IgE Immunoadsorption Knocks Down the Risk of Food-Related Anaphylaxis

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The effects of an immunoadsorption procedure, specifically designed to remove immunoglobulin E (IgE), on food-induced anaphylaxis have never been evaluated. We evaluate the effects of IgE removal on the allergic thresholds to foods. A 6-year-old boy with anaphylaxis to multiple foods and steroid-resistant unstable allergic asthma displayed serum IgE levels of 2800 to 3500 kU/L. To lower IgE serum concentrations, which could be overridden by a high dose of omalizumab, 1.5 plasma volumes were exchanged in 8 apheresis sessions. During the procedure, serum IgE levels fell to 309 kU/L. After the procedure, the threshold of reactivity to baked milk increased from 0.125 to 5 g of milk protein (full tolerance) after the first session, and the threshold of reactivity to hazelnut increased from 0.037 to 0.142 g of protein after the first session, 0.377 g after the eighth, and 1.067 g (full tolerance) after the first administration of omalizumab. Immediately after the sixth IgE immunoadsorption, we started omalizumab therapy. In the next 40 days, the threshold of reactivity to hazelnut increased to 7.730 (full tolerance). Asthma control was obtained, treatment with montelukast was stopped, and fluticasone was tapered from 500 to 175 μg/day. The boy became partially or fully tolerant to all the tested foods, and quality of life was improved. IgE immunoadsorption, used to establish the starting basis for omalizumab administration, is able to increase the tolerance threshold to foods.

Food-related anaphylaxis kills 12 people every year in the United States[1] and is a well-known risk factor for asthma-related death. Oral immunotherapy, which has been proposed to reduce such a burden, is strictly allergen-specific and has limits in case of multiple food allergy (MFA).[2] Omalizumab, a monoclonal antibody indicated for treatment of severe persistent allergic asthma inadequately controlled despite optimal controller therapy, is also effective in anaphylaxis due to MFA,[3] but serum immunoglobulin E (IgE) levels >1500 kIU/L preclude its use.[4] Total plasma exchange, anecdotally used to overcome this limitation,[5] is known to reduce allergy symptoms[6] but has never been evaluated for severe allergic conditions such as anaphylaxis. Here we report on the use of a recently developed, IgE-selective, therapeutic apheresis adsorber in the treatment of MFA. Specifically, we use it as a strategy to make possible anti-IgE therapy in patients previously considered not suitable for it. We also assess its ability to reduce the risk of anaphylaxis per se.

CASE REPORT

A 6-year-old boy with severe asthma[7] presented with a history of anaphylaxis to milk, egg, fish, nuts, shrimp, soy, and peanut. He had been diagnosed with asthma at age 4, treated with montelukast, salmeterol, and fluticasone (up to 500 μg/day) for 18 months, and despite good pharmacological compliance[8] still was

abstract

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Drs Dahdah and Fiocchi were the clinical guarantors, carried out clinical examinations and follow-up, and wrote the first draft of the manuscript; Dr Ceccarelli planned and carried out the immunoadsorption procedures; Dr Amendola administered and interpreted the quality-of-life questionnaires; Dr Campagnano was in charge of the total and specific immunoglobulin E determinations; Dr Cancrini interpreted the immunological findings; Dr Mazzina prepared the food challenges and supervised the data collection; and all authors approved the final manuscript as submitted.

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TABLE 1 Specific IgE Determinations for Each Allergen, kUI/L

Food		Inhalant	
Egg white	>100	Grass	19.4
Cow's milk	>100	Corylus	17.5
Hazelnut	>100	Birch	15.8
Egg yolk	91.3	Cupressus	12.2
Cod	88.1	Olea	7.9
Shrimp	64.8	*D farinae*	11.1
Peanut	28.9	*D pteronyssinus*	12.2
Soy	25.7	Dog dander	17.9
Chicken	15.9	Cat dander	5.5
Beef	6.30	*Alternaria*	4.6
Peach	2.72	*Aspergillus F*	2.2

