

FDA-approved peanut allergy treatment The first wave is about to crest

Stephen A. Tilles, MD; Daniel Petroni, MD, PhD

ASTHMA Inc, Clinical Research Center, Seattle, Washington

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Introduction

As the prevalence of food allergy has increased in recent years, practicing allergists have seen an explosion in food allergy patient volume. For example, according to a nationwide telephone survey, between 1997 and 2008, a 3-fold rise in peanut allergy occurred.^{1,2} Based on an informal search of electronic medical records at the Northwest Asthma and Allergy Center in Washington State, between 2006 and 2017 there was more than a 2-fold increase in the number of office visits for peanut allergy, tree nut allergy, and other food allergies (Figure 1).

Practicing allergists have adapted to the peanut allergy epidemic in several ways. Some have chosen to assume that peanut allergy is a permanent untreatable condition, electing to perform efficient counseling of patients and families regarding the life-threatening nature of the disease and the importance of strict avoidance, along with annual updating of the action plan and refilling auto-injectable epinephrine. Others have spent additional countless (and poorly reimbursed) clinical hours analyzing patient histories and test results to help clarify whether in fact each patient is truly food allergic. And still others have taken a bolder approach, offering off-label food allergy oral immunotherapy (OIT) in their offices based on published protocols involving small numbers of patients. Meanwhile, food allergy translational and clinical researchers have enjoyed a validation of their calling, including the formation of the National Institutes of Health-funded Consortium of Food Allergy Research (CoFAR), which has resulted in numerous important publications, including many focusing on peanut allergy. Unfortunately, despite more than 2 decades of rapid expansion of allergy research, food allergy remains an unmet need,

because of a long lag in the availability of validated treatments for allergists to prescribe. Indeed, the most dramatic change other than the number of food allergy patients has been the price of the leading epinephrine auto-injector—until now.

Where are We in 2018?

Thanks to both painstaking scientific progress and the product development efforts of 2 small biopharmaceutical companies, sometime in 2019 we may find ourselves able to prescribe safe and effective immunotherapy treatment for pediatric patients with peanut allergy. One of these products, called AR101,³ developed by Aimmune Pharmaceuticals, involves a traditional OIT⁴ protocol starting with 1 mg and ending with a 300-mg daily maintenance dose. The other, called Viaskin Peanut⁵ (or the “peanut patch”) from DBV Technologies, delivers a daily 250-μg dose of peanut protein as epicutaneous immunotherapy (EPIT). Both immunotherapy strategies seek to improve the threshold dose that results in symptoms from accidental peanut ingestion by desensitizing patients, although they involve fundamentally different routes of allergen exposure, peanut protein doses, and logistics.

Based on their potential to fill an unmet need for a serious medical condition, both AR101 and Viaskin Peanut have received Fast Track and Breakthrough Therapy designation from the US Food and Drug Administration (FDA). However, neither appears to be a cure for this disease. No evidence suggests that either product achieves sustained unresponsiveness to peanut,⁴ and all treated patients must continue peanut avoidance and keep auto-injectable epinephrine on hand. It is also too early to promise these treatments to our patients, because the phase 3 data have not yet been filed with the FDA. However, it is not too early to prepare ourselves for the daunting task of deciding when and how to use these treatments.

What is the Peanut Allergy Unmet Need?

A common misconception is that patients with peanut allergy would like nothing more than to eat a peanut butter and jelly

Reprints: Stephen A. Tilles, MD, ASTHMA Inc, Clinical Research Center, 9725 Third Ave NE, Suite 500, Seattle, WA 98115; E-mail: stilles@nwasthma.com.

