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Case Report

Fatal Reactivation of Hepatitis B Virus after Stopping Treatment with Nucleos(t)ide Analogues

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Abstract

Nucleos(t)ide analogues (NAs) are very efficient antiviral agents able to suppress hepatitis B virus (HBV) replication with very minor side effects.

Current data suggest that administration of these agents to cirrhotic patients should be continuous but in patients with chronic hepatitis B with long-term administration and optimal response there is a concern when the treatment will be discontinued, taking into account the potential adverse effects that may occur because of this interruption.

We present a patient, who having been on NAs treatment for 10 years, he discontinued the treatment which was followed by severe reactivation of the virus, manifesting as lethal subacute/subfulminant hepatitis.

Thus, discontinuation of the use of NAs in patients with chronic hepatitis B should be done according to the current guidelines and with a very close attendance of the patient.

Keywords: *Nucleos(t)ide Analogues (NAs); Fatal Reactivation; Hepatitis B Virus*

Introduction

NAs are very efficient therapeutic agents for the treatment of chronic hepatitis B. Their usage entails selective suppression of the HBV DNA polymerase which results in the halting of viral replication. The currently used drugs which suppress the virus are tenofovir, tenofovir alafenamide, entecavir, adefovir, telbivudine and lamivudine [1]. Side effects from the use of these agents are minimal.

The use of these agents is mandatory in cirrhotic patients [1-3]. On the contrary, for the patients with chronic hepatitis B and long-term excellent response there is the question of how long the administration will be continuing [4]. Discontinuation of treatment is usually accompanied by reactivation of the virus with inflammation in the liver which may at best result in surface antigen loss (HBsAg) [5] or significant liver damage and very rarely in the patient's death [2,6].

Consequently, discontinuation of NAs should be performed in accordance with current criteria and close monitoring of the patient.

Case Report

A 55 year old man was diagnosed with HBeAg-negative chronic liver disease following serological and histological (2 liver biopsies, 1997 and 2001) investigations. He was treated twice in the past with interferon alpha (1997 and 1999) without success. In 2000, he was started on lamivudine till 2006 and then due to the development of resistance, adefovir was added to his treatment. This combination

therapy lasted till June 2010 when the patient stopped treatment. Then HBV DNA was undetectable and the levels of transaminases were within normal limits. The patient was advised to have transaminase level measurements on a monthly basis.

Three months later, the patient was presented with jaundice, complaining of tiredness and anorexia without fever. The patient reported urine hyperpigmentation and fecal discoloration. Clinical examination revealed, BP 140/80 mm Hg, pulse 80/min, chest and heart examination normal. Abdominal examination revealed a slightly palpable liver. No splenomegaly and no ascites were detected. Neurological examination was normal and he was well orientated. The biochemical measurements were: AST 2690 IU/ml, ALT 3382 IU/ml, total bilirubin 23.7 mg%, direct bilirubin 15 mg %, PT 16.7 sec, INR 1.4, and AFP 17.3 ng/ml. HBV serological markers were: HBsAg -positive, HBeAg -positive, anti-HBc -positive, anti-HBe-negative, anti-HBs-negative. The HBV DNA level by PCR was extremely high at 10^8 IU/ML using the Taqman assay. PCR amplification of the polymerase region showed that the patient was infected with a genotype D HBV, subtype ayw. Amino-acid sequence alignment revealed no substitutions associated with NAs analogue treatment.

Course of the disease

The general health of the patient was deteriorating every day. Immediately after the patients admission into the hospital, tenofovir and entecavir treatment were initiated. On the second week of the hospitalization, there was a rise in the level of bilirubin (from 23 mg% to 35 mg%), an increase of the INR (from 1.4 to 1.6), a decrease in the levels of transaminases (from 3382 to 924 IU/ml), while the regeneration of the liver was satisfactory (AFP 286.3 from 17.3 ng/ml). By the end of the second week the patient developed ascites with a slight decrease in the size of the liver as was noted by ultrasound examination. Diuretic treatment was started with spironolactone 100 mg and furosemide 40 mg daily with reduction of ascitic fluid. At the end of the third week bilirubin was raised to 43 mg%, INR was raised to 1.8, while the transaminase levels were reduced to $1/10^{th}$ of those at presentation (SGPT 312, SGOT 251 IU/ml). HBVDNA levels were decreased to 10.000 IU/ml.