uncontrolled. He had immediate, nonanaphylactic reactions to kiwi, plum, apricot, chicken, and turkey. To prevent the risk of accidental ingestion, the child had been kept away from eating at the day care center. Total IgE ranged from 2800 to 3500 kIU/L, and specific IgE was positive for egg white, milk, hazelnut (>100 kIU/L), egg yolk, cod, shrimp (50–100 kIU/L), grass, tree pollens, mites, dog dander, peanut, soy, and chicken (10–50 kIU/L; Table 1). Molecular diagnosis indicated sensitivity to lipid transfer proteins (Pru p 3, Act c 10, Ara h 9; 38.2, 26.5, and 11.7 kIU/L, respectively) and seed storage proteins (Cor a 9, Gly m 5, Ara h 2; 24.9, 22,7, and 14.8 kIU/L, respectively). It also indicated sensitization to milk (Bos d 4, 90.8 kUI/L; Bos d 5, 59.3 kUI/L; Bos d 8, >100 kUI/L) and egg (Gal d 1, 30.8 kUI/L; Gal d 2, >100 kUI/L) components. The boy had 4 episodes of anaphylaxis in the year before the assessment, 2 of which resulted from inhalation of milk and egg in the day care center. The parents came to our center asking a solution, because the school to which he had to be admitted was requesting them to provide a personal nurse for the special needs of the child. We measured quality of life, with Pediatric Quality of Life Inventory Measurement Model (PedsQL) scores of 59.8 (parental) and 67.8 (child).[9]

After ethical approval, the following evaluations were done:

- Signal transducer and activator of transcription 3 (STAT3) score, negative (Supplemental Table 2)[10]
- Basal respiratory function, normal
- Childhood Asthma Control Test, scoring 17 despite fluticasone (500 μg/day) and montelukast (5 mg/day)[11]
- Oral food challenge (OFC) with baked milk, positive at 0.125 g (anaphylaxis necessitating epinephrine)
- OFC with hazelnut, positive at 0.037 g (urticaria)

Challenges with egg, milk, soy, and fish were contraindicated because of a recent anaphylactic reaction.

Over a 10-day period, 1.5 plasma volumes were treated in 8 apheresis sessions (2100 mL total plasma exchanged through a central venous catheter with an adsorber containing matrix-bound, mouse monoclonal, anti–human IgE antibody; Therasorb IgE, Miltenyi Biotec GmbH, Germany[12]). Briefly, 2 adsorbers were used for the immunoadsorption procedure in conjunction with a tubing set, a plasma separator, and solutions for anticoagulation, adsorber regeneration, rinsing, and preservation. An apheresis unit (LIFE 18; Miltenyi Biotec GmbH, Germany)

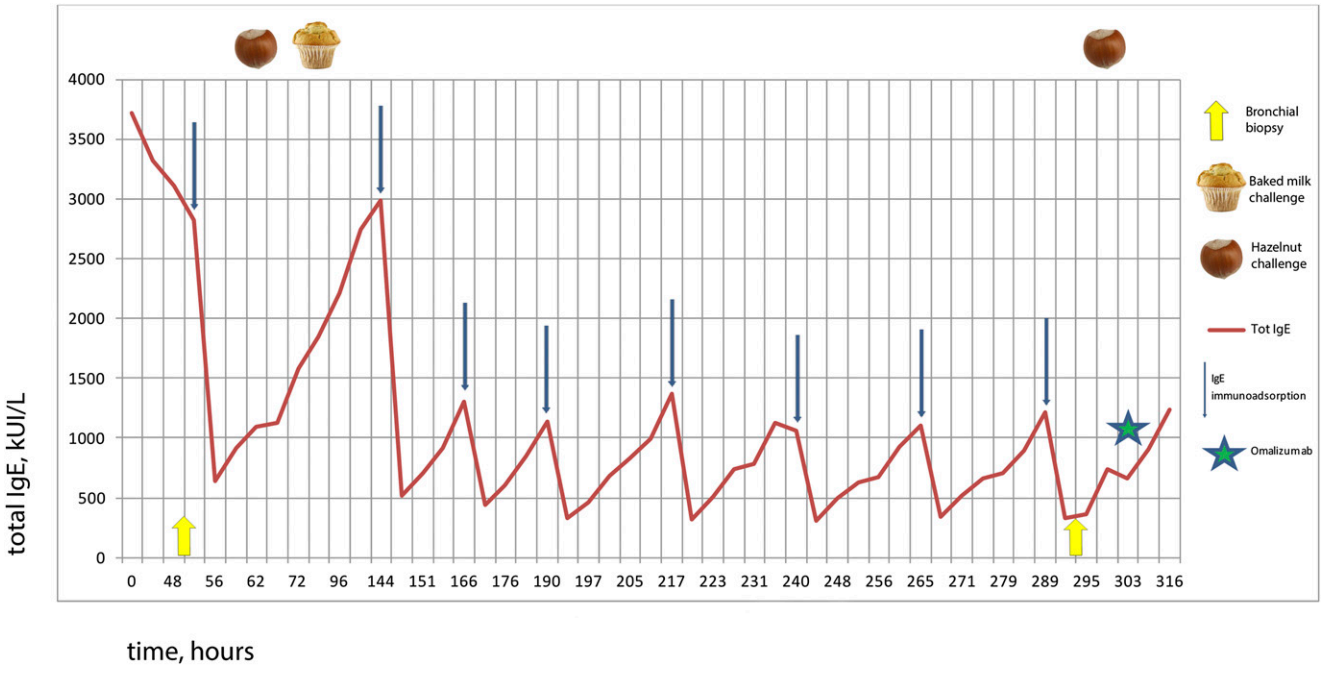

FIGURE 1
Total IgE kinetics (red line) after 8 IgE removal procedures (blue arrows), allowing treatment with omalizumab (blue star).