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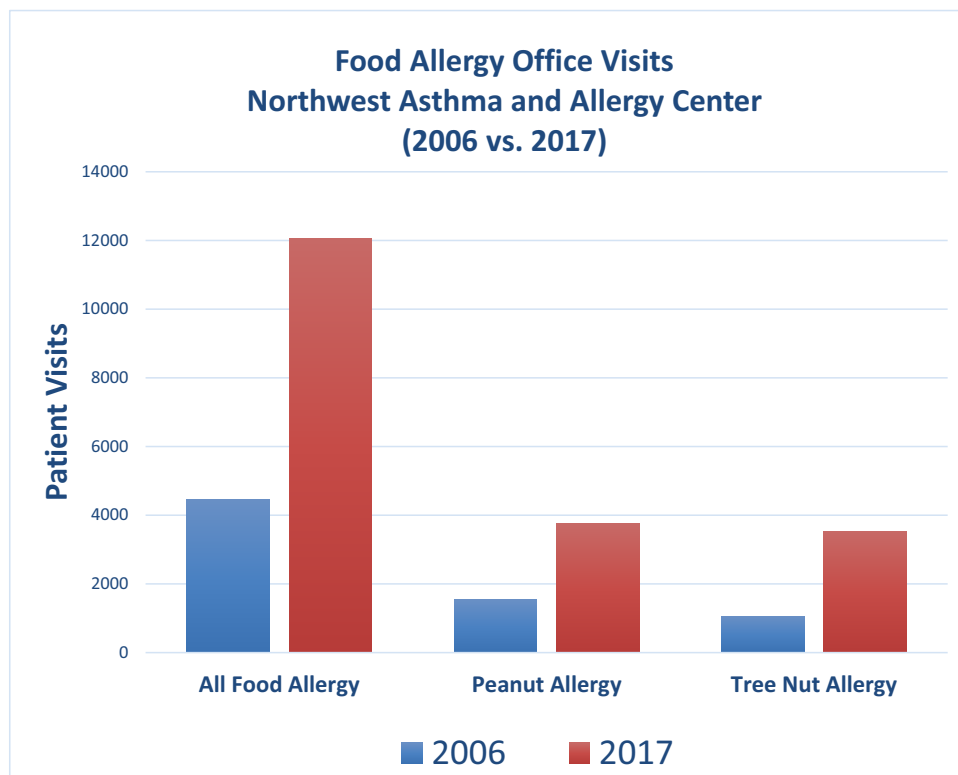


Figure 1. Numbers of food allergy visits, peanut allergy visits, and tree nut allergy visits were determined by searching clinic electronic medical records by office visit diagnosis codes used for unique patients in 2006 and 2017. The Northwest Asthma and Allergy Center has 8 offices in Washington State. There were 14 physician providers in 2006 and 15 in 2017.

sandwich. In fact, most patients with this allergy have no desire to eat peanuts. Rather, they merely wish to be able to continue avoiding peanuts without concern about accidental consumption leading to symptoms. Many patients and parents also have a lingering and disturbing fear of a fatal peanut reaction, which is understandable because anaphylaxis caused by accidental food allergen ingestion is common. However, death from accidental ingestion of food allergens is exceedingly rare. In fact, among food-allergic patients, the annual risk of a fatal food allergy reaction is nearly 100-fold lower than the annual risk of dying in an accident.⁶ The unmet need in peanut allergy therefore involves the combination of a real risk of a life-threatening anaphylactic reaction, along with the fear, anxiety, and inconvenience that results from the continuous possibility of a reaction. Separating these issues is complicated but essential to understanding both the peanut allergy unmet need and positioning of new peanut immunotherapy treatments.

Confounding a description of the peanut allergy unmet need are patients who are “sensitized but nonreactive.”² This is particularly problematic in patients who have never ingested peanut but have a positive peanut skin test or specific immunoglobulin E (IgE) in vitro test. Some of these patients are in fact peanut allergic and must be managed accordingly, but in many others the tests are “false positives,” and the patients therefore find themselves unnecessarily avoiding peanuts and potentially experiencing morbidity from peanut allergy misdiagnosis.⁷ This is a common phenomenon with foods and underscores the importance of understanding proper use of skin testing and in vitro IgE testing to foods.

