Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Goldmann G. (2015) Long-term outcome of liver transplantation in HCV/HIV coinfected haemophilia patients: A single centre study of 10 patients. *Haemostaseologie*, 35(2):175-80.
Date of Review:	Sep. 11, 2016
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☒ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☐
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☒ **Other: orthotropic liver transplant, haemophilia, HBV** **Level:** **Group** ☒ **Individual** ☐ **Other:** **Target Population: HCV or HCV/HIV infected haemophilia patients who underwent liver tranplant** **Setting: Health care setting/Clinic** ☒ **Home** ☐ **Other:** **Country of Origin: Germany** **Language:** **English** ☒ **French** ☐ **Other: German**

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Primary research; a retrospective analysis of the long-term outcome in 10 haemophilia patients who underwent liver transplant due to hepatitis-associated liver disease.
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Information was not used for decision-making.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☐	☒	☐	This study analyzed only 10 haemophilia patients (9 with haemophilia A, 1 with aemophilia B). Therefore, given the limited sample size, the results are not very generalizable.
Are the best practices/methodology/results	☐	☒	☐	Results of this study are only applicable to the 10 haemophila patients who underwent liver transplant at the University of Bonn Haemophila Centre and is not

described applicable in developed countries?				applicable in other countries.
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☐	☒	☐	
The research study/tool/data dictionary is easily accessed/available electronically	☒	☐	☐	Free PDF of the article can be found at http://haemo.schattauer.de/en/contents/archive/issue/2211/manuscript/23661.html
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	Cost effective analysis was no conducted.
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☒	☐	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☒	☐	No funding stated
Is the best practice/intervention dependent on external funds?	☐	☐	☒	
Other relevant criteria: _____	☐	☐	☐	
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☒	☐	☐	Patients were continuously followed at the Hemophilia Centre and data were collected during follow-up visits through structured questionnaires.
Are these data regularly collected at and/or below a national level?	☒	☐	☐	Below national level: at only one center

Are these data collected manually or electronically?	☐	☐	☐	Manually
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	Haemostaseologie
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	New data/information

Long-term outcome of liver transplantation in HCV/HIV coinfected haemophilia patients

A single centre study of 10 patients

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Keywords
Haemophilia, liver transplantation, hepatitis, factor VIII, inhibitor

Summary
The outcome and clinical features during long term follow-up of 10 haemophilia patients (haemophilia A n = 9, haemophilia B n = 1), who underwent successful orthotopic liver transplantation (OLT) due to hepatitis associated liver disease, are summarised. Patients: Eight patients were HIV/HCV co-infected. Despite severe postoperative complications, which were not bleeding-associated, all patients survived OLT. Results: Long-term survival was 70% after in mean 8 years follow-up. Twelve years after OLT one patient developed a cyclosporine-induced nephropathy requiring haemodialysis. HIV-HAART was initiated in all patients after OLT, and allowed a successful HCV treatment in 6 patients. Factor VIII production was sufficient in mean 72 h after OLT and remained stable at subnormal to normal FVIII levels of in median 30% (range 14–96%) also during long-term follow-up. Post-OLT spontaneous bleeding events were rare compared to pre-OLT, therefore, the performance status improved in all patients. Discussion: OLT substitutes the hepatic FVIII but has no effect on the extrahepatic endothelial FVIII production, suggesting that in case of severe tissue injury enhanced bleeding might occur. Additionally, after OLT there is no acute phase reaction of the FVIII protein. Therefore, our OLT patients received in case of a reduced FVIII activity a peri-interventional prophylactic short-term FVIII substitution in surgical and diagnostic interventions with high bleeding risk. Conclusion: Bleeding and wound healing disturbances were not seen.

