Role of lamivudine in the reactivation of hepatitis B virus infection in immunodepressed patients

E. Marín, P. Rendón, L. de Diego, Mª J. Soria, Mª C. Martínez and L. Martín

Service of Digestive Diseases. Hospital Universitario Puerta del Mar. Cádiz, Spain

ABSTRACT

Introduction: hepatitis B virus (HBV) reactivation in immunocompromised states is a well-known event that may be a serious problem in endemic areas of infection. Presently, the investigation of hepatitis B status has been recommended prior to receiving cytotoxic treatment. Lamivudine has been used in the reactivation of HBV in immunocompromised states. We report our corresponding data for lamivudine in the treatment of HBV reactivation after intensive chemotherapy in patients with lymphoma and after kidney transplantation.

Clinical observation: we present two cases of HBV reactivation after chemotherapy for lymphoma and two cases after cadaveric renal transplantation treated with lamivudine (100-150 mg/day).

Results: we observed a prompt clinical improvement in all patients after lamivudine treatment. Furthermore, laboratory data showed a rapid biochemical and antiviral response. However, the response in lymphoma patients was quicker than in patients who had post-transplantation reactivation of HBV. Therapy was well tolerated and no relevant side effects appeared during follow-up (twenty four months). The HBV remained negative in three cases.

Conclusion: lamivudine is effective and safe in the treatment of HBV reactivation in immunodepressed patients. Lamivudine therapy should be considered for the treatment of HBV reactivation in patients with prior hepatitis B or chronic hepatitis B with inactive viral replication.

Key words: Lamivudine. Hepatitis B virus. Chemotherapy. Lymphoma. Transplantation.

INTRODUCTION

According to the WHO, chronic hepatitis B virus (HBV) is one of the most frequent infectious diseases in the world, with 350 million persons affected. The reactivation of the HBV during and especially after immunosuppressive therapy in tumor patients or in those receiving a transplant, is an important cause of morbidity and mortality, particularly in those regions where the infection is endemic. Therefore, prior investigation of the status of the HBV is recommended in transplanted patients or those with cancer requiring treatment with cytotoxic agents.

Lamivudine is a nucleoside analogue of deoxycytidine currently indicated for the treatment of some virus infections such as HIV and HBV. In addition, it has been used as treatment for the reactivation of HBV infection after pharmacological immunosuppression, and currently, it is even proposed as prophylaxis of this condition.

We describe our experience with lamivudine in the treatment of patients who have suffered from reactivation of a latent infection by the HBV after immunosuppression, and more specifically we report what has occurred in patients affected by lymphoproliferative diseases treated with intensive chemotherapy and in those with renal transplants.

CASES REPORTS

Case 1

A 62 year-old woman with grade I follicular lymphoma, stage IV-A, and with positive serology for HBV infection (anti-HBc positive; anti-HBs <10 UI/L), with strictly normal hepatic tests at the time of diagnosis. One month after the fifth cycle of CHOP-type (cyclophosphamide, Adriamycin, vincristine, prednisone) chemotherapy, she presented elevated serum level of transaminases (SGPT 1600 UI) and bilirubin (22.2 mg/dl), and ascitis. It was
confirmed the presence in serum of HBsAg, anti-HBc-IgG, HBeAg and HBV-DNA, latter by polymerase chain reaction (PCR). After excluding other causes of acute hepatitis, treatment was started with 150 mg/day of lamivudine. At week 12, normalization of serum transaminases and bilirubin was observed, and at week 36, HBV-DNA (PCR) was negative in blood. At present, after 15 months of treatment with lamivudine, no adverse effects of the medication have been observed, serum transaminase levels remain normal and the HBV-DNA is negative (Fig. 1). However, remission of the hematological disease has not produced.

