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Single Case

A Fatal Outcome after Cessation of Nucleotide Analogue Therapy in a Patient with Chronic Hepatitis B: A Case Report

Sylvia M. Brakenhoff[a] Heng Chi[a] Pieter Friederich[b] Michail Doukas[c] Caroline den Hoed[a, d] Hajo J. Flink[b] Robert J. de Knegt[a] Robert A. de Man[a]

[a]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [b]Department of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, The Netherlands; [c]Department of Pathology, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [d]Erasmus MC Transplant Institute, Erasmus MC University Medical Center, Rotterdam, The Netherlands

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Hepatitis B · Liver transplantation · Nucleos(t)ide analogues cessation · Case report

Abstract
Introduction: Emerging evidence suggests that long-term nucleos(t)ide analogue (NA) therapy can be ceased in a selective group of chronic hepatitis B (CHB). This is being gradually implemented in clinical practice. ***Case Presentation:*** A 68-year-old man known with a chronic hepatitis B e antigen-positive hepatitis B infection without signs of advanced liver fibrosis or cirrhosis was admitted with acute liver failure. Two months prior to his admission, he ceased his NA therapy. During the admission, NA therapy was restarted, but the liver function worsened. The patient was put on the high-urgency liver transplantation waiting list, and the next day, he was successfully transplanted. However, the patient died 17 days later due to hemorrhagic shock that resulted from intra-abdominal bleeding and acute pancreatitis. ***Conclusion:*** Current guidelines suggest that NA therapy can be discontinued in a selective group of CHB patients. However, these guidelines suggest different stopping and follow-up criteria. This case illustrates that NA withdrawal is not without risks and that these differences in recommendations may lead to inadequate management and eventually a fatal outcome.

Correspondence to:
Sylvia M. Brakenhoff, s.brakenhoff@erasmusmc.nl

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Introduction

Worldwide, 296 million individuals are chronically infected by the hepatitis B virus (HBV) [1]. Chronic hepatitis B (CHB) is associated with significant comorbidity and mortality as those patients are at risk to develop liver cirrhosis and hepatocellular carcinoma [1]. Viral eradication is the ultimate goal to halt further progression of liver-related complications. However, a definite cure is difficult to achieve with the current treatment options.

First-line therapy includes nucleos(t)ide analogues (NAs), which can effectively achieve viral suppression. Nonetheless, clearance of hepatitis B surface antigen (HBsAg), and therefore a true functional cure of CHB, remains a rare event even after long-term therapy. Lifelong continuous treatment has therefore been the basis of management in recent years [2]. However, various studies investigated the possibility to cease NA therapy after multiple years of viral suppression. These studies have shown that the chance of HBsAg loss or durable suppression of HBV DNA load (sustained response) is higher among those who cease compared to those who remain on treatment [3–5]. Currently, the hepatitis B guideline of the European Association for the Study of the Liver (EASL) suggests that NA therapy may be ceased in a selected group of patients, including hepatitis B e antigen (HBeAg)-negative patients without signs of cirrhosis who have achieved at least 12 months on-therapy viral suppression [2].

However, cessation of NA therapy is not without risks. Off-treatment virological relapses, often followed by ALT elevations, are observed in the majority of patients [4, 6]. In this report, we present a case that experienced acute liver failure due to an HBV reactivation after NA cessation.

Case Presentation

A 68-year-old man was evaluated with jaundice and signs of encephalopathy at the emergency department. He had a history of Crohn's disease (for which he underwent an ileocecal resection and was currently in remission without any medication) and a stable CHB infection since 2005. The transmission route was identified as men who have sex with men, although the precise date of transmission was unknown. HBV had been adequately suppressed with antiviral therapy; initially with entecavir which was subsequently switched to tenofovir disoproxil (TDF) 4 years ago. Notably, in 2005, HBeAg seroconversion occurred, persisting as negative in the following years. However, an HBeAg seroreversion was observed during tenofovir administration. The most recent HBeAg quantification was performed 3 years ago and showed that the patient was HBeAg-positive, anti-HBe-negative. Five years ago, liver stiffness measurement showed F2-3 liver fibrosis (8.8 kPa, FibroScan®, Echosens, France). Two months ago, TDF was stopped since his treating physician proposed TDF cessation as he had been stable for multiple years (based on ALT and HBV DNA levels; HBeAg and HBsAg levels were not quantified, but he was assumed to be HBeAg negative). Follow-up appointments were scheduled for every 3 months.