On the fourth week of hospitalization the patient developed a respiratory infection with high fever. Radiologically there was opacity at the middle lobe of the right lung. He was given cefotaxime with quick amelioration of his condition. But the shrinkage of the liver was still ongoing, INR was raised to 2.3, there were further decreases in the levels of transaminases (SGPT 94, SGOT 91 IU/ml), cholesterol was quite low (18 mg%) and AFP was reduced to 21 ng/ml. At the end of the fifth week of the hospitalization the patient presented hepatic encephalopathy and finally died of septic shock.

Discussion and Conclusion

The administration of NAs is the most effective way to suppress HBV. The use of the newer NAs (tenofovir and entecavir) long-term have proved that both have a high barrier to resistance, being 0% for tenofovir and around 3.1% for entecavir [7]. The usage of these agents must be continuous in cirrhotic patients because the discontinuation of treatment has detrimental consequences usually with the death of the patient [2,8].

The discontinuation of the treatment in patients with chronic hepatitis B is one of the most controversial topics in the management of chronic hepatitis B. In a systematic review [4] of 25 studies with 1716 patients the durable virological remission (VR) after the discontinuation of treatment with NAs showed that for HBeAg- positive patients the VR was 62.5%, 53.34%, 51.5% at 12, 24, 36 months after the discontinuation and for HBeAg- negative the respective VR was 43.7%, 31.3%, 30.1%. After discontinuation of treatment, in all patients there is a risk of virus activation that may elicit an immune response that may at best cause surface antigen (HBsAg) loss or cause mild or severe liver inflammation with the risk of transition to cirrhosis or rarely in the development of subacute/subfulminant liver failure, leading to death [9].

In the literature [2,8], rare cases of death are reported in persons with chronic hepatitis B who stopped treatment with NAs. The existence of cirrhosis of the liver makes the situation more difficult and more dangerous. So patients with cirrhosis should never stop treatment with NAs.

Our patient had been administered a combination of adefovir with lamivudine for 4 years, subsequent to 6 years of monotherapy with lamivudine. The patient was not cirrhotic and his general health and laboratory examinations were normal with undetectable HBV DNA. Three months after cessation of the treatment the patient presented with jaundice, very high levels of viral load (10^8 IU/ml), seroconversion (from anti-HBe-positive to HBeAg-positive) and raised transaminases. These phenomena appeared after the interruption of NAs which caused an increase in viral load as well as the initiation of the immunological reaction, with reactivation of T lymphocytes against the virus. The administration of tenofovir and entecavir did not ameliorate the situation. At the end of the third week of hospitalization the level of HBVDNA dropped to 10.000 IU/ml, but in spite of this, the patient continued to deteriorate. The cascade of immunological reaction had started and was impossible to stop.

The levels of transaminases continued to decline (Figure 1), but bilirubin was stabilized around 40 mg%. The coagulation index was worsening (INR 4.5). Cholesterol was reduced from 132 to 16mg%, a sign of very severe liver damage. AFP which is an index of regeneration of the liver, had an initial rise in the middle of the second week and then progressively dropped to 10 ng/ml. This transient rise was very hopeful for a good outcome but later its fall was rapid.

