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Mini-Review

Xolair in conjunction with OIT: Highest dose reached at day of initial food introduction

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ABSTRACT

Omalizumab is an anti-IgE medication used for treating patients with moderate to severe persistent asthma. Recently it has been used in combination with oral immunotherapy (OIT) to accelerate the desensitization process. Although many studies have involved omalizumab and OIT and it has been determined to be safe in phase I trials, currently phase II trials are being conducted. However, most of the published studies have primary and secondary endpoints near the end of a participant's desensitization. Surprisingly, information published regarding the time of initial introduction to the food allergen in question has not been explicitly investigated. The objective of this study is to assess the literature and provide a statistical analysis regarding dosing information for the initial introduction of food allergen. A literature search for published omalizumab and OIT trials as well as a retrospective chart review on 40 participants in an omalizumab with OIT trial at the Sean N. Parker Center for Allergy Research was conducted. Four published trials and one case report were found and the initial day of dosing was analyzed. In addition, data from the 40 participant charts was extracted and analyzed. In trials where omalizumab was given in combination with OIT, the initial day of food allergen dosing occurred 8-22 weeks after the first omalizumab injection was given. On the initial day of dosing, the participants reached a dose of 7 mg-8000 mg of food allergen protein. More research needs to be conducted and published to determine the best time to introduce foods after the first omalizumab injection and the highest and safest dose that can be consumed during the first day of dosing. In addition, type of allergen, whether introducing multiple foods at once or a single allergen at a time, age, sex, and omalizumab dosing schedule needs to be analyzed to determine trends and possible questions on future research.

KEYWORDS: food allergy, oral immunotherapy, omalizumab, combination therapy, desensitization, Xolair

INTRODUCTION

Food allergy (FA) is an immune response mounted against non-pathogenic food antigens that is quickly becoming an increasing concern and public health problem in Westernized countries throughout the world [1]. A recent study has stated that FA is prevalent in approximately 7% of children in the United States [2]. Individuals or families living with a member who has been diagnosed with FA undergo a significant amount of stress in dealing with the disease [3]. The most common allergens in developed countries include peanut, tree-nuts, milk, eggs, wheat, soy, fish and shellfish.

The most common method of treatment for FA has been strict avoidance of the allergen in question [4]. Recently, research has started exploring

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oral immunotherapy (OIT), which involves giving small amounts of the offending allergen to the patient in increasing doses to create a desensitized state [5]. This therapy can be done with the food protein alone or in combination with a medication called Omalizumab (Xolair). Xolair (Omalizumab; Genentech, South San Francisco, CA) is a humanized monoclonal anti-IgE antibody that has been FDA approved for use in patients with moderate to severe persistent asthma with evidence of aeroallergen sensitivity and who are inadequately controlled with controller medications (i.e.-inhaled corticosteroids), as well as in patients with chronic idiopathic urticaria [6]. Xolair has been shown in phase 1 clinical research trials to be safe for use in combination with OIT to desensitize FA patients [7]. Phase 2 studies are currently being conducted to determine its efficiacy to accelerate the desensitization process as well as to minimize adverse events during the desensitization process [8]. Xolair is typically dosed based on the patient's pretreatment serum IgE level and weight, with a minimal dose of 0.016 mg/kg[IU/mL] IgE per 4 weeks in divided subcutaneous doses for approximately 8-22 weeks before introducing the offending allergen(s) [9]. The optimal dosing for Xolair to achieve the maximal dose at the introduction of foods has not yet been established.

Purpose

The purpose of this article is to summarize the published research on the combination of Xolair and OIT and present data from 36 patients at Stanford University who completed a phase 1 Xolair and OIT combination research study protocol. A statistical analysis was completed to look for trends and correlations among data related to the initial introduction of food for the 36 patients at Stanford.

METHODS

A literature search was done (Pubmed) looking for published studies on OIT, rush OIT and Xolair combination therapy. A comparison of these studies was done and summarized (Table 1). In addition, a retrospective chart review was performed on 36 patients at Stanford University who completed a phase 1 Xolair and OIT combination research trial but which all the data had not been published.

