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Vaccine development and new attempts of treatment for ragweed allergy

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***Abstract*:** Ragweeds are flowering plants in the genus Ambrosia in the aster family, Asteraceae. They are distributed in the tropical and subtropical regions of the New World, especially North America. Short ragweed is the most important weed. The ragweed flowering occurs late in the summer and the pollination period extends from the beginning of August to mid-October. Sensitization to ragweed pollen has risen in United States in the past decade and probably worldwide. The major allergenic compound in the pollen has been identified as Amb a 1. Ragweed allergies usually cause allergic rhinitis and asthma. Ragweed allergic patients may show signs of oral allergy syndrome caused by crossreactivity between ragweed allergens and food allergens. In the present article, an update about vaccine development and new knowledge for ragweed allergy is exhaustively revised.

***Keywords*:** ragweed, immunotherapy, pollen

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Introduction

Ragweeds are flowering plants in the genus Ambrosia in the aster family, Asteraceae. They are distributed in the tropical and subtropical regions of the New World, especially North America. The giant ragweed (*Ambrosia trifida*) can reach a height from 12 to 18 feet and has leaves with three lobes (hence its scientific name). Short ragweed (*A. artemisiifolia*) and other species of ragweed (*A. bidentata, A. psilostachya*) grow to about 4 feet in height and shed enormous amounts of pollen [Esch *et al.* 2001].

About 17 widely distributed species of ragweed are found in North America, but short ragweed is the most important from the allergic point of view. Short ragweed belongs to the Asteraceae (Compositae) family. It is an annual herb common to roadsides and disturbed habitats throughout most of the United States and Canada, but also in Europe [Dechamp *et al.* 1995; Dahl *et al.* 1999]. Because of its high spreading potential throughout Europe and its very allergenic pollen, a study within the framework of the ATOPICA project was designed to calculate and predict airborne concentrations of ambrosia pollen in Europe [Hamaoui-Laguel *et al.* 2014]. In Europe, the countries with the highest levels of ragweed pollen are Hungary, Italy, Croatia and France [Laaidi *et al.* 2003].

Short ragweed is monoecious, with staminate and pistillate flowers born on distinct axillary branches, allowing for independent control of allocation to sexes [Wayne *et al.* 2002]. The pistillate flowers are wind pollinated, and can remain airborne for days and travel great distances. Ragweed flowers are greenish and concealed in small heads on the leaves. Species may grow just a few centimetres tall or well exceed 4 m in height.

Ragweed flowering occurs late in the summer and the pollination period extends from the beginning of August to mid-October with a peak from mid-August to the end of September [Frenz *et al.* 1995]. Ragweed pollen is released when temperatures become lower than 60°F (maximal in sunny and dry weather) and the night length increases (when night temperature is above 10°C). The pollen of *A. artemisiifolia* is produced in enormous amounts compared with other grasses and a single plant alone may produce millions of small pollen grains (18–22 µm), which are often transported long distances. Ragweed pollen is very allergenic and very low concentrations such as 5–10 pollen/m^3 of air are sufficient to trigger allergic reactions in sensitive patients [Taramarcaz, 2006].

The Ambrosia pollen grains are somewhat flattened to nearly spherical, the opercula slightly granular, and the ora lolongate to subcircular. The sexine is tectate; the largest spines with pointed apices and broad bases, sometimes with intermixed spinules, or occasionally with very

short spinules interspersed with small piloid elements. Ambrosia pollen grains are 16–27 μm in diameter [Pollenlibrary, 2014].

Many factors can influence year-to-year changes in the pollen season, including typical local and regional variations in temperature and precipitation, extreme events such as floods and droughts, and changes in plant diversity. Climate change can affect pollen allergies in several ways. Warmer autumn temperatures extend the growing season for ragweed. Warmer temperatures and increased carbon dioxide concentrations also enable ragweed to produce more pollen [Wayne *et al.* 2002]; many locations could experience longer allergy seasons and higher pollen counts as a result of climate change.