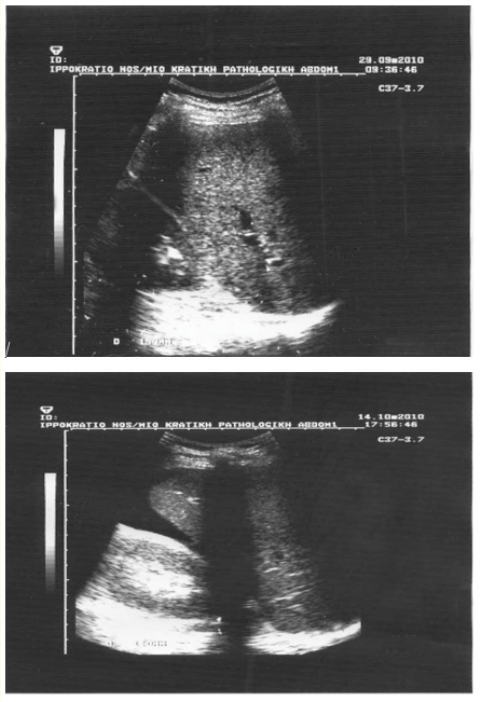

Figure 1: *Progressive shrinkage of liver size and production of ascitic fluid.*

Very impressive was the shrinkage of the liver as we noted it by performing ultrasound examination every day. Also, there was the emergence of ascites as a result of decompensation of the liver function (Figure 2). As feared, the patient presented signs of infection despite the quarantine measures taken. This affected the respiratory system. In spite of an initial improvement the patient developed septic shock and he died. The course of the patient was that of a subacute /subfulminant hepatitis, a situation that most of the times leads to patient death if liver transplantation does not take place, which is the only therapeutic approach in such patients.

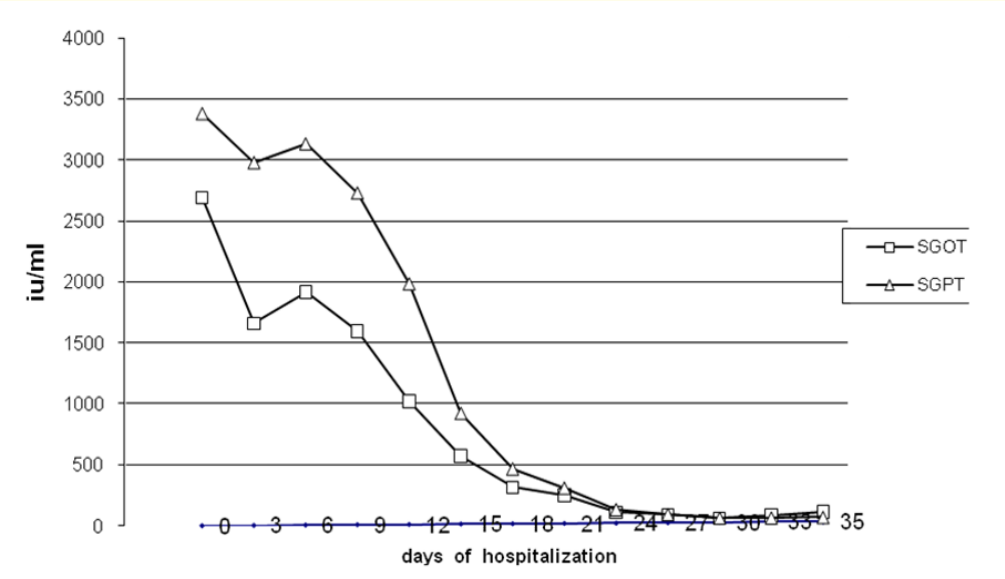

Figure 2: *The declining course in transaminase levels as indicated during the patient´s hospitalization.*

There is a great deal of concern about the strange course of this patient. There is a tremendous increase in viral load within three months and seroconversion from HBeg- negative to HBeAg- positive. Histological examinations of the liver did not reveal liver cirrhosis and there is the question if they were representative. On the other hand the sequential genome examination of the virus did not reveal any peculiarities [10].

Finally, we propose for the patients with chronic hepatitis B under NAs who are going to stop this treatment to be under strict medical attention, with at least the first three months, monthly measurement of HBV DNA and transaminases.

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