A practical focus on legume oral immunotherapy

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ABSTRACT

Legumes other than peanut are an important source of protein and consist of a wide variety of species, such as soy, peas, chickpeas, lentils, and lupin. Due to their health benefits and the rising popularity of veganism, legume consumption has increased. Legume allergy, cross-sensitization, and cross-reactivity between different species have been reported in the literature and are increasingly recognized. Unlike peanut, oral immunotherapy (OIT) for nonpeanut legumes has not been well studied and published protocols are lacking. Future studies are needed to provide real-world data on the safety and effectiveness of nonpeanut legume OIT, and whether desensitization to one legume leads to desensitization to other legumes in patients with multiple legume allergy. Nevertheless, due to the abundance of clinical trial and real-world data for peanut OIT, it is reasonable to use protocols that substitute peanut protein with other legume protein when desensitizing individuals with nonpeanut legume allergy. Clinicians who are starting to offer legume OIT in their practices may consider starting with preschoolers, an age group for whom real-world data has shown the greatest safety and effectiveness.

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Legumes belong to the Order Fabales and Family Fabaceae. Commonly consumed legumes include alfalfa, clover, pea, beans, lentils, lupins, mesquite, carob, soy, red gram, mung bean, red kidney bean, chickpea, and peanuts.[1] The epidemiology of different legume allergies, as well as their clinical cross-reactivity, varies among different jurisdictions, mainly influenced by the consumption pattern of various legumes.[2] Soy allergy is common in Israel and Australia.[3] Lentil and chickpea allergies are more common in Spain.[2] In a Portuguese study, 4.1% of the subjects had lupin sensitization, with 75% of them being cosensitized to other legumes.[4] In Canada, several cases of patients with pea anaphylaxis were reported in 2019, and 19.1% of the 68 children met strict eligibility criteria (including a reaction ≤ 12 months earlier) reported allergic reactions to legumes other than peanut.[5] The most common reactions were to green pea and lentil, and 38.5% also had a diagnosis of allergy to peanut.[6]

A Spanish study demonstrated that, among 44 children with at least one legume allergy (*i.e.*, lentil, chickpea, pea, white bean, or peanut), >80% demonstrated specific immunoglobulin E (sIgE) cross-sensitization to lentil, chickpea, and pea, >70% had cross-sensitization to peanut, and 82.1% (32/39) who received OFC had positive reactions with two or more legumes (the majority had clinical cross-reactivity to lentil, chickpea, and pea).[7] On the contrary, soy cross-sensitization with peanut has been demonstrated to be poorly correlated with clinical cross-reactivity.[2]

Discrepancies in food-labeling regulations in different jurisdictions pose a risk for accidental ingestion of legume proteins in foods without clear labeling on the package. For instance, peanut and soy are the only legumes considered priority allergens that need to be declared in prepackaged food in Canada, whereas lupine is regarded as a priority allergen in the European Union and Australia but not elsewhere.[8,9] Therefore, legume allergies could significantly impact the quality of life of individuals who are affected, and OIT to the offending legumes could be helpful to them.

PUBLISHED DOSING SCHEDULES

A question that can be difficult for the clinician to answer is whether, before OIT, a patient who is allergic to one legume should be tested and/or challenged to multiple other legumes that have not been ingested before or that have not been ingested in a long period of time. "Screening" skin or sIgE tests for legumes that

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Table 1 **Soy protein doses based on various forms of soy products**

Soy Butter, teaspoon*#	Soy Protein, mg	Unsweetened Soy Milk, teaspoon#§	Soy Protein, mg
1/128	9	1/128	1
1/64	18	1/64	2
1/32	36	1/32	5
1/16	73	1/16	9
1/8	146	1/8	18
¼	292	1/4	36
½	583	1/2	73
1	1166	1	146
2	2332	2	292
4	4664	(1 cup)	7000

**WowButter Creamy Soy Butter (Hilton Whole Grain Millers Ltd, Staffa, Ontario, Canada); 1 g of soy butter = 218.8 mg of soy protein.*
#Estimation of soy protein was provided by the original paper.[11]
§Silk Organic Unsweetened Soy Milk (Danone North America, Denver, Colorado, USA); 1 teaspoon soy milk = 4.93 mL (1 mL = 29.2 mg).

have not been ingested in a long time only represent sensitization, which may or may not be clinically relevant.[2] Because cross-sensitization (positive testing) is not the same as cross-reactivity (actual clinical reactivity), baseline oral food challenges (OFC) theoretically should be performed for every single food that has not been ingested in a long time.

