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IgE-immunoadsorption for severe allergy to multiple foods: A case series of five children

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ABSTRACT

Background: Children with severe food allergy may present high risk of fatal anaphylaxis and a highly impaired quality of life. Anti IgE-treatment has been shown to be a promising approach as monotherapy for severe allergy to multiple foods. However, very high serum total IgE levels may limit its use.
This study aims to assess the efficacy of IgE-selective immunoadsorption (IgE-IA) on total IgE levels and threshold of reactivity to the culprit foods in children with history of severe anaphylaxis due to multiple foods and allergic comorbidities.

Methods: In this single-center, prospective, open-label efficacy study we evaluated children with severe asthma, allergy to 2+foods and total IgE levels >2300 kUI/L. To establish the food reactivity threshold, each patient underwent oral food challenges (OFCs) before and after IgE-IA.

Results: Five patients (4 males; age, 12.2 ± 5 years, mean ± SD) underwent an average of 3 (range 2–4) sessions of IgE-IA. Each session reduced IgE levels by a mean of 1958.87 kUI/L. After the IgE-IA cycle, serum total IgE dropped from 3948 ± 1652.7 (mean ± SD) to 360.8 ± 71.9 kUI/L (−10.9 folds; $p = 0.01$). The threshold of reactivity (No Observed Adverse Effect Level, NOAEL) tested at OFCs for the culprit foods (4 baked-milk + 2 baked-egg + 1 lentil + 2 hazelnut + 1 wheat) increased overall from 21.5 (median, IQR 1.5–82.6) protein milligrams to 1115 (837.2–4222.8) milligrams ($p < 0.001$), ie, up to 51.8 times higher than baseline. 8/10 OFCs were negative after IgE-IA.

Conclusions: IgE-IA increased food threshold quickly. It can be considered in well-selected patients with severe food allergies and high IgE-levels especially if otherwise eligible to anti IgE treatment.

Keywords: Anti-IgE treatment, Children, IgE-immunoadsorption, Omalizumab, Severe food allergy

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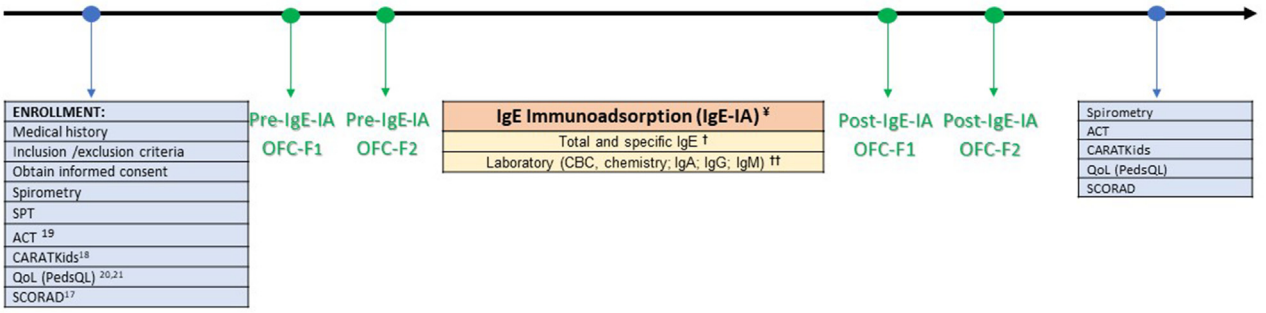
Key message

IgE-immunoadsorption can be considered in patients with severe food allergy as a safe and effective option to increase threshold reactivity, especially in those with high IgE-levels otherwise eligible to anti IgE-treatment.

INTRODUCTION

Food allergy (FA) is emerging as a relevant health and social problem. There are extensive data suggesting that FA is common with up to 10% of the population affected in industrialized countries, mainly children.[1] Even the intake of a small amount of food can induce fatal and near-fatal anaphylaxis. FA also leads to increasing hospitalizations and healthcare costs and the rate of mortality is around 0.03–0.3 deaths per million people per year.[2]