Sensitization to ragweed pollen has risen in the USA in the past decade. In the 2005–2006 US National Health and Nutrition Examination Survey (NHANES), the prevalence of specific immunoglobulin E (IgE) to ragweed was 15.6% [Gergen *et al.* 2009] compared with the rate of 0.8% detected in the 2000–2002 European Community Respiratory Health Survey [Bousquet *et al.* 2007]. In the USA and Canada, more than 15 million people suffer from ragweed pollen allergy with a prevalence of about 45% in predisposed individuals [Boulet *et al.* 1997].

Allergens described

The major allergenic compound in the pollen has been identified as Amb a 1, a 38 kDa nonglycosylated protein composed of two subunits with pectate lyase activity. It has crossreactivity with Cry j 1 (*Cryptomeria japonica*) and other members of the Cupressaceae family (Hinoki and *Juniperus ashei*), and Phl p 4 (*Phleum pratense)*.

Ragweed pollen also contains other allergens, such as profilin (Amb a 8), lipid transfer protein (Amb a 6) and polcalcin (Amb a 9 and Amb a 10) [Wopfner *et al.* 2005]. More than 90% of ragweed-sensitized subjects react to Amb a 1 in skin prick tests and at least 90% of the allergenic activity in ragweed pollen can be attributed to this protein [King *et al.* 1967]. A total of 4 isoallergens of Amb a 1 with 70–80% amino acid sequence identity have been identified [Rafnar *et al.* 1991].

The following allergens have been characterized [Allergome, 2013]:

- Amb a 1, a 38 kDa protein, a pectate lyase
- Amb a 2, a 38 kDa protein, a pectate lyase
- Amb a 3, a 11 kDa protein, plastocyanin
- Amb a 4, a 30 kDa protein, Art v1-like, defensin
- Amb a 5, a 5 kDa protein
- Amb a 6, a 10 kDa protein, a lipid transfer protein
- Amb a 7, a 10 kDa protein, plastocyanin
- Amb a 8, a 14 kDa protein, a profilin
- Amb a 9, a 10 kDa protein, a calcium-binding protein
- Amb a 10, a 18 kDa protein, a calcium-binding protein
- Amb a CPI, a cystatin proteinase inhibitor

The International Union of Immunological Societies (IUIS) Allergen Nomenclature Sub-Committee, under the auspices of the World Health Organization (WHO) and IUIS recently updated allergens from ragweed pollen [Radauer *et al.* 2014]. Amb a 2.0101 changed to Amb A 1.0501, and Amb a 2.0102 to Amb a 1.0502. These changes were made because sequence comparison of Amb a 2 and Amb a 1 isoallergens revealed identities of between 59 and 69%.

Clinical symptoms

Throughout its distribution, ragweed pollen is one of the most abundant aeroallergens in late summer. It has the largest single seasonal allergen and therefore causes about half of all cases of pollen-associated allergic rhinitis in North America [Taramarcaz *et al.* 2005].

Ragweed allergies usually cause allergic rhinitis and asthma. Allergic rhinitis is defined as a clinical symptomatic nasal inflammatory reaction induced by IgE-mediated allergen after exposure of the membranes of the nasal surface involving the following symptomatology: itch, nasal discharge, sneezing and nasal stuffiness [Bousquet *et al.* 2008]. Asthma is a chronic inflammatory disorder of the airways with participation of various types of cells and leads to recurrent episodes of wheezing, breathlessness, chest tightness and cough, usually accompanied by variable airflow obstruction usually reversible with medication as well spontaneously, and bronchial hyper-responsiveness against different stimuli [Barranco *et al.* 2007].

Some sensitive people may develop contact dermatitis when exposed to ragweed, usually a cause of sesquiterpene lactone hypersensitivity [Moller

et al. 2002; Schloemer *et al.* 2014]. Some studies has established a relationship between ragweed pollen and asthma [Zhong *et al.* 2006], but others not [Im and Schneider, 2005; Heguy *et al.* 2008; Darrow *et al.* 2012]. In the first study, the authors reported on an in-depth analysis of the autumn peak periods in an effort to determine whether there was an association between children's asthma hospital admissions and environmental variables; only weed pollen was a statistically significant predictor of children's asthma hospital admissions during the autumn peaks ($p < .001$).