RESULTS

Seven studies were reviewed during the literature search (Table 1): 3 looking at peanut allergy, 2 at milk, 1 at peach and 1 at multiple food allergens [7-8, 10-14]. The study involving peach OIT was excluded as it was written in Japanese. Of the remaining 6 studies, 5 used Xolair in a combination therapy with OIT, while one used a different monoclonal anti-IgE antibody, talizumab (TNX-901) [11]. TNX-901 is mentioned in the summary table and referred to in the Discussion section but was not used in comparison analyses. All studies used in the analysis had similar inclusion and exclusion criteria. Participants were excluded if they had eosinophilic esophagitis, chronic conditions such as heart disease or autoimmune diseases, poorly controlled asthma, had a history of severe anaphylaxis or need for intubation. All participants had a clinical reaction to their allergen(s) prior to beginning the research trial.

Schneider *et al.*, 2013

In a pilot study involving peanut allergic participants, it was shown that after pretreatment with Xolair for 12 weeks using European dosing guidelines based on weight and serum total IgE level, all 13 participants reached the maximum allowed dose of 500 mg peanut flour and were sent home on that dose to start their desensitization process [10].

Sampson *et al.*, 2011

In a phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Omalizumab in peanut allergy participants, 14 participants were enrolled, randomized at 2:1 (Omalizumab: Placebo) and treated for 20-22 weeks. The participants were introduced to their food allergens 24 weeks after initiating omalizumab or placebo treatment. The study drug was administered at a minimum dose of 0.016 mg/kg/IgE[U/mL] every 4 weeks. Participants whose dose was more than 300 mg had their dose divided and given every 2 weeks. Out of the 9 participants in the Omalizumab group, 1 (11.1%) reached a maximum allowed dose of 8000 mg peanut flour, 1 (11.1%) reached a maximum dose of 1500 mg peanut flour, 2 (22.2%) reached a maximum dose of 1000 mg peanut flour, 3 (33.3%) reached a

Table 1. Summary of studies that used combination therapies of OIT and Xolair. One study [14] was excluded as it was written in Japanese. One study in the below table [11] was excluded from statistical analyses as a different anti-IgE monoclonal antibody was used (TNX-901).

Allergen used	Study (Publication year)	Xolair pretreatment length	Xolair dosing	Max OIT dose	Additional notes on the studies
Peanut	Schneider *et al*. (2013)	12 weeks	European dosing guidelines (0.016 mg/kg/IgE [U/mL])	500 mg	
	Sampson *et al*. (2011)	20-22 weeks	Minimum of 0.016 mg/kg/IgE [U/mL]	8000 mg	Only one patient reaching maximum maintenance dose.
	Leung *et al*. (2003)	28 weeks	NA	2627 mg	Used TNX-901 anti-IgE monoclonal antibody.
Milk	Nadeau *et al*. (2011)	8 weeks	Package insert (approximately 0.016 mg/kg/IgE [U/mL])	1000 mg	All reached max. dose but 1 patient only reached 7 mg dose.
	Takahashi *et al*. (2015)	8 weeks	10 mg/kg every 2 weeks	200 mL cow's milk (approximately 170 mg of protein)	Case report of 1 participant.
Multiple	Begin *et al*. (2014)	8 weeks	Omalizumab global dosing schedule (0.006-0.18 mg/kg/IgE [U/mL])	1250 mg	Analysis of data below.

maximum dose of 500 mg, 1 (11.1%) reached a maximum dose of 250 mg, and 1 (11.1%) reached a maximum dose of 50 mg [8].

Nadeau *et al*., 2011

In a study involving milk allergic participants it was shown that after pretreatment with Xolair for 8 weeks using the product insert dosing (approximately 0.016 mg/kg/IgE[U/mL]), 9 out of 10 subjects reached the maximum allowed dose of 1,000 mg and went home on that dose to start their desensitization, while the remaining participant had a reaction after 1,000 mg and thus was sent home on 7 mg [12].

Takahashi *et al*., 2015

In a case report involving a milk allergic patient it was shown that after pretreatment with Xolair for 8 weeks at a dose of 10 mg/kg of Xolair every 2 weeks, the patient was able to reach a maximum dose of 200 mL cow's milk (approximately 170 mg of protein) [13].