Case 2
A 32 year-old woman with a mediastinal lymphoma, anti-HBs titres below the minimum protective levels (without previous HBV vaccination) and normal liver tests developed an acute hepatitis through reactivation of the HBV six months after the administration of six cycles of mega-CHOP type chemotherapy and after receiving an autogenous transfusion of peripheral blood. In this case, serum SGPT levels reached 3379 UI/L and serum bilirubin 15.5 mg/dl. Serologically, the patient presented positive HBsAg, anti-HBc-IgG, HBeAg and a HBV-DNA concentration of 3300 pg/ml by a method of molecular hybridation. After administrating 150 mg/day lamivudine, at week 12, serum transaminases and bilirubin levels were normal. Negativization of the viral DNA in peripheral blood (by PCR) was achieved at week 19. At the present time, after 60 weeks of follow-up and five months of complete remission of the hematological disease, liver tests are normal and HBV-DNA remains negative (Fig. 2).

Case 3
A 52 year-old male, asymptomatic carrier of HBsAg, recipient of a kidney transplant from cadaveric donor. He was treated with cyclophosphamide, mycophenolate and corticoids. At month 20, serum transaminase levels were found to be elevated. Liver biopsy displayed mild persistent hepatitis and the serum HBV-DNA concentration was 12000 copies/ml. He was referred to our service one year later, when SGPT level was 176 IU/L, prothrombin activity and serum bilirubin were normal and HBV-DNA level was 18000 copies/ml. Treatment with 150 mg/day lamivudine was started, and virus negativization was obtained at week 56. However, signs of cytolysis remained until week 64 (Fig. 3). Currently, after 25 months of treatment, an increased serum level of transaminases, up to 300 IU/L, positive viral DNA in peripheral blood (by PCR), together with a deterioration of the renal function (creatinine of 2.5 mg/dl) have been shown. No adverse effects have been recorded.

Case 4
A 53 year-old male, asymptomatic carrier of the HBV, was on treatment with cyclophosphamide, mycophenolate and corticoids because of renal transplantation from cadaveric donor. A raised level of serum transaminases observed after 12 months of immunosuppressive therapy confirmed the reactivation of the HBV. He was assessed by our service three months later; when serum SGPT level was 245 UI/L and the HBV-DNA load was 300 copies/ml (by molecular hybridation). Treatment was started with 100 mg of lamivudine per day. After 40 days of treatment, SGPT level was 144 and HBV-DNA remained positive (2.5 copies, by molecular hybridation). Then, lamivudine dose was increased to 150 mg/day. The viral DNA
was negative at week 25 of treatment, and serum transaminases were normal at week 29. Subsequent follow-up showed that transaminase levels were normal and HBV-DNA remained negative up to the present time, after 198 weeks of treatment with lamivudine, together with the absence of any significant adverse secondary effects (Fig. 4).

In patients receiving kidney transplantation from a cadaveric donor, the risk of reactivation during the cytotoxic therapy ranges between 5 (6) and 25%, and have been published that the mortality reaches the 60% (7). The following conditions have been defined as risk factors for the reactivation of HBV: male sex, young age, lymphomas, degree of immunosuppression, type of drug used, and presence of precore mutants (5). In vitro studies have demonstrated that corticoids stimulate the transcription of the DNA, thus increasing the expression of viral DNA and the production of HBsAg and HBeAg (8). Cyclosporine A treatment increases the viral load in vitro by means of selective inhibition of the T lymphocytes (9). However, mycophenolate mofetil inhibits the replication in vitro of some kinds of virus, including HBV (10). It appears that reactivations of precore mutants of the HBV can occur earlier and be more serious (11).

