

Cytokine profile in children with food allergy following liver transplantation

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Abstract

Background: LTX in children is associated with increased risk of food allergy, and the mechanisms underlying this are unknown. We wanted to study whether plasma cytokine profile differed in liver transplanted children, with and without food allergy, and whether it differed from untransplanted children with CLD.

Methods: Plasma cytokines, total and specific IgE in nine patients with food allergy were compared with 13 patients without food allergy following LTX, and also with seven untransplanted patients with CLD.

Results: No difference was found in the cytokine profile between liver transplanted patients with and without food allergy. Transplanted patients with food allergy having received a prescription of epinephrine had a significantly higher total IgE (2033 [234-2831] vs 10 [5-41] IU/L, $P = .002$) and MIP-1b (52 [37-96] vs 36 [32-39], $P = .035$) compared with transplanted patients without food allergy. Two patients with severe food allergy responded favorably to conversion from tacrolimus-based immunosuppression to MMF and corticosteroids with reduction in clinical symptoms, total IgE, specific IgE, IL-1ra, IL-4, RANTES, PDGF, MIP-1a, and TNF α . The transplantation group had higher levels of IL-1b, IL-5, IL-7, IL-13, GCSF, IFN γ , and MIP-1a compared with the CLD group.

Conclusions: No overall difference was found in plasma cytokine profile between patients with and without food allergy. Patients with severe food allergy had significant elevation of MIP-1b. Discontinuation of tacrolimus reduced total and specific IgE and changed plasma cytokine profile. The plasma cytokine profile in liver transplanted children was different compared with children with CLD.

KEYWORDS

children, cytokine, food allergy, immunosuppression, liver disease, LTX, tacrolimus

Abbreviations: CLD, chronic liver disease; ECP, eosinophil cationic protein; GCSF, granulocyte-colony stimulating factor; IL, interleukin; IFN, interferon; LTX, liver transplantation; MIP, macrophage inflammatory protein; MMF, mycophenolate mofetil; NK cells, natural killer cells; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T cell expressed and secreted; TAFA, transplant-acquired food allergies; TNF, tumor necrosis factor.

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1 | INTRODUCTION

LTX can be lifesaving in children, but is also associated with complications. Several studies have shown that food allergy is common in children after LTX, many of them with severe allergic reactions.¹⁻⁶ The prevalence of new-onset food allergy in liver transplanted children has been reported to be 4%-40.5%⁶⁻¹⁰ and is accompanied by an increased risk of eczema and asthma.⁶ The majority of patients with food allergy are young, and the risk of developing food allergy is highest the first year after LTX.¹¹ The mechanisms are unknown. Food allergy is an inappropriate response of the immune system triggered by the ingestion of a food protein allergen.¹² Cytokines produced by a number of cell types regulate different functions including innate immunity, acquired immunity, and inflammatory responses. In food allergy, the immune response is biased toward a type 2 cytokine-associated phenotype.¹³ Cytokines such as IL-4, IL-5, IL-10, and IL-13 are produced by Th2 cells and induce B cells differentiation into IgE-producing plasma cells. Specific IgE antibodies induce degranulation of mast cells and release of mediators including cytokines, histamine, and proteases which in turn result in allergic symptoms. T regulatory cells (Treg cells) can produce inhibitory cytokines such as IL-10 and TGF- β and play a role in developing tolerance.¹⁴ Therefore, identifying the pattern of cytokine expression can give valuable insight into the mechanisms of food allergy. It is not known whether transplanted children with food allergy have a sustained difference in cytokine profile compared with transplanted patients without food allergy or whether this profile depends on immunosuppression.

