CAS CLINIQUE / CASE REPORT

CHALLENGES IN THE TREATMENT OF ACUTE FULMINANT HEPATITIS B
Case Report and Literature Review

http://www.lebanesemedicaljournal.org/articles/63-2/case3.pdf

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Alawieh A, Eldine RN, Youssef M, Bizri AR. Challenges in the treatment of acute fulminant hepatitis B: Case report and literature review. J Med Liban 2015 ; 63 (2) : 102-106.

ABSTRACT : Acute hepatitis B is a serious cause of fulminant hepatic failure and subsequent mortality. No established guidelines are currently present for the treatment of this life threatening entity. Several therapeutic options were reported in the literature including the use of lamivudine as well as the more novel nucleoside analogue entecavir. We report an unfortunate case of fulminant hepatitis B that passed away despite intensive care unit management and treatment with entecavir in combination with steroids. Extensive review of the literature about various therapeutic approaches to manage fulminant hepatitis B was conducted. The aim of this report is to emphasize the need for larger more structured studies in order to improve the outcome of the treatment of this entity.

Keywords: fulminant hepatitis B, acute hepatitis B, fulminant hepatic failure, lamivudine, entecavir

BACKGROUND

Fulminant hepatitis (FH) has an overall incidence of 1.5 per 100,000, and the peak prevalence is among adults aged between 25-44 years [1]. FH could be idiopathic or secondary to viral infection, drug toxicity, toxins, or metabolic causes [2].

Hepatitis B virus (HBV) is the most common viral cause of acute liver failure [3]. Acute fulminant hepatitis B results in death or transplantation in 80% of affected individuals [2]. Around 5% of acute HBV infections in adults become chronic and only 1% progress to fulminant hepatitis with significant mortality [4-6]. Despite seriousness of fulminant hepatitis B (FH-B), treatment modalities remain controversial with no established guidelines or recommendations [7]. Although published guidelines focus on the management of chronic rather than FH-B [8-12], they recommend treatment for acute FH-B with no consensus on what antiviral therapy to use and the duration of therapy [13]. Liver transplantation, though expensive and limited in availability, remains the only proven therapeutic option to prevent a deadly outcome in FH-B [14-18]. Several studies have reported the significance of prompt and timely antiviral therapy in improving the outcome of FH-B [7, 19-20]. The absence of double-blinded randomized controlled trials adds to the complexity in distinguishing between various therapeutic interventions and there exist no solid evidence about the advantage of any specific agent [21].

Given the controversy and the challenges surrounding the optimal approach to the treatment of this entity, we report a case of FH-B who passed away despite intensive care management and administration of entecavir at our medical center.

CASE REPORT

A 51-year-old man who lived in the Kingdom of Saudi Arabia (KSA) presented to our hospital with decreased level of consciousness and jaundice of one-week duration. He had low grade fever, abdominal pain and has been vomiting since five days. His medical history was relevant for diabetes mellitus and hypertension. The patient had recurrent attacks of acute pancreatitis secondary to pancreatic divisum for which he was admitted to another center for stent insertion two months prior to his current illness. At that time, his hepatitis B surface antigen was negative. The patient gave no history of jaundice, ascites, or previous central nervous system problems. His social history was negative for alcohol consumption or blood transfusion. He was monogamous with no extramarital sexual relations. The patient was admitted to a hospital in KSA two days before his presentation to our center. He was diagnosed there to have acute FH-B and was started on entecavir (0.5 mg/day).

Upon admission to our center, he was stuporous, agitated, unresponsive, jaundiced, tachycardic, tachypneic and febrile. Neurologic exam revealed a Glasgow Coma Scale of 9 with preserved corneal reflexes. He was electively intubated, placed on mechanical ventilation, and transferred to intensive care unit.

His laboratory results on admission were: leukocytosis (WBC = 14,800/cu.mm; 84% segmented), platelets of 164,000/cu.mm, elevated liver and biliary enzymes (AST 6042 IU/L, ALT 5014 IU/L, GGT 109 IU/L, alkaline phosphatase 226 IU/L), INR > 6, PTT 53 seconds, bilirubin total/direct ratio: 11.2/8.4, protein/albumin ratio: 50/32 g/L, and lipase 500 IU/L. His ammonia level was 270 μg/dL that increased the second day to 500 μg/dL, and his serum creatinine was 3.4 mg/dL. Acetaminophen level was normal 1 (toxic > 200). Blood and tracheal aspirate cultures were negative.