Classically, the clearance of HBsAg had been associated with the disappearance of the HBV from the blood and the remission of the disease. However, HBV-DNA has been detected at low levels in serum, liver and/or mononuclear cells of peripheral blood in some HBsAg negative patients. It has been demonstrated that HBV infection may remain for a long time in up to 55% of the patients, even when the antiviral immune response has been effective. However, it has not been possible to find a clear correlation between the persistence of low viral load and its capacity to cause liver disease (12). Hence, the concept of “latent”, “silent” or “hidden” infection has been adopted to define those cases where the HBsAg is not detectable, but HBV infection is nevertheless present. There has been evidence of such a latent infection in patients with anti-HBc and/or anti-HBs, and even in some cases where all the serological markers are absent (13). Probably, the group of patients in which it is most difficult to accept this concept of latent infection would be those patients who have positive anti-HBs exclusively, but cases have been published that document such latent infection (14,15). Reactivation of HBV, and even fulminating hepatic failure (16), has also been reported in patients with criteria of latent infection (negative HBsAg in serum; positive anti-HBs and/or anti-HBc; absence of any serological marker of HBV infection) who had been treated with cytotoxic or immunosuppressive medication (16-18). However, the reactivation induced by immunomodulatory therapies is less frequent and serious in patients with silent infection than in those with positive HBsAg (19).

We report the case of two patients: the first one had anti-HBc-IgG and anti-HBs below the optimum level of immunity and the second had only anti-HBs. In both cases, the profound immunodepression after chemotherapy or hepatic transplantation was the main risk factor (20). Neither of the patients had an acute exacerbation of HBV liver disease, which is the most serious form of exposure to this virus (21). Although in both cases the antiviral immune response was impaired, it was able to control the HBV replication (22). The most important difference between the two cases was the risk of reactivation of HBV, which was higher in the patient who had been previously exposed to HBV (23). In this patient, the reactivation of HBV was associated with the development of a chronic liver disease (24), and the patient died of the disease 10 years after transplantation (25). However, in the patient who had never been exposed to HBV, the reactivation of HBV was associated with the development of a chronic liver disease (26), and the patient died of the disease 10 years after transplantation (27).

**DISCUSSION**

Hepatitis B virus produces liver damage through indirect mechanisms (2), after establishing a chronic infection as a result of a failure of the host immunological response. The persistent immunological assault leads to the progression of the liver disease, and between 15 and 25% of the patients die prematurely due to cirrhosis of the liver or hepatocellular carcinoma.

The reactivation of HBV is a well-documented complication in patients treated with cytotoxic agents for malignant neoplasm diseases or in transplanted patients. Mechanisms of HBV reactivation and its association with the liver damage are currently unknown. It has been postulated that iatrogenic immunosuppression permits the replication of the HBV, which results in the infection of naïve hepatocytes. When the immune system is restored, generally after the interruption of the immunomodulatory treatment, there is a rapid T lymphocytes-mediated destruction of the infected liver cells (29). Although the factors predicting the severity of the hepatic damage have still to be determined, this damage seems be proportional to the viral load stored inside the hepatocytes (3).

In the majority of cases of reactivation of HBV that have been published, malignant hematological diseases and occasionally solid tumors are involved. Thus, half of the patients with lymphoma who have had previous contact with HBV suffer a reactivation of HBV after systemic chemotherapy. The mortality rate of these patients ranges between 5 and 32% (4,32). The administration of chemotherapy regimes in patients with other malignant tumors has also resulted in a reactivation of HBV. However, no data are available on the risk of reactivation of the infection or on its prognosis. Yeo et al. found that the risk of reactivation after systemic chemotherapy is about 20% (5).
serum prior to the treatment that could confirm the presence of HBV-DNA. However, the absence of other causes of liver disease, the conversion of the serological markers, the high viral load of HBV in peripheral blood, and the publication of similar cases in the medical literature, allow the diagnosis of reactivation of a latent HBV infection following a situation of immunosuppression and justifying its treatment with lamivudine. Therefore, in all patients with serological markers indicative of previous contact with HBV, before administering systemic chemotherapy or performing transplantation, it may be necessary to determine the HBV-DNA by means of PCR, with the aim of detecting low serum HBV-DNA levels.

There are several factors that can increase the serum levels of transaminases in patients on immunomodulatory therapy: infections by other viruses (herpes simple virus, herpes zoster virus, cytomegalovirus, Epstein-Barr, Q fever, hepatitis A and C viruses, human acquired immunodeficiency virus), toxicity by drugs, tumor infiltration of the liver, autoimmunity, etc. Thus, the diagnosis of reactivation of the HBV infection during chemotherapy is defined by the increase in serum HBV-DNA count, together with data of hepatitis, without any other cause that could explain these changes.

