

Review of Selected OIT Articles 2000-21

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Leaders in Allergy & Asthma Care

A High Proportion of Canadian Allergists Offer Oral Immunotherapy but Barriers Remain. JACI Pract 2021;9:1902-8.

- Aim:
 - Survey of Canadian allergists re: OIT and barriers to implementation
- Methods:
 - survey investigating current practice, logistical and clinical barriers to OIT distributed to all 237 members of Canadian Society of Allergy/Immunol in January 2020
- Results:
 - 90 responding allergists (38%) completed survey
 - 52.2% reported offering OIT, mainly with peanut; also with TN, milk and egg
 - Working in an academic center, focusing primarily on pediatrics and having previous OIT training were significantly associated with performing OIT
 - 7% reported offering food sublingual immunotherapy
 - 47.8% reported not offering OIT

A High Proportion of Canadian Allergists ...Barriers

OIT Allergists – 47

- Lack of efficacy data (87%)
- Lack of support staff (87%)
- Need for increased clinic space (87%)
- Concerns about the need for increased OFC (87%)

Allergists not performing OIT – 43

- Concerns for safety (95%)
- After-hours support (95%)
- Efficacy (93%)
- Medicolegal risk (93%)
- Long-term practice implications (93%)

A High Proportion of Canadian Allergists ... Conclusions

- Conclusions:
 - Implementation of OIT faces many barriers, both clinical and logistical.
 - Increasing high-quality safety and efficacy data may support those hesitant to offer OIT
 - Training will help expand access for allergists interested in performing OIT

A High Proportion of Canadian Allergists ...

- Limitations of investigation:
 - Include a relatively small respondent size, even though there was a relatively high response rate reflective of the small number of Canadian allergists
- Take home messages:
 - Barriers remain to the widespread adoption of OIT in Canada
 - Nature of barriers shifting from legitimacy of OIT to pragmatic concerns
 - There is a need to address reluctance of some allergists to introduce OIT into their practices
 - Ensure that adequate infrastructure is developed to support safety of OIT in the clinic

Determinants of Omalizumab Dose-Related Efficacy in Oral Immunotherapy: Evidence from a cohort of 181 patients. JACI. 2021;147:233-43.

- Background:
 - omalizumab can improve the safety and feasibility of OIT and increase threshold of reactivity to food allergens, but use of total IgE level to guide omalizumab dose is questionable
- **Despite this - Optimal dosage strategy unknown**
- AIM:
 - to identify determinants of omalizumab dose-related efficacy in relation to OIT to foods

Omalizumab Dose-Related Efficacy ...

Methods:

- 181 patients treated with omalizumab
- Three centers
- Patients received omalizumab for at least 2 months before the initial food escalation (IFE)
- Treated with mix of up to 6 food allergens
- Progression through IFE steps assessed with survival analysis
- Continued food dose tolerance during omalizumab weaning was also documented.

Omalizumab Dose-Related Efficacy ...

Results:

- Omalizumab dose based on weight alone was strongly associated with progression through IFE; not weight and total IgE level
- Outcome of IFE was best predicted by a model that included levels of free allergen-specific IgE and their interaction with blocking omalizumab-IgE complexes and free omalizumab in serum.
- Occurrence of immediate-type reactions to food dosing subsequent to weaning of Omalizumab was associated with a greater ratio of specific IgE level to total IgE level at baseline;
- For each step of IFE, doubling the omalizumab dose per weight reduced the risk of reacting by 60%

Omalizumab Dose-Related Efficacy ...

- **Conclusions:**

- In context of OIT and IgE-mediated disease, omalizumab should be dosed by body weight alone, not total IgE
- The fraction of allergen-specific/total IgE may be useful to predict patients at greater risk of food dosing reactions subsequent to weaning

- **Limitation of study:**

- Assessment of omalizumab dose-related effect beyond the IEF was limited by lack of standardized up-dosing across the cohort

- **Take home point:**

- In context of IgE-mediated food allergy, the omalizumab dose should be based on body weight only, not body weight and total IgE level

Induction of sustained unresponsiveness after egg oral immunotherapy compared to baked egg therapy in children with egg allergy. JACI 2020;146:851-62.