Oral Immunotherapy to Peanut—Aimmune AR101

Aimmune was founded in 2011 to develop FDA-approved food allergy treatments, and it has so far focused on the development

of a standardized peanut OIT program called AR101. AR101 is highly characterized, defatted, and slightly roasted peanut flour that is dispensed in capsules.³ Before each dose, the AR101 is removed from the capsules and mixed with an age-appropriate, nonallergenic food such as applesauce or pudding. The phase 2 clinical trial³ enrolled 55 peanut-allergic patients ages 4 to 26 years. The phase 3 pivotal trial enrolled 554 patients ages 4 through 49 and performed its primary analysis in 412 patients aged 4 through 17.⁸ An ongoing phase 3 safety study that enrolled 506 patients ages 4 through 17 is expected to be completed by September 2018.⁹

Treatment Strategy

The AR101 OIT strategy requires daily dosing and involves an initial 1-mg oral dose of peanut protein (approximately 1/250 of a peanut) followed by gradual dose escalation every 2 weeks as tolerated over 20 to 36 weeks, with the goal of reaching the 300-mg daily maintenance dose. The initial dose and each “up-dose” requires post-dose observation in clinic (90 minutes in phase 3 study) to ensure no symptoms requiring rescue treatment, which is analogous to standard practice with aeroallergen subcutaneous immunotherapy injections. The time required to reach the maintenance dose varies depending on dose adjustments and re-escalations that may be required because of adverse effects such as abdominal pain, emesis, or other hypersensitivity symptoms.⁴

Efficacy

The measurement of efficacy in Aimmune’s AR101 phase 2 and 3 studies was the change in the highest tolerated peanut dose during oral challenge, and the inclusion criteria required that patients tolerate a cumulative dose of no more than 143 mg peanut protein at

baseline. The primary outcome in the AR101 phase 2 trial was the proportion of subjects who tolerated at least 443 mg at the exit challenge. Seventy-nine percent of subjects achieved this, and 62% tolerated 1,043 mg peanut protein (approximately 4 peanuts) at the month 12 oral challenge. In addition, the severity of symptoms during the month 12 food challenge was reduced in the patients receiving AR101 compared with those receiving placebo. AR101's efficacy in the recently completed phase 3 study was similarly impressive.^{8,10} The median tolerated dose of peanut protein during baseline peanut challenge was 10 mg. In the intent-to-treat analysis, 76%, 67%, and 50% tolerated an exit challenge peanut dose of 300 mg, 600 mg, and 1,000 mg, respectively. In the per protocol analysis (those subjects who completed the entire 12 months of treatment with AR101), during the exit challenges 84% tolerated 600 mg and 63% tolerated 1,000 mg.

Adverse Events

Gastrointestinal side effects were reported by approximately two thirds of the AR101-treated subjects in the phase 2 study,³ although they were most often mild and dissipated over time. The most common of these were oral pruritus, abdominal pain, and vomiting. Twenty-one percent of subjects treated with AR101 withdrew from the phase 2 study, and the most common reason for this was persistent gastrointestinal side effects. There was one patient who developed biopsy confirmed eosinophilic esophagitis. In the phase 3 study,^{8,10} the rate of serious adverse events was 1.1%, and systemic hypersensitivity reactions occurred in 14%, of which 98% were mild or moderate. No adverse events involving anaphylactic shock occurred, although 1 patient did withdraw from the study because of anaphylaxis. Subjects with high baseline peanut-specific IgE (≥ 100 ku/L) were more likely to have adverse events and were less likely to tolerate the 300-mg daily maintenance dose. One patient developed eosinophilic esophagitis during the phase 3 study, and this was an 11 year-old boy with baseline specific IgE of 352 ku/L.¹⁰ The occurrence of eosinophilic esophagitis in AR101 clinical trials has so far been less frequent than the 2.7% rate reported in previously published peanut OIT clinical trials.⁴

Epicutaneous Immunotherapy—DBV Technologies Viaskin Peanut

Founded in 2002 and dedicated to advancing treatments of food allergies and other immunologic diseases, DBV Technologies has focused on an epicutaneous immunotherapy platform called Viaskin, which is able to deliver biologically active compounds such as peanut protein to the immune system through intact skin. Ongoing food allergy development programs include Viaskin peanut (phase 3), Viaskin milk (phase 2), and Viaskin egg (preclinical). In addition, Viaskin milk is also under investigation as a treatment for eosinophilic esophagitis (proof of concept).