A definitive cure for FA still does not exist. The classic approach relies on the strict avoidance of allergenic foods, which may have a great impact on the quality of life of the patients and their families[3,4] as well as considerable increase in health direct and indirect costs.[5] Innovative therapeutic options are under investigation. Recent evidence-based international guidelines recommend to consider oral immunotherapy in patients with persistent allergy to cow's milk, egg, and/or peanut.[6,7] In addition, there is growing interest in the efficacy of monoclonal antibodies as monotherapy or combined with oral immunotherapy for increasing the threshold of reaction to the culprit food(s) and, therefore, the risk of severe anaphylaxis in case of accidental ingestion, in patients with allergy to a single or multiple food with/without concomitant allergic diseases.[8,9] The most promising monoclonal approach is the anti-IgE treatment, omalizumab, on the market since 2003; recently, other anti-IgE antibodies (ie, ligelizumab) with higher affinity for IgE and superior inhibition of IgE binding to FcεI than omalizumab are under investigation.[10] The European Medicines Agency (EMA) and United States Federal and Drug Administration (FDA)[11,12] leaflets suggest that the omalizumab applicability is limited by a weight-dependent maximum level of total IgE up to which it can be administered (ie, 1500 IU/mL). Since anti IgE-treatment is excreted through the renal emunctory, in patients who undergo such a treatment and have a high level of total IgE it has been hypothesed that considerable concentrations of IgE/anti-IgE monoclonal antibodies immune complexes might accumulate in the blood with the consequent risk of renal impairment. To overcome this limit, a few attempts of extracorporeal selective IgE-immunoadsorption (IgE-IA) preliminary to anti IgE-treatment commencement have been



† Time points for IgE determinations: immediately before; immediately after; at 2, 4, 6 and, 12 hours after the IgE-Immunoadsorption session procedure.
†† Two determinations: immediately before and immediately after the IgE-Immunoadsorption.
¥ The number of IgE-Immunoadsorption sessions was variable on individual level. When the serum total IgE levels reached values ≤ 500 kUI/L for two consecutive times, the cycle was interrupted and/or continued up to a maximum of 12 sessions.
OFCs with the most allergenic food must be administered in any case, even if the IgE cut-off is not reached.

List of abbreviation: ACT, asthma control test ; **CARATKids**, Control of Allergic Rhinitis and Asthma Test for ChildreM ; **CBC,** complete blood count; **IgE-IA**, IgE-Immunoadsorption; **OFC-F1**, oral food challenge with food 1; **OFC-F2**, oral food challenge with food 2; **PedsQL**, Pediatric Quality of Life Inventory; **SCORAD**,scoring atopic dermatitis; **SPT**, skin prick test.

Fig. 1 Study design

Total IgE (ImmunoCAP)
Adverse events (AE)
Electrolytes (serum): Na, K, total Ca, PO4, Cl
Hematology: white blood cells, erythrocytes (number, MCV, MCH, MCHC), hemoglobin, hematocrit, platelets
Liver and kidney parameters: AST, ALT, γ-GT, creatinine, bilirubin, uric acid, BUN
Protein loss: albumin
Additional immunological parameters:
IgA, IgG, IgM and specific IgE
Additional clinical parameters:
Lung function parameters: FEV1, MEF25-75
Asthma control questionnaire
Patient's diary: symptoms, medication
Skin prick test
During treatment:
Treatment time
Blood flow/plasma flow
Processed plasma volume
Heart rate
Blood pressure (every 60 min)

Table 1. Clinical and immunological parameters. *List of abbreviations: ALT, Alanine Transaminase; AST, Aspartate Transaminase; BUN, Blood Urea Nitrogen; FEV1, Forced Expiratory Volume in the 1st second; γ-GT, γ-Glutamyl Transpeptidase; MCH, Mean Cell Hemoglobin; MCHC, Mean Cell Hemoglobin Concentration; MCV, Mean Cell Volume; MEF25-75, Mean Expiratory Flow at 25–75%*

performed for atopic dermatitis[13] and severe allergic asthma,[14] including a single case report with food allergy from our group.[15]

On the other side, omalizumab has been reported to be used also in subjects with total IgE up to 2000 IU/mL without any specific safety concern.[16]

Herein, we report the first clinical series to assess the efficacy and safety of selective IgE-IA in a cohort of pediatric patients with multiple food allergies and very high IgE levels. The study hypothesis is that, throughout this procedure, children reach partial or total food tolerance to previously eliciting foods. The primary objective has been to assess food tolerance at Double Blind Placebo-Controlled Oral Food Challenges (DBPCFC) before and after IIgE-IA. As secondary endpoints, IgE levels, full clinical tolerance to food, immunological and clinical parameters were assessed.

As an extension phase of this study, we evaluated the possibility of using IA as a preliminary procedure propaedeutic to the commencement of anti IgE-treatment as potential long-term treatment for food allergies. This will be reported in another manuscript.