Schlüsselwörter
Hämophilie, Lebertransplantation, Hepatitis, Faktor VIII, Hemmkörper

Zusammenfassung
Wir berichten über 10 Hämophilie-Patienten (Hämophilie A n = 9, Hämophilie B n = 1), die sich aufgrund einer viral bedingten schwersten Lebererkrankung erfolgreich einer Lebertransplantation (OLT) unterzogen hatten. Patienten: Bei 8 Patienten bestand eine HCV/HIV-Koinfektion. Ergebnisse: Trotz z. T. schwerwiegender postoperativer Komplikationen, die nicht blutungsassoziiert waren, überlebten alle Patienten den primären Eingriff der Transplantation. Im Langzeit-Follow-up über im Median 8 Jahre betrug das Überleben in unserem Kollektiv 70%. Ein Patient entwickelte ein Cyclosporin-induziertes Nierenversagen und wurde 12 Jahre nach OLT dialysepflichtig. Die HCV-Therapie war nach Initiierung der HIV- HAART post-OLT in 6 Fällen erfolgreich. In allen Fällen erreichte die Transplantation postoperativ nach im Median 72 h einen subnormalen bis normalen FVIII-Wert von im Median 30% (Spannbreite: 14–96%), der im weiteren Verlauf stabil blieb. Die Anzahl spontaner Blutungsereignisse ging deutlich zurück, entsprechend verbesserte sich der Mobilitätsstatus aller Patienten. Diskussion: Die OLT ersetzt lediglich den hepatisch produzierten FVIII, sodass Blutungskomplikationen auch nach erfolgreicher OLT bei größeren Gefäß- und Gewebetraumata möglich sind. Insbesondere fehlt nach OLT die Akutphase-Eigenschaft des FVIII. In unserem Kollektiv wurde, sofern der FVIII-Wert unterhalb des Referenzbereichs lag, bei allen blutungsgefährdeten Eingriffen prophylaktisch perinterventionell eine kurzfristige FVIII-Substitutionstherapie durchgeführt. Schlussfolgerung: Blutungskomplikationen oder Wundheilungsstörungen traten nicht auf.

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Orthotopic liver transplantation (OLT) is an option for cirrhotic and non-cirrhotic liver diseases, especially for inborn metabolic errors. In haemophilia patients both arguments come together.

In the absence of viral inactivating processes until the early 1980s

- up to 60% of patients were infected with HIV and
- almost 100% were positive for HCV (1).

A HCV/HIV coinfection increases the estimated risk of end stage liver disease (ESLD) to 17% by 10 years, and finally 30% of these patients develop cirrhosis or hepatocellular carcinoma (2). From 1993–2013 in our haemophilia centre

- 38 patients experienced a fatal outcome of their liver disease,
- 12 of them were listed to OLT.

In haemophilia patients diffuse gastrointestinal bleeding due to portal hypertension is a dreaded complication, often presenting with melena (3). As the liver is a primary source of plasmatic FVIII and factor IX, OLT can restore blood coagulation (4). The first human OLT for haemophilia, performed in 1982, failed due to uncontrollable bleeding despite intraoperative factor supplementation. The same group achieved the first successful OLT three years later (5). At the time of writing, only about 115 haemophilia patients worldwide have undergone liver transplantation for HCV associated liver disease (1, 2, 4, 6, 7).

Data on long-term outcome in OLT haemophilia patients are therefore rare. Ragni et al. (4) recently reported a higher post-OLT 3-year-mortality in haemophilia patients as compared to non-haemophilia patients (53% vs. 38%). In the study of Yokoyama et al. (1), 9 out of 18 haemophilia patients died, five of them having been HIV/HCV co-infected. The median survival of these co-infected patients was, at 26 months compared to 118 months in HCV mono-infected haemophilia patients (1).

Factors influencing patient life span are the viral reinfection of the graft promoted by the adjunct immunosuppressive treatment, and patients' HIV status. HIV-associated infections, as well as toxicity of the adjunct highly active antiretroviral therapy (HAART), are further difficulties in the management of this special patient population.

