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Successful Anti-HCV Therapy of a Former Intravenous Drug User with Sofosbuvir and Daclatasvir in a Peritransplant Setting: A Case Report

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Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 37
Final Diagnosis: Chronic HCV-infection • hepatic decompensation
Symptoms: Esophageal varices • portal-hypertensive gastropathy • splenomegaly • recurrent ascitic decompensation • hepatorenal syndrome • hepatic encephalopathy
Medication: —
Clinical Procedure: Liver transplantation • antiviral therapy
Specialty: Gastroenterology and Hepatology

Objective: Unusual setting of medical care
Background: Direct-acting antivirals (DAAs) represent a new hallmark in antiviral therapy of hepatitis C virus (HCV). DAAs have been shown to be safe and effective after liver transplantation (LT), but there is little information about their use in peritransplant settings. Former intravenous drug users represent an increasing group seeking HCV treatment. This case report demonstrates the successful peritransplant antiviral treatment of a former intravenous drug user who had been treated in a methadone maintenance program.
Case Report: The patient was diagnosed with Child B cirrhosis for the first time in 2009. He had a Model for End-stage Liver Disease (MELD) score of 21 and started antiviral therapy with sofosbuvir (SOF) and daclatasvir (DCV) in March 2014. Due to hepatic decompensation, he received a LT in April 2014. Immunosuppression was performed with tacrolimus (TAC) and mycophenolate-mofetil (MMF), and boosted with prednisolone in the initial stage. Four weeks after his LT, the patient presented with an acute renal injury. The patient was discharged one week later after sufficient hydration, discontinuation of non-steroidal anti-phlogistics therapy, and adjustments to his immunosuppressive regimen. At the beginning of his therapy, the number of RNA copies was 13,000 IU/mL. He received 24 weeks of anti-HCV treatment with SOF and DCV; the antiviral treatment was successful and his LT was well tolerated.
Conclusions: Treatment of HCV is feasible in a peritransplant setting. The antiviral regimen we used did not seem to have any relevant interactions with the patient's immunosuppressive regimens. Still, the peritransplant setting is a very demanding environment for anti-HCV therapy, and further studies are needed.

MeSH Keywords: Antiviral Agents • Drug Users • Hepatitis C • Liver Transplantation

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Background

Chronic hepatitis C (CHC) is major health problem; 80% of infected patients will develop CHC, leading to 180 million chronically infected patients worldwide [1,2].

A chronic infection is highly correlated with an increased risk of hepatic inflammation and liver fibrosis, creating a significantly increased risk of developing liver cirrhosis and hepatocellular carcinoma [3]. CHC is currently the most common reason for liver transplantation (LT) [4–6]. At the same time, a recurrence of hepatitis C (HCV) after LT is common, and often results in a poor outcome. The rate of survival of the liver graft and the survival of the patient are reduced by hepatitis C infection [4–9]. After having minimized the risk of HCV infection via blood transfusions in the 1990s, intravenous (IV) drug use is today the most common route of infection with HCV in many countries [10,11]. Former intravenous drug users and current methadone maintenance patients are consequently a growing group of patients seeking HCV treatment and LT.

In the past, an interferon (IFN)-based antiviral therapy combined with the nucleoside analogue ribavirin (RBV) was the hallmark of treatment of CHC, but success rates remained unsatisfactory even after the introduction of the first generation of DAAs such as telaprevir and boceprevir [12–26].

Since the approval of second generation DAAs in 2014, antiviral therapy has become more feasible, with a broad arsenal of highly active DAAs available, including different drug groups with different antiviral mechanisms that affect HCV genes NS3/4A, NS5A, and NS5B [27]. There have been several studies involving the new DAAs that show sustained virologic response (SVR) is achievable for a majority of patients, dependent on the underlying genotype and stage of the liver disease [28–32]. In the context of HCV treatment after LT, the new treatment options represent a triumph for HCV research [33–35].