- **Background:**

- Egg OIT has been shown to promote desensitization and sustained unresponsiveness (SU); benefits of baked egg (BE) OIT has not been well studied.

- **Aim:**

- Evaluate safety and efficacy of BE OIT vs. egg OIT in participants allergic to unbaked egg but tolerant to BE

Sustained unresponsiveness after egg OIT...

Methods:

- Children tolerant to baked egg but allergic to unbaked egg (ages: 3-16 yrs)
- Randomized to 2 years of treatment with either BE or unbaked egg OIT
- DBPCFC conducted after 1 and 2 years of treatment to assess for desensitization
- Two years of treatment followed by 8-10 weeks off OIT to assess for SU
- Mechanistic studies conducted to assess for immune modulation
- Comparison group = children BE-reactive underwent egg OIT and identical DBPCFC as a comparison group

Sustained unresponsiveness after egg OIT...

- **Results:**

- Cohort of 50 participants (median age 7.3 yrs) were randomized and initiated treatment
- SU was achieved in 3 of 27 participants assigned to BE treatment (11.1%) versus 10 of 23 participants assigned to egg OIT (43.5%) ($p = .009$)
- In BE-reactive comparison group, 7 of 39 participants (17.9%) achieved SU
- More participants who were BE-tolerant withdrew from BE versus from egg OIT (29% vs 13%)
- Dosing symptoms were more frequent in BE-reactive participants
- Egg white-specific IgE, skin testing and basophil activation decreased similarly after BE and egg OIT

Sustained unresponsiveness after egg OIT...

- **Conclusions:**
 - Among children allergic to unbaked egg but tolerant to BE, those treated with egg OIT were significantly more likely to achieve SU than were children ingesting BE
- **Major limitation:**
 - A larger than expected number of participants failing the BE OFC leading to preferred sample size of investigation
 - Consortium for Food Allergy Research (CoFAR) developed protocol
- **Take home points:**
 - In patients who are BE-tolerant, egg OIT appears to be superior to BE ingestion, without egg OIT, for inducing SU
 - Patients tolerant to BE have a distinct, less severe phenotype of egg allergy
 - Egg OIT may be safer and more effective in children who are BE-tolerant

Patient Characteristics and Risk Factors for Home Epinephrine-Treated Reactions During Oral Immunotherapy for Food Allergy. JACI Pract 2021;9:185

Background:

- OIT is effective in desensitizing food-allergic patients, but adverse events limit its applicability

Aim:

- To identify risk factors for home epinephrine-treated reactions during the build-up phase of OIT

Patient Characteristics and Risk Factors ...

Methods:

- Retrospective, cohort study of patients older than 3.7 yrs undergoing OIT for food allergy at Shamir Medical Center, April 2010-March 2019
- All patients with a final disposition of full sensitization, partial desensitization or failure were analyzed
- Risk factors and outcome of home epinephrine-treated reactions were examined

Patient Characteristics and Risk Factors ...

Results:

- 1037 patients (mean age: 8.4 yrs) who received 1100 OIT treatments reached final disposition (milk 710; peanut 213; egg 50; sesame 57; tree nuts 70)
- Full desensitization achieved in 763 (69.4%), partial desensitization in 219 (19.9%) and 118 failed (10.7%)
- Epinephrine treated reactions (ETR) in 121 patients (11.7%) during 10.8% of treatments
- Milk OIT was a significant risk factor both for ETR (odds ratio, 2.15; 95% CI, 1.25-3.68) and for a lower rate of full desensitization following such reactions compared with other foods OIT (18.2% vs 73.9%, respectively; $P < .0001$)
- Milk OIT ETR risk factors included asthma, pre-OIT reaction severity, lower tolerated dose, and ETRs during up-dosing
- Non-milk OIT risk factors included male sex and lower tolerated dose

Patient Characteristics and Risk Factors ...

