



Apheresis in food allergies

Lamia Dahdah^a, Giovanna Leone^b, Mariacristina Artesani^a,
Carla Riccardi^a, and Oscar Mazzina^a

Purpose of review

The prevalence of IgE-mediated food allergy and anaphylaxis has risen rapidly in developed countries, and countries with rapid industrialization may follow. Therapies include elimination diets, Oral ImmunoTherapy, and the administration of biologics, but high serum IgE levels may preclude their use. Consequently, decreasing IgE becomes a rational approach and could be obtained by immunoapheresis. The aim of this review is to evaluate the rationale and advantages of immunoapheresis.

Recent findings

The majority of the available adsorbers remove aspecifically all classes of immunoglobulins. Recently, IgE-specific adsorbers have been approved. Data on immunoapheresis for the treatment of allergic diseases with pathologically elevated IgE levels are emerging. In atopic dermatitis, this therapy alone seems to be beneficial. IgE-selective apheresis appears to be sufficient to reduce the risk of anaphylaxis in multiple food allergy (MFA) and, when IgE titers are high, to open the way to treatment with Omalizumab.

Summary

Prospective studies, with well designed protocols, are needed to assess the efficacy, tolerability, and cost-effectiveness of immunoapheresis in the field of food allergy.

Keywords

anaphylaxis, immunoapheresis, multiple food allergy, severe food allergy

INTRODUCTION

The prevalence of IgE-mediated food allergy and anaphylaxis seems to have risen rapidly in developed countries. Countries with rapid industrialization may follow [1]. Possible therapeutic approaches for food allergy include elimination diets, Oral ImmunoTherapy (OIT), and the use of biologics [Fiocchi *et al.* (232–238)]. Elimination of the offending food may be difficult to maintain, in particular in older children with multiple food allergy (MFA). OIT is strictly allergen-specific [2] and has limits in case of MFA. The administration of biologics can help to overcome these limits [3], but they have limitations especially for MFA, as high serum IgE levels preclude its use.

Consequently, decreasing IgE becomes a rational therapeutic approach and could be obtained by apheresis, a technique used in different diseases aiming to remove undesirable blood components. Immunoabsorption has been successfully used in various autoantibody-mediated diseases such as systemic lupus erythematosus, myasthenia gravis, Guillain-Barré syndrome, dilated cardiomyopathy, rheumatoid arthritis, idiopathic thrombocytopenic purpura, hemophilia with inhibitors, dermatomyositis, ABO-incompatible kidney transplantation, and

autoimmune bullous disorders [4]. The active principle of most available absorbers is the nonspecific removal of immunoglobulins. More recently, new IgE-specific absorbers have been approved, and data on the treatment of allergic diseases with pathologically elevated IgE levels are emerging. The aim of this review is to evaluate the rationale behind the use of immunoabsorption in allergic diseases, up to MFA.

APHERESIS IN ALLERGIC DISEASES OTHER THAN FOOD ALLERGY

The first reports of immunoabsorption in the field of allergic diseases concerned patients affected by severe atopic dermatitis with high serum IgE levels.

^aUniversity Department of Pediatrics, Division of Allergy and ^bDepartment of Pediatric Hematology and Oncology, Unit of Immuno-Hematology and Transfusion Medicine, Pediatric Hospital Bambino Gesù, Rome, Vatican City, Italy

Correspondence to Lamia Dahdah, MD, Division of Allergy, Pediatric Hospital Bambino Gesù, Piazza Sant'Onofrio, 4, 00165 Rome, Vatican City, Italy. Tel: +39 06 69591; e-mail: lamia.dahdah@gmail.com

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KEY POINTS

- The prevalence of severe MFA has risen.
- Therapies include elimination diets, Oral ImmunoTherapy, and biologics in which serum IgE levels allow their use.
- For the treatment of allergic diseases with pathologically elevated levels, removal of IgE could be obtained by immunoapheresis (panimmunoglobulin immunoabsorption and IgE-selective immunoabsorption).
- IgE-selective immunoabsorption reduces the risk of anaphylaxis in MFA and paves the way to treatment with Omalizumab.