However, experiences with DAAs in a peritransplant setting are rare. The complexity of interactions in patients in this setting includes drug metabolism and the decompensated state of a patient that may be complicated by anti-HCV treatment. Thus the peritransplant setting is a very interesting area for research. The necessity of participation in a methadone maintenance program additionally complicates the demands of pre-transplant treatment. In our case report, we present a case of a patient who was in a methadone maintenance program and was being treated with a combination of SOF and DCV peritransplant.

Case Report

The patient was first diagnosed with CHC (genotype 3a) in 1996. Past medical history revealed intravenous drug abuse. He participated in a methadone maintenance program starting in 2007. His last withdrawal therapy took place in late 2012. The first diagnosis of Child B cirrhosis was in 2009. The patient was subsequently in medical care because of esophageal varices with several ligation therapies, portal hypertensive gastropathy, splenomegaly, recurrent ascitic decompensation, hepatorenal syndrome, and hepatic encephalopathy. The patient presented himself in February 2014 in reduced general condition for evaluation for a LT with a Model for End-stage Liver Disease (MELD) score of 21. In the following weeks, a further worsening of the patient's condition was observed, leading to a MELD score of 28 in late March. Antiviral treatment was started with sofosbuvir (SOF) 400 mg/day and daclatasvir (DCV) 60 mg/day (as compassionate use) in March 2014, just 18 days before a liver graft was available for him. The antiviral therapy was administered for 24 weeks without dose adjustments. Our patient received a liver transplant in April 2014 at the age of 37 years with a MELD score of 33. Immunosuppression was started with a combination of tacrolimus (TAC), mycophenolate mofetil (MMF), and boosted with prednisolone in the initial stage. The liver transplantation was conducted using piggy-back technique with a graft from a 45-year-old, male donor. Cold ischemic time was nine hours, warm ischemic time was 40 minutes.

The patient tolerated the transplantation well. Replacement therapy with L-polamidone had to be supplemented with dipyrone and clonidine during the patient's hospital stay. The patient received palladon retard twice daily and non-retard on demand. As was to be expected, the level of transaminases diminished postoperatively. From the second day, parameters of cholestasis increased as well as bilirubin, informing the decision to perform an endoscopic retrograde cholangiopancreatography (ERCP) on day four post-surgery. A sphincter of Oddi dysfunction was diagnosed. As the result of a papillectomy and the implantation of a stent in the ductus hepaticus communis (DHC), the parameters of cholestasis and bilirubin declined adequately.

The renal function was limited preoperatively in terms of hepatorenal syndrome. Post-LT renal function was ameliorated with drinking volume restriction and the application of toseamide 10 mg twice daily. The patient was discharged from the hospital 17 days after his LT.

One week after discharge, our patient was readmitted to the hospital because of an acute renal injury (classified as Acute Kidney Injury Network II – AKIN II). His general state and renal function changed for the better after sufficient hydration

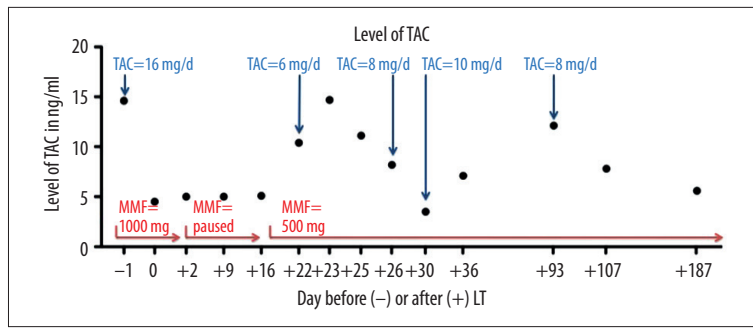


Figure 1. Time course of immunosuppressive regimen. This figure shows the time course of the patients TAC-level (black dots) and the according adaptations of the TAC dosage (in blue). Due to a massive drop of platelets observed on day 2 post-LT, MMF (in red) was paused for 14 days and the dosage reduced in the follow-up. TAC – tacrolimus; MMF – mycophenolate mofetil; LT – liver transplantation.