Several studies link immunosuppression and especially tacrolimus to the development of transplant-acquired food allergy (TAFA) in liver transplanted children.^{2-4,15} Lacaille et al² suggested that tacrolimus induced an imbalance between the Th1 and Th2 leukocyte subsets. Furthermore, a change in immunosuppression from tacrolimus to another immunosuppressive drug reduces the risk of allergy.⁴ Tacrolimus is not the only factor as food allergy is rarely seen after kidney transplantation.^{10,16,17} One study found a significant higher number of natural killer (NK) cells in liver transplanted children compared with kidney transplanted children and hypothesized that NK cells might be involved in the mechanism.¹⁸ Nahum et al¹⁹ studied stimulated leukocytes in post-liver transplant children with food allergy compared with non-allergic transplant patients and found increased levels of IL-5, but decreased levels of IL-10. We aimed to investigate whether there is a persistent change in the cytokine profile in liver transplanted children with and without food allergy, and also to investigate whether there is a difference in cytokine profile between the liver transplanted children and the children with CLD who have not been transplanted.

2 | MATERIALS AND METHODS

The study was approved by the Institutional Review Board at Oslo University Hospital and by the Regional Ethics Committee (08/324d, 2008/6203). Written informed consent was obtained from patients or parents.

2.1 | Study design and population

The study was designed as a case-control study with liver transplanted patients with ($n = 9$) and without ($n = 13$) reported food allergy, and with a group of children with CLD ($n = 7$) for comparison. Twenty-two patients who underwent orthotopic LTX at Oslo University Hospital during the period from 1995 to 2009 were included. All patients received a split liver from deceased donors. The immunosuppression protocol currently used consists of tacrolimus, mycophenolic acid, and prednisolone in tapering doses. A history of allergic reactions was recorded using a questionnaire. The type of immunosuppressive therapy was recorded.

2.2 | Allergy

Total IgE, serum eosinophilic cationic protein (ECP), and allergen-specific IgE were quantified using the Phadia(R)/Thermo Fisher Scientific ImmunoCAP (Phadia) system. The panels included specific IgE for cow's milk, egg, peanut, soybean, wheat, cod, horse, cat, grass, birch, mugwort (common wormwood), mites, molds (cladosporium and alternaria). Sensitization was defined as specific IgE levels ≥ 0.35 kU/L. *Reported food allergy* was defined as a reported history of symptoms like pruritus, tongue-, face-, or lip-edema, dyspnea or hoarseness, urticaria or anaphylaxis immediately after exposure to a food suspected to be linked to the reaction. *Eczema* was defined as reported use of treatment of eczema prescribed by a doctor. *Asthma* was defined as the patient using asthma medication (during the last 12 months) prescribed by a doctor because of asthma.

2.3 | Cytokines

Plasma samples were obtained together with routine sampling at the outpatient clinic. Samples were centrifuged and stored at -70°C until analysis. Plasma was diluted 1:3 in Bio-plex sample diluent before analysis. Cytokines were measured using enzyme-linked immunosorbent assay (ELISA)/multiplex ("Bio-Plex Assay" from Bio-Rad Laboratories Inc). A total of 27 cytokines were included: IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17A, Eotaxin, FGFbasic, GCSF, GMCSF, IFN γ , IP10, MCP1, MIP-1a, PDGF, MIP-1b, RANTES, TNF α , and VEGF. Analyses were carried out according to the manufacturer's instructions, and all samples were tested in duplicates and fitted to assay standard curve.

2.4 | Statistical analysis

Data are reported as mean and standard deviation or median and interquartile range. Statistical analyses were performed using Mann-Whitney U test for independent samples. A two-sided P value less than .05 was considered statistically significant. Statistical analyses were performed with GraphPad InStat version

03.10 for windows (GraphPad Software Inc) and IBM Statistical Package for Social Sciences (IBM SPSS SPSS statistics, version 21.0.1).

3 | RESULTS

Twenty-two children who had previously undergone LTX (nine children with food allergy and 13 without food allergy) and seven untransplanted children with CLD were included in the study. Diagnoses are given in Table 1. Median age at transplantation was 0.7 (0.6-7.5) years, and the median time from transplantation to allergy testing was 7.6 (0.5-8.9) years. Age at testing was not different between the transplanted children (10.2 [5.4-15.0] years) and the CLD group (6.7 [3.0-15.4] years; $P = .54$).

