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REVIEW

Intravenous immunoglobulins in liver transplant patients: Perspectives of clinical immune modulation

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Abstract

Shortage of appropriate donor grafts is the foremost current problem in organ transplantation. As a logical consequence, waiting times have extended and pretransplant mortality rates were significantly increasing. The implementation of a priority-based liver allocation system using the model of end-stage liver disease (MELD) score helped to reduce waiting list mortality in liver transplantation (LT). However, due to an escalating organ scarcity, pre-LT MELD scores have significantly increased and liver recipients became more complex in recent years. This has finally led to posttransplant decreasing survival rates, attributed mainly to elevated rates of infectious and immunologic complications. To meet this challenging development, an increasing number of extended criteria donor grafts are currently accepted, which may, however, aggravate the patients' infectious and immunologic risk profiles. The administration of intravenous immunoglobulins (IVIg) is an established treatment in patients with immune deficiencies and other antibody-mediated diseases. In addition, IVIg was shown to be useful in treatment of several disorders caused by deterioration of the cellular immune system. It proved to be effective in preventing hyperacute rejection in highly sensitized kidney and heart transplants. In the liver transplant setting, the administration of specific Ig against hepatitis B virus is current standard in post-LT antiviral prophylaxis. The mechanisms of action of IVIg are complex and not fully understood. However, there is increasing experimental and clinical evidence that IVIg has an immuno-balancing impact by a combination of immuno-supporting and immuno-suppressive properties. It may be suggested that, especially in the context of a worsening organ shortage with all resulting clinical implications, liver transplant patients should benefit from immuno-regulatory capabilities of IVIg. In this review, perspectives of immune modulation by IVIg and impact on outcome in liver transplant patients are described.

Key words: Intravenous immunoglobulins; Immune modulation; Hyperimmunoglobulin; Model of end-stage liver disease; Liver transplantation

Core tip: In times of an escalating organ scarcity, decreasing posttransplant survival rates following liver transplantation have been reported. Predominantly infectious and immunologic complications were identified to account for this recent outcome deterioration. Therefore, balancing the recipients' immune system is currently discussed as useful approach to improve prognosis. Intravenous immunoglobulins (IVIg) are thought to provide favorable immuno-regulatory capabilities. This paper summarizes the current available clinical data that indicate beneficial immuno-modulatory properties of IVIg in liver transplant patients.

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INTRODUCTION

Liver transplantation (LT) has evolved to become a standard procedure in the treatment of end-stage liver disease[1,2]. Due to refined surgical techniques, advancements in intensive care treatment and progress in immunosuppressive medication, post-LT outcome improved dramatically over the past decades[3]. As a result, donors' and recipients' selection criteria were considerably expanded and numbers of LTs performed were significantly increasing in recent years. Due to a dramatic donor organ shortage, growing waiting lists, prolonged waiting times and increasing pre-LT mortality rates have been reported[4-6]. To respond to this challenging situation, the model of end-stage liver disease (MELD) score was implemented to give priority to the most urgent patients on the waiting lists. The "sickest first" approach based on serum creatinine, bilirubin, and the international normalized ratio contributed to reduction of waiting list mortality[7-13]. However, the problems were rather shifted from the pre- to the posttransplant period. It was a consequence of the escalating organ shortage that final pre-LT MELD scores were significantly increasing in recent years[11-14]. Therefore, liver transplant patients became more complex with considerably higher perioperative risk profiles. Rates of early posttransplant immunologic and infectious complications have markedly increased and survival rates were, thus, significantly deteriorating in recent years[10-14]. There is evidence that the immune systems of high-MELD patients are per se compromised, which in turn, may lead to an increased risk of septical disorders. Almost 85% of patients become afflicted with early infections, which is nowadays the most common cause of death soon following LT[10-14]. To realize LT at an earlier stage of disease progression, an increasing number of so-called extended criteria donor organs (ECD; based on donor age, liver steatosis, allograft infections, living-related or non-heart beating donors) are nowadays accepted[15,16]. The use of such marginal grafts may, however, aggravate the risk of allograft dysfunction, immunologic imbalance and infectious complications[15,16]. Therefore, balancing the liver recipients' immune system has been recognized as key approach in the context of organ scarcity and resulting clinical implications. Tailoring the immunosuppressive therapy to the patients' individual need is an established strategy for an early immune regulation[17]. However, balancing between reduction of infectious risks and increased susceptibility for graft rejection may be difficult. Indeed, there are no clinical parameters that reliably define the lowest possible immunosuppressants' dose for avoiding immunologic attacks to the allograft[18]. Need of anti-rejection treatment may, in turn, increase the risk of septical complications[19]. Therefore, a combination of immuno-stimulating and immuno-suppressive properties, as were recently suggested for intravenous immunoglobulins (IVIg), could be another attractive immuno-balancing approach[20-22].

Treatment with IVIg was introduced in the 1950's, primarily for substitution of antibodies in patients with immune deficiencies[20-22]. Since the evidence that IVIg may ameliorate immune thrombocytopenic purpura in 1981, it has been used for the treatment of a wide range of autoimmune and systemic inflammatory disorders. In addition to these mainly antibody-mediated diseases, IVIg proved to be effective in several disorders caused by deterioration of the cellular immune system, like multiple sclerosis, Kawasaki disease and graft *vs* host disease[20-25]. Subsequently, IVIg was increasingly used in the transplant setting. It was shown to be effective in prophylaxis and treatment of severe allograft rejection, particularly in highly sensitized kidney and heart recipients. In addition, IVIg proved to be beneficial in the treatment of posttransplant hypogammaglobulinemia[26-28]. In the 1990's, the use of specific immunoglobulins (Ig) against hepatitis B virus (HBV) was established as standard for prophylaxis against HBV recurrence in liver transplant patients[29].

