Original Article

An Economic Analysis of a Peanut Oral Immunotherapy Study in Children

Marcus S. Shaker, MD, MS *Lebanon, NH*

What is already known about this topic? The anxiety and fear of repeat peanut exposures in children with peanut allergy impairs quality of life.

What does this article add to our knowledge? Peanut oral immunotherapy may be cost-effective but will cause more anaphylaxis than it prevents unless the annual rate of therapy-associated anaphylaxis is less than 6% or the probability of therapy-induced tolerance is 68% or greater.

How does this study impact current management guidelines? Application of peanut oral immunotherapy will involve patient preference–sensitive trade-offs. A greater understanding of longer-term risks and benefits is needed before it can be adopted into routine clinical practice.

BACKGROUND: Peanut oral immunotherapy (POIT) decreases the probability of accidental recurrent systemic reactions but reactions from the therapy itself are frequent.
OBJECTIVE: The purpose of this economic analysis was to characterize the potential cost-effectiveness of POIT.
METHODS: Cohort simulations were used to evaluate the effect of POIT for children with peanut allergy. A POIT with probiotic was used in the base-case simulation and long-term survival was modeled using age-adjusted mortality together with the risk of food allergy–associated mortality.
RESULTS: The incremental POIT cost-effectiveness ratio was $2142 per quality-adjusted life-year. A mean number of 12.3 (95% CI, 12.0-12.5) and 2.0 (95% CI, 1.9-2.1) allergic reactions occurred in the POIT and avoidance groups over 20 years of simulation, with 2.3 (95% CI, 2.2-2.3) episodes of anaphylaxis treated with intramuscular epinephrine per subject in the POIT group and 1.1 (95% CI, 1.0-1.2) episodes per subject in the avoidance group. In sensitivity analyses, POIT was associated with lower rates of anaphylaxis than strict avoidance when the annual rate of accidental allergic reactions in the peanut avoidance group exceeded 25%, the annual rate of anaphylaxis in the POIT group dropped below 6%, or the probability of sustained unresponsiveness after 4 years of POIT was 68% or greater.
CONCLUSIONS: POIT may be cost-effective in a long-term economic model. However, treated patients may experience a greater rate of peanut-associated allergic reactions and anaphylaxis. The analysis was sensitive to rates of accidental allergic reactions, therapy-associated adverse events, and likelihood of therapy-induced tolerance. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Peanut oral immunotherapy; Cost-effectiveness analysis*

Peanut allergy affects 2% of children younger than 18 years or 1.5 million children.[1,2] Because peanut allergen is difficult to avoid, approximately 12% of peanut-allergic children experience repeated allergic reactions each year and most of these reactions are potentially life threatening.[3,4] Once a systemic reaction has occurred, the threat of a repeated or progressive reaction may be a source of great anxiety for patients and caregivers. Quality-of-life (QOL) considerations are significant in patients with food allergy and impairments in health-related QOL have been found for food-allergic patients and their families, affecting family and social activities, emotional issues, and family budgets.[5-11]

Oral immunotherapy (OIT) involves a process of gradual ingestion of increasing allergen doses and has been recently reviewed.[12] Peanut oral immunotherapy (POIT) has demonstrated potential effectiveness in inducing a state of desensitization as demonstrated in open-label, randomized open-label, and randomized placebo-controlled studies.[13-21] Subjects have aged from 9 months to 18 years with the ability to consume increasing amounts of peanut protein, seen in up to 93% of subjects in the most successful OIT studies.

Tang et al[20] performed a double-blind placebo-controlled randomized trial to investigate POIT with a probiotic over a period of 18 months in children aged 1 to 10 years.[20] The primary outcome was sustained unresponsiveness to peanut challenge 2 to 5 weeks after the discontinuation of treatment. In

Section of Allergy and Clinical Immunology, Dartmouth-Hitchcock Medical Center, Lebanon, NH
Conflicts of interest: The author declares that he has no relevant conflicts of interest.
Received for publication August 13, 2016; revised March 6, 2017; accepted for publication April 12, 2017.
Available online ■■
Corresponding author: Marcus S. Shaker, MD, MS, Section of Allergy and Clinical Immunology, Dartmouth-Hitchcock Medical Center, One Medical Center Dr, Lebanon, NH 03756. E-mail: Marcus.shaker@dartmouth.edu.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2017.04.016

Abbreviations used
FAQL-PF- Food Allergy Quality of Life-Parent Form
ICER- Incremental cost-effectiveness ratio
OIT- Oral immunotherapy
POIT- Peanut oral immunotherapy
QALY- Quality-adjusted life-year
QOL- Quality of life

Glossary
Cost-effective analysis- An economic analysis that compares costs and benefits of therapies, which may be expressed in quality-adjusted life-years. Therapies can be contrasted within and across disease states from a societal perspective using this methodology that provides a common metric for comparison. In the United States, medical interventions costing less than $50,000/quality-adjusted life-year have been considered cost-effective.
Health state utility- A metric that provides an economically quantifiable patient-reported, preference-sensitive trade-off of health states under conditions of risk. More than just an estimate of health quality, it provides a standardized and comparable measure central to the derivation of a quality-adjusted life-year. Common techniques used to measure health state utility include the standard gamble and time trade-off techniques.
Incremental cost-effectiveness ratio- The economic difference between 2 contrasting therapies expressed in terms of quality-adjusted life-years.
Markov model- An economic decision tree that involves recurrent probabilistic risk and allows transitions between defined health states over a linear time frame and a specified time horizon.
Quality-adjusted life-year- A quality-of-life measure that is economically quantitative and health state utility derived.
Sensitivity analysis- A method of incorporating uncertainty into economic analyses across a range of input probabilities to provide a plausible estimate range in a cost-effectiveness analysis.

the trial 62 children were randomized, with successful desensitization found in 89.7% of subjects receiving therapy.