METHODS

Study design

This is a single-center, prospective, open label, interventional, pilot, efficacy study (IAO, Immunoadsorption for anti IgE-treatment; OPBG Ethic

	Study population (n = 5)		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	Median/n	IQR/%					
Age (y)	11.43		10	20	6	13	6
Female			no	No	no	No	yes
BMI (kg/m^2)	18.72		19.48	18.72	18.71	20.39	14.12
Allergic asthma*			Moderate persistent	Moderate persistent	Severe persistent	Moderate persistent	Severe persistent
Allergic rhinitis**			No	Mild intermittent	Mild intermittent	No	Mild intermittent
Eczema***			Mild	Previous	Previous	Moderate/ severe	Moderate
ACT (0–25)			14	17	18	15	17
PedsQoL			84.8	65.5	67.8	68	66
CARATkids			NA	10	10	NA	3
SCORAD			10.9	NA	NA	60	37
Culprit food allergen(s)			Milk, egg, walnut, hazelnut, peanut, almond, sesame, pine seed, fish	Milk, egg, fish, wheat	Milk, egg, peanut, hazelnut, fish, shellfish, soy	Egg, peanut, hazelnut, LTP	Milk, egg, fish, wheat
N. FIA in life-time			3	1	2	3	1
Anaphylaxis triggers			Peanut, milk, baked egg	Baked milk	Milk, egg	Hazelnut, peanut, egg	Baked milk
Total sIgE (kU/L)			2391	4020	3112	3511	6706
OFC food 1							
Food			Baked egg	Baked egg	Baked milk	Lentil	Wheat
sIgE (kU/L)			Egg white 16,1; egg yolk 10,6; ovomucoid 0,47; ovoalbumin 21,6	Egg white 13,4; egg yolk 7,16	>100	28	>100

NOAEL (mg)			2.09	20.88	260	58.65	4050
LOAEL (mg)			6.26	62.64	390	175.95	6750
Type of reaction			Moderate scratching, throat tightness and wheezing	Oral itching, abdominal pain	Orticaria with severe generalized involvement, hoarseness, one episode of emesis	Itchy mouth, one episode of emesis	Mild complaints of abdominal pain, one episode of emesis
Drugs administered			Steroids i.v., antihistamines i.v.	Prolonged observation	Steroids i.v., antihistamines i.v., epinephrine i.v.	Steroids i.v., antihistamines i.v.	Steroids i.v., antihistamines i.v.
OFC food 2							
Food			Baked milk	Baked milk	Hazelnut	Hazelnut	Baked milk
sIgE (kU/L)			α-lactalbumin 28,3; β-lactoglobulin 44; casein>100	milk 28,9; α-lactalbumin 3,51; β-lactoglobulin 15,2; casein 23,4	>100	>100	α-lactalbumin 15; β-lactoglobulin 22; casein>100
NOAEL (mg)			1.3	0	69	13.8	0
LOAEL (mg)			3.9	1.3	138	69	1.3
Type of reaction			Oral itching, perioral erythema, mild lip edema	Itchy mouth, throat tightness, rubbing nose and eyes, frequent sniffing	Itchy mouth, rubbing nose and eyes, frequent sniffing, faint erythema	Abdominal pain	Abdominal pain and emesis
Drugs administered			Prolonged observation	Steroids i.v., antihistamines i.v.	Steroids i.v., antihistamines i.v.	Prolonged observation	Steroids i.v., antihistamines i.v.

Table 2. Characteristics of study population at baseline. **according to GINA classification (24).*according to ARIA (Allergic Rhinitis and its Impact on Asthma) (25).*according to SCORAD classification (17).List of abbreviations: ACT, Asthma Control Test; FIA, Food-Induced Anaphylaxis; CARATKids, Control of Allergic Rhinitis and Asthma Test for Children; LOAEL, Lowest Observed Adverse Effect Levels; LTP, Lipid Transfer Protein; N., number; na, not applicable; NOAEL, No Observed Adverse Effect Level; OFC, oral food challenge; PedsQoL, Pediatric Quality of Life; SCORAD, SCORing Atopic Dermatitis; sIgE, specific Immunoglobulin E*

Committee approval 599/18) (Fig. 1). To establish the reactivity threshold before apheretic procedures, each patient underwent 2 oral food challenges (OFCs) with 2 of the foods that, based on their medical history, determined severe reactions (preOFC-F1; preOFC-F2). Spirometries were also performed to assess the degree of asthma control. In stable clinical conditions, the patients were admitted to the hospital and underwent selective IgEIA procedures.

IgE-immunoadsorption was stopped if total IgE was below 500 kU/L after 2 consecutive procedures. Before and after each IgE-IA procedure, blood cell count (CBC), chemistry, IgA, IgG, IgM, and total and specific IgE were evaluated. To assess any increase in food tolerance after the apheretic procedures, OFCs for the 2 most allergenic foods tested were repeated (postOFC-F1; postOFC-F2). The OFCs were performed on the day of IgE-IA discontinuation (1stfood) and the following day (2ndfood) only if no rescue medication was provided. Furthermore, before the procedure and at the end of the study, children underwent dermatological assessment for the definition of SCORAD[17] (in case of eczema), rhinitis control test (CARATKids),[18] Asthma Control Test (ACT)[19] and Assessment of Quality of Life (PedsQL).[20,21]

Description of the study population

The cohort design did not include comparison/reference groups nor we assessed unexposed groups. There was no randomization. Eligible children were identified by selective inclusion-exclusion criteria (IAO Protocol). The children were screened at the Allergology Service and followed-on at the Pediatric ward of the Bambino Gesù Children's Hospital (Rome, Italy). Before the enrollment, patients and their parents were informed on the methods and the aim of the study and signed an informed consent.