3.1 | Transplanted children and food allergy

Nine out of 22 transplanted patients had reported food allergy. The reported allergens were egg, kiwi, cod, nuts, caviar, chicken, turkey, salami, shrimps, coconut, chocolate, banana, tomato, cheese, and milk. All nine patients with reported allergy had sensitization to food allergens, and one of the patients without reported food allergy had sensitization to food allergens (Table 2). Sensitizations to aeroallergens (grass, birch, mugwort) occurred in four patients in the reported food allergy group and in two patients in the transplanted children without reported food allergy.

TABLE 1 Characteristics of children with CLD and liver transplanted children

	LTX N = 22	CLD N = 7	P value
Age at test (y)	10.2 (5.4-15)	6.7 (3.0-15.4)	.54
Female sex	11/22	7/7	.02
Albumin (g/L)	41 (39-43)	40 (36-44)	.98
Reported food allergy	9/22	0/7	.04
Total IgE ($\times 10E3$ IU/L)	39 (7-432)	8.3 (2-75)	.14
ECP ($\mu\text{g/L}$)	5 (8-18), n = 6	10 (6-18), n = 5	.52
Eosinophil count ($\times 10E9/L$)	0.2 (0.1-0.3)	0.1 (0.03-0.2)	.43
Diagnosis			
Biliary atresia	11	2	.41
Cholestasis	5	3	.64
Tumor	2	1	1.00
Metabolic liver disease	1	1	.47
Acute liver failure	3	0	.54

The median age at transplantation was significantly lower in the food allergy group compared to the transplanted patients without food allergy. The median age at testing for the transplanted children with and without food allergy was 8.6 (4.1-10.5) years and 12.8 (5.8-15.4) years, respectively. The median total IgE was higher in transplanted children with food allergy (581 [103-2166] IU/L) than transplanted without food allergy (13 [5-39] IU/L [$P = .002$]). The median eosinophil count in the transplanted group with food allergy (0.3 [0.15-0.55] $\times 10E9/L$) was statistically significantly higher ($P = .049$) than in the transplanted group without reported food allergy (0.1 [0.1-0.25] $\times 10E9/L$). Doctor-diagnosed asthma was significantly more frequent in the liver transplanted children with food allergy. There were no significant differences in cytokine profiles between the transplanted groups with and without food allergies (data not shown). Comparing the patients with food allergy to all those without food allergy (transplanted and CLD group), the patients with food allergy had statistically significantly higher eosinophil count, 0.3 (0.15-0.55) and 0.1 (0.1-0.2) ($P = .032$), respectively. All of the patients with food allergy were sensitized to one or more food allergens.

3.2 | Transplanted children with and without tacrolimus

Tacrolimus is associated with food allergy in liver transplanted children. In these selected transplanted patients, 17 were currently treated with tacrolimus and five were not. The liver transplanted children not currently treated with tacrolimus received either combination of cyclosporine and mycophenolic acid (n = 4), or mycophenolic acid (n = 1). All of the transplanted children with reported

TABLE 2 Characteristics of liver transplanted children with and without food allergy

	LTX food allergy N = 9	LTX no food allergy N = 13	P value
Age at test (y)	8.6 (4.1-10.5)	12.8 (5.8-15.4)	.17
Age at LTX (y)	0.6 (0.5-0.96)	1.5 (0.7-6.4)	.03
Tacrolimus at test	9/9	8/13	.166
Cyclosporine at test	0/9	4/13	.07
Asthma	4/9	0/13	.009
Eczema	6/9	4/13	.164
Total IgE ($\times 10E3$ IU/L)	581 (103-2166)	13 (5-39)	.002
Eosinophil count ($\times 10E9/L$)	0.3 (0.15-0.55)	0.1 (0.1-0.25)	.049
IgE aeroallergens	4/9	2/13	.142
IgE food	9/9	1/13	<.001
IgE mite/mold	4/9	1/13	.048
IgE animals	3/9	1/13	.134

food allergy were treated with tacrolimus. The median total IgE 58 (6-1281) IU/L and eosinophils 0.2 (0.1-0.3) $\times 10^9/L$ in transplanted patients with tacrolimus did not significantly ($P = .66$ and $P = .08$, respectively) differ from patients without current tacrolimus (total IgE 10 [5-104] IU/L, eosinophils 0.1 [0.05-0.2] $\times 10^9/L$). When comparing the patients in the transplantation group who were treated with tacrolimus to those without tacrolimus, there was no significant difference in the cytokine profile.