In real-world clinical practice, however, families with a family member who have experienced a severe reaction in the past to one legume may be reluctant to undergo OFCs to other legumes that have tested positive without a history of ingestion or recent ingestion. Therefore, an initial approach that recognizes potential hesitancy is to explore how comfortable the family is with trying other legumes (that have not been ingested before or in a long time) without testing. If the family is uncomfortable and tests are done that are positive, then whether to choose baseline OFCs first or proceed to OIT directly for all legumes with a positive test result would best be decided based on a combination of the degree of sensitization (*e.g.,* large skin-prick test wheal size > 8 mm) and shared decision-making.[10]

OIT protocols for legumes other than peanut and soy are not available in the literature. It is unclear whether desensitization to one legume (*e.g.,* peanut) leads to desensitization of other legumes in patients with clinical cross-reactivity to multiple legumes.[2] Because peanut OIT has been covered in another chapter, the current chapter will describe an OIT protocol for individuals with soy allergy, which was published in a multiple-food OIT study that provided safety outcomes. Unsweetened soy milk and soy butter were the forms of soy protein sources used.[11] The soy protein dose of the products in these studies is listed in Table 1.

In this multiple-food OIT retrospective study of 45 patients (median age, 9.8 years; range, 1.5–18.7 years) conducted by Eapen *et al.*,[11] only one of the patients received soy OIT. For all the patients, if OFC was performed before OIT, then the highest tolerated dose determined the initiation dose at the OFC. If the clinical history suggested a higher threshold for reaction and no OFC had been performed, then a graded series of doubling test doses starting from 1/64 teaspoon was initially given.[11] Patients' daily home dosing was started at the same dose as the highest tolerated dose in the clinic. Measurements were performed by volume, either in milliliters for liquid or fractions of a teaspoon. It was not explicitly mentioned in the study which source of soy protein the single patient on soy OIT used.[11] OIT updoses were given in the clinic, followed by 1 hour of monitoring afterward. Updosing visits were scheduled between 2 and 4 weeks apart, doubling the amount at each visit (Table 1).[11]

The investigators did not mention the final maintenance dose achieved for the patient on soy OIT.[11] Six months after maintenance treatment, the patients were challenged with two to four times their maintenance dose to test their tolerance to a larger quantity of the foods.[11] Daily dosing was then continued with at least the original maintenance dose. One year after initiation of maintenance treatment, the patients were challenged up to a full serving of the food. Concurrently, skin-prick tests and sIgE tests were repeated every 6 months during maintenance therapy.[11] Specific safety outcomes for the patient on soy OIT were not described. Forty-nine percent of the patients had reactions during updosing. Ninety-one percent of the reactions were mild (grade 1), 9% were moderate (grade 2), and there were no severe reactions (grade 3).[11] Three reactions were treated with epinephrine and one with albuterol.[11] In general, the patients in the study were advised to decrease dosing to two to three times weekly when the SPT wheal

Table 2 **Estimated protein content of different forms of legumes**

Legumes	Content, g protein per 100 g of food
Alfalfa seeds (raw)	3.99
Carob flour	4.62
Chickpea (raw mature seeds)	20.5
Chickpea (boiled, unsalted)	8.86
Chickpea flour	22.4
Green peas (raw)	5.42
Green peas (boiled, unsalted)	5.36
Lentils (raw)	24.6
Lentils (boiled, unsalted)	9.02
Lupin (raw mature seeds)	36.2
Lupin (boiled, unsalted)	15.6
Mung beans (raw)	23.9
Mung beans (boiled, unsalted)	7.02
Red grams (raw)	21.7
Red grams (boiled unsalted)	6.76
Red kidney beans (raw)	22.5
Red kidney beans (boiled unsalted)	8.67
Soy (defatted flour)	51.5
Soy milk	0.793 (per fluid ounce)

