throat swelling [3]).

In summary, pooled analyses that examined short-term safety (28 day studies) and long-term safety (52-week studies) provided reassurance that the ragweed sublingual tablet was well-tolerated in subjects with ragweed pollen-induced allergic rhinitis with or without allergic conjunctivitis with or without milder asthma.

Conclusion

SLIT with a ragweed tablet provides a safe and effective alternative to subcutaneous immunotherapy in patients that suffer with seasonal allergic rhinitis/conjunctivitis with or without milder asthma (Table 4). It provides the patient with an easy-to-administer treatment that can be taken by the patient in the home setting, not necessitating an office visit for treatment.

The robust results observed in the clinical trials performed with the ragweed sublingual tablet are defined by the quality of their study design, their use of a standardized allergen extract, their consistent reproducibility in demonstrating therapeutic efficacy and their properly quantified and graded safety data.

Further studies need to be performed to address adherence, concomitant safety with other allergens, optimal duration of treatment and evaluation of regimens that may provide long-lasting benefit through induction of immune tolerance.

Future perspective

Novel approaches in which the allergen itself is modified (e.g., recombinant allergens; peptide constructs; adjuvants; combinations), or in which the route of delivery is enhanced (e.g., epicutaneous; intralymphatic; topical nasal or inhaled delivery) may allow us to achieve the holy grail of immune tolerance, through rebalancing the untoward allergen-induced allergic diathesis with disease modification and induction of long-lasting clinical remission of the allergic disease state [54–57].

Financial & competing interests disclosure

PS Creticos has received research grant funding from Circassia, Merck and Stallergenes-Greer; has served as a consultant to Allergy Therapeutics, Anergis, ASIT, Circassia, OptiNose and Stallergenes-Greer; has served as a past speaker for Merck; is an editor and author for UpToDate; receives royalties from UpToDate; has received payment for development of educational presentations from WebMD, Elsevier and the AAAAI; has served on advisory panels for NIAID, PCORI and AHRQ; and serves on committees of the AAAAI and ACAAI. O Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding BV/HAL Allergie GmbH,

Executive summary

Global impact of ragweed allergy

- Ragweed (*Ambrosia artemisiifolia*) is the most relevant and prevalent fall seasonal allergen in North America and is expanding its footprint globally, with particular spread to parts of Europe.
- This noxious weed is an annual plant, has significant cross-reactivity with other members of the *Ambrosia* family, and partial cross-reactivity with several other species of plants in related genera.

Ragweed SCIT: clinical evidence of efficacy with ragweed subcutaneous immunotherapy

- Subcutaneous allergen immunotherapy has been the traditional mode for administration of an allergen vaccine, since it was first employed by Noon and Freeman in 1911 for the treatment of grass ‘hay fever’.
- The major allergenic moieties of ragweed allergen have been characterized and the allergen has been standardized based on its principal protein (Amb a 1). This work led to the development of immunologic assays that allowed a better understanding of the underlying mechanisms of effective immunotherapy.
- Randomized single and double-blinded clinical trials with ragweed extract have defined its optimal dose and demonstrated clinical improvement in field trials, allergen challenge studies (skin; nasal; bronchial provocation) and environmental exposure chambers.

Ragweed immunotherapy administered as a dissolvable sublingual tablet (ragweed sublingual immunotherapy tablet)

- A rapidly dissolving, once daily, 12 Amb a 1 unit ragweed sublingual immunotherapy (SLIT) tablet has been approved by the US FDA and Canadian HPFB.
- It is approved for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, in adult patients who have a clinical history of disease and who demonstrate positive skin test sensitivity to ragweed or to *in vitro* testing to pollen-specific IgE antibody to ragweed.

Ragweed SLIT: clinical evidence of efficacy with ragweed immunotherapy administered as a dissolvable sublingual tablet

- The therapeutic construct has demonstrated statistically significant and clinically meaningful improvement in pivotal seasonal trials of the active drug versus placebo.
- The two pivotal clinical trials demonstrated improvement in the primary outcome measurement (total combined score during the peak pollen season) and in clinically relevant secondary outcomes (daily rhinoconjunctivitis symptom score; daily medication score; Visual Analog Scale) for the 12 Amb a 1 Unit ragweed SLIT-tablet.

Safety data with the ragweed SLIT-tablet

- Safety data collected in the 28 day safety studies and 52-week pivotal clinical trials were pooled and demonstrated that the ragweed SLIT-tablet was well-tolerated in allergic rhinoconjunctivitis patients with or without milder asthma (GINA Step 2; low dose inhaled corticosteroids +/- short-acting bronchodilator).
- The most frequently reported treatment-related adverse events were throat irritation, oral pruritus, tongue pruritus, ear pruritus and swollen tongue.
- No treatment-associated asthma exacerbations or deterioration in asthma control was observed with treatment.
- The manifestation of oropharyngeal edema should not be overlooked as this can lead to airway obstruction or respiratory compromise due to local swelling of the oropharynx.

Conclusion

- Sublingual immunotherapy with a standardized ragweed tablet (12 Amb a 1 Unit ragweed SLIT-tablet) provides an effective alternative to subcutaneous immunotherapy for patients suffering with ragweed-induced allergic rhinitis, with or without conjunctivitis.

grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Nuvo, grants from Circassia, grants and personal fees from Biotech Tools SA, grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from Novartis Pharma, personal fees from MEDA Pharma, grants and personal fees from Anergis S.A., personal fees from Sanofi US Services, personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Pohl-Boskamp, personal fees from Indoor Biotechnologies, outside the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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