Two Viaskin peanut phase 2 clinical trials were conducted; 1 enrolled 74 subjects ages 4 to 75 years and was conducted by CoFAR,¹¹ and the other enrolled 221 subjects ages 6 to 55 years and was conducted by DBV Technologies.⁵ The recently completed phase 3 clinical trials enrolled 356 (pivotal efficacy/safety) and 393 (safety) subjects ages 4–11.^{12,13} An ongoing Viaskin Peanut phase 3 trial in toddlers ages 1 to 3 years will not be completed before DBV's anticipated submission of Viaskin Peanut's Biologics License Application.

Treatment Strategy

Treatment with Viaskin Peanut involves applying a daily “patch” to the upper back of the patient, rotating the patch among 6 small zones of the back such that each zone of skin is exposed to a patch

every sixth day. All of the patches are loaded with a 250- μ g dose of peanut protein. Initially, the patch is applied for 6 hours for 1 week, then 12 hours each day for 1 week, then for a full 24 hours.⁵ Dose adjustments are generally unnecessary, even for missed treatment days.

Efficacy

The primary outcomes chosen for the DBV Viaskin peanut phase 2 and 3 studies involved changes in the peanut challenge “eliciting dose” (ED), the dose resulting in “clear-cut objective symptoms.”⁵ This differed from the Aimmune AR101 OIT studies, which assessed changes in highest tolerated dose, and therefore directly comparing the thresholds reported for Viaskin Peanut and AR101 is not appropriate.

In the DBV phase 2 study, 53% of subjects ages 4 through 11 years treated with the Viaskin Peanut 250- μ g dose met the primary outcome compared with 9% of the placebo subjects.⁵ In the CoFAR phase 2 study, 48% of subjects treated with the Viaskin Peanut 250- μ g dose met the primary outcome, compared with 13% of those on placebo.¹¹ In the phase 3 study, for those subjects with baseline ED of 10 mg or less, the definition of a treatment responder was an ED of at least 300 mg after 12 months of treatment. For patients with a baseline ED greater than 10 mg, a responder was defined as a patient with a peanut protein ED equal to or greater than 1,000 mg of peanut protein after 12 months of treatment.^{12,13} In this pivotal study, 35% had a treatment response compared with 13% on placebo, and although these phase 3 efficacy findings were statistically significant, the primary endpoint did not achieve the predetermined 15% lower bound of the confidence interval. Although a setback, this result was not necessarily judged unfavorably by the FDA, which—according to a DBV Technologies press release in March 2018—has agreed that “the available efficacy and safety data for Viaskin Peanut supports the submission of a Biologics License Application for the treatment of peanut allergy in children four to 11 years of age.”¹³

Adverse Events

Adverse events with Viaskin Peanut are common and typically involve mild to moderate local patch site dermatitis that dissipates over time and may be treated with a topical corticosteroid. Discontinuation of study participation because of treatment-emergent adverse events was 1.1% in the phase 3 trial,¹³ and similar numbers of serious adverse events occurred in the Viaskin Peanut-treated and placebo-treated subjects (4.2% vs 5.1%, respectively). Three subjects treated with Viaskin Peanut experienced serious adverse events that were judged by the investigator to be “possibly” related to Viaskin Peanut, and each of these responded to outpatient treatment. Adherence to the Viaskin Peanut therapy was greater than 95%.

