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THE USE OF BIOLOGICS IN FOOD THERAPY

INTRODUCTION

In the last decade, the advent of biologic medications has transformed the practice of allergy, allowing clinicians to address unmet needs in the treatment of asthma, chronic spontaneous urticaria, atopic dermatitis and nasal polyposis.[1,2] Emerging and novel therapeutic agents in food allergy have however been slower to develop, with no biologic currently approved for this indication.

One factor has been that the low direct cost associated with food allergy created a poor incentive for pharmaceutical investment in research and development. However, the recent availability of health economic tools to quantify intangible costs and the recognition of oral immunotherapy as a valid treatment alternative has helped better define the unmet need.[3,4] This may partly explain the renewed interest in developing medications for food allergy, with ongoing trials at various stages.

In practice, clinicians are confronted with severe and/or complex cases of food allergy that could potentially benefit from treatment with biologic therapy, but there are no published studies demonstrating their proper use in these clinical scenarios and patient populations. There are various review articles available summarizing the evidence from the literature.[2,5] The objective of this article is to focus on practical knowledge regarding the off-label use of biologics in food allergies.

ANTI-IgE MONOTHERAPY

TALIZUMAB

The first biologic used for the treatment of food allergy was talizumab. This anti-IgE monoclonal antibody, which is highly similar to omalizumab, was studied in the context of peanut allergy and was shown to significantly increase the patient's reactivity threshold in a dose-dependent manner.[6] The development of talizumab was abandoned after Tanox was acquired by Genentech, which produced omalizumab.

OMALIZUMAB

Following the success of talizumab, trials were conducted on peanut allergy using omalizumab.[7] A phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted to assess the efficacy of omalizumab in reducing the risk of peanut-induced allergic reactions. The study was designed to compare changes in peanut tolerability thresholds in subjects with proven peanut allergy who were treated with either omalizumab or placebo. Although the study intended to randomize 150 subjects, it was stopped early on the recommendation of the Data Safety Monitoring Committee because of the severity of 2 anaphylactic reactions that occurred during the qualifying oral food challenges (OFCs) before the administration of the study drug. Consequently, only 14 subjects reached the study's primary endpoint before the discontinuation of the trial. Despite these small numbers, some interesting trends were observed including the 80-fold increase in reactivity threshold for patients receiving omalizumab compared to patients in the placebo group (**Table 1**).

Placebo			Omalizumab				
	Peanut Flour (mg)			Peanut flour (mg)		Free total IgE (kU/L)	
Subject Identification no.	Wk 1.	Wk 24.	Subject Identification no.	Wk 1	Wk 24	Wk 2	OFC 3
1107	15	50	1002	15	500	22	1.38
1419	15	50	1101	15	500	253	4.3
1502	50	50	1106	100	1500	40	2.44
1601	100	1000	1202	15	8000	406	3.04
1702	5	50	1407	50	500	216	11.35
Times increase from baseline: 4.07			1410	50	50	188	7.72**
			1501	100	1000	97	15.9
			1503	15	250	308	4.24
			1506	<5	1000	243	4.16
					Times increase from baseline: 80.9		

*Value at week 20.

Table 1. Change in peanut dose tolerability, per-protocol analysis, and change in free IgE in omalizumab-treated group ; adapted from Sampson et al, 2011

LIGELIZUMAB

Ligelizumab is a new anti-IgE monoclonal antibody that has demonstrated higher potency compared with omalizumab at suppressing skin prick tests in early asthma studies.[8] While the molecule didn't show clinical superiority in asthma, it has shown efficacy in chronic spontaneous urticaria and it is now being studied in clinical trials as a monotherapy in food allergy.[9]

Currently, omalizumab is the only anti-IgE biologic that is Health Canada approved for chronic spontaneous urticaria, asthma and nasal polyps. It can be used off-label in food allergy to increase a patient's reactivity threshold and reduce the risk of accidental reactions. However, this approach is rarely used because of the associated cost, which is hard to justify given the total direct and indirect healthcare costs associated with treatment. However, there have been instances when public payers have provided reimbursement on compassionate grounds in patients with recurrent episodes of severe food allergic reactions despite appropriate precautions.