At the emergency department, he complained about reduced alertness and jaundice for a couple of days and general malaise for 1–2 months. He did not use any new medication (including herbal supplements) or alcohol in the weeks before presentation. Emergency room vitals included a blood pressure of 157/93 mm Hg, heart rate of 101 beats per minute, respiratory rate of 22 breaths per minute, and temperature of 37.5°C. Physical examination was notable for jaundice, bilaterally crepitation in the lung bases, and tenderness around the umbilicus. He was also noticeably slow in his reaction. The toxicology screen was negative for drugs, and paracetamol levels were low.

Laboratory results are displayed in Table 1. These showed elevated liver enzymes, international normalized ratio, and HBV DNA load of 7.1E8 IU/mL. Abdominal ultrasound showed liver steatosis, but no signs of cirrhosis, ascites, or portal hypertension. Acute liver failure due to HBV reactivation was considered. Antiviral therapy (TDF) was restarted, and broad-spectrum antibiotics as well as N-acetylcysteine were administered. During admission, liver function worsened, international normalized ratio increased, and encephalopathy progressed for which the patient was intubated. The clinical course is depicted in Figure 1.

After 3 days, the patient was transferred to a liver transplantation unit. HBV serum makers showed an elevated HBV DNA load and a positive HBeAg. Viral co-infections (HIV, hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus) were excluded, and serum alfa-1-antitrypsin, ceruloplasmin, ANA, cANCA, pANCA, antibodies against smooth muscle, anti-SLA, anti-mitochondrial antibodies were all within the normal range.

Four days after admission, the encephalopathy progressed and the liver function deteriorated further. The patient fulfilled both the King's College and the Clichy criteria for transplantation in the setting of acute liver failure [7]. Consequently, the patient was put on the high-urgency liver transplantation waiting list. The next day, a liver (donation after brain death) became available, and the patient was successfully transplanted. Postoperative, prophylaxis with hepatitis B immunoglobulins 5,000 IE/day (Hepatect) was started next to antiviral therapy.

The liver explant showed a mottled, nutmeg appearance without signs of nodularity (Fig. 2). Histological findings (Fig. 3) showed confluent hepatocyte necrosis throughout the parenchyma, accompanied by moderate lobular infiltration and periportal ductular reaction. The portal/periportal regions showed lymphoplasmacytic infiltration with interface activity. There were no signs of significant fibrosis. Immunohistochemistry was positive for HBsAg. Thus, histological findings showed signs of acute liver failure which could be consistent with an HBV reactivation without signs of advanced fibrosis or cirrhosis.

One day after the transplantation, the liver enzymes increased. CT abdomen showed infarction of liver segment 6 and stenosis of the hepatic artery, suggesting allograft dysfunction. The liver function improved in the following days, but the kidney function worsened (creatinine of 454 μmol/L) for which continuous veno-venous hemofiltration was started. Five days postoperative, inflammation parameters increased (C-reactive protein: 150 mg/L, leukocytes: 32×10^9/L, temperature: 36.8°C) and a CT showed signs of acute pancreatitis, for which supportive management was initiated.

Seventeen days posttransplantation, the patient became progressively hemodynamically unstable, which was caused by intra-abdominal bleeding. The patient was hemodynamically supported at the ICU. A re-laparotomy was performed and showed peripancreatic necrosis, bile duct injury, and bleeding from the vena cava inferior due to a dissolved suture caused by pancreatic necrosis. Hemostasis could not be achieved, the bleeding was packed with gauzes, and the patient was returned to the intensive care unit. Total blood loss was 15 L. Postoperatively, the patient developed multi-organ failure due to ischemia of the liver, stomach, head of the pancreas, cecum, sigmoid, kidneys, and parts of the small intestine. This all resulted from hemorrhagic shock due to the vena cava bleeding. Supportive treatment was stopped because there was no prospect of recovery, and the patient died. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538342).