Conclusions:

- Milk OIT poses a significant risk for home EPI-treated reactions during OIT and for poor outcome following such reactions
- Together with the additional risk factors described for both milk and nonmilk OIT, the information may assist in patient selection for OIT treatment

Limitations:

- ETRs did not reflect all of the most severe reactions
- This study examined reactions during the build-up phase only
- Data on AR and AD not consistently available and not included in analysis

Take home point:

- Milk and Non-Milk OIT differ significantly, both in risk they pose for severe anaphylaxis and subsequent outcomes

The Use of Biologics in Food Allergy

Fiocchi A, Vickery BP, Wood RA. Clin Exp Allergy 2021

Etokimab, antagonist of IL-33, in patients with peanut allergy confirmed by DBPCFC; Single dose Etokimab administered

- Increase proportion patients tolerating peanut: 73% tolerated 275 mg peanut at 14 days, 57% at 45 days; tolerance to higher doses inferior
- Reduction of IL-4, IL-5, IL-9 and IL-13
- No side effects; very small study

Tezepelumab, a TSLP antagonist used in asthma and AD, potential use but no clinical trials in food allergy currently

The Use of Biologics in Food Allergy

Dupilumab:

- Monoclonal antibody targeting the alpha-chain of the IL-4 receptor (IL-4Ra), which is also common to IL-13; results in blockade of signaling by both IL-4 and IL-13
- Two studies are underway to assess effectiveness in food allergy
- First aim: to evaluate how much dupilumab increases the proportion of peanut allergic subjects treated with OIT who pass an OFC at 4 months
- Second aim: to assess how many peanut allergic subjects can achieve full tolerance to OFC at 24 weeks without OIT
- Results due in 2021

The Use of Biologics in Food Allergy

Omalizumab is the most widely studied biologic for treatment of food allergy

- Reduces basophil histamine release in peanut allergy
- 2011, JACI - Sampson et al, revealed 80.9% increase in the peanut threshold over 24 weeks
- 2012, Pediatrics – Fleischer et al., thresholds for egg, cow milk, baked milk and wheat increased by 17.8%; rate of food reactions decreased and QOL improved
- OutMatch NIAID investigation underway to evaluate the effectiveness of Omalizumab plus multi-food OIT

The Use of Biologics in Food Allergy

Effects of using Omalizumab as adjuvant during milk OIT:

- Faster build-up phase without completely preventing OIT side effects
- Reduction of cow milk-specific basophil activation in patient with CMA
- May accelerate OIT with CM with increased safety
- Possible speeding up the overall execution of CM OIT

Effects of using Omalizumab as adjuvant during peanut OIT:

- Enhances oral desensitization in high-risk patients with peanut allergy
- Vast majority of patients able to reach maximal PNT dose of 8g/day
- Few reactions during the dose escalation
- FASTX (Severe Peanut Allergy with Omalizumab and Oral Immunotherapy) revealed all 23 patients with severe PNT allergy able to reach target dose of 2800 mg of PNT in 10 wks
- PRROTECT (Peanut Reactivity Reduced by Oral Tolerance in an Anti-IgE Clinical Trial) prospective study in 40 high risk PNT allergic patients; rapid OIT tolerating up to 2000 mg of PNT protein; tolerance continued after OMZ stopped; 10% rate of EoE

The Use of Biologics in Food Allergy

- OutMatch NIAID investigation (underway currently)
 - Compare treatment with OMZ with placebo OIT to placebo for OMZ plus multi-allergen OIT
 - Stage three of investigation:
 - Long-term follow-up with dietary consumption of a food
 - Long-term follow-up with avoidance of food
 - Rescue OIT for a food
- In past, OMZ has been able to improve the efficacy of multi-food OIT and to enable safe and rapid desensitization
- Food tolerance with OMZ-treated multi-food OIT was demonstrated to be most effective through maintenance of OIT (either 300 mg or 1 gram) as opposed to discontinuation of multi-food OIT

