Liver transplantation reverses hypergammaglobulinemia in patients with chronic hepatic failure

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Abstract

Introduction: Sparse data are available about the effect of therapy methods on antibody levels in patients with liver failure. The aim of this study was to determine serum immunoglobulin concentrations in patients with chronic hepatic failure (CHF), acute- (ALF), or acute-on-chronic liver failure (ACLF) and to evaluate the impact of MARS treatment or liver transplantation (LT) on antibody levels.

Materials and methods: We followed ten patients with ALF, twelve with ACLF and 18 with CHF. Eight patients with ALF and seven with ACLF underwent MARS therapy, whereas the rest received LT. 13 healthy volunteers served as controls. Serum antibody concentrations were measured using ELISA-technique.

Results: Median serum levels of IgA, IgG and IgM were significantly increased in patients with CHF compared to ALF or controls ($P < 0.02$, $P < 0.01$, and $P < 0.01$). IgM and IgG concentrations were also significantly elevated in patients with CHF compared to ACLF (IgM, 3.7 *vs.* 1 g/L, $P < 0.001$; IgG, 8.7 *vs.* 3.1 g/L, $P = 0.004$). Immediately after LT a significant decrease of IgA (6.9 *vs.* 3.1 g/L, $P = 0.004$), IgG (8.7 *vs.* 5.1 g/L, $P = 0.02$) and IgM (3.7 *vs.* 1.8 g/L, $P = 0.001$) was detected in patients with CHF and antibody levels further decreased the days after LT reaching levels comparable to healthy individuals. MARS treatment had no apparent effect on the immunoglobulin profile in patients with ALF or ACLF.

Conclusion: We provide evidence that LT reverses hypergammaglobulinemia in patients suffering from CHF within one day, which could be explained to a reconstituted hepatic antibody clearance, whereas MARS treatment has no immediate effect on immunoglobulin levels.

Key words: antibodies; immunoglobulins; liver failure; liver transplantation; artificial liver support system, molecular adsorbent recirculating system

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Introduction

Chronic hepatic failure (CHF) and cirrhosis are mostly caused by chronic hepatitis C, alcohol abuse, or non-alcoholic fatty liver disease and are leading causes of morbidity and death (1). Most patients suffering from cirrhosis are asymptomatic over a long period of time until, e.g. variceal bleeding and bacterial peritonitis cause decompensation leading to ascites, encephalopathy, portal hypertension, and hepatorenal syndrome (2). A common observation in patients suffering from CHF is the occurrence of hypergammaglobulinemia, described for the first time in the early 1970s (3). These elevated immunoglobulin concentrations even seem to add to the pathogenesis of hepatic fibrosis (4). Immunoglobulin serum levels correlate with histological findings of advanced forms of he-

patic fibrosis as well as with the progression of liver disease (5,6) and may add to the compromised immune status (2). Thus liver transplantation (LT) is the ultimate therapy for patients when standard therapy has failed and liver dysfunction is irreversible (2). According to the United Network of Organ Sharing (UNOS) only 6,000 liver transplantations are performed every year in the United States and about 16,000 patients are currently awaiting transplantation (7).

In contrast to CHF, acute liver failure (ALF) is the clinical manifestation of a sudden and severe liver damage and acute-on-chronic liver failure (ACLF) describes a sudden exacerbation of liver dysfunction in patients with pre-existing hepatic disease. Despite continuous research and improvement in intensive care, ALF and ACLF still represent life threatening conditions, associated with mortality rates up to 60% (8,9). Patients suffering from acute liver dysfunction are especially susceptible to infections, due to multiple immunologic defects resulting either from hepatic dysfunction as well as from side effects of the high dependency care they receive. About half of those patients recover spontaneously after intensive care, which also includes the application of artificial liver assist devices like the molecular adsorbent recirculating system (MARS) (10). Those devices were developed to support or bridge hepatic function especially in patients with an acute exacerbation of hepatic dysfunction. In contrast to patients suffering from CHF, only a few patients with acute liver dysfunction undergo LT as ultimate therapy. Several days after LT, hypogammaglobulinemia can occur, adding to overall mortality in transplant recipients by increasing the risk of postoperative infection (11,12).

