Severe peripheral neuropathy in patients with chronic HBV infection receiving long-term nucleos(t)ide analogues (NAs) therapy

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ABSTRACT: The goal of HBV treatment is to improve survival by preventing disease progression to decompenated cirrhosis and HCC. This goal can be achieved if HBV replication is suppressed in a sustained manner. For these reasons the prolonged treatment with oral nucleos(t)ide analogues is recommended for selected patients with chronic HBV infection. These therapies have to be continued until the possible seroconversion (HBsAg/anti-HBsAg) which is actually an uncommon event. Therefore, NA-therapy can assume a lifelong duration. A variety of long-term adverse events have been reported in patients with HIV infection on antiretroviral therapy including one or more nucleoside reverse transcriptase inhibitors. Here we describe 3 clinical cases of peripheral neuropathy related to long-term anti-HBV treatment possibly due to mitochondrial toxicity related to long-term NA treatment in HBV-infected patients.

— Key words: HBV infection, Nucleos(t)ide analogues, Severe peripheral neuropathy, Mitochondrial toxicity.

INTRODUCTION

The hepatitis B virus (HBV) is estimated to have infected more than 2 billion people worldwide, of whom 400 million are chronically infected today and are at an increased risk of liver-related complications, including cirrhosis, liver failure, hepatocellular carcinoma (HCC) and death1,2.

Treatment end-points are complete viral suppression (undetectable levels of HBV DNA replication), hepatitis B e antigen (HBeAg) clearance and seroconversion in HBeAg-positive patients, and if possible HBsAg clearance and development of anti-HBs antibody3,4.

The goal of HBV treatment is to improve survival by preventing disease progression to decompensated cirrhosis and HCC5.

This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients6.

For these reasons the prolonged treatment with oral nucleos(t)ide analogues (NAs) is recommended for selected patients with chronic HBV infection. These therapies have to be continued until the possible seroconversion (HBsAg/anti-HBsAg) which is actually an uncommon event. Therefore, NA-therapy can assume a lifelong duration.

Then prolonged treatment with oral nucleos(t)ide analogues is recommended for selected patients with chronic HBV infection.

However, there are compelling evidence linking the development of HIV-lipodystrophy one related with the use of some medications including the nucleoside reverse transcriptase inhibitors6.

CASE REPORTS

Here we describe 3 clinical cases of peripheral neuropathy related to long-term anti HBV treatment.

The first patient was a woman of 71 years of age who was receiving NA therapy for 147 months (LAM, ADF, TDF). He received ADV+LAM for 132 months. His last therapeutic schedule was lamivudine 100 mg once daily with full virologic success (HBV DNA <20 IU). The patient referred the progressive onset of neuropathic pain involving the legs reaching Grade 4 with burning pain at the last visit. She also complained of difficulty on walking requiring the need of help by others.

The second patient was a male of 67 years of age who was in therapy with NAs from 102 months with NUC (LAM, ADF, ETV and TDF). He received ADV+LAM for 60 months and his last therapeutic schedule was TDF 245 mg once a day with HBV-DNA not detectable.
He also complained of peripheral neuropathy involving both inferior limbs with bilateral Grade 3-4 pain and great difficulty on walk unaided.

The third patient was a 66 years man, who has been in therapy with NAs (LAM, ADV, TDF) for 153 months. He received ADV+LAM for 108 month whereas his last schedule at the time of event was TDF 245 mg once a day with HBV-DNA not detectable.

His symptoms were characterized by peripheral neuropathy mainly involving the left lower limb, with Grade 2-3 local pain and difficulty on walking.

In our three patients the onset of neuropathy was definitely not related to progression of liver disease.

Other potential causes of peripheral neuropathy were also excluded including alcohol abuse, assumption of other drugs, including chemotherapies in the 12 preceding months, diabetes and autoimmune diseases. In all cases the peripheral neuropathy was confirmed by a neurological examination with electromyography and electronueroigraphy consistent with the diagnosis of peripheral neuropathy of probable iatrogenic etiology.

In the three reported cases NA therapy was discontinued with progressive resolution of the neuropathic pain.

They started peg-interferon alfa-2a 180 mcg once a week which was subsequently discontinued 4-6 months after the start for different reasons.

**DISCUSSION**

As previously discussed, NA therapy can assume a life-long duration, even if some long-term adverse events can occur such as those relating to mitochondrial toxicity in HIV-patients known as “lipodystrophy syndrome” that could increase cardiovascular risk7,8.

Indeed, a variety of adverse long-term as peripheral polyneuropathy predominantly of the lower limbs, lactic acidosis, hepatic steatosis, pancreatitis and lipodystrophy are highlighted in patients with HIV infection on antiretroviral therapy including one or more nucleoside reverse transcriptase inhibitors (NAs)9.

In our center 54 HBV-infected patients in chronic therapy with NAs were actively seen for care with a median duration of therapy of 38 (range 20-60) months when the 3 described clinical cases occurred.

In all 3 cases of peripheral neuropathy developed during the last 3 years of clinical monitoring and they taking Tenofir disoproxil monotherapy at the onset of their symptoms.

They all came to our attention complaining about signs and symptoms localized at the lower extremities, closely resembling NRTI-related peripheral neuropathy seen in HIV-infected patients.

Our group have previously demonstrated that NA treatment (especially if including ADV + LAM) can result in mitochondrial (mt) toxicity with a significant reduction in mitochondrial RNA expression in terms of mtRNA values10.

We hypothesize that, similarly to what happens in patients with HIV infection treated with NRTI, the long-term exposure to drugs associated with potential mitochondrial toxicity such as lamivudine and adefovir can promote the occurrence of clinical adverse events such as severe peripheral neuropathy also in the treatment of patients with chronic HBV infection even if currently receiving medication with less toxic potential such as TDF.

**CONCLUSIONS**

Our observations suggest an intensification of monitoring in patients with chronic HBV infection receiving long-term therapy with NAs in order to evaluate the possible occurrence of peripheral neuropathy onset. This particularly applies to patients who have had a long history of drug therapy with LAM alone or in combination with ADV.

**CONFLICT OF INTERESTS:**

The Authors declare that they have no conflict of interests.

**REFERENCES**