Lamivudine treatment for Hepatitis B in dialysis population : Case reports and literature review

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Abstract

It is well known that chronic hepatitis B plays a detrimental role on survival in patients on long-term dialysis and after kidney transplantation. The advent of nucleos(t)ide analogues offers the opportunity to change the natural history of hepatitis B in patients with chronic kidney disease. We report our experience on lamivudine use in two patients with HBV-related liver disease on long-term dialysis. At the beginning, both the patients were HBsAg positive and HBeAg positive with high viral load ; after long-term lamivudine therapy, clearance of HBV viremia from serum was observed in both. Raised aminotransferase levels fell into the normal range and one patient experienced clearance of HBsAg by anti-HBV therapy. Tolerance to lamivudine was satisfactory and lamivudine resistance was not detected. Information on antiviral therapy with lamivudine in HBsAg positive patients on regular dialysis is extremely limited ; we identified by an extensive review of the literature five studies with a total of 38 unique patients, most of them being renal transplant candidates. Lamivudine proved to be effective as the clearance of HBV viraemia from serum ranged between 56% and 100% ; the clearance of HBeAg from serum was less evident (between 37.5% and 100%). No significant side-effects due to lamivudine were observed and emergence of lamivudine-resistant strains was observed in two (5%) patients. Only a minority of patients experienced HBsAg loss (13%). We conclude that anti-HBV treatment with a nucleoside analogue such as lamivudine gives satisfactory results in some patients on long-term dialysis. Clinical trials are in progress to assess efficacy and safety of last-generation nucleos(t)ide analogues for anti-HBV therapy in dialysis population. (Acta gastroenterol. belg., **2013**, 76, **423-428**).

Key words : hepatitis b, hbv viraemia, lamivudine, dialysis.

Introduction

Controlling the spread of hepatitis B virus (HBV) infection within dialysis units has been a major advance in the management of patients with chronic kidney disease (CKD) undergoing long-term dialysis. The prevalence of HBsAg positive patients in dialysis population and after renal transplant is currently low (1-3) ; according to the DOOPS data, the rate of HBsAg positive patients on dialysis range between 0 and 5% (4). Evidence accumulated in the last decade has shown an accelerated course of hepatitis B in patients with uraemia and a negative impact on survival. A large meta-analysis of observational studies ($n = 6$, 6050 unique RT recipients) found that positive HBsAg status in serum is an independent and significant risk factor for death and graft failure after RT ; the summary estimate for relative risk was 2.49 (95% CI, 1.64-3.78) and 1.44 (95% CI, 1.02 ; 2.04), respectively (5). The impact of HBV upon survival in dialysis population is less evident but a high mortality rate among HBsAg positive patients on dialysis has been already observed (6).

Several oral nucleos(t)ide analogues have been recently introduced in the routine clinical practice and novel information has been collected on antiviral therapy for HBV in individuals provided with intact kidney function (7-8). On the contrary, data on anti-HBV therapy in chronic kidney disease population is extremely poor. We report the outcome of therapy for HBV infection in two patients on maintenance dialysis ; in addition, a systematic review of the available literature was made.

Case report n. 1

The patient was an African male with end-stage renal disease of unknown origin who started regular haemodialysis since the age of 21. He had underwent kidney biopsy in his own country ; the procedure was complicated by bleeding whereas the results of kidney histology remained unknown. He underwent long-term haemodialysis (HD) in his country for four years and moved at the age of 25 to Italy where he continued long-term HD three times weekly. His initial hepatitis work up revealed positive hepatitis B surface antigen (HBsAg), positive hepatitis B e antigen (HBeAg), and hepatitis C antibody negative ; moreover, no detectable antibody for immunodeficiency virus in serum was seen. An intermittent increase in serum aminotransferase levels was noted. Ultrasonography examination revealed enlarged liver and spleen with normal structure, intact biliary ducts were present. Endoscopy of gastro-intestinal (GI) tract showed gastric esophageal reflux (grade 1) and uremic gastritis. Other medications at that time included inhibitors of protonic pump, phosphate binders, iron supplements, intravenous erythropoietin, oral calcitriol, beta-blockers and nifedipine. Twenty-two months after his arrival in Italy, blood chemistries revealed an important