The exact modes of action of IVIg are complex and not yet fully understood. However, there is increasing experimental and clinical evidence that, beyond clearing pathogenic autoantibodies, IVIg may establish long lasting modulations of the cellular immune system[21,22]. The nature of these immuno-regulatory capabilities suggest that, particularly in these times of higher immunologic and septical risks, liver transplant patients might benefit from early post-LT treatment with IVIg[30,31].

The aim of this review was to report on current available data indicating prognostically favourable immuno-modulatory properties of IVIg and, thereby, improved outcome following LT. For this purpose, an extensive review of the English literature using the PubMed database was performed by selecting papers according to the following key terms: "liver transplantation", "immunoglobulin", "hyperimmunoglobulin", and "immune

modulation".

MECHANISMS OF IMMUNE MODULATION BY IVIG

Therapeutically administered Ig consist of a polyspecific IgG preparation with small amounts of IgA and IgM. It is obtained from plasma pools of either thousands of healthy blood donors or donors with specifically high antibody titers directed against several viruses[20-22]. Treatment with IVIg was shown to be safe. Only mild generalized symptoms like headache, fever and nausea have been described in a small number of patients, but serious adverse effects are mostly uncommon. The half-life of IVIg is about three weeks. The clinical effects of IVIg were, however, proven beyond this period. Therefore, immuno-regulatory capabilities by IVIg were suggested to be based not only on antibody-mediated mechanisms but rather on interactions with the cellular immune system[20-22]. The modes of action of IVIg are very complex and still elusive[30]. They are triggered *via* selective and distinct molecular mechanisms of biological processes that are implicated in innate or acquired immune responses[20-22,30]. There are some excellent reviews on the specific effects of IVIg on the immune system[21,22,30,31]. Thus, only some of the most important immuno-regulatory properties of IVIg are mentioned below.

Fab-mediated modes of action

Neutralization of auto-antibodies by anti-idiotype antibodies present in IVIg was one of the first explanations for the anti-inflammatory impact of IVIg. Apart from well-known microbial antigen-specific binding effects, IVIg is supposed to convert a pro-inflammatory trigger into an anti-inflammatory condition by neutralization of endogenous inflammatory chemokines and cytokines and apoptosis-inducing molecules *via* naturally occurring auto-reactive antibodies[32-34].

Targeting of Fc receptors

Fc gamma receptors (FcγRs) are the main receptors for IgG and, thus, very likely to be involved in clinically relevant immuno-regulatory actions of IVIg. They are found on almost all immune cells (B- and T-cells, natural kille cells, dendritic cells, macrophages, monocytes neutrophils, eosinophils, and platelets). They mediate a wide range of biological immune response, like phagocytosis of IgG-opsonized microorganisms or immune complexes, antibody-dependent cellular cytotoxicity, activation of the NADPH oxidase, and the release of cytokines[21,22,33]. Based on their affinity for monomeric IgG, they can be divided in high-affinity FcγRI and the low-affinity FcγRII and FcγRIIII. Biological pathways may be mediated by activating (FcγRI and FcγRIII) or inhibiting (FγRII) mechanisms[34-36]. Blockade of activating FcγRs by high doses of IVIg and, thereby, saturation of FcγRs is discussed as one possible way of immune modulation. Up-regulation of the inhibitory FcγRII as a result of sialylated IgG-Fc is another prevailing theory for immunologic impact of IVIg[36]. Furthermore, saturation of the neonatal FcR (FcRn) may increase the clearance of pathogenic antibodies[37]. FcRn is expressed by human endothelial cells to recycle IgG and, thus, extends its half-life. Saturation of these receptors with high-doses of IVIg is supposed to shorten the half-life of all circulating IgG including harmful auto-antibodies[34,37].

Inhibition of the complement cascade

IVIg was shown to contain antibodies against several components of the classical complement pathways, like C1, C3a, C3b and C4[38]. Apart from that, the Fc portion of IgG was shown to inhibit C5 convertase, an enzyme that is required for subsequent formation of the membrane attack complex[21,22,27].

Effects on cytokines

Modulating the production of cytokines and cytokine antagonists is supposed to be another important immuno-modulatory mechanism of IVIg. This capability is not only triggered by affecting monocytic cytokine production, but also *via* increase of T 1 helper (Th1) and Th2 cytokine gene expression and production[21,39]. IVIg was shown to reduce the level of several cytokines, like interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and nuclear factor κB. Furthermore, it may selectively trigger the production of IL-1-receptor antagonist, the natural antagonist of IL-1[21,33,40]. The anti-inflammatory cytokine IL-11 was, by contrast, shown to be up-regulated by IVIg[41]. Recently, it has been demonstrated that plasma levels of IL-33, IL-4 and IL-13 are increased by IVIg. This molecular mechanism may, in turn, lead to inhibition of inflammatory processes *via* Th2-cytokine-mediated down-regulation of FcγRIIa[42].