In our pilot study we investigated serum immunoglobulin levels in patients suffering from chronic, acute or acute-on-chronic liver failure and compared the concentrations to healthy probands, who served as controls. We further studied the immediate effect of LT on immunoglobulin levels in patients with CHF and ALF/ACLF to assess separately prompt changes in postoperative antibody concentrations. Furthermore, we compared immunoglobulin serum levels before and after treatment with the artificial liver assist device MARS, since immunoglobulin elimination by the MARS system seems likely.

Materials and methods

Patients and clinical features

The study was approved by the institutional ethics committee and is in accordance with the Helsinki Declaration of 1975. After informed consent, samples were prospectively collected within one year and retrospectively analyzed. We followed ten patients with ALF, twelve patients with ACLF, and 18 patients suffering from CHF. 13 healthy volunteers (10 male / 3 female, range age 21–56, median age 25) served as controls. Liver diseases, abdominal pain over the last four weeks, food intake within the last six hours, or pregnancy have been excluded in the control group via anamnesis. The patients' diagnosis, baseline demographics and initial laboratory values are shown in Table 1. Pre- and postoperative liver parameters of all patients who underwent LT are given in Table 2 and 3.

CHF was characterized by the continuous fibrosis of liver tissue due to chronic liver damage over a longer time period (1). As a consequence, liver function got increasingly impaired and fibrotic changes finally led to cirrhosis, apparent among others by massive ascites at the end-stage of CHF. ALF was defined with the onset of coagulopathy with international normalized ratio (INR) of greater than 1.5 and mental alteration in a patient without pre-existing liver cirrhosis and with an illness of less than 26 weeks duration (13). Patients suffering from ALF were susceptible to develop severe complications, like cerebral oedema, due to an impaired protein synthesis of the liver, in turn indicating a loss of liver function of about 80%. ACLF was defined as acute deterioration of liver function followed by other end organs in a patient with previously compensated chronic liver disease (9). A prior episode of decompensation was no exclusion criterion in this group.

In our study eight patients with ALF and seven with ACLF were treated with MARS. MARS is a two-circuit detoxification system to remove albumin-

Table 1. Underlying liver disease, baseline demographic data and initial laboratory variables

	Acute liver failure (N = 10)	Acute-on-chronic liver failure (N = 12)	Chronic hepatic failure (N = 18)
Unknown	3		
Traumatic liver rupture after blunt abdominal trauma	1		
Protozoan infection	1		
Mushroom poisoning	1		
Liver embolism	1		
Partial liver resection	1		
Liver metastasis	1	1	
Wilson's disease	1	1	
Hereditary hemorrhagic telangiectasia		1	
Haemochromatosis		1	
Autoimmune hepatitis		1	
Primary biliary cirrhosis		1	
Hepatitis C cirrhosis		5	5
Alcoholic liver cirrhosis		1	10
Hepatocellular carcinoma (chronic Hepatitis B)			3
Gender (male / female)	5 / 5	8 / 4	13 / 5
Age	33 (18-62)	55 (27-67)	57 (47-66)
Underwent LT	2	5	18
Underwent MARS	8	7	
Survived / Died	5 / 5	7 / 5	16 / 2
Bilirubin (µmol/L)	266 (64-750)	80 (2-313)	32 (6-233)
Creatinine (µmol/L)	139 (67-347)	95 (34-344)	93 (50-680)
AST (U/L)	635 (72-5771)	219.5 (27-10973)	60 (28-672)
ALT (U/L)	339 (22-3997)	152 (19-6646)	33 (11-538)
PT (% activity)	28 (< 5-71)	50 (21-> 150)	58.5 (21-94)

Data are given as median and range.
AST - aspartate aminotransferase; ALT - alanine aminotransferase; PT - prothrombin time; LT - liver transplantation; MARS - molecular adsorbent recirculating system.

