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Adefovir dipivoxil (ADV) – the management of particular difficult problems in patients with chronic HBV infection

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Summary

Prolonged lamivudine therapy for chronic hepatitis B may induce mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) locus of the HBV DNA polymerase gene in both immunosuppressed and immunocompetent patients, often leading to exacerbation of the disease. Patients with HBV-related cirrhosis should be treated to improve fibrosis, prevent decompensation, and suppress HBV replication in the pretransplant setting. It is well confirmed that some patients with lamivudine resistance awaiting for liver transplantation treated with ADV were stable or improved and were not transplanted. Therapy with ADV resulted in a delay of hepatic decompensation and liver transplantation as final treatment. Thus, in patients with pre-existing liver cirrhosis an early switch to ADV appears to be indicated after emergence of lamivudine resistance. In majority of cirrhotic patients, IFN alfa therapy is contraindicated. Failure of prophylaxis for hepatitis B virus (HBV) recurrence in liver transplant patients with HBV immunoglobulin (HBIG), or lamivudine, or both can be associated with rapid development of liver failure. ADV should be considered to be a safe and effective choice for prophylaxis of recurrent HBV infections in liver transplant patients. It is confirmed that cccDNA persists throughout the natural history of chronic hepatitis B, even in patients with serologic evidence of viral clearance. Long-term ADV therapy significantly decreased cccDNA levels by a primarily noncytolytic mechanism, diminishing possibility of reactivation. In the absence of prophylaxis with LAM or ADV, the reactivation of HBV infection in oncology patients who are HBsAg carriers is a well-known and often serious complication of chemotherapy. The current recommendations of antiviral prophylaxis prior to chemotherapy in the USA are patients who are positive for HBsAg. Patients who are negative for HBsAg but positive for antibodies anti-HBc are still at risk for reactivation of latent HBV infection during and after chemotherapy and may be considered for prophylaxis. Successful treatment of fibrosing cholestatic hepatitis (FCH) using ADV in a patient with cirrhosis and renal insufficiency where observed. Moreover ADV can be safe and effective treatment of renal transplant patients with lamivudine-resistant hepatitis B. Adefovir does not share cross-resistance with nucleoside compounds such as lamivudine, emtricitabine, telbivudine and entecavir.

key words: **chronic hepatitis B • reinfections • antiviral treatment • adefovir**

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Despite long experience in the management of HBV chronic infections we still find it difficult to treat some patients in clinical practice. These are cases with advanced liver cirrhosis with serious concomitant diseases, patients with tumors growth, immunocompromised, organ transplant recipients or dialysed. The most successful way to decrease the risk of chronic infection complications and prevent liver failure is HBV eradication. Effective antiviral treatment results in improvement in necroinflammatory assessment, reduction of fibrosis progression and improves quality of life. However in some cases prolonged antiviral therapy may induce mutations that result in treatment resistance and progression of liver disease.

Chronic liver failure

Therapy with a nucleoside analogue may lead to treatment resistance. Prolonged administration of lamivudine (LAM) in patients with chronic hepatitis B may induce mutations in tyrosine-methionine-aspartate-aspartate (YMDD) locus of HBV DNA polymerase gene. Lamivudine resistance occurs in about 25% after one year of treatment, in 66% after four years; average 20% per year [1]. YMDD mutation often leads to clinical severe exacerbation of liver disease. These patients may be successfully treated with adefovir dipivoxil (ADV) - nucleotide analogue. Prolonged therapy with ADV induces HBV mutations and treatment resistance only in 15% of patients with chronic hepatitis B after 192 weeks of administration [2]. ADV was effective in cases with YMDD mutation as well as in patients with proved YSDD mutation. Patients with exacerbation of liver disease during lamivudine therapy with YMDD mutation improved after additional ADV administration. Early LAM resistance detection and ADV therapy may delay transplantation. Clinical, biochemical and virological improvement was observed also in 324 patients with LAM-resistant HBV infection before and after liver transplantation, treated with ADV in 10 mg daily dose, for 48 weeks [3].

The main reason for antiviral treatment failure and lack of sustained virological response is ineffective elimination of microsomal DNA (cccDNA) from the infected hepatocyte nucleus. Prolonged ADV therapy does not inhibit amplification of microsomal DNA but significantly reduces cccDNA [4].