An open-label pilot study enrolled 12 patients with severe atopic dermatitis and high IgE serum levels to investigate clinical efficacy, safety, and immunologic effects of panimmunoglobulin immunoabsorption [5]. All patients displayed total serum IgE levels more than 4500 kU/l and a history of no significant or long-term Scoring Atopic Dermatitis (SCORAD) reduction after treatment with topical corticosteroids/calcineurin inhibitors, ultraviolet light therapy, systemic corticosteroids, and cyclosporine A. Patients were treated with a total of 10 immunoabsorptions on days 1–5 (week 1) and days 29–33 (week 5) by using adsorption columns that contained polyclonal sheep antihuman Ig antibodies binding the different human Igs with similar affinity (Ig-Therasorb; Miltenyi Biotec, Teterow, Germany). Each immunoabsorption cycle induced an average reduction of total IgE levels of more than 90%. IgE levels started to rise again approximately 12 h after each immunoabsorption, but with repetitive apheresis continuously decreased in a sawtooth-like manner. In all patients, a 24–82% individual SCORAD reduction was observed between week 1 and 13. Although immunoabsorption was found to be associated with continuous clinical improvement of atopic dermatitis, only a short-term depletion of serum IgE, followed by recovery within 3 weeks, was observed. Similar patterns were seen for circulating total IgG, IgM, and IgA with a mean reduction of more than 90%. Authors speculated that because neosynthesis of IgE within this short period appears unlikely, the rapid recovery of serum IgE levels may rather be a result of a redistribution from the interstitial into the intravascular compartment. In line, intensity of IgE deposits in the skin almost halved after panimmunoglobulin immunoabsorption, justifying the clinical improvement.

The same group reported the first study on the use of IgE-specific immunoabsorption [6¹¹]. Two

consecutively recruited patients with atopic dermatitis displayed high serum IgE levels of 40 848 and 111 696 $\mu\text{g/l}$, SCORAD scores of 66 and 77, respectively, and a history of no substantial response to the therapies mentioned above. Again, two cycles of five immunoabsorption sessions were performed. In each immunoabsorption session, plasma was separated using a blood cell separation technique (Life-18 Apheresis Unit; Miltenyi Biotec) followed by alternate application of two patient plasma volumes to two adsorption columns containing matrix-bound, mouse monoclonal, antihuman IgE antibody (Therasorb IgE; Miltenyi Biotec GmbH, Bergisch Gladbach, Germany). Both patients tolerated well the treatment and showed a good response in terms of SCORAD improvement. The mean reduction in circulating IgE for each immunoabsorption cycle was 92%. Less substantial reductions in IgM, IgG, and IgA were observed (49, 37, and 36%, respectively). All Ig levels started to increase again approximately 12 h later, reaching concentrations similar to baseline within 3 weeks. The authors speculated that this decrease may likely be attributed to common unspecific protein loss during elution processes and immunoabsorption-related dilution procedures.

Following their two studies, they concluded that IgE-immunoabsorption is a well tolerated therapy, and an advantage over Omalizumab therapy in atopic dermatitis may be the greater benefit in patients with extremely high serum IgE levels, which are often present in severe cases, thereby overcoming possible treatment challenges.

For the same kind of patients, repetitive cycles of panimmunoglobulin immunoabsorption were tested [7]. A total of seven patients with severe atopic dermatitis with a history of no significant or long-term SCORAD reduction and total serum IgE levels more than 700 IU/ml were enrolled. The patients received one to five series of immunoabsorption (Ig-Therasorb), each consisting of five consecutive treatments that were performed on a monthly regimen. Overall, one patient received one, two patients two, one patient three, two patients four, and one patient five cycles of immunoabsorption. Immunoabsorption led to a significant decrease of SCORAD and IgE levels during each immunoabsorption cycle in all the patients. One of the patients exhibited a long-lasting clinical benefit over more than 12 months after the fifth immunoabsorption cycle. Repetitive immunoabsorption with more than two cycles at intervals of 4 weeks induced a profound and persisting IgE reduction and a remarkable clinical efficacy, improving SCORAD in severe atopic dermatitis with high serum IgE levels. This study was the first to demonstrate that allergic

patients can benefit from repetitive panimmunoglobulin immunoabsorption with long-term effects.