With monotherapy, treatment duration is indefinite, which can be costly. The usual dosing strategy has been to follow asthma dosing regimens based on total IgE. This approach was recently shown to be inadequate in food allergy, where omalizumab dosages should be adjusted for body weight alone, independent of total IgE levels.[10] Therefore, rather than using the asthma dosing table, one approach could be to aim for a dose of 12mg/kg, which was the average dosage used in that cohort. Given the cost of the medication, the aim should be to start with the lowest effective dose, knowing that higher dosages will increase reactivity threshold in a linear fashion.

Oral food challenges in the clinic can be useful to help determine dosing. The use of omalizumab in food challenges reveals a dual mechanism of action. The main mechanism of action is that the molecule disarms mast cells, both by directly displacing IgE from its receptor and by preventing free IgE from binding to it.[11] The expected effect of this is a dose-dependent increase in reactivity threshold. The second mechanism is that the molecule creates food specific IgE-IgG complexes that can neutralize the allergen upon entry into the circulation, similar to IgG4.[12] This offers a protection against systemic reactions but not against local reactions. Contrary to the first mechanism, IgE-IgG complexes are formed at relatively low dosages.[10] In practice, low dosages tend to provide a significant increase in the reactivity threshold, but the symptoms are often localized to the oral and gastro-intestinal tract. If challenge is pursued despite local symptoms, the neutralizing capacity of IgE-IgG complexes appears to saturate and systemic reactions eventually occur.

ANTI-IgE TO SUPPORT ORAL IMMUNOTHERAPY

A more common use of omalizumab in food therapy has been to use it to enable otherwise difficult oral immunotherapy treatments. This approach was first described by researchers in 2010 and has since been extended to other foods.[13-19] The main advantage of this approach is that omalizumab is used for a limited duration, and therefore is potentially more cost-effective.

Protocols involving omalizumab-enabled oral immunotherapy generally include a pre-treatment phase of two to three months, which is the time required to reach a plateau effect for reactivity threshold reduction. The medication is typically continued during the oral immunotherapy up-dosing phase and discontinued when the patient reaches maintenance.

When combined with a standard "slow" oral immunotherapy-to-milk algorithm, this approach has been shown to decrease dosing reactions by half and markedly reduce the incidence of severe reactions.[20] However, this involves prolonged use of the medication, which may not be affordable. When combined with an accelerated oral immunotherapy protocol, a short treatment with

omalizumab has been shown to allow patients to reach maintenance doses in a few weeks, making it much more cost-effective.[21,22]

Clinical trials are ongoing to further establish the potential for omalizumab in oral food therapy and to help elucidate the optimal dosage.

PATIENT SELECTION AND DOSAGE

The Canadian guidelines on oral immunotherapy suggest that omalizumab may be warranted for complex cases of oral immunotherapy.[23] However, the guidelines do not offer a firm definition of what constitutes a complex case.

In practice, omalizumab will usually be considered as an adjunct to oral immunotherapy in the following situations:

- ✓ Previous failure of regular oral immunotherapy
- ✓ Patients desensitized to multiple foods simultaneously
- ✓ Patients with low baseline reactivity thresholds or very high IgE levels
- ✓ Patients with a history of severe reactions
- ✓ Patients in rural areas where reducing the number of up-dosing visits can offset the cost of medication
- ✓ Patients willing to pay out-of-pocket despite their case not being "challenging"

OMALIZUMAB DISCONTINUATION ONCE ON MAINTENANCE

About 40% of patients experience dosing reactions approximately 6 to 8 weeks following the discontinuation of omalizumab.[10] Due to ineluctable rise in free IgE, it is important that patients keep dosing regularly to prevent rapid loss of protection when this happens. One strategy is to pre-medicate with anti-histamines, proton-pump inhibitors or disodium cromoglycate during this transition period. Another, potentially more effective approach has been to take the full allergen twice a day during this period, but it is often difficult for active patients to avoid co-factors twice every day.

The risk of reaction or OIT failure upon discontinuation of omalizumab appears significantly higher in patients with a high specific-to-total IgE ratio.[10] For these patients, one option can be to wean omalizumab progressively. Importantly, the specific-to-total IgE ratio should be considered when OIT is an option and potentially treated as a relative contra-indication.