Clinical evaluation

We evaluated clinical conditions of patients during the entire study (Table 1). Specifically, we used validated questionnaires to assess comorbidities' control status at the beginning and at the end of our study. For asthma, we used Asthma Control Test (ACT, uncontrolled asthma if score$\leq$19)[21] forms: 1 form, specifically, filled in by the child and one by the parents. We used CARATKids Test to determine the allergic rhinitis (uncontrolled if score$\geq$6).[18] For the assessment of eczema, we used the SCORAD test[17](mild disease: SCORAD $<$25; moderate: 25$\leq$SCORAD$\leq$50; severe: SCORAD$>$50). Moreover, we administered a Pediatric Quality of Life questionnaire (PedsQL)[20,21] to children and their parents. It consists of 4 domains: physical, emotional, social, and cognitive functioning. Items were scored and linearly transformed into a 0 to 100 scale. Higher scores indicate a better quality of life.

Laboratory tests

Total and allergen-specific IgE were measured by ImmunoCAP (Phadia). For the specific IgE we used 0.35 kU/L as the cut-off value. Levels of total serum IgG, IgA, IgM, CBC, albumin, and electrolytes were obtained before and immediately after immunoadsorption cycle to assess any variation (Table 1).

Oral food challenges (OFC)

To establish the food reactivity threshold, each patient underwent OFCs before and at the end of the apheretic procedure[22,23] with the same foods to evaluate if there was any increase in the food tolerance.

Prior to the OFC, we instructed parents about the child's preparation according with the Work Group report indications.[22] We performed a seven-step open OFC with a semi-logarithmic increase according to the internal protocol (Table S1), at intervals of about 15–20 min as suggested by the PRACTALL consensus document.[23] Food tolerance was evaluated in terms of threshold of reactivity: we designated the initial point at which symptoms occur at a specific dose as the lowest observed adverse effect level (LOAEL) and the highest dose that does not lead to objective symptoms as the no observed adverse effect level (NOAEL). The reactive symptoms observed were pruritus, urticaria, skin rash, laryngeal and nasal symptoms (rhinorrhea and nasal congestion), respiratory symptoms (wheezing), and gastrointestinal symptoms (subjective and objective). According

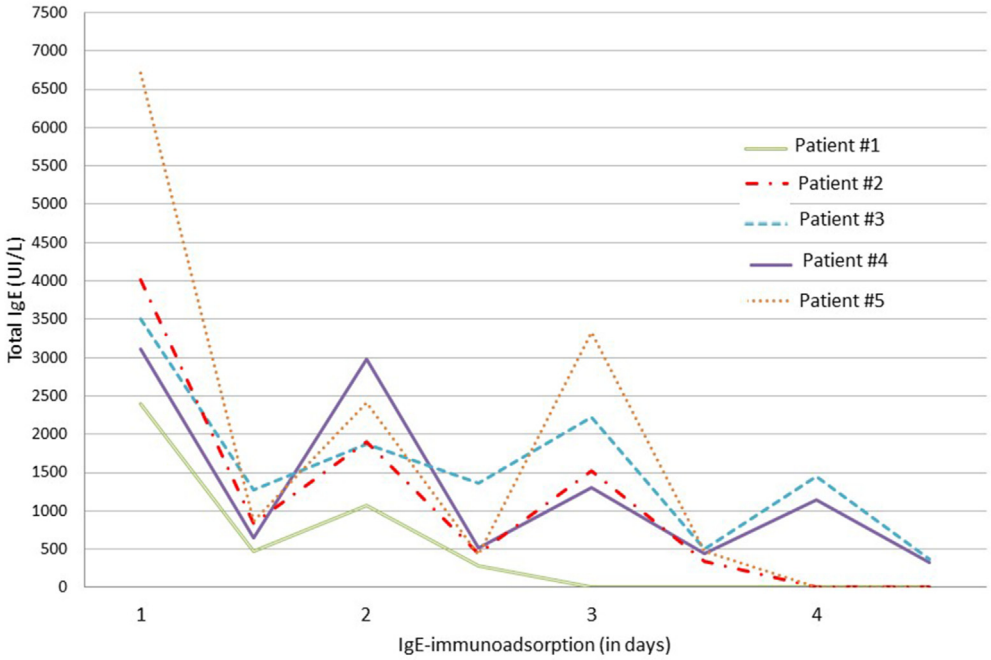


Fig. 2 Total IgE kinetics during IgE – immunoadsorption. Trajectories represent the longitudinal evaluation of total IgE during the IgE-immunoadsorption cycle and assessed before and immediately after each session at individual level (n = 5)