In a Korean study [5], results of ADV 10mg daily treatment in two groups of patients with liver cirrhosis and HBV infection were compared - 48 cases with compensated cirrhosis and 53 in end stage liver disease. Good tolerance, efficiency and safety were demonstrated in both groups of patients including lamivudine-resistant cases. However, the efficiency of the therapy may be worse in liver decompensation, there was no ALT values improvement differences in both groups. Loss of HBeAg and anti-HBe seroconversion did not differ either. The amounts of HBV DNA copies lower than 0.5pg/ml in the serum were more often observed in patients with compensated liver function than in end stage disease cases. ADV therapy in patients with LAM-resistant HBV infection significantly decreases viral load and leads to YMDD mutation change for wild-type virus in more than 22% of cases after 16 weeks of treatment [6].

Child-Turcotte-Pugh score (CTP) is useful in evaluation of the degree of liver failure in clinical practice. Model for End-Stage Liver Disease (MELD) is more useful in evaluating expected clinical problems and surgical death rate (10) and is helpful in qualification for liver transplantation. Well evaluated MELD may significantly reduce death rate among patients waiting for liver transplantation [7].

In one study [8], 226 patients awaiting for orthotopic liver transplantation (OLT) with LAM-resistant HBV infection and with average CTP model 7.0 and MELD 12 were included into study evaluating results of additional ADV (10mg daily) treatment (LAM + ADV). Clinical and biochemical improvement were achieved with HBV DNA below 1000 copies/mL in 65% of patients and normalization of ALT activity in 77%, after 96 weeks of the therapy. Average MELD model was 3.8 lower after 48 weeks of treatment and 5.1 in week 96. The survival rate in week 96 was 77% of the evaluated patients. ADV treatment decreases MELD value, some patients improve and may be successfully crossed out from the OLT candidates list.

Prevention of hepatitis B virus recurrence after liver transplantation

All candidates for liver transplantation due to HBV-related liver disease should get antiviral treatment prior to the surgery. HBV reactivation in immunosuppressed transplant recipients may lead to graft failure. Combination prophylaxis with LAM and hyperimmune globulin (HBIG), the current standard of care after transplantation, reduces the rate of HBV reinfections. Patients with LAM-resistant mutations may be treated with ADV as “rescue” therapy [9].

Sixteen patients with YMDD mutation were treated with LAM and ADV before and after liver transplantation [10]. Eight of them received additionally HBIG for about 24 months. In 14 cases, HBsAg loss was observed, two patients who were treated with LAM and ADV only, were still HBsAg positive. One patient died, but of unrelated cause. 15 patients have undetectable serum HBV DNA and no biochemical and histological evidence of hepatitis. The average follow-up after transplantation was 21.1 mo. ADV was generally well-tolerated. Further study to evaluate benefits of antiviral therapy (LAM + ADV) with or without expensive HBIG is needed.

A number of studies proved successful ADV treatment with HBIG in posttransplant patients with LAM resistant HBV infection even in cases with advanced disease with progressive liver failure due to severe HBV reinfection or fibrosing cholestatic hepatitis [9-11].

Other difficult clinical cases

Reactivation of HBV infection is common in immuno-compromised patients; during chemotherapy, after organ transplantations, in HIV positive individuals, even in cases negative for HBsAg but with detectable anti - HBc antibodies. Antiviral prophylaxis (LAM or ADV) is recommended prior and during immunosuppressive therapy in so called “HBsAg carriers” without clinical and biochemical symptoms of hepatitis [12-14].

Two interesting examples are as follows: a patient after renal transplantation was treated with LAM due to HBV reactivation. Two years after the transplantation and antiviral

therapy, clinical and biochemical symptoms of exacerbated hepatitis and renal graft dysfunction were observed with high viral load. ADV (10mg every 72 hours) was used as "rescue" therapy with good result [15]; a patient with prostatic adenoma with metastases in bones (D2) during chemotherapy (mitoxantrone + prednisone) manifested recurrent hepatitis B successfully treated with ADV [16].

Conclusions

Effective therapy of HBV infection should lead to sustained viral eradication. The currently accepted treatment of patients with chronic HBV infection includes agents with immunomodulatory and antiviral (or) only antiviral activities – interferon alfa, nucleoside analogue (LAM) or nucleotide analogue (ADV). Interferon is associated with many side effects so it is often poorly tolerated and contraindicated. Long-term use of LAM may induce YMDD mutations with LAM resistance.

Adefovir dipivoxil is well tolerated and effective in HBeAg positive and negative patients infected with wild-type or LAM resistant HBV. It may be used in decompensated liver cirrhosis, in patients with renal dysfunction and HIV co-infection. It is also effective in HBV re-infection prophylaxis after liver transplantation and in immunosuppressive therapy. The benefits of ADV therapy are also associated with a delayed and infrequent emergence of resistance due to HBV mutations in prolonged treatment.

Adefovir dipivoxil is still relatively new drug and at present its use is limited to patients with LAM resistant HBV infection but provides a promising new option in the management of this disease.

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