controlled the whole procedure. Blood was withdrawn via the catheter, anticoagulated, and separated into its liquid and cellular components in the centrifugal plasma separator. The separated plasma was perfused through the first adsorber, where binding of the IgE to the monoclonal antibody took place (under saturation conditions achievable in the laboratory, 1 mL of the functional matrix binds ≥100 000 IU of human immunoglobulin). After a predefined volume of plasma had been processed with the first adsorber, the plasma was directed to the other adsorber. The initial adsorber was automatically regenerated by the LIFE 18 apheresis unit, which lowered the pH to elute the previously bound target molecules and then restored the pH to neutral to enable binding of the target molecule in the next adsorption cycle. Automatic cycling between the 2 adsorbers was continued until the intended plasma volume had been processed. The IgE-depleted plasma was reunited with the previously separated blood cells each time and reinfused into the patient. After the treatment, the patient was disconnected, and after final regeneration the adsorbers were preserved with a solution containing sodium azide and stored at +4°C until needed for the next treatment session.

Serum IgE progressively fell to 309 kIU/L (Fig 1), allowing omalizumab administration immediately after the eighth procedure (375 mg every 14 days; patient's weight 28 kg, calculated level of total IgE 1500 kUI/L). Omalizumab is licensed in Europe for children from age 6. Asthma was kept under control (score 25 1 month after the eighth procedure), montelukast withdrawn, and fluticasone tapered to 175 μg/day. OFCs showed full tolerance to 5 g baked milk protein (1 muffin) after the first session. Hazelnut was tolerated up to 0.142 g protein after the first session, 0.377 g after the eighth, and 1.067 g (full tolerance, 8 hazelnuts) after the first administration of omalizumab.

The boy became partially or fully tolerant to all the tested foods. PedsQL scores increased to 78.7 (parental) and 90 (child). During the procedures, the red blood cell count progressively decreased from 5 960 000 to 3 860 000/mm^3, platelets from 282 000 to 166 000/mm^3, and hemoglobin from 13.2 to 10.3 g/L. Immunoglobulin A levels fell from 157 to 95 mg/dL, immunoglobulin M from 64 to 47 mg/dL, and immunoglobulin G from 701 to 376 mg/dL. These reductions, smaller than in our previous experience using total plasma exchange, reverted in 14 days.

COMMENTS

This is the first clinical evaluation of IgE-selective immunoadsorption in asthma and food allergy. The boy's asthma was brought under control, and pharmacotherapy could be reduced. Forty days after the last procedure, the boy's diet included baked milk, hazelnuts, soy, and chicken. Other foods are being avoided as a cautionary measure, but oral food challenges are being performed in hopes of introducing foods previously not tolerated. An increase in PedsQL scores (data not shown) reflects a reduction of anxiety toward possible anaphylactic reactions. The boy was able to go to school without anaphylactic accidents during his first year.

A full evaluation of other immunologic parameters is ongoing; we report here on the kinetics of IgE. The reduction of IgE after each procedure was prompt but not persistent: After the first apheresis, IgE increased to 3000 kIU/L within 4 days. In a similar previous report it was speculated that "neosynthesis of IgE within this short period appears unlikely, [and] the rapid recovery may reflect a redistribution of IgE from the interstitial into the intravascular compartment."[6] If so, repeated procedures would achieve a progressive depletion of circulating IgE. With this possibility in mind, we performed the subsequent apheretic procedures every 24 to 48 hours. The curve of the reduction of IgE proved comparable to the first, but total IgE never went below 300 kIU/L, indicating a vigorous IgE neosynthesis. The apparently worrisome finding of reduction of immunoglobulin A, M, and G can be explained by the transient hemodilution due to the procedures, and it is promptly reversible.

If these clinical results will be replicated, therapeutic IgE-selective apheresis appears to be sufficient to reduce the risk of food anaphylaxis in MFA and, when IgE titers are high, to open the way to treatment with omalizumab.

ABBREVIATIONS

IgE: immunoglobulin E
MFA: multiple food allergy
OFC: oral food challenge
PedsQL: Pediatric Quality of Life Inventory Measurement Model
STAT3: signal transducer and activator of transcription 3

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