If Both AR101 and Viaskin Peanut are FDA Approved, Which Product Should I Prescribe for My Patients?

Assuming that both AR101 and Viaskin Peanut are approved by the FDA, the integration of these products into routine clinical practice by the end of 2019 is an exciting yet somewhat unsettling notion, because of both the significance associated with being the first FDA-approved food allergy treatments and the challenges associated with the proper and safe use of these products. Based on pivotal trial inclusion criteria, we anticipate that AR101 will be approved in peanut-allergic patients ages 4 through 17 years, whereas Viaskin Peanut will be restricted to ages 4 through 11 years. Therefore, for peanut-allergic patients ages 12 through 17 years, OIT with AR101 will likely be the only FDA-approved option. In younger patients, likely multiple factors will influence the choice of product.

Table 1
Advantages and Disadvantages of AR101 OIT and Viaskin Peanut EPIT

	AR101 (OIT)	Viaskin peanut (EPIT)
Advantages	Most of patients reach maintenance dose easily Desensitization is certain in those tolerating the maintenance dose Affords protection from accidental exposures exceeding 1–4 peanuts	Systemic side effects exceedingly rare No up-dosing visits Affords likely protection from small accidental exposures to peanut
Disadvantages	Q2 week up-dosing visits in the allergist's office Possible anaphylaxis requiring epi Frequent minor GI side effects 15%–20% of patients do not remain on therapy Small risk of eosinophilic esophagitis	One-third of subjects have no benefit in first year Efficacy not known in an individual patient unless oral challenge performed Frequent minor local side effects
Treatment protocol	Day 1: initial dose escalation starting with 1 mg and ending with 6 mg Day 2: single 3-mg dose administered in clinic followed by daily home dosing Q2 week dose escalation office visits until reaching 300 mg daily maintenance dose	Application of 250- μ g patch to upper back each day Daily patch duration: 6 hours $\times$ 1 week, then 12 hours $\times$ 1 week, then 24 hours

Tables 1 and 2 summarize the advantages, disadvantages, and practical considerations associated with AR101 and Viaskin Peanut. The main advantage of AR101 is the near 100% certainty that patients tolerating the daily maintenance dose will also tolerate accidental ingestion of at least 1 peanut. This outcome is likely for most peanut allergy patients who decide to proceed with AR101 treatment, and achieving this degree of desensitization will address a significant portion of the peanut allergy unmet need, because peanut-allergic patients generally wish to continue avoiding peanuts and are unlikely to accidentally ingest a quantity larger than 1 peanut.¹⁴ In addition, based on the phase 2 and 3 clinical trial oral challenge data, even if accidental peanut ingestion exceeds the patient's new symptom threshold, likely the symptoms experienced would be less severe than the symptoms the patient experienced before OIT.¹⁰ The main disadvantages of the AR101 OIT program include the inconvenience of every-2-week office visits for up-dosing and the risk of allergic reactions to home doses of AR101. The logistics of AR101 dosing require careful education of patients and their parents to make sure they are fully informed regarding the procedure's time commitment and relative likelihood of various side effects of this treatment. In addition, allergy clinics must have appropriate infrastructure, and "on call" providers must have adequate experience with OIT, including the management of acute hypersensitivity reactions. These logistics are analogous—but not identical—to routine steps taken by allergists who prescribe respiratory allergen subcutaneous immunotherapy (SCIT). For example, standard practice is for allergy clinics to have strict and systematized protocols for SCIT, including an informed consent process that includes a thorough description of the procedure and its risks. A similar process should emerge for AR101 OIT administration, including ensuring that up-dosing visits begin with a careful assessment of whether the recent home doses were sufficiently tolerated to warrant up-dosing. In addition, patients and providers must be aware of factors that increase the likelihood of adverse reactions during peanut OIT, including exercise or hot showers immediately before or after AR101 doses, viral respiratory infections,

menses, and nonsteroidal anti-inflammatory drug use.¹⁵ As mentioned earlier, the gastrointestinal symptoms associated with AR101 are usually mild and dissipate over time, such that most patients can comfortably reach the 300-mg maintenance dose, but a clear subset of patients will not tolerate this dose and therefore will have to discontinue AR101 therapy or perhaps be treated with a lower daily maintenance dose.