Clinicians should be extra cautious when treating patients with asthma who may have discontinued controller medication during omalizumab treatment due to improved response with omalizumab. If controller medication is not re-initiated these patients can be at a risk of a severe asthma attack when omalizumab is eventually discontinued.

LOW-DOSE OMALIZUMAB TO PREVENT CO-FACTOR INDUCED ANAPHYLAXIS

Co-factor induced anaphylaxis is a frequent cause of systemic reactions during oral immunotherapy. These reactions usually become less frequent after the first year of therapy, likely owing to the development of neutralizing IgG4 antibodies. However, some patients may experience anaphylaxis on their maintenance dose with minor co-factors. An effective approach has been to administer a low dose of omalizumab (150 mg or 75 mg every 4 weeks) to gain protection from food-specific IgE-IgG complexes without incurring the cost of a full dose. Currently, this strategy is limited by the poor access to allergen-specific IgG4 outside the research setting.

DUPILUMAB MONOTHERAPY

Dupilumab is monoclonal antibody that blocks the IL-4 and IL-13 signaling pathways, two of the sources of Type 2 inflammation.

Because specific IgE decreases by up to 70% in patients receiving dupilumab for the treatment of atopic dermatitis[24], it has been suggested that it could potentially help improve IgE-mediated allergy in a similar fashion to omalizumab. However, in practice, patients receiving dupilumab for atopic dermatitis do not appear to significantly increase their tolerance threshold to their food. One explanation could be that this effect is canceled out by a proportional decrease in total IgE and loss of the associated protection.

On the other hand, dupilumab appears highly effective at suppressing cellular-mediated food allergy. Phase 2 and preliminary phase 3 trial results are promising for eosinophilic oesophagitis, which is likely the next indication for this biologic medication.[25]

In practice, dupilumab has been used successfully for the off-label treatment of patients with primary severe eosinophilic gastrointestinal disease, where omalizumab has not demonstrated efficacy. Reimbursement for this indication is often difficult but is generally approved in pediatric patients when the impact on growth and development is demonstrated.

The following criteria have been used to justify the off-label use of dupilumab in patients with primary eosinophilic gastrointestinal disease:

- ✓ Growth and developmental delay
- ✓ Delayed puberty
- ✓ Low bone density
- ✓ Hypoalbuminemia
- ✓ Vitamin deficiencies
- ✓ Active inflammation on biopsies despite previous treatments
- ✓ Disabling symptoms despite other treatments
- ✓ Impact on quality of life

The dosage for patients with primary eosinophilic gastrointestinal disease is the same dosage as is used for asthma or atopic dermatitis. Symptoms generally improve progressively and usually quite dramatically over the initial months following initiation of treatment. Treatment response can be measured by following the various parameters, including albumin, bone density and endoscopy. Clinically, parents will usually report an improvement in appetite and energy, a growth spurt and the successful reintroduction of multiple foods that had been previously restricted from the diet. The optimal duration of therapy is unknown, but therapy should ideally be maintained until puberty is completed.

DUPILUMAB AND ORAL IMMUNOTHERAPY

In patients with IgE-mediated food allergy, oral immunotherapy will sometimes uncover an unknown cellular-mediated allergy to the food that had been avoided to date. In patients desensitized for multiple foods simultaneously, atopy patch testing can be helpful to identify the culprit.[26] Omalizumab is not effective in preventing these symptoms. In fact, patients with severe eosinophilic gastrointestinal disease in the course of omalizumab-enabled OIT have successfully transitioned to dupilumab, allowing them to reintroduce the culprit allergen.[10] However, dupilumab therapy must be continued over the long term in order to maintain tolerance. It is possible that cellular tolerance may develop over many years, but it is rare for this to occur in the short term.

In addition to omalizumab, ligelizumab and dupilumab, there has been positive proof-of-concept trial results with etokimab, an anti-IL-33 monoclonal antibody[27], and there is an ongoing trial with abatacept, a CTLA-4 fusion protein (NCT04872218). In the next decade, new indications for food allergy will likely be established for some of these, and potentially other, biologic drugs, which could transform the way clinicians currently manage food allergy. In the meantime, the use of biologics in food allergy should be reserved for challenging cases, in which they have the potential to greatly improve patient health and quality of life.

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