3.3 | Transplanted children with and without tacrolimus and with and without food allergy

There was no significant difference in the cytokines in the transplantation group without food allergy, compared with the untransplanted group without food allergy. When looking at the transplantation group treated with tacrolimus but without food allergy, compared with the untransplanted group without food allergy, there was a significant difference in IL-7, IL-13, and MIP-1b ($P = .003$, $.003$, and $.012$, respectively) with higher concentration of IL-7 and IL-13 in the transplanted group with tacrolimus and without food allergy and lower levels of MIP-1b compared with the untransplanted group without food allergy.

3.4 | Patients with epinephrine

Six out of the nine children with reported food allergy had been prescribed epinephrine and three of the six patients with prescribed epinephrine had used epinephrine. Liver transplanted patients with food allergy that had received a prescription of epinephrine had significantly higher total IgE (2033 [234-2831] vs 13 [5-39] IU/L, $P = .002$) and MIP-1b (52 [37-96] vs 36 [32-39], $P = .035$) compared with liver transplanted patients without food allergy. No significant difference was found in eosinophil count and ECP between the two groups.

3.5 | Clinical and biochemical effects of changing immunosuppression

Two patients had severe food allergy and had to be converted from tacrolimus-based immunosuppression to MMF and corticosteroids.

Patient 1 was a 3-year-old boy. The preconversion blood test was taken 6 days before conversion, and the post-conversion blood test was taken 2 months after conversion. The patient was liver transplanted 2.5 years before conversion. He had severe food allergy (allergens caviar, tree nut, and shrimp) with a history of anaphylactic reaction and was converted from tacrolimus, MMF and corticosteroid to only MMF and corticosteroid. There was a clinical improvement in his food allergy after conversion, and he had reduction in total and specific IgE (Figures 1 and 2). Patient 1 had an increase in IL-6, GM-CSF, IP10, and MIP1b, while IL-1ra, IL-1b, IL-4, IL-5, IL-9,

