Long-term add-on therapy with adefovir in lamivudine-resistant kidney graft recipients with chronic hepatitis B

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Abstract

Background. To assess the long-term effectiveness and safety of adefovir (ADV) plus lamivudine (LMV) in LMV-resistant (R) kidney transplants with chronic hepatitis B, 11 such patients were treated with add-on ADV.

Methods. Serum alanine aminotransferase, renal function and serum hepatitis B virus (HBV) DNA levels were assessed every 3 months; ADV mutations were searched for by INNO-LiPA HBV DR v2 assay.

Results. During 36 months (12–48), nine patients cleared serum HBV DNA with a 3-year cumulative virological response rate of 88%, without the emergence of ADV mutations. ADV dose was reduced in six patients (55%) showing a decline of creatinine clearance, in the absence of proximal tubulopathy.

Conclusions. In LMV-R kidney graft recipients, long-term add-on therapy with ADV is efficacious and safe with timely adaptation of ADV dose.

Keywords: adefovir dipivoxil; hepatitis B virus; lamivudine-resistance; renal transplantation

Introduction

In hepatitis B virus (HBV)-infected kidney graft recipients, lamivudine (LMV) suppressed viral replication satisfactorily in the short term only, as high rates of resistance and severe complications emerged upon long-term administration [1–10]. Add-on therapy with ADV is the recommended strategy for LMV-resistant (R) patients, since a combined therapy with a non-cross-resistant drug inhibits HBV replication and minimizes the risk of multiple drug-resistant strains long term [11,12]. However, no studies have assessed this strategy in the setting of kidney transplantation [13–16] where the risk of proximal tubular cell toxicity and Fanconi syndrome should be carefully assessed [17–19]. To gain more insights on this issue, we assessed the efficacy and safety of ADV add-on strategy in LMV-R renal transplants followed for 36 months.

Materials and methods

Eleven renal transplant recipients with LMV-R chronic hepatitis B, consecutively referred to our Liver Unit for rescue therapy, were enrolled in this prospective, open-labelled uncontrolled study. Table 1 shows the baseline features of the patients. The appropriate dose of ADV was selected based upon creatinine clearance (CLcr), according to manufacturer’s instructions [20] (Table 1). All patients gave their written informed consent. Details of the study were approved by the local Institutional Review Committee.

Routine biochemistries and HBV serology were measured by standard laboratory procedures. CLcr was calculated with the Cockcroft–Gault (CG) method using ideal body weight and Modification of Diet in Renal Disease (MDRD) formula [21,22]. Hepatitis C virus (HCV) RNA was assessed by Amplicor HCV (Roche Molecular System, Branchburg, NJ). Serum HBV DNA was assessed every 3 months by COBAS TaqMan HBV test (Roche Molecular Systems, Inc.), with a lower limit of quantification of 12 IU/mL. LMV and ADV (rtA181T/V and rtN236T) mutations were determined by INNO-LiPA HBV DR v2 (Innogenetics NV, Belgium) at baseline and at yearly intervals.

Data were expressed as counts and percentages, median and range or mean and SEM as appropriate; differences in their distribution were assessed with Student’s t-test or the Wilcoxon rank sum test (Stata Statistical Software: Release 7.0. Collage Station, TX: Stata Corporation).

Results

Virological and biochemical response

During 36 months (range: 12–48), serum HBV DNA became undetectable (<12 IU/mL) in nine patients (82%) (Table 2) with a 3-year cumulative probability of 88% (Figure 1). In the two partial virological responders, tenofovir (TDF) + LMV rapidly and completely inhibited viral replication (Figure 2, patients #1 and #2). None of the patients developed ADV-R while the pattern of LMV-R remained unchanged (Figure 2). In the only patient with
Virological and biochemical response to add-on therapy with ADV

Cumulative probability of achieving a virological response (HBV DNA <12 IU/mL) to LMV plus ADV combination therapy throughout the study. Two partial virological responders were censored at the time of rescue with TDF.