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Table 1. Laboratory results

	NA cessation	Day 0	Day 3	Day 4 (referral*)	Day 4.5	Day 5
AST, U/L	22	2,800	2,500	1,839	1,871	1,740
ALT, U/L	33	3,500	4,000	3,339	3,333	3,203
Bilirubin, µmol/L	6.9	190	330	406	414	412
Alkaline phosphatase, U/L	91			1,887	187	166
GGT, U/L	36			122	120	114
Albumin, g/L		38		21	21	19
Creatinine, µmol/L	80	59	55	81	103	115
Hemoglobin, mmol/L	9.2			8.7	8.4	8.2
Leukocyte, $\times 10^9$/L	9.5			14.6	14.1	12.7
Platelet count, $\times 10^9$/L	340			347	343	366
CRP, mg/L	<6.0			25	26	27
INR		2.7	4.1	3.3	3.7	4.0
PT, s				37.3	42.0	44.8
aPTT, s				36		
Factor V, U/mL				0.31	0.21	0.19
Ammonia, µmol/L				98		93
HBV DNA, IU/mL	<10		7.1E8		4.4E7	
HBeAg			positive			

AST, aspartate transaminase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; INR, international normalized ratio; CRP, C-reactive protein; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; U, units; IU, international units; L, liter; mL, milliliter; µmol, micromole; g, gram.

*Referral to the liver transplantation center.

Discussion

Current guidelines suggest that NA therapy can be ceased after long-term viral suppression in a selective group of CHB patients [2, 8]. This case demonstrated, however, that NA cessation is not without risks. Currently, different guidelines suggest different stopping and follow-up criteria. This case illustrates that these different criteria may lead to inadequate management and even – in this case – death.

First, a full workup of the patient is important before NA discontinuation, including the assessment of HBeAg status. Our patient was HBeAg-positive. The current EASL guideline does not recommend NA cessation in this group of patients; it can only be considered at least 1 year after a patient experienced HBeAg seroconversion. In our case, the most recent HBeAg status was quantified 3 years ago but not at the time of NA discontinuation. If performed shortly before NA withdrawal, this might have prevented NA cessation. Therefore, a complete HBV virology and serology quantification should be performed if NA cessation is considered, including HBV DNA, HBeAg, quantitative HBsAg, and (if not performed in the past) hepatitis C, hepatitis D, and HIV serology to exclude a co-infection. In addition, emerging evidence suggests that HBsAg levels are the best reliable predictor for off-treatment outcomes. These should therefore also be included in patient selection, excluding patients with high HBsAg levels (for instance >1,000 IU/mL and possible >100 IU/mL among Asian patients) as these patients have very limited chance of favorable outcomes but an increased risk of ALT flares [9].