**From Ref. 14.*

size reached < 8 mm and an sIgE level of <1 kUA/L, and the patient was confirmed to tolerate a full serving of the food.[11]

Apart from the above study, to our knowledge, no other outcomes from nonpeanut legume OIT have been published. The protein content of soy (without any accompanying specific OIT protocols for soy) has been included in the Canadian Society of Allergy and Clinical Immunology (CSACI) OIT guidelines and a recent review of practical OIT experience of clinicians across the United States and Canada, which suggests that some experts are comfortable with the idea of offering soy OIT outside of research.[12,13] The protein contents of other various legumes are listed in Table 2, with reference to U.S. Department of Agriculture data.[14] With the median eliciting protein dose that 5% of the allergic population would experience an allergic reaction for lupine and soy being 15.3 mg and 10.1 mg, respectively, legume OIT should provide adequate protection from accidental exposures.[8] However, because legumes often have a high protein content both in raw and boiled forms (Table 2), whether legume OIT allows free eating is unclear. It is hoped that future studies will provide data for the risk of reaction at thresholds higher than the cumulative dose in typical OFCs that assess OIT effectiveness.[15]

Table 3 **Generic buildup protocol for OIT (which can be applied to legumes other than peanut)**

Dose No.	Protein, mg*
Optional	1
Optional	2.5
Optional	5
1	10
2	20
3	40
4	80
5	120
6	160
7	240
8	300

**Dose increment every 2 – 4 wk.*

APPLYING PEANUT OIT PROTOCOLS TO LEGUME OIT

There are multiple types of legume proteins, including seed storage proteins and lipid transfer proteins, that can be cross-sensitized.[2] Although OIT protocols specifically for legumes other than peanut and soy are lacking, it is reasonable to follow peanut buildup and maintenance protocols for other legumes because they are all in the same botanical family (Table 3).[16] Because peanut OIT has proven to be safe and effective,[17–19] applying proven real-world peanut OIT protocols (when risks and benefits have been clearly described) to nonpeanut legumes is likely safe, especially in preschoolers. In addition, the CSACI OIT guidelines uniquely stated that OIT can be offered broadly in clinical practice to all food allergens, supported by the lack of biologic plausibility that the mechanism of OIT would differ from one allergen to another.[12,16]

CONCLUSION: CHALLENGES AND FUTURE CONSIDERATIONS FOR OIT TO LEGUMES OTHER THAN PEANUT

There is a paucity of literature on specific OIT protocols for legumes other than peanut, as well as on safety and effectiveness outcomes for OIT to nonpeanut legumes. Phase III clinical trials for nonpeanut legumes are unlikely to be done anytime soon, given the significant expense and impracticality of doing trials for every single legume individually. However, given the abundance of clinical trial data for peanut OIT and, moreover, no biologic reason why the safety and efficacy of OIT to other members of the same botanical family would be any different,[20] separate phase III clinical trials for each individual legume are unnecessary. Instead, research and quality-improvement efforts

going forward should focus on publishing real-world safety and effectiveness outcomes for nonpeanut legume OIT in as many patients as possible, which take into account important real-world factors such as cost and adherence. In the meantime, it is reasonable for clinicians to offer nonpeanut legume OIT by using generic protocols such as a maintenance dose of 300 mg of each legume protein achieved over 8–11 buildup visits (Table 3), a maintenance dose that has been well established for peanut OIT in, not only clinical trials but also large real-world studies.[16,17,20] It may be prudent for clinicians who are starting to offer legume OIT in their practice to gather initial experience in preschoolers, an age group in which real-world OIT data has shown the greatest safety and effectiveness.[16,17]

CLINICAL PEARLS

- Allergy to legumes other than peanut is not uncommon, and cross-sensitization and cross-reactivity have been reported.
- Published OIT protocols for legumes other than peanuts are lacking, and real-world data for nonpeanut legume OIT are needed. However, it is likely that the safety and effectiveness of legume OIT are the highest in preschoolers based on peanut OIT data.
- With the abundance of clinical trial and real-world data for peanut OIT, it is reasonable to use protocols that substitute peanut protein with other legume protein when desensitizing patients with nonpeanut legume allergy.

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