Interaction with dendritic cells

Dendritic cells (DC) are a heterogeneous group of antigen-presenting cells that are involved in the pathogenesis of several immune-mediated diseases and allograft rejection[22,43]. IVIg was shown to inhibit differentiation and maturation of human DCs. It may prevent up-regulation of the co-stimulatory molecules CD80 and CD86 that play a crucial role in the interaction between DCs and T-cells[22,43,44]. It is able to minimize the capability of mature DCs to secrete the pro-inflammatory cytokine IL-12, while simultaneously increasing the production of the anti-inflammatory cytokine IL-10[45]. Apart from that, IVIg suppresses DC-related activation and proliferation of auto- and allo-reactive T-cells. Thus, the immunosuppressive properties of IVIg are suggested to be mainly triggered by suppression of DC-specific properties[45,46].

Effects on B-cells

It has been shown that B lymphocytes, unique cells with an Ig as part of the B-cell receptor (BCR), may interact

with IVIg in different ways[47]. Antigen binding to BCR leads to modulation of gene expression, finally resulting in activation, anergy or apoptosis of B-cells. Several co-receptors on the B-cell surface are able to either positively or negatively affect BCR signaling. It has been demonstrated that IVIg may interact with almost all of these co-receptors on the B-cell surface[30,47]. This may lead to other highly relevant B-cell mediated mechanisms of IVIg, including inhibition of B-cell differentiation, inhibition of IL-6 and TNF-α production, induction of B-cell apoptosis, and down-regulation of specific auto-reactive B cells. In addition, IVIg is able to induce secretion of *de-novo* IgG, which may be beneficial in controlling reactivities of pathogenic auto-antibodies[30,47,48].

Effects on T-cells

The capability of IVIg to inhibit human T cell proliferation and cytokine production *in vitro* was shown to be comparable to that of calcineurin inhibitors[46,49]. It is supposed that this inhibitory effect of IVIg on T cells is at least partly caused by suppression of antigen-presenting cells, but also mediated by direct interactions[49,50]. IVIg was shown to suppress proliferation and cytokine production of T-cells by inhibition of IL-2 and interferon-γ production[22,49,50]. In addition, IVIg was demonstrated to contain antibodies against CD4 cells, soluble human leukocyte antigen (HLA) class Ⅰ and Ⅱ molecules, chemokines-receptor CCR-5 and T-cell receptor β chain[21,22,51-53]. It has recently been suggested that a major mechanism of IVIg to suppress cellular immunity is mediated by activating $CD4^+CD25^+$forkhead box protein 3 ($FoxP3^+$) regulatory T cells (Tregs). Tregs have been identified as crucial regulators of cell mediated immune responses[22,54]. They are able to suppress pathogenic immune activities, which play an important role in the context of autoimmune diseases, transplantation and GVHD. Activation of Tregs by IVIg leads to an increased ability of these regulatory cells to suppress allogeneic T cell proliferation *in vitro*[22,54]. High-dose IVIg treatment was demonstrated to stimulate Tregs and, thus, to enhance their suppressive function in humans. This mechanism is currently suggested to be crucial for IVIg-induced restoring of imbalanced immune homeostasis[55]. Regulatory T cell epitopes (Tregitopes) on IgG have been recently identified to trigger the interaction between Tregs and IVIg[56].

HBV HYPERIMMUNOGLOBULIN AFTER LT

HBV hyperimmunoglobulin and HBV-positive liver recipients

HBV-related liver cirrhosis was initially considered as contraindication for LT, due to high rates of fulminant recurrent hepatitis B and posttransplant mortality[57,58]. The introduction of anti-HBsIg (hepatitis B hyperimmunoglobulin; HBIg) in the early 1990's marked a breakthrough for establishing HBV-related liver cirrhosis as standard indication for LT[59].

HBIg is a polyclonal antibody to HBsAg, derived from pooled human plasma[60,61]. It is supposed to bind and to neutralize HBsAg expressing virions. Furthermore, it may prevent cell-to-cell infection within the liver and destruct infected hepatocytes *via* cell-mediated immunity[61]. However, it has only little impact on viral replication. Besides producing significant costs, long-term HBIg monotherapy may promote the development of viral mutations[62,63]. Therefore, a combination of HBIg with potent nucleos(t)ide analogues (NA) is considered as gold standard in prophylaxis of recurrent HBV[62-67].

Currently, the combination of anti-HBs Ig with tenofovir or entecavir is under clinical evaluation[62,68]. These novel drugs are characterized by higher antiviral potency than lamivudine (Lam) or adefovir and, thus, decrease the risk of viral resistances[68]. In combination with high costs and inconvenience of HBIg treatment, strategies of HBIg minimization/withdrawal or even anti-HBs Ig-free prophylaxis may be reasonable. Small sample sizes, short follow-up periods, different virologic risk profiles and inconsistent definitions of viral relapse were major limitations of previous studies. In addition, most trials were predominantly focusing on virologic outcome results, but not on survival data. It became, however, evident in recent years that, with availability of very effective antimicrobial agents, recurrent viral disease no longer reduces patients' long-term prognosis[58,60,68-79]. In order to appropriately assess the prognostic value of HBIg, the focus should, thus, be rather turned on variables like organ acceptance, graft rejection, infectious complications and survival[21,22].

Despite an obvious lack of randomized controlled trials, several clinical studies have in the past demonstrated beneficial immuno-regulatory properties by HBIg which are beyond its antiviral efficacies (Table 1).

Already in 1996, Farges *et al*[80] noticed that 116 HBV-positive liver transplant patients were on a lower risk for acute and chronic graft rejection compared to patients with other indications ($P < 0.05$). Since the immunologic benefit was not paid with an increased risk of infections, these data obviously indicated beneficial immuno-balancing capabilities of HBIg[67]. In contrast, the risk of bacterial infections was significantly higher in 21 patients with alcoholic liver cirrhosis ($P < 0.05$), although their immunologic outcome was comparable to that of HBV-positive liver recipients (Table 1). Apart from that, the incidence of death or retransplantation from rejection or either sepsis or de novo malignancies was significantly lower in HBV-positive liver recipients (3.5%) compared to patients with alcoholic liver cirrhosis (19%; $P < 0.05$; Table 1).