It has been observed that reactivation of the HBV infection after transplantation of solid organs is manifested clinically and analytically later or more slowly than in tumor patients treated with chemotherapy (6,24). We have also observed these differences in the onset of the reactivation in our patients: less than six months after ending chemotherapy in tumor patients, and more than one year in the two cases of immunosuppression indicated because of transplantation. This difference is likely due to the degree of immunosuppression and the type of drug used in each condition, particularly the high doses of corticoids used in the treatment of lymphomas.

Lamivudine is an analogue of nucleosides with major activity against HBV; it inhibits reverse transcriptase and effectively reduces viral load in chronic hepatitis B (20). In the published cases of reactivation of HBV by immunosuppression, lamivudine has been shown to be effective in reducing the risk of hepatitis (21). Early use of lamivudine as a treatment for the reactivation of HBV in transplanted patients can increase survival of these patients from 40 to 75% (32). This drug induces a rapid antiviral response, both biochemical and clinical (32), and with no adverse effects of any consideration (23). To date, no consensus has been reached on the optimum dose and the duration of the therapy. For some authors, the administration of 100-150 mg/day for at least 4-6 months after finishing the last cycle of chemotherapy appears to be effective in tumor patients. Subsequently, monitoring of patients would be necessary, with periodical determination of serum transaminases and DNA viral load, to diagnose a possible relapse after the suspension of lamivudine (23). However, in transplanted patients, lamivudine therapy should be maintained for life. Prolonged treatment is safe and well tolerated (24,25); the problem lies in the emergence of lamivudine resistant mutants in the YMDD motif of the HBV polymerase gene.

In the treatment of chronic hepatitis B, a decreased effectiveness of lamivudine therapy has been described that is directly proportional to the time of administration. The rate of YMDD mutations is of 19% after one year of treatment and of 44 and 57% after two and three years, respectively (26,27). However, despite the emergence of mutants, serum HBV-DNA levels are lower than before initiating the treatment with lamivudine, which may reflect the poor replicative capacity of these mutants. On the other hand, it is not at all clear that the seroconversion can be maintained, although the presence of YMDD strains does not prevent this. Withdrawal of lamivudine treatment gives rise to a prompt reappearence of the wild strains. New analogues of nucleosides –such as adefovir dipivoxil– with synergic or additive properties when used in association with lamivudine in non-responding patients, or for use in monotherapy are currently under investigation (28).

In our experience, evolution after lamivudine was excellent, with a rapid clinical and analytical recovery following the suppression of the viral load. In all patients there was an early clinical improvement. Biochemical normalization occurred between weeks 12 and 64, and the HBV-DNA was disappeared between weeks 19 and 56. The mean times of response in patients with lymphoma were considerably shorter, the liver tests normalized at week 12 and the HBV-DNA was not detected at week 28 of treatment, against weeks 47 and 41, respectively, for the renal transplanted patients. After a mean monitoring of 24 months, in three of these patients, the HBV-DNA remained negative (by PCR determination) and no patients had adverse effects.

Currently, is being considered the possible prophylactic use of lamivudine in patients previously in contact with HBV who need to receive chemotherapy or a transplantation (4,29-32). The main purpose of this proposal is to avoid fulminating hepatitis by reactivation of HBV in situations of immunosuppression, where lamivudine may fail due to a late administration (33). This is the case of early relapses after intensive chemotherapy in patients with malignant hematological diseases. The use of lamivudine would allow the chemotherapy protocol to be completed without the need to reduce the dose, and the decreased probability of cure associated with dose reduction.

Due to all of the reasons presented herein, we believe that lamivudine is a good therapeutic option in cases of the reactivation of HBV in situations of immunodepression, in particular after chemotherapy in tumor and in transplanted patients.
REFERENCES