Begin *et al*., 2014

In a phase I research trial involving 36 patients with multiple food allergies it was shown that after pretreatment with Xolair for 8 weeks using the Omalizumab global dosing schedule, 22 (61%) patients reached the maximum allowed

dose of 1250 mg total food protein, 5 (14%) reached a maximum dose of 625 mg total food protein, 4 (11%) reached a maximum dose of 300 mg total food protein, 2 (5.5%) reached a maximum dose of 150 mg total food protein, 2 (5.5%) reached a maximum dose of 50 mg total food protein, and 1 (2.8%) reached a maximum dose of 5 mg total food protein. Since these participants included multiple foods in their OIT, all protein was expressed as total food protein; to determine individual allergen protein the total protein must be divided equally by the number of allergens included in the patient's OIT (maximum 5 foods) [7].

Begin *et al*., 2014 in more detail: Statistical analysis of Xolair dose vs highest dose reached at multiple allergen initial dosing day

Of the 36 participant charts reviewed, the number of allergens included in OIT, Xolair dose and interval, weight, total IgE, and cumulative total and highest dose consumed at the initial dosing day were collected. From this information, highest allergen dose per allergen was calculated as well as total Xolair received before the initial introduction of food and standardized Xolair dose (mg/kg/IgE [U/mL]). A Pearson correlation was performed using SPSS software and it was found that there was a negative correlation between the highest total tolerated allergen dose at the initial dosing day and the number of allergens included in OIT ($p = 0.005$). There was no correlation among the highest tolerated allergen dose at the initial dosing day and specific food allergens included in OIT, the weight of the patient, total IgE, total Xolair received before the initial introduction of food or standardized Xolair dose (mg/kg/IgE[U/mL]).

DISCUSSION

In 2003, Leung *et al*. published a landmark study involving TNX-901 which showed that it may prevent or reduce the severity of allergic symptoms caused by an accidental ingestion of an allergen [11]. Interestingly, in this study, patients were given varying doses of the medication and only patients given the highest dose of TNX-901 showed a statistically significant increase in the mean amount of peanut flour that elicited objective symptoms after 20 weeks of treatment. This study sparked an increase in research with other monoclonal anti-IgE antibodies, i.e. Xolair, thought to prevent or reduce the severity of allergic symptoms due to accidental ingestions and/or during a desensitization process. Based on the study conducted by Leung *et al*. it could be hypothesized that higher the dose of Xolair given, higher would be the dose of food allergen safely reached without a reaction during the initial introduction of food. This analysis of 36 patients showed that the dose of Xolair given does not correlate with the total dose of allergen protein reached at the initial introduction of food protein. Although some studies restricted their patients to a lower dose of food protein on their initial day, research tends to show that those participants may very well have been able to tolerate more protein if the protocol would allow for it. This analysis of 36 patients is the only study to do an initial dosing day with multiple allergenic foods simultaneously. It was found that a negative correlation existed between the highest total tolerated allergen dose at the initial dosing day and the number of allergens included in OIT ($p = 0.005$) meaning that higher the number of individual allergens in a patient's OIT the less likely they were to reach a high total allergen protein dose. This means that those with more allergens included in their OIT started their desensitization process at a lower dose.

CONCLUSION

Looking at this data prompts many more questions. If total IgE, weight, and Xolair dose do not correlate with the maximal dose a patient reaches at the day on which food is introduced, then what does? What determines the maximal dose a patient can reach at their introduction to food? More research needs to be conducted to look at other factors that may contribute to or limit the maximal dose a patient is able to reach at the initial introduction to food allergen protein. Some possibilities to be explored are: number of accidental exposures, time of year and/or age at time of introduction to foods, other mechanisms in the blood, and skin prick test results for food included in OIT. In addition, the best Xolair dosing schedule as well as the OIT dosing schedule at the day food is initially introduced should be explored. The best practice of the initial

introduction to foods to start an OIT desensitization process using combination OIT plus Xolair would be potentially beneficial to allergists everywhere.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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