Table 1. Course of laboratory parameters prior and after LT.

	-18 (days)	-11	-4	LT	+7	+16	+22	+30	+36	+42
INR	1.88	1.87	1.68	1.76	1.30	1.03	1.18	1.16	1.13	1.13
BIL	21.7	17.1	21.7	19.2	4.1	2.4	2.4	1.8	1.4	1.5
ALB	2.3	2.3	2.4	2.7	2.6	2.7	2.6	3.2	3.2	4.0
CREA	1.2	1.2	1.3	1.6	1.2	–	–	3.0	1.3	1.1
AST	72	50	53	1074	22	16	18	24	25	30
ALT	44	32	33	412	45	19	17	21	14	18
gGT	50	48	43	32	722	392	123	193	111	93
eGFR	>60	>60	>60	49	>60	>60	>60	23	>60	>60

This table shows the time course of all important laboratory parameters, starting from the beginning of the antiviral therapy. Parameters were collected prior to and after LT. The successful clinical course after LT under antiviral therapy as well as the transient renal injury (AKIN II) were noticeable. LT – liver transplantation; INR – international normalized ratio; BIL – bilirubin; ALB – albumin; CREA – creatinine; GOT – glutamic oxaloacetic transaminase; GPT – glutamic-pyruvic transaminase; gGT – gamma-glutamyl transferase; eGFR – estimated glomerular filtration rate; bold values – pathologic values.

and discontinuation of therapy with non-steroidal antiphlogistics (NSAPs). Furthermore, the dose of both immunosuppressive agents was reduced.

In the course of the following months, our patient presented himself regularly to our hospital for control esophagogastroduodenoscopies (EGDs) and ERCPs. A stent exchange as well as treatment of a mucosal irritation with proton-pump inhibitors (PPIs) became necessary. The time course of TAC (FK506) levels and dosages of TAC and MMF are presented in Figure 1. Laboratory parameters for the first six weeks after LT are presented in Table 1. Reactivation of CMV or EBV did not occur. Further, follow-up after LT was satisfactory, and no major complications occurred.

The antiviral treatment was: SOF (400 mg/day) and DCV (60 mg/day) for 24 weeks until September 2014. Our patient started treatment with 13,000 IU/mL detectable RNA copies. The therapy was started 18 days prior to the transplantation. Five days post-LT, a small number of RNA copies (65 IU/mL) was detected. In the further course of treatment, HCV-RNA remained

undetectable, yielding a SVR for our patient. The antiviral treatment provoked no severe adverse events in our patient, who had been treatment-naive previously.

Our patient tolerated the combined liver transplantation and antiviral therapy very well, which is remarkable given his complicated circumstances. In the follow-up period, a liver biopsy showed no episode of transplant rejection reaction, and according to laboratory parameters and ultrasonography, the function of his liver graft has been normal. HCV-RNA has remained undetectable for more than 18 months.

Discussion

HCV infection is very common among intravenous drug users, as IV drug use is the major route of transmission of HCV in Western countries [35–44]. Participation in a methadone maintenance program is the most effective and common mode of treatment for these patients [45,46]. Listing patients participating in a methadone maintenance program for liver transplantation is

still a highly controversial topic. Thus, experience in the outcome of LT in this subset of patients is limited, but the results do not seem to differ from other LT patients [47–50]. The accessibility of the new DAAs for former drug-users is another topic of contestation, due to the high cost of new regimens and required compliance of patients. Treatment and follow-up of a methadone patient in the context of concurrent antiviral therapy and a liver transplantation can be very demanding.