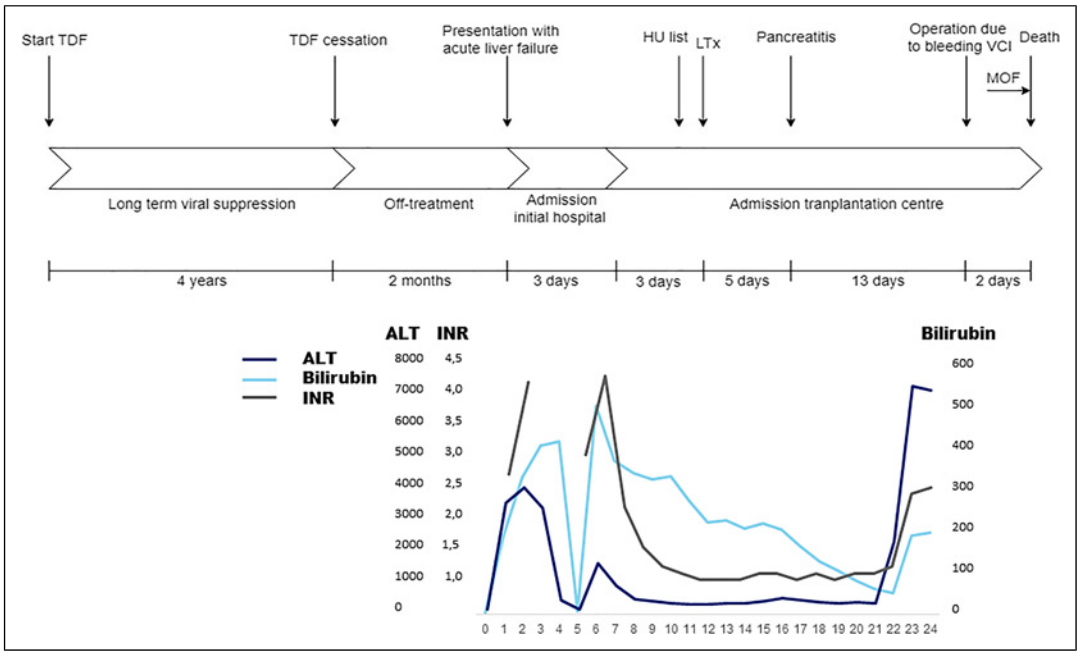

Fig. 1. Clinical course. TDF, tenofovir disoproxil; HU, high urgency; VCI, vena cava inferior; MOF, multi-organ failure; ALT, alanine aminotransferase; INR, international normalized ratio.

Additionally, a liver stiffness measurement should be included in this workup to exclude cirrhotic patients because these patients have a higher risk of hepatic decompensation in case of HBV reactivation [4]. However, the absence of cirrhosis does not warrant an off-treatment complication-free course. In our case, histology of the liver explant showed no/minimal signs of liver fibrosis. Thus, liver failure can also occur in non-cirrhotic (or even non-fibrotic) livers if an HBV reactivation or severe ALT flare is not detected in an early stage. This highlights the urge for strict and close off-treatment follow-up management.

The current EASL guideline states that NA cessation can be considered among patients who can be followed "closely" with ALT and HBV DNA monitoring during (at least) the first year. No exact time frame has been provided for this off-treatment follow-up period. In our case, the first follow-up appointment was scheduled 3 months after NA discontinuation. Although some studies also used this time frame [3], most studies used a closer follow-up monitoring plan, which demonstrated that HBV reactivation can already occur 4 weeks off-treatment [5, 10]. A study conducted by Choi et al. [11] underscores that clinical relapse (i.e., concomitant elevation in HBV DNA and alanine aminotransferase) could occur within a few weeks following NA cessation, particularly among individuals previously treated with tenofovir. Our patient presented himself 2 months after TDF withdrawal with acute liver failure and an HBV DNA load of 7.1E8 IU/mL. It could be hypothesized that in the weeks before this presentation, the viral load might already be elevated, as well as ALT levels. In case of closer follow-up management, for instance, every 4 weeks during the first 3 months, a severe flare could have been identified in an earlier stage. Possibly, re-treatment with antiviral therapy could then have prevented liver failure.

In conclusion, NA cessation in highly selected patients is possible but not without risks. It could be considered in a highly selective group of CHB patients after a full assessment of fibrosis stage, serum HBV DNA, HBsAg, HBeAg and should be executed only if close follow-up

Fig. 2. Macroscopy of the liver explant. A slice of the liver specimen with a nutmeg appearance.