Recently, Caillaud and colleagues investigated the dose–response relationship between ragweed exposure in patients sensitized to this pollen and daily rhinitis symptoms in five towns in France and one in Switzerland using generalized estimating equations (GEE) [Caillaud *et al.* 2014]. Patients completed a symptom diary from July to October 2009 and/or from August to October 2010. The study shows that there is a linear relationship, without thresholds or plateaus, between the level of airborne ragweed pollen and nasal, ocular and respiratory symptoms. Curiously, nasal symptoms differed between weekdays and weekends.

To assess the risk of sensitization and allergy, a follow up of 20 volunteers for ragweed eradication campaigns was performed in Germany [Brandt *et al.* 2014]. The authors established that intensive contact and exposure to high ragweed pollen concentrations did not necessarily result in sensitization and/or allergy, meaning that the allergenic potential of this weed might be lower than expected. They thought that continuous exposure to high allergen levels induced tolerance in the ragweed workers.

Ragweed allergic patients may show signs of oral allergy syndrome [Egger *et al.* 2006]. This is caused by crossreacting allergens found in both pollen and raw fruits and vegetables. The immune system recognizes allergens presented in the pollen with structural homology within proteins in the food. These patients can usually eat the same fruits or vegetables in cooked form because the proteins are denaturated during the heating process, so that the immune system no longer recognizes the food [Zarkadas *et al.* 1999]. Ragweed has showed crossreactivity with the following foods: banana, melon, chamomile, watermelon, cucumber and zucchini. Oral allergy syndrome can include itching, burning, and swelling of the mouth and throat, and less frequently conjunctivitis, rhinitis, urticaria and rarely, vomiting, diarrhoea, asthma and other signs/symptoms of anaphylaxis.

Treatment

Treatment of allergic rhinitis and asthma has four cornerstones: education of the patient; allergen avoidance measures; symptomatic treatment; and allergen immunotherapy. In addition to avoidance and environmental control measures, patients should start an individualized pharmacological treatment [El-Qutob Lopez, 2012]. Pollen avoidance measures include keeping windows closed, bathing to remove allergens from the hair and body, and high-efficiency particulate absorption (HEPA) air filtration [Baxi *et al.* 2010].

Today, allergic rhinitis can be treated with oral and topical antihistamines, topical and oral corticosteroids, topical cromones, topical and oral vasoconstrictors, anticholinergics and leukotriene modifiers. Of these, the most used are second and third generation antihistamines, both oral and topical, and topical nasal corticosteroids [Scadding *et al.* 2008]. Allergen-specific immunotherapy (SIT) is the only etiologic treatment of allergic disorders that can alter the natural course of the disease [Abramson *et al.* 2010; Viswanathan and Busse, 2012]. Furthermore, specific allergy vaccination has preventive effects reducing the risk of hay fever developing into asthma and reducing the risk of development of new allergen sensitivities [Creticos, 1992]. The recommended duration of immunotherapy is usually between 3 and 5 years. For seasonal allergens, such as pollens, updosing is usually started and completed well in advance of the specific pollen season to avoid initiating the treatment of allergic patients with ongoing symptoms and hence to minimize the risk of side effects. In addition, a review of publications comparing the costs of allergic immunotherapy (AIT) to symptomatic drug treatment (SDT) demonstrated cost savings conferred by AIT over SDT [Hankin and Cox, 2014].

El-Qutob and colleagues recently published a review of recent patents for immunotherapy [El-Qutob *et al.* 2014]. In the present article, an update about vaccine development and new knowledge for ragweed allergy is exhaustively revised.