The study presented here analyses retrospectively the long-term outcome in 10 haemophilia patients (9 with haemophilia A, one case with aemophilia B) who underwent OLT due to advanced hepatitis-associated liver diseases. Beside the infection and treatment-associated complications, the focus of the study was directed at haemophilia-specific symptoms, e. g. post-OLT coagulation status, patients' performance and bleeding phenotype. Since OLT only substitutes intrahepatic FVIII, bleeding complications can occur after OLT. Therefore, information about post-OLT bleeding events, patients' handling prior to and during high bleeding risk interven-

Tab. 1 Patients' characteristics before and after orthotopic liver transplantation (OLT); 4* suffered from liver failure due to hepatitis B; 9* incompliant with regard to virustatic treatment

GI: gastrointestinal bleeding; 0: death; 1: survival; HAART: high active antiviral treatment; IS: immunosuppressive treatment first line (IS1) and at study end (IS2); Hep C/ PCR status pre/ post OLT, HCV treatment post OLT;

ID	before orthotopic liver transplantation										
	age (years)	age (years) infection	infection	haemophilia	FVIII	CD 4/µl	HCV	MELD	clinical symptoms of end stage liver disease	outcome	follow-up (years)
1	31	8	HIV/HCV/HBV	A	<1%	161	1a	13	ascites, hepatic hydrothorax, GI bleedings	1	10
2	43	22	HIV/HCV/HBV	A	<1%	210	2a/2c	15	fatigue, continous deteoriation of liver function test	0	12
3	58	35	HIV/HCV/HBV	A	<1%	190	3a	13	hepatic cell carcinoma	1	14
4*	34	8	HIV/HCV/HBV	A	<1%	254	1a	HU	acute liver failure due to hepatitis B	1	8
5	34	8	HIV/HCV/HBV	A	<1%	239	1a	16	ascites, hepatic hydrothorax, GI bleedings	1	10
6	51	18	HCV	A	<1%		1a	16	ascites, GI bleedings	1	1
7	36	15	HIV/HCV	A	<1%	162	1a	18	ascites, GI bleedings	0	3
8	59	36	HIV/HCV/HCC	A	<1%	442	1a	13	hepatic cell carcinoma	1	2
9*	44	26	HIV/HCV/HBV	B		239	1a	23	ascites, continous deteoriation of liver function test	0	2
10	19	8	HCV/HBV/HDV	A	<1%		1a	20	continous deteoriation of liver function test ,GI bleedings	1	22

tions, like surgery and invasive diagnostic procedures, are of great interest and so far not available.

Patients and methods

Patients

Between 1993 and 2013 a series of ten patients underwent liver transplantation at the University of Bonn Haemophilia Centre. Data were analyzed retrospectively. All patients gave their informed consent. There were no other liver transplants in haemophilia patients during the observation period.

Criteria for accepting a candidate for OLT were a CD4 count of >100 cells/µl, lower than the limit of detection HIV RNA, and end-stage liver disease or acute liver failure. As a model of end stage liver disease (MELD) score (UNOS) (8) was used for assessing the severity of liver disease in patients with end stage liver disease. A score >15 was required for listing. Patients suffering from hepatocellular carcinoma were listed regardless of their MELD score.

Data, data analysis

All patients underwent long-term follow-up after OLT during regular visits in our Hemophilia Centre. Data were collected during follow-up visits and from patients' records by means of a structured questionnaire, which was composed of general demographic data (gender, body weight, age), characteristics of the HIV infection (CD4 count, HIV RNA level, HAART) as well as details of concomitant liver disease (viral type, reason for OLT, biochemical and clinical signs of liver disease). To evaluate patients physically the Karnofsky performance status was determined (9). Pre-/postoperative general coagulation parameters were measuredData concerning the post-OLT factor supplementation during invasive procedures and surgical interventions were collected and analyzed.

The clinical course of the immunosuppressive treatment, the adjunct antiretroviral treatment (HAART), and the treatment of concomitant viral hepatitis were documented after OLT and during long-term follow-up. Laboratory tests concerning status were performed during regular follow-up visits.

All statistical analyses were performed using the Statistical Package for Social Sciences IBM SPSS, version 19.0 (SPSS, Inc., Chicago, Illinois, USA). Descriptive statistics have been used to characterize the study population.