Peritransplant setting, preexisting renal insufficiency, history of former IV drug abuse, and ongoing necessity of participation in a methadone maintenance program complicated the anti-HCV therapy in our patient. Whereas studies have proved the efficiency and safety of DAAs in patients who already have a LT, experiences with patients on antiviral therapy peritransplant are absent. A decreasing liver function requires dose adjustments for most drugs, and unlike other DAAs (simeprevir, paritaprevir, ombitasvir, dasabuvir) for which a contraindication exists in cases of cirrhosis more severe than Child A, SOF is safe even in case of Child C cirrhosis [51]. In addition, DCV can also be administered in patients with hepatic failure. Due to its very low median effective dose, it is the most potent of the existing DAAs [51]. Therefore, starting the antiviral therapy with SOF and DCV seemed feasible in our patient, even though the increasing MELD score indicated aggravating hepatic failure.

Acute renal injury is common among liver transplant recipients, in particular, shortly after transplantation [52]. In our patient, a renal insufficiency was already present prior to LT and recurred in the form of an acute renal injury after LT. The acute kidney injury (AKIN II) after LT additionally complicated our patient's therapy. In the presence of an estimated glomerular filtration rate (eGFR) <30 mL/minute, which was observed in our patient at the beginning of the fourth week after LT, there is no existing dose recommendation for SOF [51]. However, a dose reduction was assumed to be necessary for all DAAs. Studies suggest that for DCV, no dose reduction is necessary in cases of both hepatic and renal failure [51,53,54]. For our patient renal function could be recovered, and hence there was no indication for a change in the dose of SOF.

Kidney function affects immunosuppressive therapy, too. It is common among liver transplant recipients to administer an immunosuppressive regimen with a calcineurin inhibitor (TAC), and MMF as an inhibitor of inosine monophosphate through its active metabolite mycophenolic acid. Glucocorticoids are known to encourage a recurrence of HCV after LT and therefore are abandoned as possible therapy in immunosuppressive regimens for HCV patients [55].

In our patient's case, adaption of immunosuppressive medication was necessary, and, indeed, rescued the patient from

renal failure in combination with sufficient hydration and discontinuation of NSAPs. Because TAC is known to have a possible harmful effect on renal function and the levels of TAC were too high in our patient's blood, the dose was reduced. In the presence of renal failure, the dosage of MMF also has to be reduced [56]. In addition, an accumulation of TAC is known to occur in the presence of MMF and vice versa [57,58]. In our patient, the reduction of both dosages yielded a satisfactory level of TAC in the patient's blood and an improved condition of the patient.

Despite the complicated peritransplant setting, including an increasing MELD score and an acute renal injury in a patient on methadone, the treatment with SOF and DCV was successful and required no dose adjustments. The results of recent studies on HCV therapy with DAAs represent an extraordinary opportunity for progress in the history of HCV infection and in the history of infectious diseases in general. Obviously, these advances will diminish the quantity of HCV-infected patients who will need a LT in the future. CHC may be replaced by other hepatological diseases as the most common reason for LT. Despite of all the triumphs in transplant-naïve patients concerning the rate of SVR, the necessity of a liver transplantation may not be prevented but only postponed. The recommendation to prioritize fibrotic patients with a METAVIR (Meta-analysis of Histological Data in Viral Hepatitis) score of 3–4 for treatment with DAAs is surely understandable considering the high healthcare system cost of these treatments [59]. Nevertheless, a restriction of treatment to fibrotic patients may lead to reduced prevention of the necessity of a LT. An increasing frequency of peritransplant anti-HCV treatments is assumable. Consequently, the number of anti-HCV therapies in patients with a high MELD score and/or an acute kidney injury is also likely to grow. More experience in anti-HCV therapy in these complex patients is needed.

Conclusions

Despite the aggravating circumstances in the peritransplant setting for our patient, anti-HCV therapy was successfully administered. In our patient's case, the necessity of a LT was foreseeable and viral clearance was desired before the LT to improve the patient and graft outcomes post-LT. A combination therapy with SOF (400 mg/day) and DCV (60 mg/day) seemed to be safe and effective in a peritransplant setting. Patients on methadone may need psychological therapy to ensure continuation of the treatment and to reduce the risk of reinfection via IV drug use. Further treatment experiences in this patient population are needed, as the number of peritransplant anti-HCV treatments will likely increase within the next few years.

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