Given that health care expenditures are rising faster than the gross domestic product in most developed countries, economic analyses of the value of new medical therapies are warranted.[22] Cost-effectiveness analyses are useful because they allow comparisons of therapies across a wide range of health care delivery systems and circumstances.[23] In an effort to maximize health care delivery in environments in which resources are limited, it is important to weigh different therapies against their respective opportunity costs. Decision analysis provides a common metric to compare the costs of therapies used in different medical conditions.[24] The purpose of this economic analysis was to characterize the potential cost-effectiveness of POIT.

METHODS

A computer-based mathematical model (TreeAge Pro, Williamstown, Mass) was used to perform Markov modeling of transitional health states to compare POIT with the natural history of peanut allergy in children. Markov modeling is a decision-analytic model useful in clinical circumstances characterized by recurring probabilistic risk because it can describe transitions experienced by hypothetical cohorts of patients between defined health states over a linear time frame.[23] Markov modeling allows hypothetical patients to re-experience risks of anaphylaxis and all-cause mortality each year. With this technique risk-reduction can be evaluated in terms of costs of anaphylaxis preparedness.

The model included clinical and market assumptions. Health states were based on the natural history of peanut allergy. Long-term survival was modeled using age-adjusted mortality[25] in tandem with probabilities of subsequent peanut exposures[3] and spontaneous peanut allergy resolution.[26] Vander Leek et al[3] described 31 of 53 subjects who experienced an accidental reaction over 5 years. Most (31 of 60) of the subsequent reactions involved potentially life-threatening symptoms. Yu et al[4] described similar rates of allergic reactions in children practicing strict avoidance, with 35 exposures in 29 children over 244 patient-years for an annual incidence rate of 14.3% per year (95% CI, 10%-19.9%). With similar rates as described in Vander Leek et al, 20 of 35 reactions were characterized as moderate to severe.[4] Skolnik et al[26] described a 21.5% probability of peanut resolution, which was modeled over a 20-year time horizon.

Health states are depicted in Figure 1. Health states were defined to incorporate probabilities, costs, benefits, and risks associated with POIT and strict avoidance. Hypothetical subjects were randomized to POIT or avoidance of peanut. The natural history of peanut allergy was used to estimate risks of future reactions and progression from the incident case for hypothetical cohorts of patients receiving immunotherapy and those choosing not to begin therapy. Model parameters are presented in Table I. Costs were represented from a societal perspective and future costs were discounted equally at 3% per annum to reflect the average annual consumer price index for all goods and services.[27]

The initial simulation was modeled using the study described by Tang et al.[20] Market costs of oral desensitization included costs of *Lactobacillus rhamnossus*[28] (monthly cost $33.98 based on $16.99 per 30 count Culturelle 1×10^{10}), peanut flour[29] (annual cost $18.65 based on 5 lb peanut flour light, 28%), and supervised challenge visits (cpt 95076, $117.80 per initial 120 minutes and cpt 95079, $83.78 per additional 60 minutes for a total cost of $285.36).[30] Costs of treating allergic reactions were modeled using commercial costs of epinephrine ($268.63 direct cost for 1 epinephrine autoinjector based on $537.26 per twinpack[31]) and costs of hospitalization[32] ($4719.00), emergency department visits[32] ($553.00), outpatient visits[32] ($193.00), and ambulance runs[32] ($469.50). For the analysis, costs were converted to 2016 dollars using the US Department of Labor Bureau of Labor Statistics inflation calculator.[27]

Probability of response to oral desensitization was modeled on the basis of results from Tang et al[20] who reported that 26 of 29 subjects receiving POIT were desensitized, so base-case probability of response was modeled at 89.7%. In this study, 3 of 31 patients randomized to therapy withdrew; therefore, a rate of 9.7% was used over the time horizon of the model. Fourteen of 31 subjects experienced a severe adverse event over 18 months (with similar rates reported between buildup and maintenance phases); 1 subject had 13 events, 1 had 4 events, 1 had 3 events, 3 had 2 events, and 8 had 1 event, for a total of 34 events in 31 subjects over 18 months. To account for the probability that a patient may experience multiple allergic reactions in a given year, these data were used to model a 73% probability that a patient may experience a significant allergic reaction to POIT in any given year. These allergic reactions consisted of local oropharyngeal symptoms in 2.9% of subjects, rhinoconjunctivitis in 2.9%, urticaria in 20.6%, abdominal pain in 8.8%, diarrhea in 2.9%, cough with urticaria in 17.7%, asthma in 26.5%, and eczema in 2.9% of subjects.[20] Of 31 subjects, 3 experienced