Results

Ten male haemophilia patients were liver-transplanted between 1993 and 2013. Nine patients suffered from severe haemophilia A, whereas haemophilia B occurred in one patient. Transplantation data are shown (▶Tab. 1). The mean age at OLT was 47.3 years (±15.2 years), the mean follow-up

CyA: cyclosporine; Pred: prednisolone; Tac: tacrolimus; Int: PEG interferon; Riba: Ribavirine; na: information not available; TDF: tenofovir; 3TC: lamivudine; LPV/r: Lopinavir/ ritonavir; SQV: saquinavir; NFV: nelfinavir; AZT: Zidovudin; SUV: Saquinavi; HAT: arterial hepatica thrombosis; CKD: chronic kidney disease; RJ: rejection episodes treated with steroids or OKT3

after orthotopic liver transplantation						bleedings events	
ISI	ISII	Hep C / PCR status pre/post OLT therapy	HAART	clinical complications	RJ	before OLT	after OLT
CyA/Pred	CyA	Int / Riba +/–	TDF / 3TC / LPV / r	ascites, hydrothorax, biliary tract leakage, HAT, TIPS	2	7	2
CyA/Pred	Eve/MMF	Int / Riba +/–	LPV / r / SQV / 3TC	cholestatic hepatitis, central venous thrombosis, CNI nephritis, haemodialysis	1	6	0
CyA/Pred	Rapa/MMF	Int / Riba +/–	NFV / 3TC / TDF	ascites, Tbc, CKD, basalioma	0	0	0
Tac/Pred	CyA/MMF	–/–	3TC / Truvada / Kaletra	neuopathy, CKD, HAT, hepatic abcess, ascites, TIPS	3OKT3	4	0
CyA/Pred	Tac	Int / Riba +/–	Abacavir / Tenovir / Fosampavir / Ritonavir	CMV enteritis, anal fistula, AZT induced hepatotoxicity, Riba-induced anaemia	1	5	0
CyA/Pred/ MMF	Eve/MMF	Int / Riba +/+		sepsis, SIRS, haemodialysis, bacterial spondylitis, CMV pneumonitis and colitis, critical illness neuropathy with tetraparesis, CyA hepatotoxicity	1	4	0
CyA /Pred	CyA	+/+	na	M. Hodgkin	0	4	0
Tac/Pred	CyA	Int / Riba +/–	Nelfinavir / Tenofovir / Abacavir / Cotrim	pleura effusion, pneumonia, HAT, ascites, TIPS hepatic abcess, pericardial effusion	1	6	2
Tac/Pred	Tac	Int / Riba+/–		cholestatic hepatiis, choledochostenosis T-tube drainage, Riba-induced anaemia		4	1
CyA/Pred/ Imurek	CyA	-/-			1OKT3	15	0

was 8.4 years (±6.6 years). Reasons for OLT were

- end stage liver disease due to hepatitis C (n = 7),
- hepatitis C induced hepatocellular carcinoma (n = 2), or
- a high urgency status due to fulminant hepatitis B infection (n = 1).

Eight patients were co-infected with HIV. Only one patient suffered from an AIDS-defining event in terms of oesophageal candidiasis prior to OLT, which could be resolved by HAART three months before listing. Patient 10 had post-hepatitis B/C and D cirrhosis and suffered from severe gastrointestinal bleedings due to portal hypertension. After three years on a waiting list he underwent OLT in a non-replicative stage of hepatitis. He was the first OLT patient of the haemophilia centre in Bonn.

All patients had been infected with hepatitis B/C and/or HIV during factor supplementation therapy in the 1970s and early 1980s when they received pooled plasma derived products. The median age of infection was 16.5 years (range 8–36 years).

Complications of OLT

Data on post-OLT complications are summarized (▶Tab. 1). Despite severe complications in 9 out of 10 patients, all patients survived initial OLT.

Ten episodes of organ rejection were seen in seven patients. Two of them were steroid-refractory and were successfully controlled by T cell depletion with OKT3 (patients 4, 10). Prolonged refractory postoperative ascites occurred in three patients, requiring recurrent paracentesis (patients 1, 4, 8) and a TIPS implantation in two of them (patients 1, 8). The ascites subsided spontaneously 36 respectively 12 and 24 months post-OLT. Partial liver lobe necrosis due to late arterial hepatica thrombosis was seen and required an operative revision in three patients (patient 1, 4, 8) complicated by liver abscess formation in two patients (patient 4, 8). The hepatic abscess could successfully be treated by antibiotics and nasobiliary probe (patient 8). In one patient (patient 6) the postoperative course was complicated due to systemic inflammatory response syndrome, requiring artificial ventilation and haemodialysis. Furthermore, he suffered from critical illness neuropathy. Two months after his operation the patient developed a spondylodiscitis induced by *Staphylococcus epidermidis*, which was successfully controlled with antibiotics. A cholestatic hepatitis based on choledochal stenosis was seen in another patient and successfully treated by T tube drainage (patient 9).