New advances and clinical trials in 2014

Crossreactivity at the level of T cells and IgE antibodies was investigated using ragweed Amb a 1 and mugwort Art v 6 purified from pollen sources [Jahn-Schmid *et al.* 2012]. Enzyme-linked immunosorbent assay (ELISA) inhibition experiments showed that Amb a 1 contains more IgE epitopes than Art v 6, suggesting an important role of Amb a 1 as primary sensitizer. However, in another study, Asero and colleagues studied the concomitant sensitization to ragweed (Art) and mugwort (Amb) pollen [Asero *et al.* 2014]. The study found that Art v 6 plays an important role in mugwort allergy and that the crossreactivity between Art v 6 and Amb a 1 is frequent, bidirectional and clinically relevant in the area of study (Milan).The authors found that Amb+/Art+ patients reactive to Art v 1 should be prescribed mugwort immunotherapy, whereas Amb+/Art+ patients not reactive to Art v 1 should be prescribed ragweed immunotherapy because ragweed is probably the primary sensitizer.

In the 2014 meeting of the American Academy of Allergy, Asthma & Immunology (AAAAI), Moingeon and colleagues presented a study of 70 individual sera from ragweed pollen-allergic donors (from the USA and central Europe) [Moingeon, 2014]. They identified a new cysteine protease, Amb a x, as a novel major allergen from short ragweed pollen (*Ambrosia artemisiifolia*). Amb a x showed high sequence homology with known cysteine proteases, such as the house dust mite Der p 1 allergen. Amb a x was purified, fully characterized by mass spectrometry and its three-dimensional structure established by homology modelling. IgE reactivity was confirmed on purified natural and recombinant forms of Amb a x. More than 60% of patients were sensitized to this new allergen and therefore it should be considered an essential component for diagnosis and specific immunotherapy of ragweed pollen allergy. The patent of this new allergen has been registered [Bordas *et al.* 2014].

Some nonallergic rhinitis patients have locally increased IgE levels in their nose or nasal lavage and this type of rhinitis is defined as local allergic rhinitis (LAR) [Rondon *et al.* 2012]. Kato and colleagues investigated the pathophysiology of mice with allergic rhinitis that initially sensitized with ragweed pollen through the nasal route [Kato *et al.* 2014]. The results demonstrated that nasal sensitization with an allergen induced systemic atopy, which can adversely affect the onset of other allergic diseases when the individuals encounter the same allergen. Local Th2 cell accumulation is the first sign of the disease and IgE mediated signalling is essential for inducing sneezing, but is not sufficient for recruitment and activation of inflammatory cells. So, the authors propose T-cell-based diagnosis and therapy which may improve LAR treatment.

In 2014, Nolte and colleagues published the results of four clinical trials evaluating the safety and tolerability of MK-3641 (*Ambrosia artemisiifolia*; Merck Sharp & Dohme Corp, Whitehouse Station, NJ; ALK-Abelló, Hørsholm, Denmark) [Nolte *et al.* 2014]. MK-3641 is a short ragweed sublingual tablet being developed for the prevention of ragweed (*Ambrosia artemisiifolia*) pollen-induced rhinoconjunctivitis. Across all studies, 757, 198, 454 and 1058 subjects were randomized to placebo or 1.5, 6 or 12 Amb a 1-U of MK-3641, respectively. Results from the individual trials and the pooled safety analyses indicate that MK-3641 is well tolerated during up to 1 year of treatment. The US Food and Drug Administration (FDA) has approved MK-3641, commercially named Ragwitek®. Treatment with Ragwitek is started 12 weeks before the start of ragweed pollen season and continued throughout the season. The first dose is taken in a healthcare professional's office where the patient has to be observed for at least 30 minutes for potential adverse reactions. After the first dose, patients can take Ragwitek at home.

Srivastava and colleagues have studied the effects of antiasthma simplified herbal medicine intervention (ASHMI), a traditional Chinese medicine formula, on a murine model with neutrophil predominant ragweed asthma [Srivastava *et al.* 2014]. They demonstrated that standard ASHMI and refined formula ASHMI^{II} treatment significantly suppressed both neutrophil and eosinophil airway inflammation *via* regulation of associated chemokine and cytokines such as tumour necrosis factor-α (TNF-α), interleukin 8 (IL-8) and IL-17.