A Brazilian group reported in 2001 on less acute rejection episodes ($P < 0.05$) in 12 HBV-positive liver recipients following long-term HBIg treatment (rejection rate 25%; Table 1) compared to both, HBsAg-positive patients without HBIg treatment ($n = 10$; rejection rate 70%) and HBV-naïve liver recipients ($n = 238$; rejection

Table 1 Clinical data of prognostic relevant immune modulation by hepatitis B hyperimmunoglobulin after liver transplantation

Ref.	No. of patients receiving HBIg	Efficacy of HBIg on immunology/survival
Farges *et al*[80]	n = 116	Significant reduction (P < 0.05) of acute and chronic rejection rate (1.7%) compared to other indications like PBC (6.1%), PSC (13%), AIC (17%), and HCV (9.2%), without increased risk of bacterial infection; significantly lower risk (P < 0.05) of death or retransplantation from rejection or either sepsis or de novo malignancy (3.5%) compared to patients with alcoholic cirrhosis (19%)
Couto *et al*[81]	n = 12	Significantly less acute rejection episodes (0.3 ± 0.5) as compared to HBsAg-positive (0.9 ± 0.7; P = 0.02) and HBsAg-naïve (0.7 ± 0.7; P = 0.03) liver transplant patients without HBIg therapy
Kwekkeboom *et al*[82]	n = 40	Sigificantly lower rate of acute rejection (12%) as compared to patients without viral hepatitis (34%; P = 0.012); only HBIg treatment (HR = 0.39, 95%CI: 0.16-0.99, P = 0.047) and year of LT (HR = 0.87, 95%CI: 0.78-0.98, P = 0.017) were identified as independent predictors of acute rejection
Wang *et al*[83]	n = 1000	Reduction of HBV recurrence rate and of viral mutants; significantly improved 1-yr (P = 0.03) and 3-yr survival (P = 0.005) as compared to an antiviral prophylaxis without HBIg

HBIg: Hepatitis B hyperimmunoglobulin; HBV: Hepatitis B virus; HCV: Hepatitis C virus; LT: Liver transplantation; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cirrhosis; AIC: Autoimmune cirrhosis; HBsAg: Hepatitis B surface antigen.

Table 2 Clinical data of prognostic relevant immune modulation by hepatitis B hyperimmunoglobulin in recipients of hepatitis B virus-positive liver allografts

Ref.	HBV characteristics donor/recipient	Antiviral prophylaxis	Impact of HBIg on outcome
Brock *et al*[94]	HBc+/HBsAg- (n = 958)	HBIg alone: n = 61 HBIg + Lam: n = 66 Lam alone: n = 116 None: n = 509 Missing data: n = 206	70% reduction in risk of mortality by HBIg prophylaxis; (HR = 0.29, 95%CI: 0.10-0.86, P = 0.026)
Li *et al*[112]	HBsAg+/ HBsAg- (n = 63) HBsAg+/HBsAg+ (n = 15)	With HBIg: n = 17 Without HBIg: n = 61 With Lam: n = 14 Without Lam: n = 64	HBIg independently associated with superior posttransplant graft survival; (HR = 0.23, 95%CI: 0.06-0.81) and patient survival (HR = 0.16, 95%CI: 0.04-0.759)

HBV: Hepatitis B virus; HBIg: Hepatitis B hyperimmunoglobulin; HBc+: Hepatitis B core +; HBsAg: Hepatitis B surface antigen.

rate 56%), respectively[81].

In 2005, Kwekkeboom *et al*[82] suggested beneficial immuno-regulatory capabilities of anti-HBsIg. In their study, 40 HBsAg-positive liver transplant patients had a significantly lower incidence of acute rejection (12%) compared with 147 liver recipients without viral diseases (34%; P = 0.012; Table 1). In multivariate analysis, only treatment with HBIg and the year of transplantation were identified as independent factors for reduced risk of acute rejection[82].

And recently, Wang *et al*[83] reported on results of a meta-analysis including 19 studies and 1484 HBV-positive liver transplant patients. Treatment with HBIg was not only associated with reduced risk of viral relapse and development of mutants but lead to a significantly better overall patients' 1- (P = 0.03) and 3-year (P = 0.005; Table 1) survival compared to HBIg-free antiviral prophylaxis. The authors did, however, not find a benefit of HBIg on long-term survival[83].

HBIg and HBV-positive donor livers

The worsening scarcity of donor organs recently prompted several transplant centers to accept donor livers with pre-existing exposition to HBV[15,16]. Particularly anti-HBc-positive/HbsAg-negative donor grafts were increasingly accepted, mainly for HBsAg-positive patients who per se were requiring lifelong antiviral prophylaxis[84-87]. Currently, there seems to be growing need to allocate Hbc+ livers also to HBsAg- patients, especially to those with progressive liver function deterioration or advancing HCC[3,15,16]. In the absence of antiviral prophylaxis, incidences of viral reactivation up to 13%[85-87] and *de novo* HBV infection rates up to 100%[88-95] have been reported. There is currently no standard recommendation for antiviral prophylaxis in this special transplant matching, mainly since well designed studies are lacking. Treatment with HBIg either as monotherapy or in combination with Lam was demonstrated to significantly lower the risk of viral re-activation and infection[96-102]. Recently, monotherapy with potent NAs instead of an HBIg containing antiviral prophylaxis has been proposed[55,99,103]. There are only few trials that have focused on immuno-modulatory impact of HBIg in this special transplant setting (Table 2).