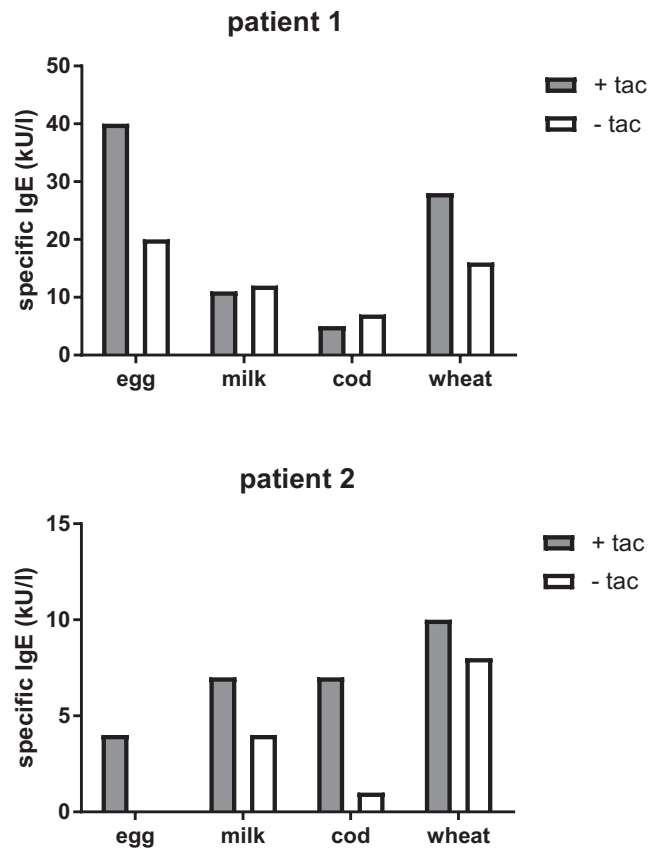


FIGURE 1 Specific IgE levels for food allergens in patient 1 (tacrolimus, MMF and corticosteroids) and patient 2 (tacrolimus and corticosteroids) before (+tac) and after (-tac) discontinuation of tacrolimus and conversion to MMF and corticosteroids

IL-12, IL-13, IL-17A, FGf, G-CSF, IFN γ , MIP-1a, PDGF, RANTES, TNF α , and VEGF were decreased (Figure 2).

Patient 2 was a girl aged 6 years at conversion. She was liver transplanted 5 years prior to the conversion. The pre conversion blood test was taken 2.5 months before conversion, and the post-blood test was taken 4 years after conversion. She had a history of severe food allergy (allergens kiwi, tree nut, coconut) after transplantation and numerous reactions with angioedema. She was converted from tacrolimus and corticosteroid to MMF and corticosteroid. Her allergy clinically improved after conversion. Patient 2 had a decrease in total and specific IgE and in IL-1ra, IL-4, IL-8, IP10, MIP-1a, PDGF, MIP-1b, RANTES, and TNF α (Figures 1 and 2). Both these patients had a decrease in IL-1ra, IL-4, MIP-1a, PDGF, RANTES, and TNF α after changing immunosuppression paralleling the clinical improvement in food allergy and reduction in total and specific IgE (Figure 2).

3.6 | Transplantation group and CLD group

Nine out of the 22 patients had food allergy, and none of the controls had reported food allergy. Ten out of 22 patients in the transplantation group and one of seven patients in the CLD group had