Creticos and colleagues determined the efficacy and tolerability of standardized glycerinated short ragweed sublingual allergen immunotherapy liquid (RW-SAIL) extract in subjects with ragweed-related allergic rhinoconjunctivitis [Creticos *et al.* 2014]. A phase III randomized, placebo-controlled trial was conducted and subjects self-administered the maximum tolerated dose of RW-SAIL or placebo daily beginning approximately 8–16 weeks before and through to the end

of the ragweed pollen season. The subjects who received active treatment reported a 42% reduction in medication and symptoms scores during the peak season relative to placebo recipients. The occurrence of adverse events was similar between the treatment groups; most were mild in severity.

In 2007, a double-blind, placebo-controlled trial over two ragweed seasons compared carried out by Creticos and colleagues compared the safety and efficacy of two dosing regimens of Amb a 1 immunostimulatory oligodeoxyribonucleotide conjugate (TOLAMBA) in ragweed allergic adults [Bernstein *et al.* 2007]. In this study, 738 subjects were randomized (1:1:1) to receive 6 weekly doses of placebo or high (TOLAMBA: 3, 9, 30, 30, 30, 30 mg) or low total dose (TOLAMBA: 1.2, 3, 6, 15, 21, 30 mg). Both active treatment regimens were safe and well-tolerated.

Campbell and colleagues studied a chronic ragweed allergic-asthma murine model exposed weekly to intranasal ragweed [Campbell *et al.* 2014]. Using this model, the effects of a limited series of weekly intranasal CpG-containing oligodeoxynucleotides (CpG-ODN) treatments were evaluated. CpG-ODNs stimulate innate immune responses through toll-like receptor 9 (TLR9) expressed principally by plasmacytoid dendritic cells (pDCs) and B cells in humans [Krieg, 2002]. Treatment induced significant suppression of bronchoalveolar lavage eosinophilia and IL-4, IL-5 and IL-13 levels. This suppression of allergic T helper 2 parameters was maintained through 13 weekly ragweed exposures administered after treatment cessation. This study supports the development of inhaled CpG-ODNs as a novel disease-modifying therapy for allergic asthma.

A randomized, double-blind, placebo-controlled phase IIb study of 228 patients ($n = 228$) evaluated the clinical efficacy and safety of ragweed MATA MPL (short ragweed pollen allergoid adsorbed to L-tyrosine + monophosphoryl lipid A) compared with placebo by using controlled ragweed pollen exposure in an environmental exposure chamber [Patel *et al.* 2014]. This is a novel ultrashort-course SIT for the treatment of seasonal allergic rhinitis caused by ragweed pollen allergen that is administered in only 4 weekly preseasonal injections. Mean improvement in total symptom scores in the ragweed MATA MPL group was statistically significantly greater than in the placebo group (relative mean improvement of active *versus* placebo, 48%; $p < 0.05$; median improvement, 82%). There were no statistically significant differences in ragweed-specific immunoglobulin (IgG) levels at baseline between the active and placebo groups. After treatment, ragweed-specific IgG levels increased considerably in the ragweed MATA MPL group, whereas they remained relatively unchanged in the placebo group. The majority of adverse events experienced by subjects were mild injection site reactions (mostly pruritus, swelling and pain). No severe systemic or serious adverse events occurred during the study. No subject discontinued from the study because of a treatment-related adverse event.

In the 2013 World Allergy Organization (WAO) Symposium on Immunotherapy and Biologics, a poster presentation showed a prospective multicentre, double-blind, randomized dose-ranging study conducted in patients with history of ragweed-related moderate-to-severe allergic rhinoconjunctivitis for at least 2 years, with or without controlled seasonal allergic asthma and positive response to allergen specific nasal provocation test (NPT) [Compalati *et al.* 2014]. This study was designed to compare the efficacy and safety of three different daily dosages. Before the 2013 ragweed pollen season, adult patients were assigned to different daily dosages (300, 1000 and 2000 UA) of tablets of ragweed pollen carbamylated extract given for 4 months. Carbamylated allergoids are chemically modified extracts developed to reduce the immunoglobulin E (IgE) binding activity and consequently improve the sublingual immunotherapy (SLIT) tolerability. The mean improvement and the incidence of treatment-related adverse event suggested that the 1000 UA dosage appears to be the ideal dose of carbamylated allergoid for treating ragweed pollen allergic patients.

Conflict of interest statement

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