Saab *et al*[102] reported in 2003 on the UCLA experience with 22 HBc+/HCV+ liver allografts. They noted a significant survival benefit in recipients who received a combination of HBIg and Lam compared with those receiving either therapy alone or none of them. However, sample size was rather small and analysis was mixed up with data of other subpopulations[102].

Brock *et al*[94] have specifically addressed this issue in 958 HBsAg-negative liver recipients who received HBc+ liver allografts. Evaluating the UNOS STAR registry data

set, they reported on a 75%-80% risk reduction in graft failure and mortality in HBIg treatment-only compared to Lam therapy-only ($P < 0.001$). Furthermore, improved graft survival was observed for HBIg *vs* Lam-only recipients (HR = 0.34, 95%CI: 0.07-1.56), though data was not statistically significant (Table 2). No allograft failures in this series were attributed to *de novo* hepatitis B infection. Therefore, the authors drew the conclusion that patient and graft survival benefits were rather resulting from anti-inflammatory and immunomodulatory properties than from antiviral efficacies of HBIg treatment[94].

To further expand the available donor pool, the focus recently shifted towards a greater use of HBsAg-positive liver grafts from donors with overt HBV infection, but with normal graft morphology and liver function. Current experiences with these high-risk ECD allografts are still limited, particularly because allocation of HBsAg+ liver grafts is rejected in many transplant centers[104-113]. Therefore, the prognostic value of HBIg and its immunomodulatory efficacies in this special transplant setting is still undefined.

Just recently, however, Li *et al*[112] reported on outcome results of the so far largest series including 78 patients who received HBsAg-positive grafts. By using the US Scientific Registry of Transplant Recipients database, the authors performed a matched analysis and demonstrated comparable long-term patient and graft survival rates between recipients of HBsAg+ ($n = 78$) and those receiving HBsAg- ($n = 312$) liver grafts. Posttransplant outcome of recipients of HBsAg+ livers was significantly better after HBIg prophylaxis as compared to no HBIg treatment (92% *vs* 65% at 5 years for patient survival, $P = 0.01$; 87% *vs* 60% at 5 years for graft survival, $P = 0.02$). In contrast, patient death and graft loss were unrelated to Lam treatment. In multivariate analysis, only the administration of anti-HBs Ig predicted independently posttransplant patient and graft survival in these high risk patients (Table 2).

CYTOMEGALOVIRUS HYPERIMMUNOGLOBULIN AFTER LT

The introduction of specific IVIg against cytomegalovirus (CMV) infection about two decades ago resulted in a significant reduction of viral infection rates posttransplantation[114]. Important developments have since changed the perspectives of CMV infection, like assessment of specific donor (D)/recipient (R) risk constellations and the introduction of potent antiviral drugs (ganciclovir; valganciclovir). Between 1% and 30% of liver transplant patients are supposed to develop CMV disease in the absence of preventive strategies[115,116].

Indirect virus efficacies were demonstrated to account essentially for CMV-related morbidity and mortality[115,116]. These are mainly triggered by the capability of CMV to adversely modulate the recipients' immune system. The virus was demonstrated to up-regulate alloantigens and to increase the risk of acute and chronic allograft rejection[115,116]. It may be associated with vanishing bile duct syndrome and ductopenic chronic rejection and, thus, with risk of cholestatic allograft dysfunction[117,118]. Infection of endothelial vascular cells with CMV promotes the risk of hepatic artery thrombosis and subsequent liver allograft failure[119,120]. In addition, CMV-induced immunologic imbalance increases the susceptibility for other opportunistic fungal and bacterial infections. Apart from that, risk of allograft fibrosis and inflammation may be enhanced and incidence of metabolic disorders was shown to be increased by CMV infection[115,116,120].

Looking at this harmful impact of CMV on the immune system, immuno-modulatory properties by CMVIg could be particularly useful for patients with an increased immunologic and infectious risk profile[21,22]. However, treatment with anti-CMV Ig is currently not a recommended standard in liver transplant recipients[115]. Although well-designed studies on this issue are rare, some larger clinical trials have in the past suggested favourable immuno-balancing capabilities of CMVIg, which are beyond its established antiviral efficacies[80,119-126] (Table 3).

Farges *et al*[80] reported already in 1996 on a significantly reduced incidence of acute rejection in liver recipients who received a 3-mo course of CMVIg (19%) compared to those who did not (48%; $P = 0.01$). Treatment with anti-CMV Ig had no impact on chronic rejection, possibly due to a limited application period. Incidence or severity of bacterial infections was not influenced by treatment with CMVIg[80].

Falagas *et al*[121] demonstrated in 1997 the results of their double-blinded, placebo-controlled CMVIg prophylaxis trial (CMVIg $n = 90$ *vs* Placebo $n = 72$). They reported on a significantly better 1-year survival (86% *vs* 72%; $P = 0.029$) and an obvious trend toward improved long-term survival (68% *vs* 54%; $P = 0.055$) in the CMVIg-population. Furthermore, treatment with anti-CMV Ig was identified as independent predictor of beneficial outcome at one year post-LT in multivariate analysis ($P = 0.042$), and a trend toward increased long-term survival ($P = 0.098$) was also shown[121].