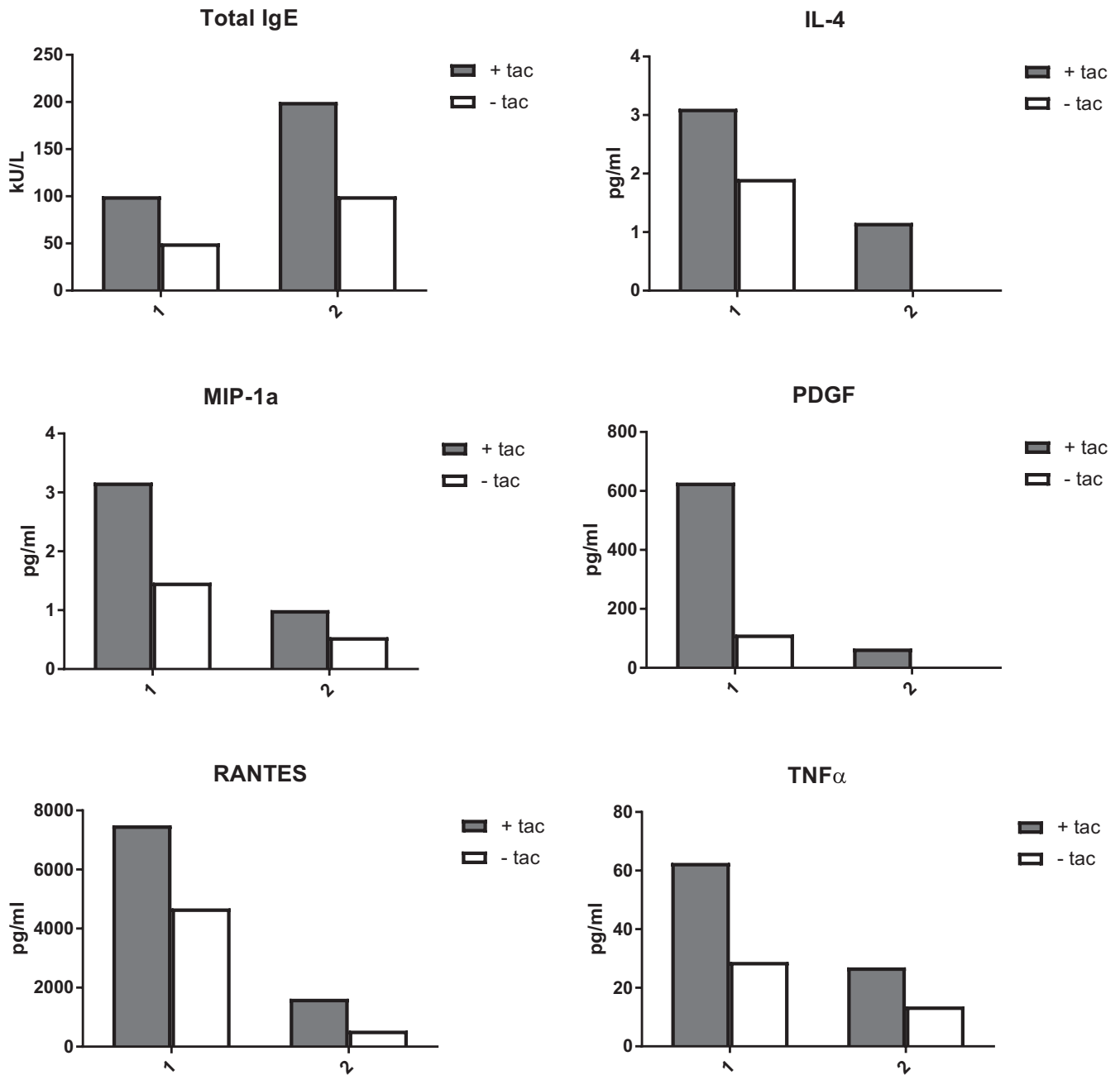


FIGURE 2 Total IgE and selected cytokine levels in patient 1 (tacrolimus, MMF and corticosteroids) and patient 2 (tacrolimus and corticosteroids) before (+tac) and after (-tac) discontinuation of tacrolimus and conversion to MMF and corticosteroids

eczema, and four of the transplanted patients with food allergy had asthma (Table 1). The median total IgE in liver transplanted patients was 39 (6-432) IU/L (n = 22) and 8.3 (2-75) IU/L in the CLD group (n = 7). The liver transplanted children had significantly higher levels of IL-1b, IL-5, IL-7, IL-13, GCSF, IFN γ , and MIP-1a compared with the CLD group, but lower levels of MIP-1b (Figure 3).

4 | DISCUSSION

Food allergy is common in liver transplanted children, and the mechanisms are poorly understood. Comparison of liver transplanted

children with food allergy and transplanted children without food allergy revealed no significant difference in the cytokine profile. However, the patients with the most severe food allergy, having been prescribed epinephrine, had increased MIP-1b compared to transplanted patients without food allergy. Discontinuation of tacrolimus in two patients with severe food allergy resulted in clinical improvement in food allergy, reduction in total and specific IgE and a decrease in IL-1ra, IL-4, MIP-1a, PDGF, RANTES, and TNF α . Liver transplanted children had a significantly different cytokine profile compared to untransplanted children with CLD.

No overall difference in the cytokine profile was found when comparing liver transplanted children with food allergy and liver