Immunosuppression, HAART

Cyclosporine A (CyA) and prednisolone were chosen as first line immunosuppressive treatment in seven patients, whereas three patients received tacrolimus (Tac) / prednisolone (▶Tab. 1). Prednisolone could be tapered down in all patients after a median of three months post-OLT, and was replaced by mycophenolate (MMF) in four patients. One patient was treated with azathioprine (▶Tab. 1). In HIV patients HAART was delayed until transaminases had normalized to lower than three times the upper normal limit, and bilirubin level to less than 2 mg/dl. Furthermore, stable blood levels of CyA (100–150 ng/ml) or Tac (8–10 ng/ml) were desired. Dose adjustments to prevent over-immunosuppression was necessary in all patients, requiring a dose reduction of in mean 5–20% of CyA or Tac. In one patient, HAART induced neurological symptoms and renal deterioration due to difficulties in achieving appropriate Tac levels. Therefore, he was shifted to CyA. Elevated liver enzymes under Zidovudine (AZT) required a shift of HAART to less hepatotoxic therapy in another patient (patient 4).

Infectious complications

Hepatitis C reoccurred in all patients except patient 10 who underwent OLT in a non-replicative stage of hepatitis. Elevated liver enzymes and a cholestatic hepatitis were seen after in mean 23 d (std 45 d) post OLT. The diagnosis was confirmed by liver biopsies intended to exclude organ rejection. HCV treatment was successfully initiated in six patients after in mean seven weeks (3–12) post-OLT, mainly with a combined schedule of PEG interferon and ribavirin (▶Tab. 1). Severe side effects induced by ribavirin required treatment interruption in two patients: severe anaemia and two episodes of central venous thrombosis were seen. In one patient treatment was interrupted due to comorbidities (patients 7). CMV enteritis/pneumonitis and a pulmonic infection with *Mycobacterium avium* after OLT were further infectious complications (patients 3, 5, 8). Patient 4, suffering from fulminant hepatitis B, was treated with HBs hyperimmunoglobulin at initially 10000 U i.v. once a day started in the an-hepatic phase followed by a maintenance therapy with monthly infusions to keep serum levels of anti HBs at >100 U. Lamivudine 300 mg once a day was given in addition to HAART.

Coagulation status

Before OLT all patients were on regular prophylaxis therapy with an annual FVIII consumption varying from $2–5 \times 10^5$ IE FVIII per year. After transplantation FVIII was given only in case of surgery. During intervention FVIII concentrates were calculated to raise the level of the deficient FVIII > 60%. In average the total amount of FVIII concentrate, which was used for surgery, was approximately half of the treatment of factor concentrate that was used for surgery before OLTx. Post OLT the factor supplementation could be stopped in median 72 h postoperatively. During long-term follow-up FVIII concentrations remained stable at subnormal to normal levels (▶Fig. 1). Bleedings were common before OLT, with in median 5.5 events / year (range: 4–15), but rarely occurred after OLT, with only five reported events during the entire follow-up period within the whole collective. Patients' performance status improved remarkably in all patients as shown (▶Fig. 1).

Post-OLT the peri-interventional factor supplementation allowed invasive procedures like PTCA, TEP implantation, coronary bypass operation, surgical excision of basalioma, anal fistula resection and shimono shunt implantations without bleeding and wound healing complications. None of the transplanted patients required post OLT further prophylaxis.