In a meta-analysis including 11 randomized controlled trials, Bonaros *et al*[122] reported about improved overall survival [RR = 0.67 (95%CI: 0.47-0.95)] and reduced CMV-related death [RR = 0.45 (95%CI: 0.24-0.84) after prophylactic administration of CMVIg in solid organ transplantation. However, in the all-cause death analysis, only one liver transplant study has been included[122].

Kwekkeboom *et al*[82] did not observe an outcome benefit by CMVIg in 18 liver transplant patients, which was contrary to their experiences with HBIg treatment. Just recently, differences in the manufacturing process were identified to account for discrepant immunoregulatory capabilities between both Ig-preparations described[123]. The newly manufactured CMVIg was subsequently shown to provide immuno-modulatory capabilities that were comparable to that of HBIg[123].

Two large registry studies recently added data that

Table 3 Clinical data of prognostic relevant immune modulation by cytomegalovirus immune globulin after liver transplantation

Ref.	No. of patients receiving CMVIg	Efficacy of CMVIg on immunology/survival
Farges *et al*[80]	n = 19	Significant reduction of acute rejection rate (19%) compared to recipients without CMVIg (48%; P = 0.01); no impact of on incidence of chronic rejection and bacterial infections
Falagas *et al*[121]	n = 90	Improved 1-yr survival (86% *vs* 72%; P = 0.029) and a clear trend towards improved long-term survival (68% *vs* 54%; P = 0.055). CMVIg as independent predictor of beneficial outcome at one year post-LT (P = 0.042)
Bucuvalas *et al*[124]	n = 336	Lower rate of acute rejection at 3-mo (31% *vs* 40%; P = 0.02); (CMV)Ig treatment as independent predictor for absence of acute rejection (HR = 0.73; P = 0.0019); significantly increased death-free allograft survival (HR = 0.57; P = 0.014) by (CMV)Ig
Fisher *et al*[125]	n = 2805	Significantly lower risk of graft loss and recipients' death (with or without additional antiviral agents; P < 0.001) at 7 yr post-LT; significantly higher 7-yr-survival rate after CMVIg monoprophylaxis (72%) *vs* no prophylaxis (67%; P = 0.02)

CMVIg: Cytomegalovirus immune globulin; LT: Liver transplantation.

emphasized on beneficial immuno-modulatory efficacies of anti-CMVIg[113,114]. Using the Studies of Pediatric LT Registry, Bucuvalas *et al*[124] performed a comparative trial on 336 pediatric liver transplant patients who received either CMVIg or unspecific IVIg for the first week post-LT and 1612 pediatric liver recipients who did not receive any of them[124]. While overall patient survival was comparable between both groups, death-free allograft survival was significantly better in patients treated with (specific or unspecific) Ig (HR = 0.57; P = 0.014). The risk of allograft rejection at 3 mo was 31% for patients receiving, but 40% for those without Ig administration (HR = 0.81, P = 0.029), respectively. The proportion of patients with 2 or more episodes of liver rejection was significantly lower in patients receiving Ig treatment (13.1% *vs* 19.2%; P = 0.009). In multivariate analysis, treatment with IVIg was identified as an independent predictor for absence of allograft rejection (HR = 0.73; P = 0.0019)[124].

Fisher *et al*[125] reported in 2012 on the so far largest study in this special context. Using data of the Scientific Registry of Transplant Recipients, a total of 64.252 liver transplant patients were analyzed, with 2805 of them receiving CMVIg post-LT[125]. The administration of anti-CMVIg (with or without additional antiviral therapy) was associated with lower rates of graft loss and recipients' death at 7 years post-LT (P < 0.0019). Apart from that, CMVIg prophylaxis alone (n = 4559) resulted in a significantly higher survival rate at 7 years post-LT (72%) compared to no antiviral prophylaxis (n = 28508; 67%; P = 0.02), which emphasized on beneficial immune regulation by CMVIg[125].

IVIG AND LT ACROSS IMMUNOLOGIC BARRIERS

Without effective down-regulation of the immune system, transplantation across immunologic barriers may result in hyperacute and antibody-mediated rejection (AMR) and, thus, in organ loss and patients' death. Immunologic incompatibility was, therefore, originally considered as a contraindication in all organ transplants, except LT[127-134]. A positive T-lymphocytotoxic crossmatch, presence of preformed donor specific HLA antibodies and ABO blood group incompatibility are considered as prognostically relevant immunologic barriers in the transplant setting[127,128]. In times of an escalating organ scarcity there is, however, increasing need to accept immunologic incompatible ECD liver allografts[15,16]. Therefore, the issue of implementing immuno-modulatory protocols has gained clinical relevance in recent years[127].

IVIg and LT with positive T-lymphocytotoxic crossmatch

A positive lymphocytotoxic crossmatch indicates the presence of donor-specific antibodies directed either against class Ⅰ or class Ⅱ HLA[127,128]. Increased immunologic sensitization may result from pregnancy, transfusion or previous transplants[127]. The implementation of immune modulation protocols including high doses of IVIg, plasmapheresis and potent immunosuppressive drugs resulted in attenuation of the humoral alloimmune response and in acceptable outcome in highly sensitized kidney and heart transplants[127-133].