with the provisions of the PRACTALL Consensus,[23] the challenge suspension occurred after the appearance of objective symptoms. In case of reported subjective symptoms, the test was continued by lengthening the interval of administration between the doses; whenever the subjective symptoms continued, the test was considered positive and, therefore, interrupted. Any reaction was treated according to this scheme: oral antihistamines at the onset of the symptoms, intramuscular administration in case of persistence; oral and then intramuscular corticosteroids in case of further persistence of the symptoms; aerosol epinephrine in case of laryngospasm and intramuscular administration in case of anaphylaxis. Patients were then monitored for at least 4 h.

IgE-immunoadsorption (IgE-IA)

During hospitalization, patients underwent daily sessions of immunoadsorption, approximately 180 min each one, using the IgE-adsorber Therasorb IgE, Myltenyi Biotec. It consists of a pair of adsorbers that contain Sepharose spheres to which murine monoclonal antibodies are bound, which bind selectively IgE from the plasma of

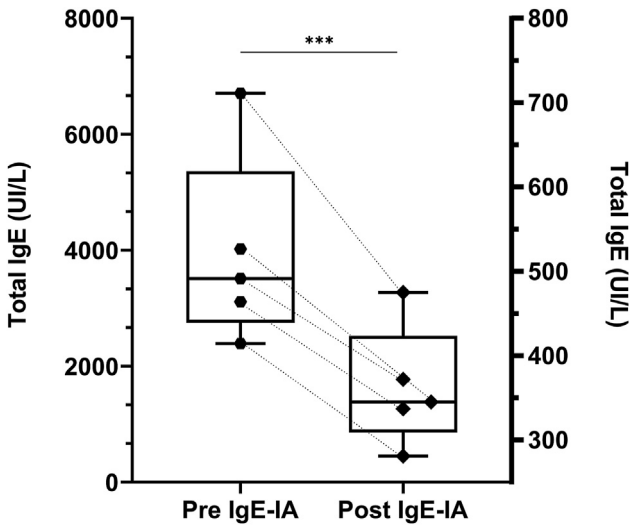


Fig. 3 Concentration of serum total IgE(kUI/L) across the entire IgE-immunoadsorption cycle. Absolute total IgE-levels (y-axis: kUI/L) are shown as box-and-whisker plots for the first (pre-IgE IA) and the last visits (post-IgE IA)) of the entire treatment cycle (x-axis). The box-and-whisker plot on the left side (pre-IgE IA) shows IgE levels immediately before the first IgE-immunoadsorption session with individual values represented each as an hexagon; the box-and-whisker plot on the right side (post-IgE IA) shows IgE levels immediately after the last IgE-immunoadsorption session, with individual values represented each as a rhombus. Median, 0^{th} (minimum) and 100th (maximum) percentiles of serum total IgE-levels are shown for both time points. The dashed lines connect individual values for each patient. Significant differences between start and end of the entire cycle of the IgE-immunoadsorbtion procedure are indicated (***$p \leq 0.01$)

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	pre-IA	post-IA	pre-IA	post-IA	pre-IA	post-IA	pre-IA	post-IA	pre-IA	post-IA
OFC food 1										
Food	Baked egg		Baked egg		Baked milk		Lentil		Wheat	
NOAEL - single dose (mg)	2.088	584.64	20.88	584.64	260	390	58.65	4685.1	4050	6750
LOAEL - single dose (mg)	6.264	NA	62.64	NA	390	NA	175.95	NA	6750	NA
NOAEL - cumulative dose (mg)	2.088	1114.99	29.232	1114.99	447.2	837.2	82.11	7289.16	6311.25	13061.3
LOAEL - cumulative dose (mg)	8.352	NA	91.872	NA	837.2	NA	258.06	NA	13061.3	NA
OFC food 2										
Food	Baked milk		Baked milk		Hazelnut		Hazelnut		Baked milk	
NOAEL - single dose (mg)	1.3	130	0	39	69	2070	13.8	2070	0	390
LOAEL - single dose (mg)	3.9	260	1.3	130	138	NA	69	NA	1.3	NA
NOAEL - cumulative dose (mg)	1.3	187.2	0	57.2	82.8	4222.8	13.8	4222.8	0	837.2
LOAEL - cumulative dose (mg)	5.2	447.2	1.3	187.2	220.8	NA	82.8	NA	1.3	NA

