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Grains of Wisdom: Transgenic Rice for Oral Allergen Immunotherapy in Japanese Cedar Pollen-Allergic Patients

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Allergen-specific immunotherapy (AIT) has been considered to date the only disease-modifying treatment in allergic rhinitis. In this issue of *International Archives of Allergy and Immunology* (IAAI), Endo et al. [1] report the first use of transgenic rice to deliver high doses of allergen for oral immunotherapy of Japanese cedar allergic rhinitis patients. Vaccine development is among the greatest achievements in the history of medicine. The goal of immunotherapy by vaccine is to harness broad and specific immune responses involving B- and/or T-cells depending on the approach. In AIT, administration of allergenic preparations aims to restore tolerance and reduce allergic symptoms. AIT can be delivered intramuscularly, subcutaneously, sublingually, orally, or intralymphatically with increasing doses as the patient's tolerance grows over time [2]. AIT has been used to treat IgE-mediated allergic diseases since the early 1900s [3], but it still remains fraught with problems. For example, optimal dosing, length, different up-dosing regiments, improving adherence and management of polyallergies in patients, and the comparative efficacy of various adjuvants and routes of administration are continuously discussed [4]. The danger of anaphylaxis occurring during the administration of AIT also remains high. When successful however, AIT treats and prevents the development of allergic asthma, rhinitis, and venom-induced anaphylaxis, and was demonstrated to prevent sensitization with new allergens for up to 12 years [5, 6]. In fact AIT has been considered the only disease-modifying treatment in allergic rhinitis [7]. Therefore, the quest to develop safer and more effective AIT continues today.

In an allergen-triggered immediate reaction, B-cell-secreted IgE activates mast cells and basophils. Allergen-specific T-helper type 2 (Th2) cells are also activated, leading to a delayed and prolonged inflammatory reaction. AIT induces an increased number and activation of allergen-specific CD4+CD25+ regulatory T-cells [8] that produce IL-10, an immunosuppressive cytokine, thereby attaining immune tolerance. Since the discovery of its principle in 1911, several approaches to immunotherapy have been tested. One of the most recent ones is to use allergenic T-cell epitope peptides. The first successful immunotherapy that used T-cell epitope peptides of bee venom phospholipase A2 was shown to induce specific T-cell anergy and tolerance to bee venom in allergic patients [9]. Peptide AIT approaches appear to be efficacious, often shorter than the classical methods and also safer, because T-cell epitopes do not cross-link cell-bound IgE, eliminating the risk of anaphylaxis.

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Oral administration of allergens for immunotherapy could be achieved using plants, especially rice seeds, recognized as superior allergen carriers because of their high productivity, stability, and safety. Transgenic rice seeds in which major epitopes of cedar pollen allergens or house dust mites are expressed have been recently developed [10]. The most common allergen responsible for allergic rhinitis in Japan is Japanese cedar (*Cryptomeria japonica*) pollinosis, [11]. Takaishi et al. [12, 13] recently developed transgenic rice that expresses all possible T-cell epitope repertoires of Cry j 1 and Cry j 2, the molecular determinants of Japanese cedar. They showed that allergen-sensitized mice that ate transgenic rice daily for 3 weeks had a marked suppression of allergen-specific CD4+ T-cell proliferation, IgE and IgG levels compared with mice fed non-transgenic rice, in response to challenge with crude *C. japonica* pollen allergen.

In this issue of IAAI, Endo et al. [1] present a study on the T-cell peptide mucosal route of immunotherapy for cedar pollinosis patients. They used transgenic rice expressing 7 overlapping epitope T-cell peptides (7Crp) to deliver a high dose of allergen for specific T-cell tolerance induction. Allergen-specific T-cell proliferation against Japanese cedar pollen allergens, Cry j 1 and Cry j 2, were significantly downregulated by this treatment. The suppressive effect of transgenic rice on allergen-specific T-cell proliferation was dose dependent, appeared within 2 weeks, and remained during the pollen season. However, T-cell tolerogenicity such as IL-10 upregulation and IL-13 downregulation was not associated with either decreased cedar pollen-specific IgE antibodies, or increased IgG blocking antibodies upon 20 weeks of transgenic rice intake. There was no effect on the IFN-γ and IL-5 secretions from Th1 and Th2 cells and the effect on IL-4 was also minimal, in contrast to what was seen in previous peptide AIT studies [14]. This treatment did not accomplish improvement of clinical symptoms (as measured by the Japanese rhinitis quality of life score or the total nasal symptom and medication scores) either. The effect on improving of symptom score was only significant for nasal and eyes itching without significant improvement on the rest of nasal symptoms. Thus, even though T-cell proliferative activities to Cry j 1 and Cry j 2 were highly suppressed, 20 weeks of transgenic rice consumption did not show a profound clinical improvement.

The authors speculate that the partial effects seen may be due to the possibility that 7Crp does not cover the full repertoire of T-cell epitopes localized in Cry j 1 and Cry j 2 molecules due to the diversity of MHC (HLA) class II alleles in patients. Although 92% of Japanese cedar pollinosis patients are covered by 7Crp, some Cry j 1- and Cry j 2-specific T-cells that are not suppressed by the 7Crp peptide may proliferate in some patients during the pollen season. Furthermore, it might take a longer course (more than 2 seasons) to accomplish full tolerance and improve clinical symptoms. Thus, inclusion of additional T-cell epitopes to address MHC diversity and a more prolonged preseasonal treatment and longer-term treatment may be necessary to accomplish significant clinical improvement.

Nonetheless, it is important to distinguish this study as it is the first clinical trial to administer transgenic rice to human subjects exploring the T-cell epitope peptides as a future mode of allergen immunotherapy. Peptide immunotherapy is safe due to a lack of IgE crosslinking and minimal inflammatory potential. Indeed, with administration of different doses of transgenic rice containing the 7Crp peptide to human subjects (with or without Japanese cedar allergy), no adverse effects including immediate or late-phase allergic reactions were observed. This is a major improvement over previous reports of T-cell-mediated late-phase side effects for birch pollen and cat peptide vaccines [15].

In conclusion, while allergen immunotherapy is still being explored by different mechanistic approaches, the study by Endo et al. [1] supports a potential future for an effective and safer mucosal route of T-cell peptide immunotherapy with transgenic rice technology. Because of its potential impact on the improvement of quality of life in allergic disease, AIT will certainly stay a present and future therapy for respiratory and food allergies. Larger clinical studies are needed to reliably assess the added benefit for the patient of using transgenic rice for delivering peptide allergens for AIT.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.I. drafted the manuscript and A.H. edited and finalized it.

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