The prognostic relevance of a positive T-lymphocytotoxic crossmatch in LT is, however, still discussed controversially[127,134-144]. Originally, the liver was considered to be less susceptible to immunologic attacks. Therefore, pretransplant T-cell crossmatch was either not required, or did not affect the indication for LT[127]. Nowadays, there is increasing evidence that a highly positive lymphocytotoxic crossmatch promotes the risk of acute and chronic allograft rejection, cholestatic liver dysfunction and impaired allograft and patient survival[141-147]. Direct clinical implications of the organ shortage, like pre-LT rising transfusion need, prolonged waiting times and increasing MELD scores, have shown to promote the risk of immunologic imbalance[127,134,148]. This could be one explanation for the reported outcome deterioration in the MELD era[5,10-14]. As a consequence, pre-LT immunologic screening has been recently recommended, particularly in high-risk liver patients[137,138,149].

The prognostic importance of IVIg in highly sensitized liver transplant recipients is currently undefined, since comparative trials are still lacking. In some smaller

Table 4 Clinical data of immune modulation by intravenous immunoglobulins in liver transplant recipients with positive lymphocytotoxic crossmatch

Ref.	Transplant procedure	No. of patients receiving IVIg (pre-LT/post-LT)	Additional immune modulation	Efficacy of IVIg on outcome
Watson *et al*[150]	LT	*n* = 1; post-LT, after detection of AMR	Plasmapheresis, rituximab	Intermittent decrease of Bili, liver enzymes and DSAs'; no survival
Dar et al[151]	SLKT	*n* = 6; pre- and post-LT desensitization	-	Survival rate 83.3%
Kozlowski *et al*[142]	LT	*n* = 3; post-LT, after detection of AMR	Plasmapheresis, rituximab	Transient decrease of Bili, yGT and DSAs' in 2 patients; survival rate 33.3%
Koch *et al*[153]	SLKT	*n* = 1; post-LT, after liver function deterioration and detection of DSAs'	Splenectomy, plasmapheresis, bortezomid	Improvement of liver/kidney function; decrease of DSAs'; survived
Shindoh *et al*[154]	LDLT	*n* = 1; post-LT, after decrease of platelet count and increase of attacking IgG	-	Recovery of platelet count; decrease of attacking IgG; survived
Leonard *et al*[137]	LT	*n* = 2; post-LT, after liver function deterioration	-	Recovery of allograft function; survival rate 100%
Hong *et al*[155]	LDLT	*n* = 1; post-LT, desensitization	-	Survived

IVIg: Intravenous immunoglobulins; LT: Liver transplantation (full size deceased); SLKT: Simultaneous liver-kidney transplantation; LDLT: Living donor liver transplantation; AMR: Antibody-mediated rejection; DSAs: Donor-specific antibodies.

studies of desensitization or treatment, decreasing levels of cytotoxic antibodies and improved allograft function (Table 4) were reported[142,149-155]. Well-designed studies on this subject are needed.

IVIg and ABO incompatible LT

Early results of LT across the ABO blood type barrier were devastation, due to high rates of hyperacute cellular rejection, AMR, vascular thrombosis and ischemic-type biliary lesions (ITBL). As a consequence, ABO-incompatible (ABO-I) LT was originally considered as contraindication[156-158]. In the last decade, ABO-I living-donor LT (LDLT) was implemented in those Asian countries where patients have no chance of receiving a deceased donor graft[159,160]. The escalating discrepancy between growing waiting lists and available donor organs recently put this transplant approach also into the focus in Western countries, mainly for rescue treatment of liver failure and advanced malignancy[161].

Historically, kidney transplantation first broke the ABO barrier and novel immune modulation protocols containing high doses of specific or unspecific IVIg essentially contributed to this success[162-164]. Since immunologic barriers may be even higher in ABO-I LT, its establishment as clinical routine has been more demanding[165].

The introduction of B-cell depletion by a chimeric anti-CD20 antibody (rituximab) and local graft perfusion of vasoactive substances added significantly to improved allograft acceptance in the early 2000's. However, their combination with established immuno-depressive strategies (plasmapheresis, splenectomy, intensified immunosuppression) resulted frequently in aggressive down-regulation of the immune system and, thus, in increasing risks of life threatening infections and vascular complications[165,166].

More recently, treatment with high doses of IVIg was successfully introduced in ABO-I LT[165,166]. The implementation of beneficial immuno-regulatory properties by IVIg encouraged many transplant groups to perform ABO-I LT without complicating local graft catheterization and/or splenectomy[161,165-177].

Testa *et al*[169] reported in 2008 on survival of 4 of 5 patients at mean of 43 mo after ABO-I LDLT following a combination of pretransplant IVIg, pre- and post-LT plasmapheresis and splenectomy.

In the same year, Urbani *et al*[171] demonstrated excellent outcome in 8 patients after ABO-I LT without any case of acute or chronic rejection by using plasma exchange and IVIg. In contrast, there were 3 cases of AMR (27.3%), 5 cases of acute biopsy-proven rejection (45.4%), 1 case of chronic rejection (9.1%) and 3 cases of ITBL (27.3%) following ABO-I LT in 11 patients without IVIg, respectively. Since plasma exchange was performed in both study groups, these results provided some good evidence on beneficial immuno-modulatory capabilities of IVIg, which were beyond its antibody-depleting properties[171].

Ikegami *et al*[172] reported in 2009 on their novel ABO-I LDLT immuno protocol containing rituximab, IVIg, plasmaexchange and splenectomy, but without local graft perfusion. This immuno-regulatory approach was effective and safe in 4 patients after ABO-I LDLT, who were all alive after 26, 8, 6, and 5 mo, respectively. In contrast, two severe catheter-associated complications were reported in 3 historic patients receiving local graft infusion, including one of them suffering from allograft loss[172].