Table 2. Laboratory values in all patients suffering from CHF who underwent LT (18 patients).

	post LT	d1	d2	d3	d4	d5
Bilirubin (µmol/L)	47 (12-157)	84 (16-238)	65 (10-274)	65 (10-256)	76 (20-262)	60 (20-314)
Creatinine (µmol/L)	91 (58-278)	122 (7 -217)	114 (73-207)	89 (60-188)	88 (58-249)	90 (59-178)
AST (U/L)	701 (97-5377)	777 (291-6763)	481 (136-4943)	169 (62-1802)	128 (38-596)	136.5 (26-239)
ALT (U/L)	461 (74-3476)	886 (229-4201)	713 (183-6000)	550 (156-6470)	428 (106-2782)	307.5 (66-1450)
PT (% activity)	39.5 (17-90)	39 (11-80)	60 (7-133)	65 (17-119)	63.5 (32-96)	62.5 (36-88)

Data are given as median and range, preoperative values are shown in table 1.
CHF - chronic hepatic failure; AST - aspartate aminotransferase; ALT - alanine aminotransferase; PT - prothrombin time; LT - liver transplantation; d1–d5, day 1 to day 5 postoperative.

Table 3. Laboratory values in all patients suffering from ALF or ACLF who underwent LT (7 patients).

	pre LT	post LT	d1	d2	d3	d4	d5
Bilirubin (µmol/L)	202 (2-750)	142 (16-263)	112 (13-183)	70 (15-202)	69 (14-286)	154 (18-285)	95 (21-275)
Creatinine (µmol/L)	92 (34-347)	98 (75-453)	124 (78-683)	103 (65-355)	88 (58-209)	82 (53-181)	112 (57-193)
AST (U/L)	635 (27-10973)	1190 (488-6117)	1639 (314-3454)	875 (183-2190)	262 (88-920)	196 (78-436)	89 (54-245)
ALT (U/L)	488 (29-6646)	999 (358-4260)	1143 (358-2183)	1139 (304-2018)	829 (212-1418)	736 (219-913)	467 (117-591)
PT (% activity)	23 (<5->150)	40 (31-96)	48 (27-88)	50 (23-88)	69 (11-87)	80 (21-97)	73 (29-88)

Data are given as median with range.
ALF - acute liver failure; ACLF - acute-on-chronic liver failure; CHF - chronic hepatic failure; AST - aspartate aminotransferase; ALT - alanine aminotransferase; PT - prothrombin time; LT - liver transplantation; d1–d5, day 1 to day 5 postoperative.

bound molecules like bilirubin and ammonia (14), and has been shown to improve renal function, systemic hemodynamic and hepatic encephalopathy (15). Indications for MARS therapy were ammonia levels of 100 µmol/L or higher with hepatic encephalopathy grade 3. Each eligible patient received 1 to 5 MARS treatments lasting 15-22 hours. The treatment was conducted via a conventional hemodialysis catheter (14), a dialysis machine equipment (BM 25, Edwards Life Sciences, Irvine, CA, USA), and a highly permeable dialyzer (MARS-Flux, Gambro, Lund, Sweden). The MARS cycle was filled with a 20% human albumin solution and the blood flow from the dialysis machine and the albumin dialysate circuit were equal, at rates of 120-150 mL/min. Prostaglandin I2 (3-5 ng/kg/min) was applied continuously extracorporeal after the blood pump of the MARS circuit. To maintain the activated clotting time between 120 and 140 seconds unfractioned heparin was adjusted if required by the intensivist on duty (16).

All patients with CHF, two patients with ALF, and five with ACLF included in our study underwent LT. Patients with CHF suffered from end stage liver disease receiving LT and were clinically stable at the time of blood sampling. After LT all patients received immunosuppressive medication following the center-specific standard therapy, starting with an intraoperative dose of 200 mg methylprednisone followed by a steroid taper and withdrawal after 3 months. Further, all patients received induction with 2.5 mg *per* kilogram bodyweight thymoglobulin (2.5 mg/kgBW/d) for three days, starting immediately after transplantation. The beginning of maintenance immunosuppression with low-dose cyclosporine (trough level 130-150 ng / mL for month 1, 100-130 ng/mL month 2-3, < 100 ng/mL beyond month 3) was delayed for 3-4 days. Patients suffering from Hepatitis B additionally received 10000 IE Hepatect medication during LT as well as on 7 postoperative days. Hepatect medication consists of human hepatitis B immunoglobulins (IgG only).