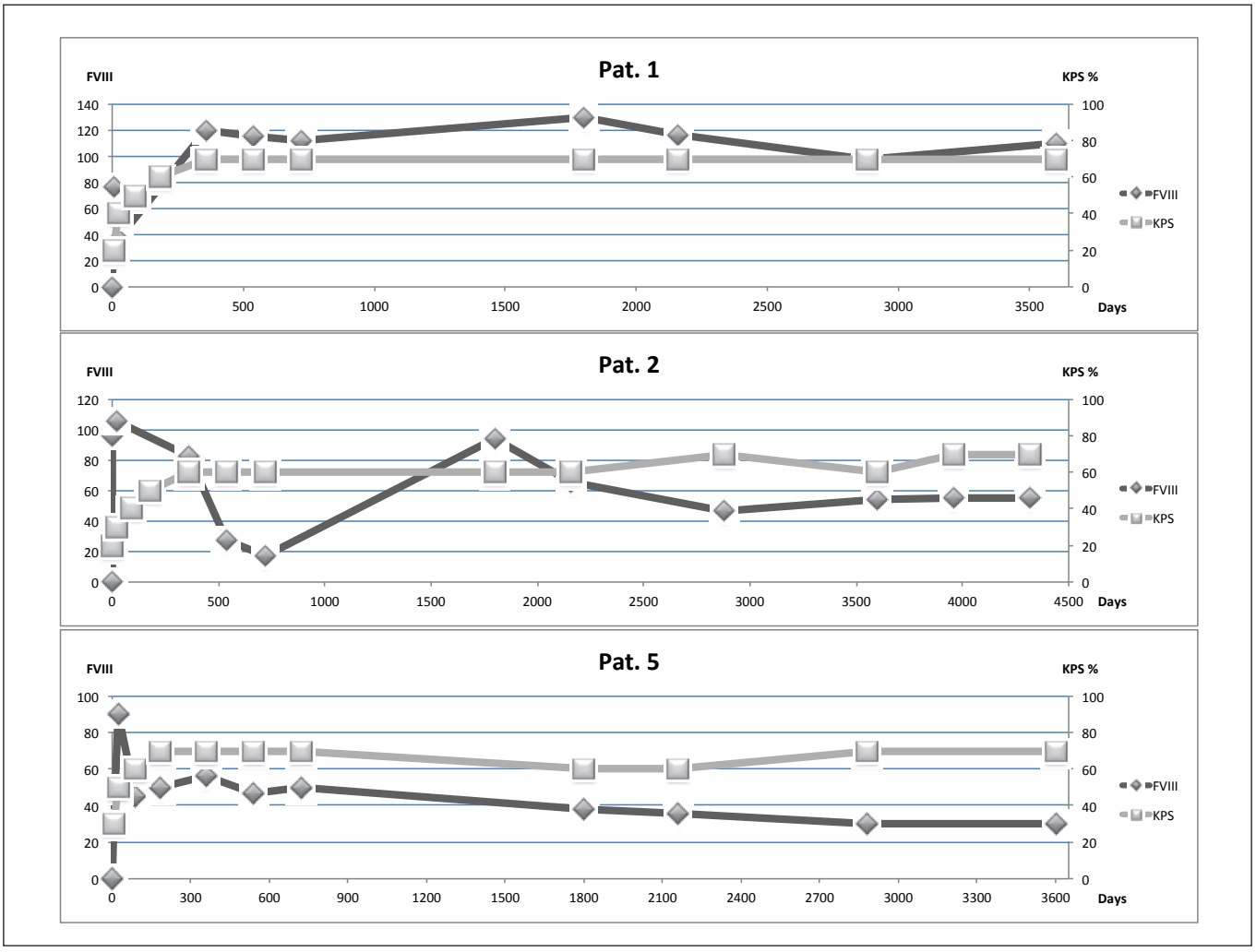

Fig. 1 Factor VIII concentration (%) and the course of the Karnofsky performance status (%) during long-term follow-up after orthotopic liver transplantation in three representative patients.

Long-term outcome

Three patients died during long-term follow-up of in median eight years:

- Patient 7 suffered from Hodgkin lymphoma 30 months after OLT and died in consequence of infectious complications during chemotherapy. He was HCV/HIV co-infected.
- The second patient was suffering from haemophilia B and had been wheelchair-bound since childhood due to an accident. He was HIV/HCV co-infected and incompliant concerning the HAART and HCV treatment. He died of infection two years after OLT.
- The third patient developed CNI-induced nephropathy 12 years after OL, finally requiring haemodialysis.