Mendes *et al*[174] reported on a single center experience of emergency ABO-I LT in 10 patients with severe hepatic failure, immediately leading to death without intervention. Plasmapheresis and IVIg were implemented for immune modulation before and after LT. At a mean follow-up of 19.6 mo post-LT, 5 of these

Table 5 Clinical data of immune modulation by intravenous immunoglobulins in ABO-incompatible liver transplant recipients

Ref.	Transplant procedure	No. of patients receiving IVIg (pre-LT/post-LT)	Additional immune modulation	Efficacy of IVIg on immunology/survival
Morioka *et al*[167]	LDLT	*n* = 2; post-LDLT; treatment of AMR	Plasmapheresis	Normalization of liver function; survived
Urbani *et al*[170]	LT	*n* = 1; post-LT; treatment of AMR	Plasmapheresis	Normalization of liver function; survived
Ikegami *et al*[168]	LDLT	*n* = 1; post-LDLT; treatment of AMR	Rituximab, plasma exchange, splenectomy	Normalization of liver function; survived
Testa *et al*[169]	LDLT	*n* = 5; pre-LDLT	Plasmapheresis, splenectomy	Patient and graft survival 80% at mean of 43 mo post-LDLT
Urbani *et al*[172]	LT	*n* = 8; pre- and post-LT	Plasma exchange	Patient and graft survival 87.5% at 18 mo; no case of acute or chronic rejection, no ITBL
Ikegami *et al*[161]	LDLT	*n* = 4; post-LDLT	Rituximab, plasma exchange, splenectomy	Survival rate 100% (28, 8, 6, 5 mo post-LDLT)
Takeda *et al*[173]	LDLT	*n* = 3; post-LDLT; treatment of AMR	Plasma exchange	Normalization liver function; survived
Mendes *et al*[174]	LT	*n* = 10; pre- and post-LT	Rituximab, plasmapheresis	Survival rate 50%; death mainly related to MOF and sepsis
Kim *et al*[175]	LDLT	*n* = 14; post-LDLT	Rituximab, plasma exchange	Survival 100%; no case of acute or chronic rejection
Lee *et al*[176]	LDLT	*n* = 15; post-LT	Rituximab, plasma exchange	Survival 100%; no case of bacterial or fungal infection; 3 cases of biliary strictures
Shen *et al*[177]	LT	*n* = 35; pre- and post-LT	Rituximab	Survival rate 83.1% at 3-yr; one case of acute celluar rejection; two cases of AMR

IVIg: Intravenous immunoglobulins; LT: Liver transplantation (full size deceased); AMR: Antibody-mediated rejection; LDLT: Living donor liver transplantation; MOF: Multi organ failure; ITBL: Ischemic-type biliary lesions.

high-risk liver recipients were still alive[174].

Kim *et al*[175] presented in 2014 excellent outcome results in 14 patients after ABO-I LDLT using a simplified protocol. It consisted of pretransplant rituximab and plasma exchange, and post-LT treatment with IVIg, but without splenectomy and local graft perfusion[175]. Neither AMR nor biliary strictures have been reported after a mean follow-up of 16.2 ± 9.4 mo[175].

Lee *et al*[176] reported on 15 patients after ABO-I LDLT by using rituximab, plasma exchange and IVIg, but without local graft infusion and splenectomy. They demonstrated excellent survival without any case of hyperacute rejection or AMR. Furthermore, the authors did not observe any case of prognostic relevant bacterial or fungal infection[176].

And just recently, Shen *et al*[177] presented their results of a study comparing outcome between emergency ABO-compatible (*n* = 66) and ABO-I LT (*n* = 35). They have adopted a very simplified protocol, consisting of a single dose rituximab and of IVIg at the beginning of LT and for 10 d post-LT, respectively. Plasma exchange, splenectomy and local graft perfusion were not implemented[177]. The 3-year survival rates in these high-risk patients were excellent (86.3% *vs* 83.1%) and rates of complications were comparable between both subsets[177].

Large comparative trials on this issue are not yet available, mainly since ABO-I LT is a highly demanding and very exclusive procedure. Apart from that, the interpretation of previous studies are hampered by differences regarding indications, transplant techniques, recipients' characteristics, immunosuppressive treatments and immune modulation protocols (Table 5). Nonetheless, current available data suggest that the implementation of IVIg and its immuno-modulatory properties contributed significantly to recent outcome improvement in ABO-I LT[165-177].

CONCLUSION

There is increasing experimental and clinical body of evidence that IVIg provides beneficial immuno-modulatory capabilities beyond its antibody-mediated mechanisms. The combination of immuno-stimulating and immuno-suppressive efficacies might be particularly attractive for liver transplant patients with increased infectious and immunologic risk profiles. Although number of immuno-compromised liver recipients was continuously increasing in recent years, well-designed studies on this subject are still rare. Only treatment with specific anti-HBs Ig in HBV-positive liver transplant patients is a recommended standard, but mainly due to its antiviral potency and less for its immuno-regulatory properties.

Current available clinical data on valuable immuno-balancing efficacies of IVIg is intriguing and encouraging, but still based on smaller monocentric studies, larger retrospective registry data and on different outcome variables. However, particularly the identified data on specific IVIg suggest that immuno-modulatory approaches with hyperimmunoglobulins may become more important in times of an escalating organ shortage and its negative clinical consequences. At the very least, they should prompt discussion and emphasize the need to conduct larger prospective trials. It would be very important that future investigations include appropriate risk stratifications, in order to identify subsets that particularly benefit from IVIg. Apart from that, adequate

cost-benefit analyses are needed, since treatment with IVIg may be a rather expensive treatment.

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