Laboratory data

A venous blood sample was initially obtained from each patient before LT or the first MARS treatment as well as from healthy controls. From 15 patients suffering from ALF or ACLF another sample was taken immediately after detaching the patient from the MARS system after the first treatment with the artificial liver support system. Venous blood from patients who underwent LT was obtained directly before and immediately after transplantation, as well as on five following days after the procedure. Right after collection in a 9 mL Z Serum Clot Activator Tube (Greiner Bio-One International GmbH, Austria), blood was allowed to clot for up to 60 minutes at room temperature (22 °C) and afterwards centrifuged at 2000 RCF for 10 min at 4 °C. Serum aliquots were transferred in tubes and stored at –70 °C until further analyzed within

the next months. Samples were thawed once simultaneously and randomized before analysis. Immunoglobulin levels were determined by using the Human Immunoglobulin ELISA Quantitation Set of Bethyl Laboratories (Montgomery, Texas, US) according to the manufacturer instruction. Color reaction was gained adding tetramethylbenzidin (TMB; Sigma, St. Louis, Missouri, US, www.sigmaaldrich.com) and stopped with 1% sulfuric acid solution (in aqua bidest. diluted 95–98% sulfuric acid, Merck KGaA, Darmstadt, Germany). The optical density was measured with a microplate reader (Victor 3, Perkin Elmer, Waltham, US) at a wavelength of 450 nm. Coefficients of variation of the used ELISA sets are according to the manufacturer: 0.4–9.8% for IgA, 0.3–15.4% for IgM, 0.3–3.5% for IgG, and 0.6–4.2% for IgE. IgG, IgM and IgA serum levels were quantified in gram *per* liter (g/L) and IgE in nanogram *per* milliliter (ng/mL).

Following additional parameters were determined *via* routine tests and in the course of routine clinical work: aspartate aminotransferase, alanine aminotransferase, bilirubin, serum creatinine, and prothrombin time. The aminotransferases were determined *via* enzymatic reaction with pyridoxal phosphate according to the recommendations of the German Society for Clinical Chemistry (17). Bilirubin was quantified *via* diazotization and creatinine with the Jaffe reaction (18). The prothrombin time was measured with a coagulometer according to Quick *et al.* (19) and Barthels *et al.* (20). All parameters were routinely quantified at a certified laboratory in the Department of Laboratory Medicine at the Medical University of Vienna.

Statistical analysis

Immunoglobulin levels were compared between healthy individuals and patients suffering from CHF, ACLF and ALF before transplantation or the first MARS treatment. Gaussian distribution was assessed with the Shapiro-Wilk normality test. Since Gaussian distribution could not be verified for all analyzed groups, especially for that with fewer patients, the non-parametric Mann-Whitney-test (two-tailed) was used to compare initial immunoglobulin concentrations. According to the Bonferroni adjustment for multiple comparisons, an individual $P < 0.013$ was necessary to achieve statistical significance at the 5% level. The immunoglobulin concentrations in patients with ALF or ACLF under MARS treatment, as well as globulin levels before and after LT were compared using paired Wilcoxon's signed rank tests (two-tailed). A $P < 0.05$ was necessary to achieve statistical significance at the 5% level. Correlation between immunoglobulin levels and liver enzymes were calculated in patients suffering from CHF by using Spearman's correlation coefficient. Unless otherwise stated data are given as median with range. Statistical analysis was performed using GraphPad Prism Version 5.01 (GraphPad Software, Inc. California, US).

Results

Initial serum immunoglobulin levels in patients with ALF, ACLF, or CHF

In patients suffering from CHF initial serum IgG and IgM levels were significantly increased in comparison to ALF, ACLF or healthy individuals (8.67 *vs*. 3.18, 3.11 or 4.44 g/L for IgG, 3.71 *vs*. 0.74, 0.95 or 1.54 g/L for IgM), (Figure 1A and 1B). Increased IgA serum levels were found in patients suffering from CHF as compared to patients with ALF or controls (6.86 *vs*. 1.72 or 2.51 g/L), (Figure 1C). However, no significant difference could be found for IgE serum levels. Healthy individuals had a median IgE serum concentration of 96 ng/mL (range 28–381), patients with ALF 429 ng/mL (range 49–11842), with ACLF 131 ng/mL (range 30–502) and with CHF 75 ng/mL (range 23–1667).