The main advantages of Viaskin Peanut are its safety and convenience, which reflects the fact that the dose of peanut (250 μ g) used in EPIT is exceedingly low compared with food OIT. In fact, the maintenance dose of Viaskin Peanut EPIT is more than 10-fold lower than the starting dose for AR101 OIT. Although local side effects are common with Viaskin Peanut, they are typically mild, respond to topical corticosteroid treatment, and dissipate over time. Discontinuation of Viaskin Peanut because of adverse reactions to the patch has been rare in clinical studies. Frequent medical office visits are not necessary with Viaskin Peanut, because of a very simple treatment protocol that involves applying a 250- μ g patch for 6 hours for 1 week, then 12 hours for 1 week, then for 24 hours.³ Viaskin Peanut therefore may be an attractive option for peanut-allergic children whose families do not have schedule flexibility for OIT up-dosing. The main drawback of Viaskin Peanut is the lack of certainty about whether a treated patient is in fact desensitized, and on average the degree of desensitization in patients treated with Viaskin Peanut for 12 months appears to be less than that for patients treated with AR101 OIT.^{10,13} Therefore, in a given patient treated with Viaskin Peanut, oral challenge with peanut is necessary to assess the symptom threshold of ingested peanut. As mentioned earlier, peanut-allergic patients do not, in general, wish to safely eat peanuts. Rather, they wish to continue avoiding peanuts with less fear of an accidental ingestion resulting in a severe, possibly fatal, reaction. In this context, patients and families of patients treated with Viaskin Peanut may feel reassured and satisfied by the Viaskin Peanut treatment even without advancing to oral challenge. Others may choose to begin with Viaskin Peanut and possibly switch to AR101 OIT later as life circumstances change.

Table 2
Practical Considerations When Choosing Between Peanut Immunotherapy Strategies

	AR101 (OIT)	Viaskin peanut (EPIT)
Office visits	Every 2 weeks for 20–36 weeks with observation Must follow dose escalation protocol	No specified interval
On call provider	Occasional after-hours calls for acute reactions Rare after-hours calls for advice whether to dose during upper respiratory infection, etc.	Rare if any after-hours calls
Precautions on home dosing days	Avoid dosing while body temperature elevated from exercise After dosing avoid exercise and hot showers Hold dose or reduce dose during upper respiratory infections Use nonsteroidal anti-inflammatory drugs with caution	Patch may fall off while swimming Treat local dermatitis reactions with topical corticosteroid

Summary

For the past 2 decades a rapid and sustained increase in food allergy prevalence has occurred without availability of any FDA-approved treatment options for literally millions of food-allergic patients. The AR101 OIT and Viaskin Peanut EPIT are the first products to reach development phase 3, and assuming 1 or both are approved, we should celebrate this momentous event as the “first wave” of FDA-approved treatments developed in response to the food allergy epidemic. Because peanut-allergic patients typically have no desire to eat peanuts, treatment with AR101 or Viaskin Peanut should directly address a significant portion of the peanut allergy unmet need despite falling short of curing peanut allergy. The appropriate and safe integration of these immunotherapy treatments into widespread clinical practice will require close collaboration between patients, allergists, allergy specialty societies, patient advocacy groups, and the product manufacturers. However, more work remains to be done. Fortunately, just as a large cresting wave shields our view of even larger waves on the horizon, in 2018 we are appropriately focused on AR101 and Viaskin Peanut, while development of additional food allergy treatments has already gained substantial—yet largely unpublicized—momentum. The coming years will undoubtedly yield more potent and durable treatments for peanut and other food allergies.

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