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increase in serum aminotransferase levels (alanine aminotransferase up to 1251 IU/L, and aspartate aminotranferase up to 561). Other laboratory results included serum albumin 3.8 gr/dL, cholinesterase 7712 IU/L, total bilirubin 1.26 mg/dL, and gamma glutamyltranspeptidase 249 IU/L. Quantitative polymerase chain reaction showed detectable viral load in serum with HBV DNA levels ranging between 40×10^6 and 2×10^5 copies/mL. IgM antibody to hepatitis B core antigen tested negative. Diagnosis of acute on chronic HBV was suspected- he started antiviral therapy with oral lamivudine (100 mg every other day) without side-effects. Antiviral therapy was associated with a slow decrease of serum aminotransferase and HBV DNA levels, the patient remaining HBeAg positive. Fifteen months after lamivudine therapy he underwent evaluation for kidney transplant and performed liver biopsy. Important changes in the lobular structure of liver tissue were found- moderate portal inflammation with focal interface necrosis, mild to moderate lobular inflammation with frequent focal necrosis and evidence of acidophilic inclusions, activation of Kuppfer cells, numerous hepatocytes having ground glass appearance, and peri-portal fibrosis with significant bridging. Stainable iron was observed in seventy-five percent of hepatocytes. Twenty months after lamivudine therapy he resulted HBsAg positive, HBeAg negative, with no detectable HBV DNA in serum. Two years after the first biopsy while on lamivudine, he underwent repeat liver biopsy which revealed a decrease in necro-inflammation activity. Bleeding from small esophageal varices was observed by GI endoscopy four years later. No evidence of lamivudine resistant strains with molecular biology techniques was noticed. After long-term lamivudine use (eight years), he is currently on long-term dialysis waiting for kidney/liver transplant. His last chemistries included HBsAg positive, HBeAg negative, HBV DNA negative [Table 1], normal coagulation tests, cholinesterase 4675 IU/L, total protein 9.7 gr/dL, and serum albumin 4.2 gr/dL. White blood cells are 2180/μL, platelet 69000/mm^3, Hb 10.8 gr/dL. AST and ALT are 39 and 37 IU/L respectively ; and gamma-GT 63 IU/L.

Case report n. 2

The patient was a 71-year-old Caucasian male with multiple myeloma (MM, IgG*k* stage III) since the age of 53. He was in charge at the Nephrology Division at the age of 68 years for evaluation and treatment of acute renal failure with significant decrease of urine output. At that time, he underwent kidney biopsy showing tubulointerstitial nephritis and started long-term dialysis. A few weeks after long-term dialysis, immunosuppressive therapy for MM was initiated and several courses of chemotherapy over the subsequent two years were made. His initial hepatitis work-up included HBsAg negative, HBc antibody positive, anti-HCV negative ; moreover, no antibody against human immunodeficiency virus was found. He was referred to hepatology service at the age of 70 when he revealed positive HBsAg and HBeAg and detectable HBV DNA in serum, 110×10^6 IU/mL by PCR (TaqMan). Other pertinent chemistries included normal aminotransferase levels, normal total serum proteins and albumin, coagulation tests and gamma-GT were in the normal range. Ultrasonography did not show significant liver damage. A shift from occult to overt HBV infection due to the immunosuppressive courses for the treatment of MM was suspected, and diagnosis of acute HBV was made. He started antiviral therapy with oral lamivudine (100 mg every other day) with a rapid reduction of HBV DNA levels, he became HBV DNA negative after seven months of lamivudine therapy. Ten and thirteen months after the initiation of antiviral therapy he became HBeAg negative and HBsAg negative, respectively. No detectable antibody towards HBsAg (HBsAb) was found [Table 1]. Last blood chemistries showed normal total bilirubin (0.3 mg/dL), AST and ALT levels 12 and 13 IU/L respectively, gamma-GT 10 IU/L, cholinesterase 7217 IU/L, total protein 7.1 gr/dL, and serum albumin 4.2 gr/dL. White blood cells and platelet count were in the normal range. No evidence of lamivudine resistant strains with molecular biology techniques was found. He is still on long-term haemodialysis ; MM being mostly remitted but no evaluation for kidney transplant was made to date. His current medications include phosphate binders, oral calcitriol, amlodipine, intravenous erythropoietin, ranitidine, and lamivudine.