Impact of LT or MARS treatment on serum immunoglobulin levels

In patients suffering from CHF a significant decrease in serum IgG, IgM and IgA levels could be observed immediately after liver transplantation (8.67 *vs*. 5.06 g/L for IgG, 3.71 *vs*. 1.77 g/L for IgM, 6.86 *vs*. 3.07 g/L for IgA) and the first postoperative day, (Figure 2). Further, serum immunoglobulin levels on the second to the fifth postoperative day differed significantly as compared to preoperative values ($P < 0.001$, $P = 0.011$, 0.009, 0.008 for IgG; $P =$

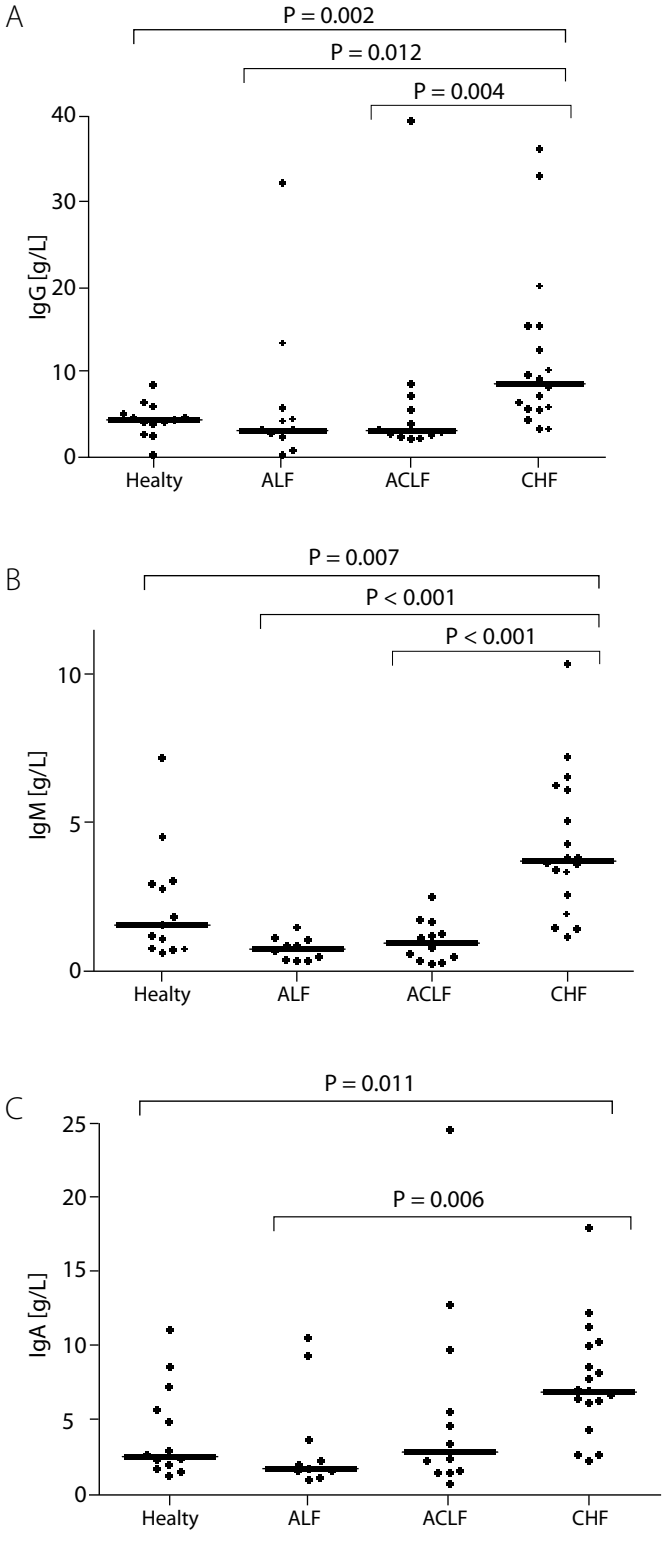

Figure 1. IgG (A), IgM (B) and IgA (C) serum levels in all patients suffering from chronic hepatic failure (CHF), acute (ALF) or acute-on-chronic liver failure (ACLF), as well as from healthy individuals (13 volunteers). Each dot represents an individual patient. The line indicates the median. Only significant P values are specified.