In the wake of previous studies, panimmunoglobulin immunoabsorption and IgE-selective immunoabsorption were compared. Extracorporeal pan-Ig ($n=24$) and IgE-selective immunoabsorption ($n=26$) were managed, and each patient received a total of 10 immunoabsorption sessions over a 2-month period divided into three cycles of 4 consecutive days in week 1, 3 days in week 4, and 3 days in week 8. The mean Eczema Area and Severity Index was 21.3, and the majority of patients had excessive IgE levels of between 5000 and 10000 kU/l before therapy. Both immunoabsorption types reduced peripheral IgE levels by approximately 85–90% per cycle, but only pan-Ig immunoabsorption had significant effects on circulating IgG levels. Although there were no major differences in clinical effects between the two immunoabsorption treatment groups, only in the pan-Ig immunoabsorption group eight AEs in seven patients were recorded, all of which were considered to be related to immunoabsorption. They included two mild cases of herpes labialis and three severe infections that required systemic therapy. Pan-Ig immunoabsorption is potentially associated with removal of protective Ig, a drawback in patients with severe atopic dermatitis, who have an increased susceptibility to skin infections by pathogens such as *Staphylococcus aureus* and Herpes simplex. The results of the current study in conjunction with earlier case reports indicate that IgE-selective immunoabsorption is indeed as effective as pan-Ig immunoabsorption but probably safer with regard to infectious events to which patients with atopic dermatitis are more prone [8].

The most recent study targeting IgE levels in severe atopic dermatitis combined extracorporeal pan-immunoabsorption and anti-IgE antibody Omalizumab in 10 patients with severe, therapy-refractory atopic dermatitis [9]. All patients first underwent nonselective immunoabsorption (Life 18 Ig-flex TheraSorb, Miltenyi Biotec GmbH, Bergisch Gladbach, Germany) depending on their respective baseline IgE levels on 2 (IgE level <6000 kU/l), 3 (IgE level 6000–20 000 kU/l), or 4 (IgE level >20 000 kU/l) consecutive days to reduce IgE levels as much as possible, followed by regular administration of Omalizumab every 2 weeks for 24 weeks. After this treatment period, patients were followed up biweekly for another 24 weeks. Free IgE levels decreased after immunoabsorption and decreased continuously in all patients during anti-IgE therapy. The reverse trend was observed during 6 months follow-up. In parallel with these observations, an improvement in atopic dermatitis, measured with SCORAD and visual

analog scale severity, was observed during the treatment period, with aggravation during follow-up. These findings reinforce the concept of a pathophysiological relevance of high IgE serum levels in atopic dermatitis and showed how immunoabsorption paved the way for the use of anti-IgE as already had been done in a case reported below.

In the early 2000s, a small randomized pilot study examined the effect of one cycle of full plasmapheresis alone in four adult asthma patients [10]. After removing humoral inflammatory factors over a 10-day period, none of the four patients displayed a significant amelioration of the clinical condition. Therefore, authors concluded that plasmapheresis is no treatment option in asthma. Ten years later, a study [11] re-evaluated the issue, performing plasmapheresis before anti-IgE therapy in a 15-year-old boy with severe allergic asthma whose serum IgE levels varied between 3000 and 8000 kU/l. The lowest serum IgE value obtained was 483 kU/l after three plasmapheresis sessions, immediately after which, the patient began an Omalizumab therapy with 450 mg Omalizumab biweekly. Upon cessation of plasmapheresis, total serum IgE levels began to rise despite the anti-IgE therapy, reaching pretreatment values after 2 months. In contrast to total IgE (sum of free IgE and IgE-containing immune complexes with Omalizumab), free IgE remained stable on a remarkably low level of about 80 kU/l during anti-IgE therapy. The anti-IgE treatment was accompanied by a noticeable clinical improvement. Patient's lung function improved 1 month after therapy start, and 9 months later, he displayed a normal lung function analysis without obstruction.