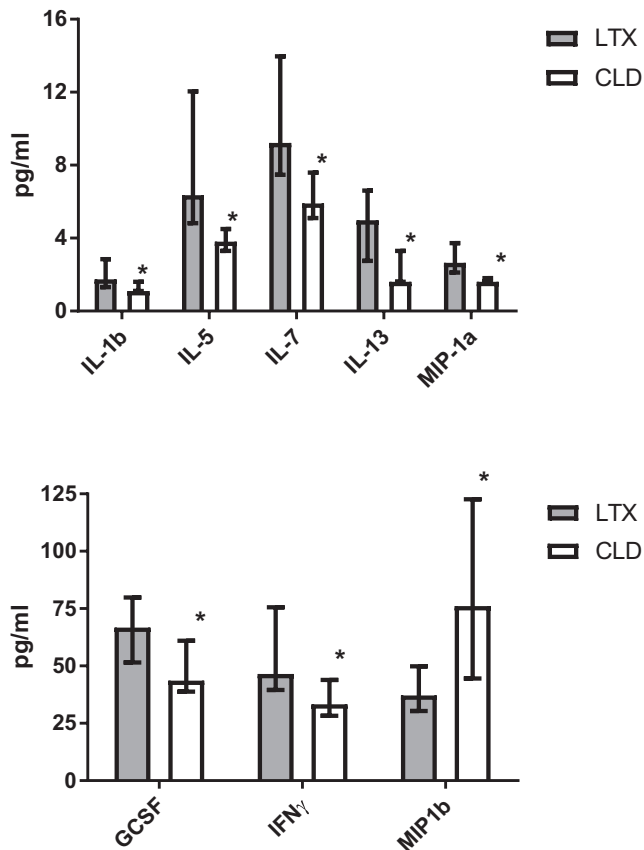


FIGURE 3 Cytokine levels in the LTX group and the CLD group

transplanted children without food allergy. Although the food allergy group had higher total IgE, eosinophils, and specific food IgE than the non-allergic transplanted patients, there was a considerable time interval between the last episode of food allergy reaction and testing time in some of the patients. Thus, it is a possibility that cytokine response after an allergic episode has been normalized at the time of sampling. Rather than assessing acute plasma cytokine changes related to food reactions, the study reveals more chronic alterations in the groups. Other studies have found a difference in the cytokine profile of food allergic children compared with healthy controls, but it should be noted that these children were not transplanted. Oral food challenge was followed by an increase in IL-4 and IL-5 after 4 and 24 hours.²⁰ Increased levels of IL-4 and IL-13 and decreased levels of IL-9, IL-17A, and IFN γ were recorded in children with cow's milk allergy compared with healthy controls. After 120 days of elimination diet, these patients had a decrease in IL-4, IL-9, IL-13 and IL-22, and an increase in IL-17A.²¹

The patients with the most severe food allergy, having been prescribed epinephrine, had increased MIP-1b compared to transplanted patients without food allergy. In the transplantation group, MIP-1b was lower compared with the CLD group. These findings could possibly be explained by opposite effects of two factors affecting these patients. Firstly, tacrolimus down-regulates the expression of MIP-1b²² and may explain why the

transplantation group had lower levels of MIP-1b compared with the CLD group. The other factor is that allergy and asthma are associated with high MIP-1b²³⁻²⁵ and even though these patients were treated with tacrolimus, MIP-1b was elevated because of allergy. MIP-1b is a pro-inflammatory cytokine involved in immune responses toward inflammation and infection.²⁶ Change in immunosuppression may affect both factors. The levels of MIP-1b increased in patient 1 after conversion, but decreased in patient 2. Of note, the time frame in the two patients was different as the blood test was taken 2.5 months following conversion in patient 1, but after 4 years in patient 2. Our hypothesis is that MIP-1b decreases after some time following conversion when the allergy effect disappears.