Table 3. Individual thresholds for food allergens at oral food challenges performed before and immediately after the IgE immuno-adsorption. *List of abbreviations: IA, IgE-immunoapheresis; LOAEL, Lowest Observed Adverse Effect Levels; NA, Not Applicable; NOAEL, No Observed Adverse Effect Level*

Patient	ACT		SCORAD		PedsQoL		CARATkids	
	pre	Post	pre	post	pre	post	pre	post
1	14	20	10.9	8.9	84.8	90.2	NA	NA
2	17	23	NA	NA	65.5	86.9	10	0
3	17	25	NA	NA	67.8	90	10	4
4	12	14	60	49.8	68	90.9	NA	NA
5	13	15	37	16.8	66	90.9	3	0

Table 4. Score values of allergic comorbidities assessed before and after IgE-immunoadsorption at individual level. *List of abbreviations: ACT, Asthma Control Test; CARATKids, Control of Allergic Rhinitis and Asthma Test for Children; na, not applicable; PedsQoL, Pediatric Quality of Life Inventory; SCORAD, SCORing Atopic Dermatitis*

allergic patients. About 2 volumes of plasma were treated in each session. Blood was drawn via a midline Powerglide 18G positioned in the brachial vein. During treatment, anticoagulation therapy was administered by a solution of ACD-A (anticoagulant citrate Dextrose-A) and low molecular weight heparin. Plasma was separated from blood cells by centrifugation-assisted filtration and then conveyed to the IgE-adsorber. After the adsorption, plasma was reunified with the blood cells and then reinfused to the patient by a second peripheral venous access at the opposite arm than the one used for blood aspiration.

More details are provided in the supplementary material.

Statistical evaluation

Due to the absence of a control group, the statistical plan mainly included an evaluation pre-post- of clinical parameters. A *t*-test (Mann-Whitney *U* test) was used to analyze the difference in amount of tolerated food expressed in grams and of IgE levels. A $p < 0.05$ was considered statistically significant.

RESULTS

Study population

A cohort of 5 children, aged 6–19 years, with severe allergic asthma,[24] multiple food anaphylaxis, and serum total IgE levels>2300 kUI/L was enrolled in a period of 12 months between October 2018 and September 2019 (Table 2). The mean age was 12.2 ± 5 years (mean ± SD); 4 of them were males. As comorbidities, 3 of them were suffering from atopic dermatitis, with 1 classified as having mild (patient# 5, SCORAD 10.9), 1 moderate (patient# 5, SCORAD 37), and 1 as having severe eczema (patient# 4, SCORAD 60). Three patients suffered from allergic rhinitis, classified as mild intermittent according to ARIA guidelines[25] [CARATKids[18] (mean ± SD), 7.67 ± 4.04; the maximum score is 13, representing bad control, and the minimum score is 0 representing optimal control]. Based on the respiratory function tests performed at the recruitment, all patients suffered from persistent asthma [ACT (mean ± SD), 14.6 ± 2.3; normal: >19].

IgE-selective immunoadsorption (IgE-IA) and IgE kinetics

Patients received 2 to 4 sessions of selective IgE-immunoabsorption: 1 patient received 2 (patient #1), 2 patients 3 (patients #2 & #5), and the remaining 2 underwent 4 sessions (patients #3 & #4), specifically.

Decrease in the IgE levels at each session was similar in all patients, with a mean IgE reduction per cycle of 1958.87 kUI/L. After the cycle sections, total IgE dropped from 3948 ± 1652.7 (mean ± SD) to 360.8 ± 71.9 kUI/L (−10.9 folds; $p = 0.01$). Overall, IgE-IA induced an average IgE reduction by 90% (Figs. 2 and 3, Table S2).

Increase in the food threshold of reactivity

Each patient underwent 2 OFCs for each of the main allergenic foods based on clinical history, immediately before and after the entire cycle of IgE-IA. OFCs performed at the end of the apheretic procedures demonstrated an increase in the

Patient	pre-IgE-IA	post-IgE-IA	pre-IgE-IA	post-IgE-IA	pre-IgE-IA	post-IgE-IA	pre-IgE-IA	post-IgE-IA
	Hb (g/dl)		Ht (%)		PLT ($\times 10^3$/uL)		Eo (/uL)	
1	13.5	12.6	41.2	37.1	161	118	430	460
2	15.1	14.6	45.9	43.9	252	135	1320	720
3	13.3	13.2	40.1	39.3	282	282	100	380
4	14.5	13.7	42.6	40.5	414	272	400	60
5	13.1	12.5	40	36.2	206	78	680	700

Table 5. Main immunological data detected in each patient pre- and post- IgE-immunoadsorption. *List of abbreviations: Eo, eosinophils; Hb, hemoglobin; Ht, hematocrit; IgE-IA, IgE-immunoadsorption; PLT, platelets*

reactivity threshold and allowed patients to reintroduce tested foods in their diet in small quantities. Specifically, the threshold of reactivity (No Observed Adverse Effect Level, NOAEL) tested at OFCs for the culprit foods (four baked milk, two baked egg, one lentil, two hazelnut, and one wheat) increased from 21.5 (median, IQR 1.5–82.6) protein milligrams to 1114.99 (837.2–4222.8) milligrams ($P < 0.001$); overall, it increased up to 51.8 times from baseline. Eight out of 10 OFCs were negative after IgE-IA (Table 3).