Discussion

The case reports described above add emphasis on efficacy and safety of lamivudine treatment for HBV in patients on long-term dialysis. As shown in Table 1, at the beginning both the patients were positive for the conventional markers of HBV replication (hepatitis B e antigen, HBV DNA) and showed a very high load. With anti-HBV therapy, HBV DNA was no longer detectable in serum ; HBeAg clearance with detectable HBeAb antibody occurred in both ; HBsAg loss was observed in patient n. 2. Patient n. 1 is currently in the waiting list for liver/kidney transplant- he likely initiated anti-HBV

Table 1. — **Biochemical and virological parameters before/ after lamivudine therapy**

Pt. No.	AST Pre/Post	ALT Pre/post	HBsAg Pre/Post	HBeAg Pre/Post	HBV DNA Pre/Post	HBsAb Pre/Post	HBeAb Pre/Post
1	561/39	1251/37	+/+	+/-	+/-	-/-	-/+
2	22/32	24/27	+/-	+/-	+/-	-/-	-/+

Table 2. — **Anti-HBV therapy by lamivudine in patients on long-term dialysis: clinical and viral parameters**

Author	Ben-Ari Z., *et al.*	Fontaine H., *et al.*	Boyacioglu S., *et al.*	Schmilovitz-Weiss H., *et al.*	Lapinski T., *et al.*
Reference number	9	10	11	12	13
Year	2000	2000	2002	2003	2005
Patients, n	6	5	7	4	16
Country	Israel	France	Turkey	Israel	Poland
Baseline age, years	40.2+9.9	50 (34; 58)	30 (22; 46)	43+8.9	NA
Male, n	6 (100%)	4 (80%)	4 (57%)	4 (100%)	12 (75%)
Baseline anti-HCV positive, n	0	1 (20%)	0	2 (50%)	8 (50%)
Baseline HBeAg positive, n	5 (83.3%)	5 (100%)	3 (43%)	4 (100%)	16 (100%)
Baseline cirrhosis, n	2 (33%)	2 (40%)	0	0	NA
Lamivudine therapy, duration (mo)	14 (1; 26)	12 (7; 28)	NA	10.2 (7; 14)	12
Lamivudine dose, mg	20 mg/day	10 mg/day	100 mg × 3/week	10 mg/day	100 mg × 3/week
HBsAg clearance by lamivudine, n	2 (33%)	0	0	3 (75%)	0
HBeAg clearance by lamivudine, n	3 (60%)	1 (20%)	3 (100%)	4 (100%)	6 (37.5%)
Lamivudine Resistance, n	0	2 (40%)	0	0	0

treatment by lamivudine after significant liver damage occurred.

Current licensed drugs for the treatment of chronic HBV infection include peg-interferon α-2a and nucleos(t)ide analogues. The nucleoside analogues which are currently approved for the treatment of chronic HBV include lamivudine, telbivudine, and entecavir. The currently available nucleotide analogues are adefovir and tenofovir. Antiviral therapy for hepatitis B among patients receiving regular dialysis is mostly based on lamivudine, the first oral drug approved for the treatment of chronic HBV. Our extensive analysis of the published medical literature on the antiviral activity against HBV in dialysis population identified five small, uncontrolled studies only (9-13) [Table 2]. This is in contrast with that observed after renal transplant where there is abundant information on lamivudine therapy against HBV over short and long follow-ups after transplant (14-18).

As listed in Table 2, a total of 38 chronic HBsAg carrier patients on regular haemodialysis was found ; most of them in the active waiting list for kidney transplant. In an attempt to make a quantitative evaluation of the response to lamivudine therapy, Figures 1 and 2 show the virological response to lamivudine in dialysis population. The primary outcome of interest in our review was viral and serologic response to lamivudine, these definitions being now standards (19).