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CT scan of brain showed diffuse edema. Imaging of the liver did not show any extra or intrabiliary dilatation or the presence of stones.

Liver specific auto-antibodies were negative. Hepatitis serology profile revealed positive HBs antigen, positive anti-HBc IgM antibodies > 200 (normal < 5) and positive HBe antigen by ELISA. Anti-HBs and anti-HBe antibodies were negative. Hepatitis C and HIV serology were negative.

Entecavir therapy, started in KSA, was continued at the same dose and the patient was given steroids, transfused with fresh frozen plasma, received vitamin K injections, and started on lactulose and antibiotics (piperacillin/tazobactam).

He developed generalized tonic-clonic seizures treated with anti-epileptics and passed away four days after hospitalization at our medical center.

DISCUSSION

The patient developed acute hepatitis B as evident by positive anti-HBc IgM antibodies and a recent conversion from negative HBsAg to positive. He could have acquired the viral infection via the endoscopic retrograde cholangiopancreatography that took place two months ago at another hospital knowing that the incubation period of the virus is between 1 to 6 months [22]. The differential of new onset jaundice includes viral hepatitis, alcoholic liver disease, autoimmune hepatitis, drug-induced liver disease, common bile duct stones, pancreatic cancer, primary biliary cirrhosis, and primary sclerosing cholangitis [23-24]. However, the differential of jaundice emergencies is quite narrow including fulminant hepatic failure, acetaminophen toxicity, and ascending cholangitis. The latter two diagnostic options are unlikely in our patient following the results of acetaminophen blood level and liver imaging.

Fulminant hepatic failure (FHF) has been defined as the development of encephalopathy within eight weeks of the onset of symptoms in a patient with a previously healthy liver [23] or the appearance of encephalopathy within two weeks of developing jaundice, even in a patient with previous underlying liver dysfunction [24]. Many complications contribute to the dismal prognosis of FHF including: cerebral edema, infections and sepsis, acute renal failure, circulatory dysfunction, coagulopathy, gastrointestinal bleeding, metabolic disturbances, pulmonary complications and malnutrition [25]. The damage in fulminant hepatitis B is believed to be due to the massive immune-mediated lysis of infected hepatocytes and not to the acute infection per se [26].

The pathogenesis of fulminant hepatitis is still undisclosed; however, it was proposed that the complications that arise from this infection are mostly inflammatory mediated and this is why steroids were thought to be helpful [27-28].

The treatment of acute hepatitis B is mainly supportive since it is a self-limiting illness [4]. In fulminant cases, patients should receive aggressive medical management that includes electrolyte and fluids, plasma, blood, and vitamin K supplement to correct coagulation defects, proper diet, acid base control, and neomycin sulfate [29]. However, some patients may need antiviral treatment, mainly those with a severe or protracted course, a preexisting liver disease, advanced age, concomitant infection with hepatitis C or D viruses, or those who are immunocompromised. Evidence has shown that treatment in fulminant hepatitis may improve survival without the need for transplant and reduces the likelihood of reinfection post-liver transplant [4, 7]. Treatment modalities include mainly the administration of certain nucleoside analogues; however, the use of interferon, prostaglandin G2, Foscarnet, and steroids was also reported [4].

Old and new nucleoside analogues were studied in FH-B including lamivudine (Table I), entecavir [30-32], adefovir [32], and tenofovir [33]. Lamivudine is the most studied modality, yet successful outcome was not always achieved [34]. Lamivudine was found to improve survival and brings upon prompt clinical, biochemical, serological and virological responses [7, 19-20, 30, 35-42] (Table I). In addition to improving survival, lamivudine was also used in FH prophylaxis to prevent the recurrence of infection following liver transplant [7]. Double lamivudine dosage (200 mg/day) was used to reach a rapid decrease in viral load and a faster recovery [35]. Meanwhile, a case control study has reported the failure of lamivudine in improving survival in infected patients with hematological malignancies [34]. Moreover lamivudine was recently found to reduce viral replication and control disease progression rather than achieving cure [33, 42-43]. Lamivudine resistance has also been documented in the past few years especially with genotype C [44-46]. Antiviral resistance to lamivudine as well as delayed therapy have led to treatment failure in several settings [21, 32-33]. Entecavir, with the lowest rates of drug resistance among nucleoside analogues [47], has been also reported to be successful in treatment of FH-B [48]. Three case reports have described the success of entecavir in FH-B [30-32]. Adefovir and Tenofovir were also found to be effective in cases that failed lamivudine therapy [32-33]. Telbivudine was reported to be helpful in acute-on-chronic hepatitis B liver failure compared to control, but there are no reports of on use in acute FH-B [49].