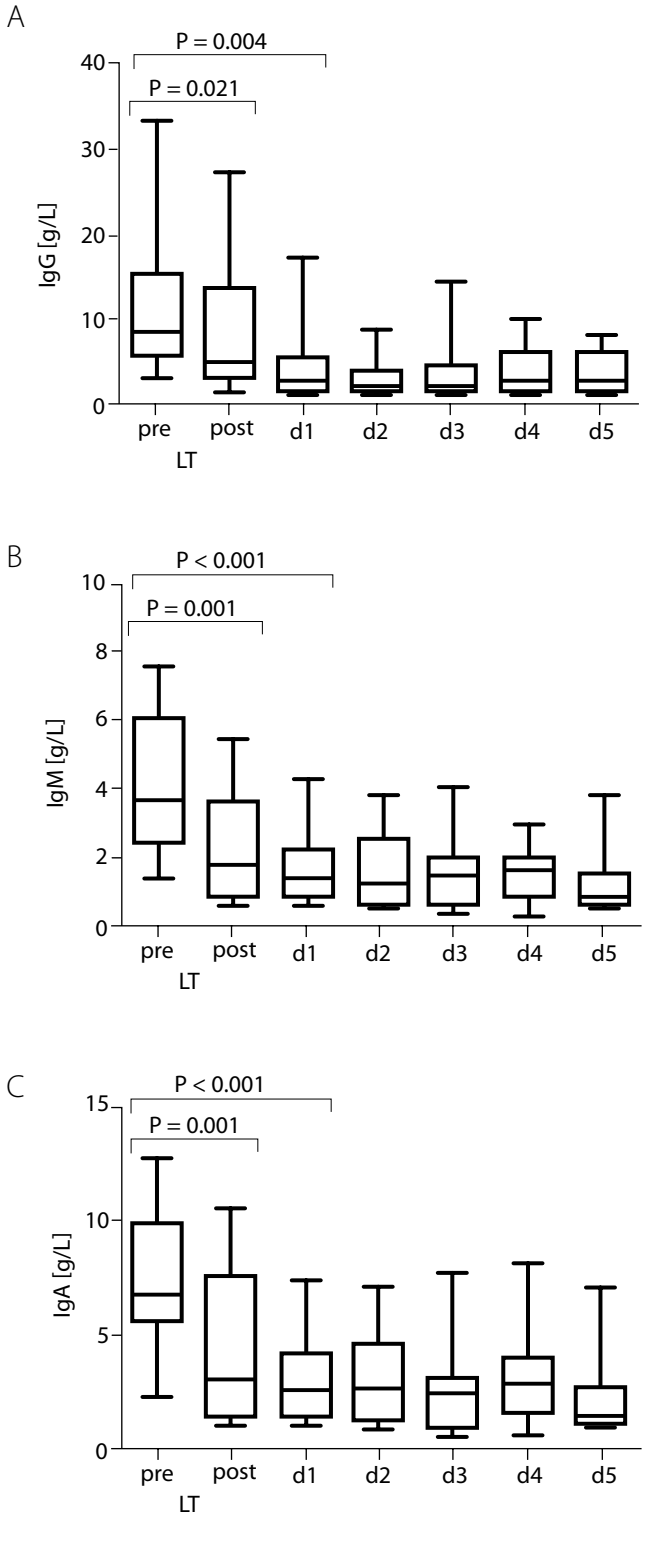

Figure 2. Immunoglobulin levels in patients with chronic hepatic failure (18 patients) before and after liver transplantation (LT) as well as on five following days (d1-d5). Median with range. Whiskers indicate the 10-90 percentiles.