Lately, a randomized, open-label, controlled pilot trial (registered at clinicaltrials.gov NCT02096237) in patients with allergic asthma evaluated safety and efficacy of selective depletion of IgE with an immunoabsorber column based on a single-chain variable fragment, ScFv12 (IgEnio; Fresenius Medical Care, Bad Homburg, Germany) [12]. It also investigated if IgEnio can bind IgE–Omalizumab immune complexes *in vitro*. Fifteen patients were enrolled and randomly assigned to the treatment group ($n=10$) or to the control group ($n=5$). Patients aged 18–50 years underwent cycles of three immunoabsorptions within 1 week and were followed by intervals of 4 weeks without intervention. Each patient was subjected to three cycles. IgE immunoabsorption with IgEnio selectively depleted 86.2% ($\pm 5.1\%$ SD) of IgE until the end of the last cycle ($P < 0.0001$). The therapy under investigation was safe and well tolerated. During a total of 81 aphereses, two severe adverse events were recorded, one of which, an episode of acute dyspnea, possibly was related to the treatment and resolved after administration of antihistamines

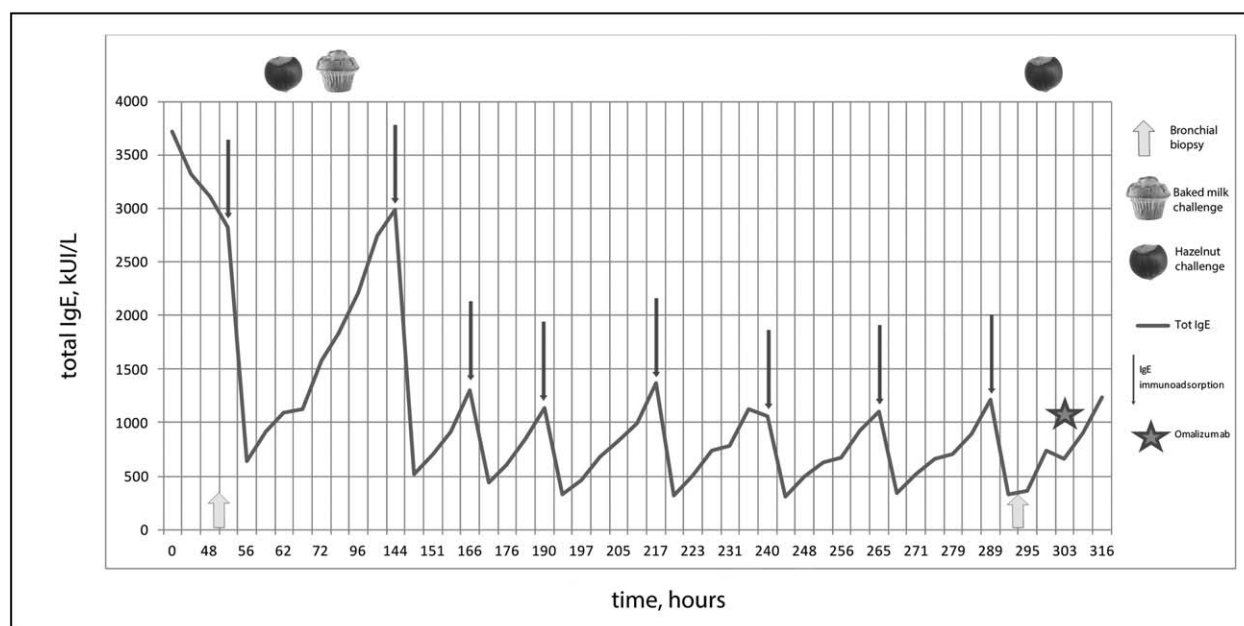


FIGURE 1. Total IgE kinetics after eight IgE removal procedures (thin arrows), allowing treatment with Omalizumab (star). Reproduced with permission from [13[■]].