Clinical evaluations

Patients underwent continuous clinical visits, including the evaluation of the control of allergic comorbidities. Overall, they experienced a prompt and global improvement with reduced need of relief therapies (eg, β2-agonists, topical and systemic steroids) in terms of atopic dermatitis [SCORAD[17] (mean ± SD), 36 ± 24.6 pre-IA→ 25.2 ± 21.7 post-IA; mild disease: SCORAD<15; severe disease: SCORAD>40], allergic rhinitis [CARATKids[18] (mean ± SD), 7.67 ± 4.04 pre-IA→ 1.3 ± 2.3 post-IA; with 0 representing optimal control], and asthma [ACT (mean ± SD), 14.6 ± 2.3 pre-IA→ 19.4 ± 4.8 post-IA; normal >19], as well. Health-related quality of life improved after IgE-IA when compared to baseline, with an immediate reduction of the anxiety and worries of the children and their families (Table 4).

IgE-immunoadsorption safety and tolerability

Immunoadsorptions were very well tolerated. Mild deviations of some laboratory parameters were observed. They were potentially caused by dilution with physiologic sodium chloride solution used for displacement of plasma prior to regeneration of the adsorber during each cycle and some unspecific plasma loss during the procedure. They were clinically irrelevant and resolved without any treatment. During the follow-up evaluations, hematocrit, albumin, total protein, and immunoglobulin classes and subclasses in serum values normalized and were back to baseline at 1 month follow-up visit (Table 5).

DISCUSSION

Our pilot study demonstrates the therapeutic efficacy and safety of IgE-IA in pediatric patients suffering from multiple severe food allergies. The efficacy is shown both in terms of laboratory results (eg, mean IgE-reduction rate of 90.86%) and clinical data (the threshold of reactivity increased up to 51.8 times from baseline, as well as clinical improvement of allergic comorbidities). We have previously showed that IgE-IA decreased IgE levels and improved the patient's allergic condition in a single boy, whose case has not been included in this study cohort.[15] IgE-IA appears to be able to reduce the risk of anaphylaxis in multiple food allergy and, when IgE titers are high, to open the way to treatment with biological treatment. Previous studies[26–28] have already confirmed that IgE-IA is safe, especially for the infection risk. Adverse event of IgE-IA procedure may rely on the specificity of selective depletion of different serological components, such as immunoglobulin of classes different from IgE. Temporary reductions of the levels of IgA, IgG, and IgM had already been highlighted in other studies that described the use of IgE-IA.[15] This reduction might be mainly related to the unspecific loss of proteins occurring due to the repeated the elution processes of the

pre-IgE-IA	post-IgE-IA	pre-IgE-IA	post -IgE-IA	pre -IgE-IA	post -IgE-IA	pre -IgE-IA	post-IgE-IA	pre-IgE-IA	post-IgE-IA
albumin (mg)		calcemia (mg)		IgA (mg/dL)		IgG (mg/dL)		IgM (mg/dL)	
4.5	4.3	10.2	9.8	90	92	961	832	77	58
4.4	3.7	9.4	9.4	123	92	1239	913	83	50
4.6	3.2	10.2	9.1	157	100	701	405	64	60
4.2	4.1	9.7	9.4	92	86	858	809	89	81
3.4	3	9.8	9.6	92	53	1041	625	135	61

Table 5. Main immunological data detected in each patient pre- and post- IgE-immunoadsorption. *List of abbreviations: Eo, eosinophils; Hb, hemoglobin; Ht, hematocrit; IgE-IA, IgE-immunoadsorption; PLT, platelets*

aphaeresis procedures.[27] Certainly, the variation of laboratory parameters during IgE-IA is much less relevant than those happening in the course of other unselective aphaeretic techniques. In our cohort, this variation was transient and resolved without any treatment within a few days and no clinical consequences (eg, infections). Our results are aligned with reports from a few cases series previously reported on IgE-IA in patients with allergic diseases.[26,28–30] Our data highlighted that selective IgE-immunoadsorption is as effective as other non-selective aphaeretic procedures, but it is safer, particularly with regard to infection risk especially when peripheral venous accesses are used. Therefore, the main advantage of IgE-IA is that, except the ones intentionally removed, all plasmatic substances are overall preserved. Of note, the adherence of patients was high, as indicated by the absence of drop-outs, although each IA section required 3 h on average and two peripheral venous accesses.