The low number of patients and the significant heterogeneity found by us precluded a full reporting of the results by our meta-analysis of clinical studies. Lamivudine proved to be effective as the clearance of HBV viraemia (HBV DNA) from serum ranged between 56% and 100% (Fig. 1). The clearance of HBeAg from serum was less important (between 37.5% and 100%) (Fig. 2). Antiviral therapy was safe as no significant adverse events attributable to lamivudine were identified ; however, emergence of lamivudine-resistant strains was noted in two patients (2/38 = 5%). Only a minority of individuals experienced HBsAg loss (5/38 = 13%) [Table 2] and it remains unclear if they developed anti-HBc antibody.

Some preliminary evidence exists on treatment of HBV in chronic kidney disease patients at pre-dialysis stage by nucleos(t)ide analogues other than lamivudine-anecdotal information on adefovir (20-22) or entecavir (23) has been published. This kind of information does not exist among patients receiving long-term dialysis. Data on efficacy and safety of nucleos(t)ide analogues including lamivudine (14-18), adefovir (24-26), or entecavir (27) for HBV after kidney transplant are more abundant even if controlled clinical trials (CCTs) have not been made so far. The benefits of successful antiviral therapy for HBV after RT in terms of better survival have been recently emphasized (28).

Several questions on lamivudine use in dialysis patients remain unanswered. For example, the optimal duration of therapy and the predictors of treatment response have not well defined. Challenges to the development of effective treatment regimens include emergence of antiviral-resistant HBV mutants during prolonged mono-therapy, and although lamivudine significantly reduces viral replication, relapse after treatment cessation seems common. The rate of lamivudine resistance in end-stage renal disease compared to individuals with intact kidney function is still unknown. In addition, it is difficult to know which CKD patients with HBV should be treated. No information has been published on histology during therapy. An important point is HBsAg loss ; it appears infrequently in HD patients on lamivudine, but it is a desirable viral end-point because is associated with the

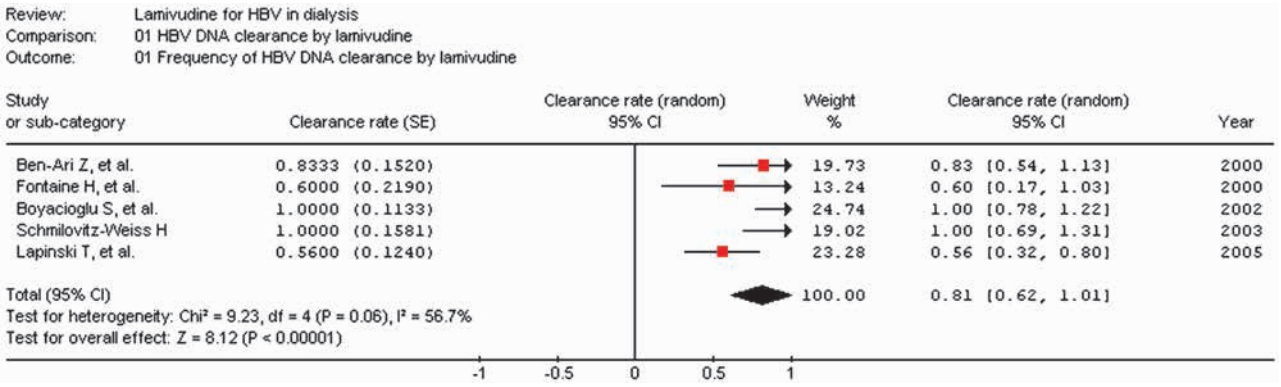

Fig. 1. — Summary estimate of frequency of clearance of HBV DNA from serum by lamivudine therapy (random-effects model)