and corticosteroids. Removal of pollen allergen-specific IgE was associated with a reduction of allergen-specific basophil sensitivity and prevented increases of allergen-specific skin sensitivity and clinical symptoms during pollen seasons. IgEnio also depleted IgE–Omalizumab immune complexes *in vitro*. Again, this pilot study indicates that IgE immunoabsorption could render allergic patients with highly elevated IgE-levels eligible for the administration of Omalizumab. It also shows that this therapy facilitates the desorption of IgE–Omalizumab complexes.

APHERESIS IN FOOD ALLERGY

The only use of IgE-selective immunoabsorption in the treatment of food allergy is a case report of a 6-year-old boy with severe asthma and MFA with anaphylaxis (milk, egg, fish, nuts, shrimp, soy, and peanut) [13[■]]. Total IgE ranged from 2800 to 3500 kIU/L. The boy had presented four episodes of anaphylaxis in the year before assessment, two of whom from inhalation of milk and egg in the daycare center where he had been kept away from eating to prevent the risk of accidental ingestion. Quality of life was very poor [Pediatric Quality of Life Inventory Measurement Model (PedsQL) 59.8 (parental) and 67.8 (child)]. Childhood Asthma Control Test, scored 17 despite fluticasone, 500 µg/day, and montelukast (5 mg/day). Oral food challenge (OFC) with baked milk was positive at 0.125 g (anaphylaxis requiring epinephrine), and

OFC with hazelnut was positive at 0.037 g (urticaria). OFCs with egg, milk, soy, and fish were contraindicated due to recent anaphylactic reactions. Over a 10-day period, 1.5 plasma volumes were treated in eight apheresis sessions (2100 ml total plasma exchanged) using Therasorb IgE.

After the treatment, serum IgE progressively fell to 309 kIU/L (Fig. 1), allowing immediate administration of Omalizumab (375 mg biweekly). 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 1.5 g baked milk protein (one 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, eight hazelnuts) after the first administration of Omalizumab.

PedsQL increased to 78.7 (parental) and 90 (child). During the procedures, IgA levels fell from 157 to 95, IgM from 64 to 47, and IgG from 701 to 376 mg/dL. These reductions, smaller than in previous experiences using total plasma exchange, reverted in 14 days.

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. Pursuing therapy with Omalizumab, the boy became tolerant to all the offending foods. Continuous increases in PedsQL reflected a reduction of anxiety toward possible anaphylactic reactions. The boy was able

to go to the school without anaphylactic accidents during his first year.

In this case, 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. If what Kasperkiewicz speculated about this recovery is true, repeated procedures would obtain a progressive depletion of circulating IgE. With this in mind, we performed the subsequent apheretic procedures every 24–48 h. The curve of the reduction of IgE proved comparable with the first, but total IgE never went below 300 kIU/l, indicating a vigorous IgE neosynthesis. 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. More cases following well designed protocols are needed to perform prospective studies evaluating cost-effectiveness, efficiency, and tolerability of this therapeutic approach in MFA with anaphylaxis.

CONCLUSION

Data on immunoapheresis for the treatment of allergic diseases with pathologically elevated IgE levels are emerging. In atopic dermatitis, this therapy alone seems to be beneficial. IgE-selective apheresis appears to be sufficient to reduce the risk of anaphylaxis in MFA and, when IgE titers are high, to open the way to treatment with Omalizumab. Prospective studies, with well designed protocols, are needed to assess the efficacy, tolerability, and cost-effectiveness of immunoapheresis in the field of food allergy.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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