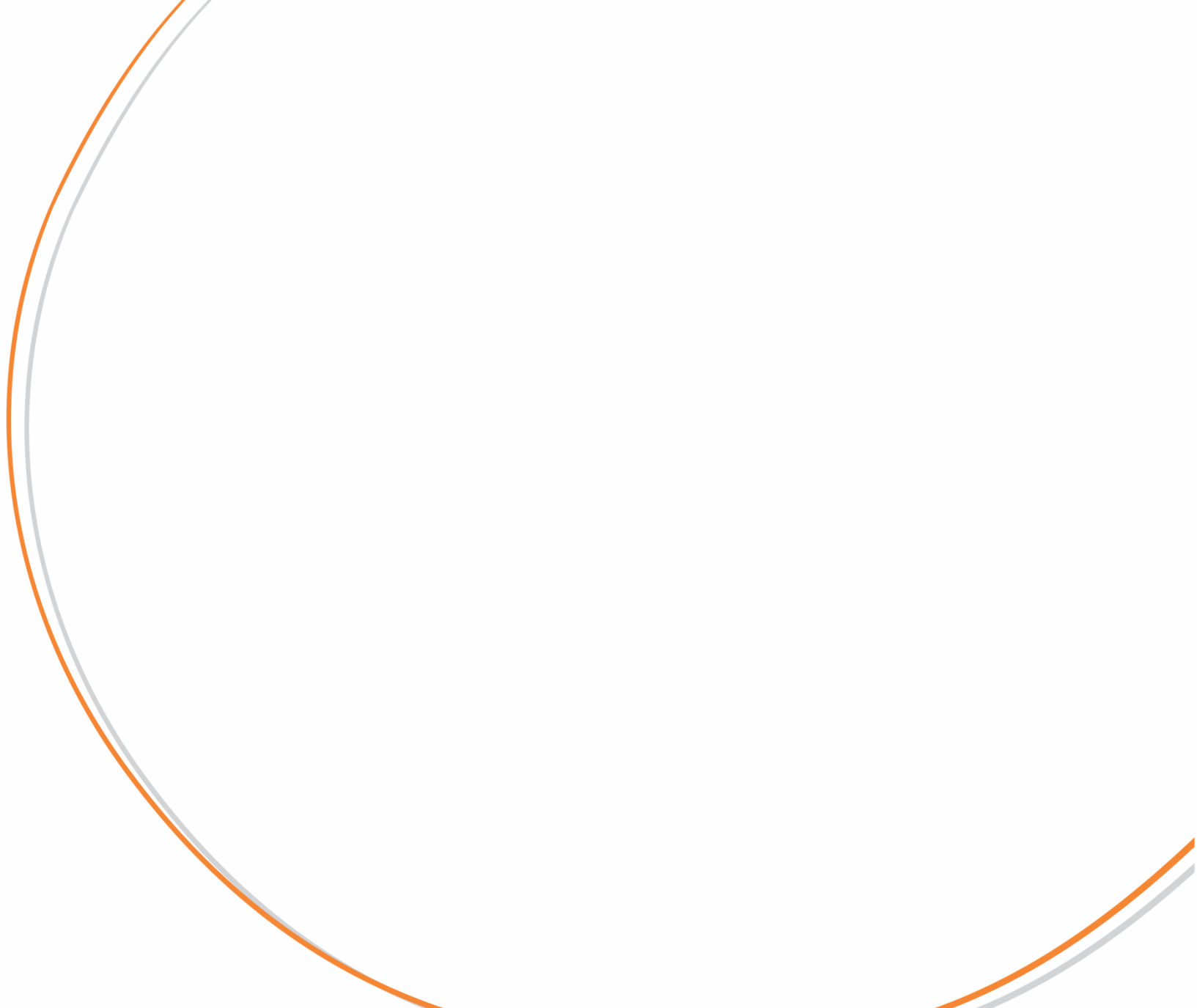
The Use of Biologics in Food Allergy

- Protana Investigation (Protection from Food Induced Anaphylaxis by Reducing the Serum Level of Specific IgE)
 - Included children with very high IgE levels
 - Reduction of total IgE by serum IgE immunoabsorption allowing safe use of OMZ in these children
- BOOM study (OMZ to Accelerate Symptom-driven Multi-Food Study)
 - How to maximize treatment speed and examining patient safety
 - First research study to address question of whether OMZ doses can be individualized for patients with food allergy

The Use of Biologics in Food Allergy...