In addition to nucleoside analogues, both steroids and prostaglandins were tested for their effectiveness in treatment of FH-B. A preliminary report on the use of prostaglandin E (PGE) by Sinclair *et al*. showed no relapse after a 4-week course of treatment in six patients with FH-B [50]. Fujiwara *et al*. reported recovery in 88.2% of 17 patients with severe exacerbation of chronic hepatitis B following treatment with corticosteroids with or without antiviral agents [51]. Foscarnet, a pyrophosphate analogue, was also reported to be successful in the treatment of FH-B [52-53].

TABLEAU I

PUBLISHED REPORTS ABOUT LAMIVUDINE IN TREATMENT OF ACUTE FULMINANT HEPATITIS B

Study Type	Year	Sample Case Description	Treatment group Case	Control	*Result*
Case Report[36]	1999	One patient	150 mg/day	–	*Successful treatment*
C-C* Study[32]	2001	10 patients with HM♦	150 mg/day (n = 5)	Supportive (n = 5)	*No prognostic advantage*
Case Series[37]	2002	3 patients	150 mg/day	–	*Enhanced recovery*
Case Series[34]	2004	15 patients	150 mg/day	–	*Favorable response in 86.6%*
Case Report[35]	2005	An infantile patient	8 mg/kg/day	–	*Effective treatment and recovery*
RCT■ [33]	2006	71 patients	100 mg/day (n = 31)	Placebo (n = 40)	*Virological response without biochemical/clinical improvement*
C-C* Study[7]	2006	17 patients	100-150 mg/day (n = 17)	Historical sample	*Full recovery in 82.4%*
RCo▼ study[51]	2008	33 patients	100 mg/day (n = 10)	Untreated (n = 23)	*70% survival with lamivudine versus 26% in untreated*
Case Report[28]	2008	A female patient	100 mg/day	– –	*Prompt clinical, biochemical, serological and virological response*
Case Series[18]	2008	4 patients	100 or 200 mg/day	–	*Successful treatment*
Case Report[38]	2009	Young pregnant woman	100 mg/day	– –	*Lamivudine is safe and effective in pregnancy*
Case Report[39]	2010	An infantile patient	3 mg/kg/day from day 3	–	*Recovery during a follow-up of 4 years*
RCo▼ study[40]	2010	80 patients	100 mg/day (n = 40)	Standard care (n = 40)	*Successful treatment with decreased mortality*
MRCo▲ Study[19]	2011	77 patients	100 mg/day (n = 38)	Untreated (n = 39)	*Decreased mortality by 28%*

*Case control ■ Randomized controlled trial ▼ Retrospective cohort ▲ Matched retrospective cohort ♦ Hematological malignancies

Our patient died despite receiving entecavir in combination with steroids and aggressive medical therapy in intensive care.

This doesn't necessarily mean failure of entecavir but may be due to delay in initiating antiviral therapy where serious complications occurred before entecavir had time to act.

CONCLUSION

Successful therapy in acute FH-B requires early recognition, prompt administration of antiviral therapy, and identifying patients who require emergent liver transplant [2]. Choosing the best antiviral agent remains a challenge in the absence of large-scale randomized controlled trials (RCTs) and the low methodological quality in many published reports. RCTs are hard to conduct given the scarcity of cases of FH-B and bounding ethical considerations. Multicenter studies and sharing data might be one possible option [21]. Prevention through vaccination and proper infection control practices can prevent this entity [5-6].

FUNDING: None
COMPETING INTERESTS: None declared.
ETHICAL APPROVAL: Not required.

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