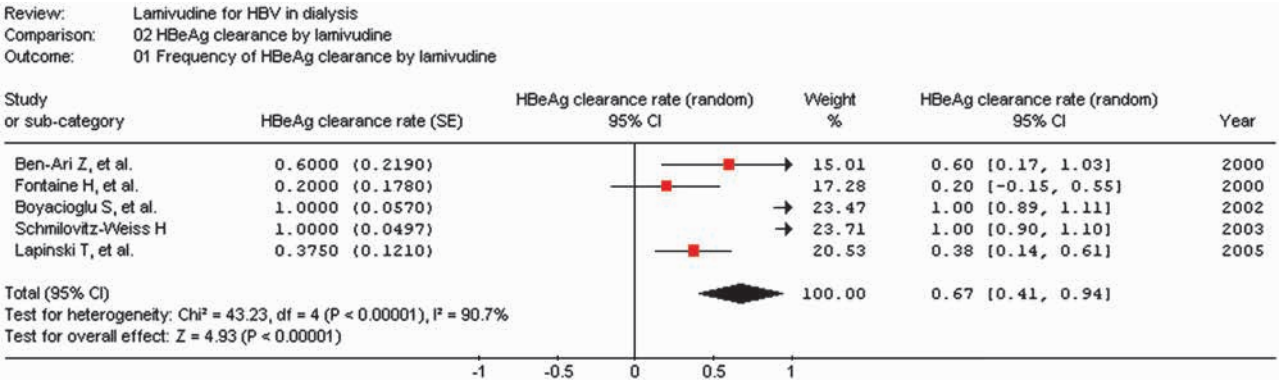

Fig. 2. — Summary estimate of frequency of clearance of HBeAg from serum by lamivudine therapy (random-effects model)

prevention of hepatitis delta super-infection, a reduced risk of complications and improved survival in cirrhotic patients (29).

Recent guidelines on the management of hepatitis B in immunocompromised patients have been issued, including chronic kidney disease patients (30). It has been suggested antiviral therapy be started in active HBsAg positive carriers (i.e., HBV DNA positive with raised aminotransferase values and liver damage confirmed by histology) with chronic kidney disease before renal transplant, regardless of whether the patients are dialysis-dependent or not. In inactive HBsAg positive carriers (i.e., HBsAg positive, HBV DNA negative) pre-transplant and during dialysis, only serologic and viral monitoring is recommended.

The case of patient n. 2 gives emphasis to the issue of occult HBV infection. It has been defined as the long-lasting persistence of HBV DNA in individuals negative for HBsAg, these patients being frequently anti-HBc positive. We suggested the presence of occult HBV infection in this patient- he was HBsAg negative, anti-HBcAb positive at initial work-up and shifted to overt HBV (HBsAg positive) after prolonged immunosuppressive therapy for multiple myeloma. Occult HBV is common in dialysis population and strict surveillance is recommended (31). Acute reactivation of HBV in patients with occult HBV infection has been also observed in liver and kidney transplants due to intense immunosuppressive therapy after solid-organ transplantation (31).

A good safety profile and the ease of administration (one pill daily) are important advantages of antiviral therapy based on lamivudine or other nucleos(t)ide analogues. These benefits are particularly appreciated in dialysis patients as conventional (or pegylated) interferons (IFN) are not well tolerated. IFN-based therapy for HBV in non-uraemic population is still appreciated by various clinicians (32). Graft rejection is a frequent complication of IFN-based therapy after renal transplant and many dialysis patients may not be good candidates for IFN therapy due to age and other co-morbid conditions. A recent meta-analysis of clinical studies found a high rate of drop-outs in dialysis patients compared to individuals with intact kidney function who underwent mono-therapy with conventional IFN for chronic hepatitis C (33).

No information has been published so far on the rate of spontaneous clearance of HBV after kidney transplant. Studies in kidney transplant recipients demonstrate that post-transplant immunosuppressive therapy has a permissive role on viral replication ; this has the potential to influence HBV infection, both in terms of reactivation and in terms of the acceleration of a pre-existing liver injury. In this situation, the possibility of spontaneous

HBV viral clearance appears to be quite low ; this phenomenon has been sometimes noted among long-term dialysis patients (31).

In conclusion, our case reports and literature review suggest that anti-HBV treatment by lamivudine provides satisfactory results in some patients on long-term dialysis. Hepatitis B is relatively uncommon among patients on maintenance dialysis of developed countries and this clearly hampers prospective clinical trials aimed at evaluating efficacy and safety of anti-HBV therapy with novel nucleos(t)ide analogues in this population.

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Conflict of Interest Statement

Dr. Fabrizi, Dr. Mangano, Dr. Stellato reported no relevant financial relationships ; Dr. Martin received financial support from Gilead and Bristol Meyers Squibb (consultant, investigator, and speaker) ; Dr. Messa received financial support for Roche (consultant ; speaker).

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