0.003, 0.003, 0.001, 0.008 for IgM; P < 0.001, P = 0.002, 0.002, 0.008 for IgA). To reveal errors due to peri- and postoperative administered Hepatect medication (human IgG), three patients suffering from Hepatitis B were tentatively excluded from the statistic calculation, with no obvious effects on significance. Therefore all values given in Tables or Graphs include all patients of the stated group, also those suffering from Hepatits B. For the sake of completeness, P values for IgG serum levels of the patient collective without Hepatect medication were as followed: 0.041 immediately after LT, and 0.005, < 0.001, 0.032, 0.023, and 0.031 on five postoperative days as compared to preoperative concentrations. For IgE no significant changes after LT could be detected. IgE serum levels immediately after LT and on five following days were 58 ng/mL (range 32–842), 86 ng/mL (range 31–855), 89 ng/mL (range 27–860), 104 ng/mL (33–908), 124 ng/mL (range 31–800) and 102 ng/mL (range 32–740).

In seven patients with ALF or ACLF who underwent LT no significant changes in immunoglobulin serum concentrations were observed (Table 4).

In a subgroup of 15 patients with ALF or ACLF immunoglobulin measurements were performed immediately before and after the first MARS session, whereby no obvious effect of the treatment on immunoglobulin serum concentrations could be detected. Median serum immunoglobulin levels before and after MARS treatment are shown in Table 4.

Correlation of immunoglobulin concentrations with liver parameters

A significant positive correlation in patients suffering from CHF can be found for preoperative bilirubin and IgM serum concentrations with a P value < 0.05 and a correlation coefficient of 0.534. IgG serum levels show a significant correlation to albumin levels immediately after LT (P = 0.026, r = 0.523) and on the fifth day after operation (P = 0.023, r = 0.779). For IgA a significant negative correlation was found to creatinine concentrations on the first postoperative day with a P of 0.031 and a correlation coefficient of –0.524. IgE values significantly correlate with bilirubin levels postoperative (P = 0.017, r = 0.588), on the first (P = 0.012, r = 0.632) and the second day after LT (P = 0.025, r = 0.575).

Discussion

Our data show increased immunoglobulin serum concentrations in patients suffering from CHF in comparison to healthy individuals, or patients with ALF or ACLF. We further found a decrease in immunoglobulin serum levels in patients with CHF immediately after LT, whereas in patients with ALF or ACLF no comparable effect was observed. In addition we could demonstrate that MARS treatment has no apparent effect on the immunoglobulin profile in patients suffering from acute liver dysfunction.

Hypergammaglobulinemia is frequently observed in patients suffering from CHF. A reason for this finding might be either the reduced liver clearance of antigens via the portal venous system leading to an increased systemic antibody production (21,22) or the impaired removal of antibodies by the diseased liver (23). Immunoglobulins also seem to play an important role in the pathogenesis of hepatic fibrosis as exposure to IgG stimulates the differentiation and proliferation of hepatic stellate cells (4), the major cell type in the development of liver fibrosis. In patients with CHF serum immunoglobulin concentration even correlates with histological findings of advanced forms of hepatic fibrosis (6), with more elevated levels in patients with decompensated cirrhosis as compared to patients with compensated CHF (5). In accordance to literature, our data also show increased immunoglobulin serum levels in patients suffering from CHF as compared to ALF or healthy individuals. Antibody levels were also significantly elevated in patients with CHF in comparison to patients with an acute exacerbation of an initial chronic liver disease.

In contrast to CHF, ALF and ACLF are caused by the abrupt onset of liver dysfunction. Patients suffering from ALF or ACLF are highly vulnerable for infections, due to multiple immunological defects, influencing hepatic injury as well as the progression of encephalopathy and systemic inflammato-

Table 4. Serum immunoglobulin levels in all patients suffering from ALF or ACLF before and after LT (23 patients) or MARS treatment (15 patients).

	pre LT	post LT	pre MARS	post MARS
IgG (g/L)	4.33 (2.21-39.43)	3.49 (1.93-59.79)	2.74 (0.33-32.07)	3.20 (0.61-32.62)
IgM (g/L)	0.94 (0.24-2.49)	0.64 (0.40-3.60)	0.59 (0.25-1.61)	0.80 (0.24-6.2)
IgA (g/L)	5.70 (0.48-24.51)	4.51 (1.04-12.74)	2.30 (0.89-10.32)	1.74 (0.83-18.54)
IgE (ng/mL)	40 (30-251)	86 (41-125)	218 (57-5973)	187 (70-3337)