Our study has some limitations. One is the small number of participants due to the severity of the disease and the selectivity of inclusion criteria. However, data showed that the decrease of IgE levels, proportionally to the baseline situation of each patient, had a similar trend among patients. Nevertheless, we also saw that after the depletion of circulating IgE, they tend to go up quickly. The mechanisms underlying this trend need to be clarified; notwithstanding, one could speculate that the IgE-production is not interrupted by the IgE-IA and in highly atopic patients is usually increased. Conversely, IgE^{+} plasma cells might unlikely produce such a massive IgE-production in such a short timeframe. Therefore, the rapid IgE increase could depend on the redistribution of interstitial IgE in the intravascular compartment. This could also explain why consecutive IgE-IA sessions can lead to ever-lower levels of circulating IgE.[13] Further studies will be necessary to explain the mechanism(s) responsible for the IgE refilling despite their mechanic depletion and could pave the way for new potential therapeutic targets.

Based on current knowledge and our results, 2 possible therapeutic scenarios emerge. On one side, when serum total IgE levels are particularly high, and it is difficult to reach and maintain lower values than 1500 kUI/L, it could be possible to repeat IgE-IA sessions at regular intervals. This could allow to maintain IgE levels and oral tolerance stable as long as possible, as already assessed in patients with severe atopic diseases.[26,28–30] The other therapeutic option concerns severe allergic patients that could benefit from anti IgE-treatment but are not eligible for this treatment because of their high IgE levels. In these patients, IgE-selective immunoadsorption could be used to reduce the IgE level under 1500 kUI/L and thereafter to commence anti IgE-treatment. The anti-IgE monoclonal antibody will bind the newly produced circulating IgE and keep their level reduced with the aim to further increase the patients' threshold of reactivity and keep it over time. A similar strategy was analyzed in studies on patients with severe asthma[26] and atopic dermatitis[13] and they highlighted the efficacy of the combination of an apheretic procedure (non-selective in this case) with a monoclonal antibody.

In conclusion, our study shows that IgE-selective immunoadsorption has been an efficient therapeutic option in patients with persistent multiple food allergy, severe asthma, and high serum IgE levels. These patients could benefit by tolerating a larger

amount of culprit food(s), better asthma control, and health-related quality of life. However, given the rapid rebound of the IgE level, we expect this effect to be transitory and not lasting over time. Since this is a prospective study, we evaluated the immediate effects of the treatment, while the long-term effects in this kind of patient will be investigated in further studies and maybe on a larger scale.

CONCLUSIONS

Food allergy may be a severe and potentially fatal disease that still does not have a cure. The results of this study highlight that IgE-IA could be a strategy to treat well-selected pediatric patients with persistent multiple food allergy and high levels of IgE to reduce the risk of severe anaphylaxis. IgE depletion through sessions of selective immunoadsorption determines an immediate clinical improvement and an increase of food tolerance in children with severe asthma, anaphylaxis and IgE levels>2300 kUI/L. The procedure was safe and well tolerated in our population.

Furthermore, anti IgE-treatment is emerging as a potential therapeutic approach in patients with food allergy, mainly if with concomitant allergic comorbidities such as asthma. IgE-IA could be used preliminarily to anti IgE-treatment, when its commencement would be otherwise contraindicated by too high serum total IgE levels. Further well-designed clinical investigations on a higher sample size are needed to confirm our results and to further improve treatment efficacy.

Abbreviations

OFC, Oral Food Challenge; NOAEL:, No Observed Adverse Effect Level; FA, Food Allergy; IgE-IA, IgE-selective immunoadsorption; SCORAD, SCORing Atopic Dermatitis; CARATKids, Control of Allergic Rhinitis and Asthma Test for Children; ACT, Asthma Control Test; PedsQL:, Pediatric Quality of Life Inventory™; AE, Adverse Events.

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Availability of data and materials

Only with the authors.

Author contributions

AF conceived the study. SA designed the manuscript. SA, LD, VP, BM, GL performed and supervised the collection of clinical data in the study. SA, AC and ALP performed the data management. SA and ALP performed statistical analyses. AF, LD, VP, BM, GL, SA participated in the clinical coordination, patients' recruitment/treatment. SA, AC and ALP wrote the first draft of the paper. SA reviewed and provided feedback. All authors read and approved the final version of the manuscript.

Ethics approval

The study was submitted to and approved by the local Research Ethics Committee at Bambino Gesù Children's Research Hospital (approval n. 599/18).

Authors' consent for publication

All authors have approved the submission of this manuscript.

Declaration of competing interest

Authors declare no conflict of interest related to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100750.

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