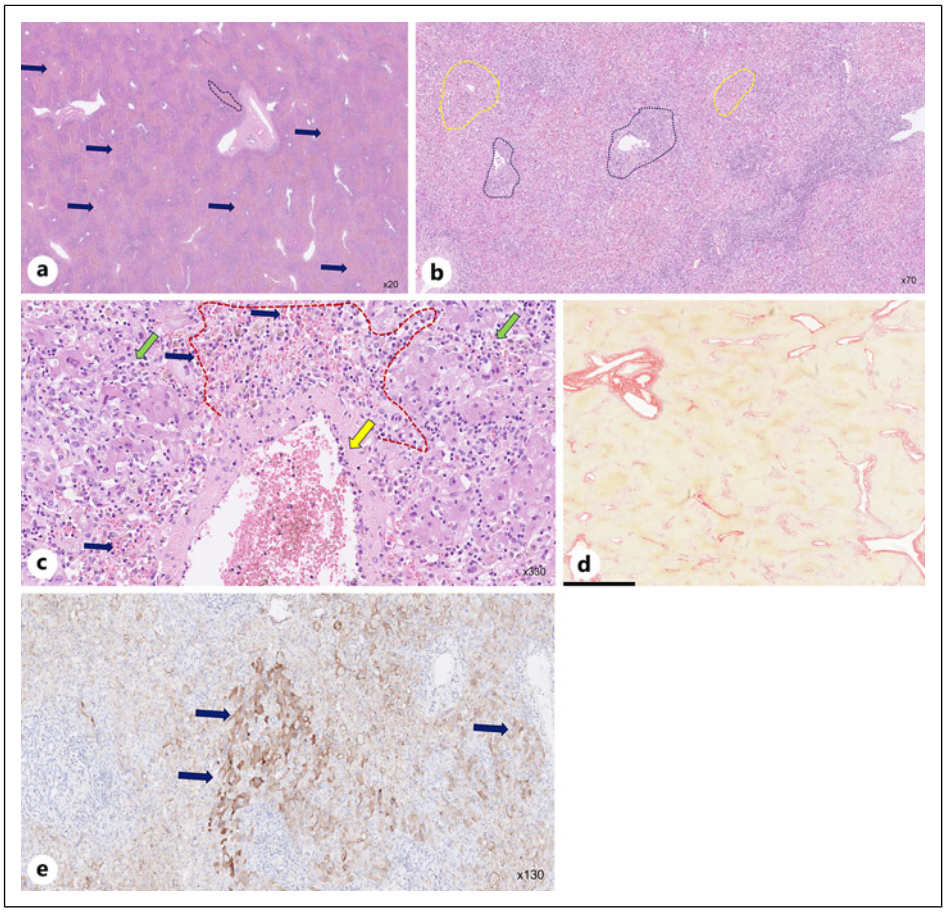

Fig. 3. Microscopic findings of liver explant. Microscopic findings, using hematoxylin and eosin (H&E) stained tissue, showed the preserved architecture of the liver parenchyma, regularly areas of necrosis (areas with sinusoidal congestion and extravasation of blood cells; blue arrows) (**a**); areas with confluent necrosis (yellow dotted line) and portal inflammation (blue dotted line) (**b**); central perivenulitis (yellow arrow) and dropout of hepatocytes (red dotted line), congestion (blue arrows), and lymphoplasmacytic infiltrates (green arrows) (**c**); and the preserved architecture of the liver parenchyma, regularly areas of necrosis (areas with sinusoidal congestion and extravasation of blood cells; arrows) (**d**). **e** In addition, immunohistochemistry showed HBsAg-positive hepatocytes (arrows).

(for instance, every 4 weeks during the first 3–6 months) can be guaranteed. In addition, due to the high complexity of HBV course and close monitoring plan, it could be considered that NA cessation should only be performed in (or after consultation with) specialized expert (academic) hospitals.

Statement of Ethics

As the patient has died, written informed consent was obtained from the patient's spouse for publication of the details of this medical case and accompanying images. Ethical approval was not required for this study in accordance with national guidelines.

Conflict of Interest Statement

Robert de Knegt has received honoraria for consulting/speaking from Gilead, Janssen, Echosens, AbbVie, and Norgine and received research grants form Gilead and Janssen. The other authors report no disclosures.

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Author Contributions

S.M.B.: conceptualization, investigation, visualization, and writing – original draft. H.C.: conceptualization, investigation, and writing – original draft. P.F., C.d.H., and H.J.F.: clinical involvement and writing – review and editing. M.D.: visualization and writing – original draft. R.J.d.K. and R.A.d.M.: conceptualization, supervision, and writing – review and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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