Summary

- Published data with OMZ suggest it is close to entering clinic with indication of food allergy
- Use of biologics in food allergy will be clinically useful in future
- Still need more data on QOL, adverse side effects including anaphylaxis and most appropriate dosing (likely different from doses used in asthma)
- Real life allergy symptoms may re-occur upon discontinuation of OMZ
- Overall, effects may be similar to use of OMZ and allergen I.T.

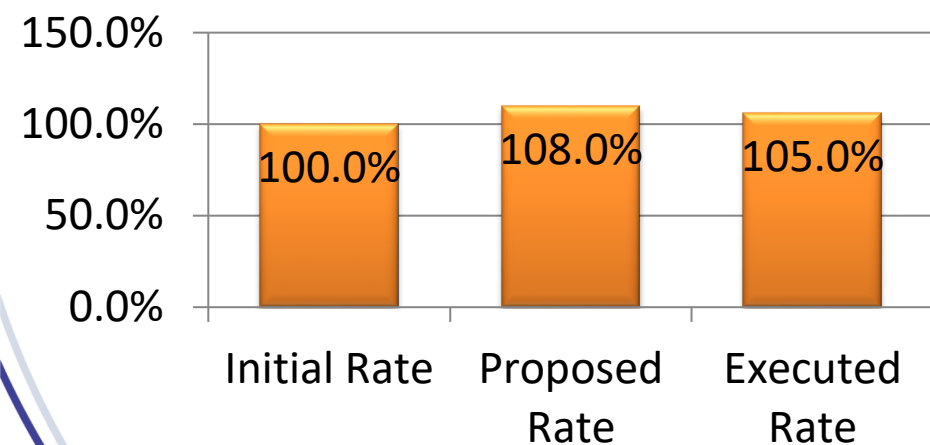




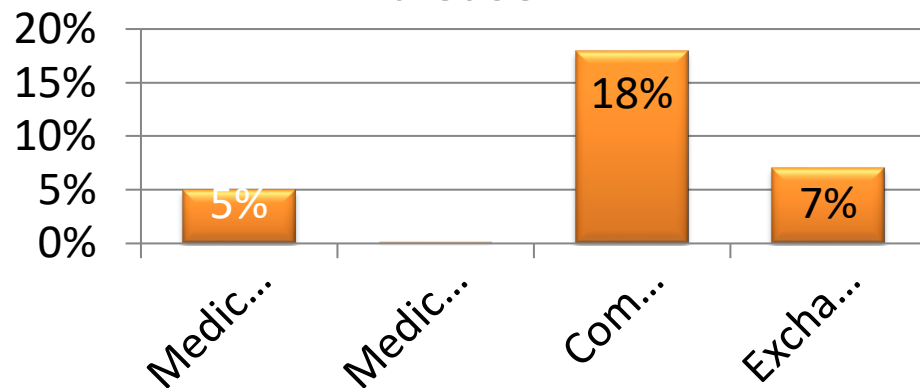


New Contract Negotiations - 2015

New Negotiations Average



Average Negotiation Rate Increase



Hylanex



Development

Increase your practice's
profit margin and patient growth by
entering into strategically beneficial
agreements with payers

Timely completion of contracts
and contract transitions

Annual review of charges
versus payer allowables

Applications

Identify and execute favorable
contracts in partnership with Hubs

Strengthen partnership
between Hubs, CBO and Managed Care

Continuously look for opportunities
to improve existing contracts and streamline
contract transition processes