Data are given as median with range.
ALF - acute liver failure; ACLF - acute-on-chronic liver failure; LT - liver transplantation; MARS - molecular adsorbent recirculating system.

ry responses (24,25). However, the immunoglobulin profile in patients suffering from acute liver failure differs between the underlying hepatic diseases (26). While no difference of IgG and IgA levels in patients with non-paracetamol induced liver failure could be found, IgM was significantly elevated in patients with viral disease. Patients suffering from ALF caused by paracetamol intoxication had significant lower immunoglobulin levels, which explained the authors through direct drug-related effects on the liver. Autoantibodies were also detected in coexistence with elevated IgG and especially IgM serum levels (26). However, in our study we could not find any significant differences in serum immunoglobulin levels of patients suffering from ALF in comparison to ACLF or healthy individuals.

In the United States, 45% of patients suffering from acute liver dysfunction recover spontaneously after intensive care, which also includes the application of artificial liver assist devices (10). 25% undergo LT (10), which is the ultimate therapy of patients suffering from CHF too. After LT, hypogammaglobulinemia can be detected in about 30% of patients, increasing the risk of infection and adding to overall mortality (11,12). Gonzáles-Quintela *et al.* demonstrated a decrease in serum immunoglobulin levels during and immediately after LT in 18 patients with alcoholic cirrhosis (27). A drop in immunoglobulin levels can be detected even during hepatectomy and especially after portal vein declamping suggesting an immediate increased liver catabolism (27). Months after transplantation levels of IgA, IgG and IgM remained within normal or near-normal concentrations (27). In accordance with these findings we could also show a sudden drop of immunoglobulin concentrations in patients suffering from CHF also including non-alcoholic patients, immediately after LT. Furthermore, antibody levels remained in the same range of healthy individuals over the observed period of five days after transplantation. In contrast to those findings we could not detect any changes in immunoglobulin concentrations in patients with ALF or ACLF who underwent LT. However, at first we showed that patients with acute hepatic injury had initial antibody profile comparable with healthy individuals in contrast to patients with CHF.

Antibodies have a half-life of several days. Therefore, it is likely that the observed immediate decrease of immunoglobulin levels in CHF patients derived from the reconstituted hepatic removal of antibodies, than from less antigens passing through the portal venous system into systemic circulation. This assumption is further strengthened by the fact, that inclusion of Hepatitis B patients, who received high concentrated IgG, into statistical analysis caused no change in significance.

The main target of peri- and postoperative immunosuppressive therapy is the cell-mediated immune response. Thymoglobulin and cyclosporine - which is given three days after LT for the first time - mainly lower the activity of T cells and their immune response. The glucocorticoid methylprednisone lowers the activity and number of T- and B cells. Hence, the effect of methylprednisone on

immunoglobulin levels only becomes apparent after several days (28). Therefore, an instant diminishing effect caused by the immunosuppressive therapy seems implausible, since immunosuppression does not directly affect circulating antibodies. In addition, immunosuppressive therapy was administered to all patients after LT, also including patients with ALF or ACLF. Nevertheless, the effect of perioperative volume administration with consecutive dilution cannot be entirely excluded, even though the diminishing effect was not obvious in patients with ALF or ACLF after LT. Moreover, there is no continuous trend regarding the correlation between serum antibody levels and other liver parameters, since significant correlations were only found sporadically after transplantation.

We further investigated the effect of MARS therapy on the immunoglobulin profile in patients with an acute aggravation of hepatic failure, since the removal of antibodies by MARS treatment might be an unintended side effect. Patients with liver dysfunction are especially prone to infections. As a consequence, elimination of circulating antibodies by MARS treatment would further increase the risk of infection and add to overall mortality. However, we could not find any significant effects on the immunoglobulin profile caused by the artificial liver assist device treatment.

In conclusion we provide evidence for elevated immunoglobulin concentration in the sera of patients suffering from CHF and a reverse effect through LT. In contrast, MARS treatment had no effect on the immunoglobulin profile in patients with ALF or ACLF after one treatment cycle. However, our results warrant further larger clinical studies and longitudinal investigation including a higher number of patients and matched controls to assess the role of immunoglobulins in CHF versus ALF/ACLF after LT.

Potential conflict of interest

None declared.

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