Use of tacrolimus in liver transplanted children has been linked to de novo food allergy. Tacrolimus causes a shift toward a Th2 cytokine profile by inhibiting IL-2.^{2,19} We did not however find a significant difference in the cytokine profile in the liver transplanted children treated with tacrolimus compared with those treated with cyclosporine or MMF. This may be due to a small number of patients in these subgroups. Tacrolimus is not the only factor as food allergy is rarely seen after kidney transplantation.^{16,17} A study by Mori et al¹⁸ found no significant difference in the serum cytokine profile between liver transplanted children and kidney transplanted children. All the patients except one in the liver transplant group were treated with tacrolimus. With this in mind, it is interesting to notice the change in the cytokine profile of two allergic patients in the transplantation group who were converted from tacrolimus. There are previous reports that change in the immunosuppression from tacrolimus to cyclosporine decrease IgE and reduce the symptoms of allergy in liver transplanted patients.^{27,28} Our two patients who had their immunosuppression changed because of food allergy also experienced a marked clinical improvement of food allergy and reduction in total and specific IgE after conversion. Furthermore, they had strikingly similar changes in cytokine profile after conversion with a decrease in IL-1ra, IL-4, MIP-1a, PDGF, RANTES, and TNF α . The changes of several cytokines upon conversion from tacrolimus indicate a decrease in inflammation. Increased levels of IL-4 play a role in the Th2 driven inflammation in food allergy.²⁹ Reduced levels of the pro-inflammatory MIP-1a also indicate that Th1 inflammation is affected. PDGF is a growth factor highly involved in the development of liver fibrosis and is associated with chronic inflammation.^{30,31} Chemokines (as RANTES or chemokine ligand 5) are relevant in allergy because of their role in regulating leukocyte recruitment, but also for cellular activation, inflammatory mediator release, promotion of Th2 inflammatory responses, and regulation of IgE.³² RANTES has been linked to recruitment of Th2 cells,³³ and TNF α is thought to play a major role in the pathogenesis of allergy and inflammatory diseases as it is produced at an early stage of allergen sensitization and continues to promote the inflammation cascade throughout the allergy development.³⁴

The clinical improvement in food allergy, the reduction of total and specific IgE, and the change in cytokine profile support that

tacrolimus plays a significant role in the development of transplant-acquired food allergy as reported by several other studies.^{2-4,7,15}

Few studies, to our knowledge, have investigated the plasma cytokine profile after LTX in children.³⁵⁻³⁷ Ganschow et al demonstrated that a tendency toward a Th2 cytokine profile corresponded with a better graft survival in infants after LTX³⁵ and early cytokine measurements after LTX showed lower levels of Th2 cytokines in patients with graft rejection.^{36,37} In the current study, we found that there was a significant difference in the cytokine profile between liver transplanted children and children with CLD. The transplantation group had higher levels of IL-1b, IL-5, IL-7, IL-13, GCSF, IFN γ , and MIP-1a compared with the CLD group, but lower levels of MIP-1b. Th2-driven inflammation is associated with increased levels of IL-4, IL-5, and IL-13.²⁹ IL-5 influences the growth, maturation, recruitment, and activation of eosinophils, and IL-13 induces IgE synthesis, eosinophil and basophil recruitment, and epithelial cell mucus production and activity.³⁸ Thus, our findings with increased levels of IL-5 and IL-13 are in accordance with a tacrolimus associated shift toward an increased production of Th2 cytokines. However, we also found elevated levels of MIP-1a (or chemokine ligand 3), which is a pro-inflammatory chemokine, and is a protein released upon the induction of Th1 responses.³⁹ Our findings are in keeping with a study by Manuyakorn et al⁴⁰ demonstrating an increase in stimulated peripheral blood mononuclear cells cytokine production of both Th1 and Th2 cytokines 6 months after LTX compared with pretransplantation levels in children. Comparison of cytokine profile between transplanted and untransplanted children with CLD thus indicated both a Th1 and a Th2 response. On the other hand, De Bruyne et al⁴¹ found decreased levels of Th1 in favor of Th2 cells within circulating follicular T-helper cells in liver transplanted children.

In this study, we compared transplanted children with and without food allergy and the transplanted group with untransplanted children with CLD. No significant difference in the cytokine profile was found between transplanted children with and without food allergy. Transplanted patients with severe food allergy that had received a prescription of epinephrine had a significantly higher MIP-1b compared with liver transplanted patients without food allergy. Changing immunosuppression causes improvement in allergic symptoms, reduction in total and specific IgE, and a change in cytokine profile. However, a longitudinal study to investigate the cytokine profile of patients awaiting LTX before initiation of immunosuppression and later after transplantation would be interesting. This could give valuable insight into a particular phenotype more prone to develop food allergy than others making it possible to tailor a more personalized immunosuppression regimen. Further studies are needed to assess this.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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