Patients' clinical benefit is also documented by an increase of the Karnosfky performance status, with a median scale score of 26% prior to OLT index (range 10–40%) increasing to in median 63% (range 40–80%) 12 months post OLT as shown in detail (▶Fig. 1).

Discussion

During long-term follow-up over in median eight years, factor VIII levels remained subnormal to normal with in median 30% (range: 14–96%) in all patients.

> Therefore, OLT might "cure" the haemophilia patient.

In our collective, severe spontaneous bleeding events post-OLT were rare compared to the pre-OLT period, with patients' performance status improving remarkably. As OLT substitutes only intrahepatic endothelial FVIII it has no influence on extrahepatic endothelial FVIII production, which is estimated to account for up to 50% of total FVIII production in humans (10). To protect post-OLT patients from bleedings and wound healing disturbances, an adjunct, peri-interventional, FVIII substitution was given in case of high bleeding risk interventions. In our patients, this management successfully allowed invasive procedures as above without any complications.

Post-OLT factor VIII levels were stable even in situations of acute hepatocyte injury such as graft reinfection. This might

be supported by recently published data from Fahs et al. favouring the sinusoidal endothelial cell rather than the hepatocyte as the main source of FVIII synthesis (11,12). Most interestingly, haemophilia A patients who underwent OLT were unable to restore the acute phase reaction of FVIII or DDAVP-response (13), most likely because these mechanisms are depending on FVIII synthesis in extra hepatic endothelial cells (14). For example patient 5 expired between 2010 and 2011 (d1800-d2100) 5 episodes of anal fistula infections requiring several surgical interventions. During these periods an adequate FVIII response to the severe infection stimulus was not seen.

However, OLT in haemophiliacs does not correct the extra hepatic FVIII synthesis. Therefore, bleeding leads directly to a linear decrease of FVIII. This observation represents the rational for peri-interventional FVIII replacement therapy, even if the initial FVIII:C levels were within the subnormal range (13).

The acceptance of "donor" FVIII by the recipients' immune systems remains remarkable, and so far a de novo alloantibody formation against the graft FVIII has not been reported. An increased incidence of autoantibody formation, despite adjunctive immunosuppressive treatment, has been reported in patients who received OLT for autoimmune and non-autoimmune liver disease (15, 16).

Antibody formation in severe haemophilia (inhibitors) occurs during factor substitution in up to 30% in the first 50 exposure days, and is a severe complication of the substitution (17, 18). Although our patients suffered from severe haemophilia, an inhibitor was not described in the anamnesis. OLT in the presence of a high titer inhibitor requires a haemostatic therapy based mainly on bypassing treatment, and has been reported with fatal outcome. Gregg et al. recently described a catastrophic microangiopathy complicated by arterial hepatica thrombosis with fatal outcome in a high titer patient after OLT (19). The reoccurrence of a low inhibitor post-OLT was described by Stabler et al. (20), whereas Horton et al. (21) speculated on a de novo inhibitor synthesis to the graft FVIII protein. Finally, in both situations the adjunct immunosuppressive treatment mainly consisting of TAC, MMF and prednisone, was not sufficient to suppress antibody synthesis (20). Finally, our results suggest a low risk of post-OLT inhibitor formation in the absence an anamnestic inhibitor prior to OLT.

The FDA has recently approved the second-generation HCV protease inhibitors, such as sofosbuvir and simeprevir. The future treatment strategies of HCV allow sustained viral response rates of 90–100%, even in HCV/HIV co-infected patients (22). Improved viral inactivation procedures and recombinant coagulation factors further diminishe the de novo infection rates to <2%, especially in industrial countries (23) so that the requirement for OLT in haemophilia patients will decrease.

The clinical reports of this rare collective should preserve information about patients' outcome and coagulation status post-OLT. The results might influence the future role of OLT in haemophilia patients. Improved immunosuppressive treatment, the opportunity of living donor and split liver transplantation might offer options for selected haemophilia patients, e.g. in those with a high risk of inhibitor formation based on their genetic background (17, 18, 24).

Conclusion

The role of orthotopic liver transplantation in improving patient's coagulation functions under life-long immunosuppressive treatment is not predictable at present.

Conflict of interest

The authors declare that they have no conflict of interest.

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