Renal safety and survival

Median CLcr, calculated by the CG method using ideal body weight and the MDRD formula, did not significantly change from baseline to the last available visit (from 57 to 39 mL/min), nor did serum phosphorus (from 2.6 to 3.0 mg/dL) or urinary protein level (from 0.23 to 0.32 g/L). However, six patients (54%) had to reduce ADV dose because of CLcr decline after a median of 11 months (range: 9–42) (Figure 3). Twenty-two months (range: 6–34) after dose adjustment, CLcr either remained stable (n = 5) or improved (n = 1). None of the patients had to change immunosuppressive regimen therapy or suffered chronic rejection, requiring chronic haemodialysis or ADV discontinuation.

In the two patients with decompensated cirrhosis, liver function significantly and rapidly improved (Child-Pugh score from 9 to 5) following HBV suppression, but one patient died of hepatocellular carcinoma. Child-Pugh scores remained unchanged in the four patients with compensated cirrhosis.

Discussion

Our study demonstrates the long-term efficacy and safety of add-on ADV in LMV-R kidney graft recipients. Undetectable serum HBV DNA in 55% of the patients after 1-year of add-on ADV therapy compares well with the results of ADV monotherapy in similar patients [14–16]. However, at variance to previous studies on ADV monotherapy showing partial response in a significant proportion of patients beyond year one [14,16], serum HBV DNA progressively declined in all viraemic patients with no emergence of ADV resistance. The only two patients with partial response, rapidly responded to a switch from ADV to TDF, confirming recent results in immunocompetent patients [23] and suggesting a potential role for TDF in the renal transplant setting. As a consequence of viral suppression, liver function either improved or remained stable in all patients with cirrhosis.

While ~50% of our renal graft recipients had to reduce ADV dose because of a decline of CLcr, none developed

Table 1. Demographic, clinical and virological features of the 11 LMV-R kidney graft recipients with chronic hepatitis B enrolled in the study

<table>
<thead>
<tr>
<th>Patient features</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57 (32–64)</td>
<td>53 (3.3)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Males, No.</td>
<td>3 (27%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>HBsAg-negative, No.</td>
<td>3 (27%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Hepatitis C virus co-infection, No.</td>
<td>3 (27%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Cirrhosis, No.</td>
<td>6 (55%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>ALT, IU/L&quot;</td>
<td>30 (17–75)</td>
<td>30 (17–75)</td>
<td>30 (17–75)</td>
<td>30 (17–75)</td>
</tr>
<tr>
<td>HBV DNA, log10 IU/mL</td>
<td>4.9 (3.0–7.3)</td>
<td>4.9 (0.5)</td>
<td>4.9 (3.0–7.3)</td>
<td>4.9 (0.5)</td>
</tr>
<tr>
<td>HBV genotype D, No.</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Lamivudine resistance pattern</td>
<td>10 (91%)</td>
<td>1 (9%)</td>
<td>10 (91%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL*</td>
<td>1.3 (0.8–3.0)</td>
<td>1.3 (0.8–3.0)</td>
<td>1.3 (0.8–3.0)</td>
<td>1.3 (0.8–3.0)</td>
</tr>
<tr>
<td>CLcr, mL/min</td>
<td>57 (18–98)</td>
<td>57 (7.5)</td>
<td>34 (8–83)</td>
<td>16 (6–60)</td>
</tr>
<tr>
<td>Time on LMV monotherapy, monthsa</td>
<td>10 (91%)</td>
<td>1 (9%)</td>
<td>10 (91%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Time with virological response on LMV, monthsa</td>
<td>2 (0–47)</td>
<td>2 (0–47)</td>
<td>2 (0–47)</td>
<td>2 (0–47)</td>
</tr>
</tbody>
</table>

"ADV = adefovir dipivoxil; LMV = Lamivudine.

*Median (range).

Table 2. Virological and biochemical response to add-on therapy with ADV in 11 LMV-R patients who were followed for a median of 36 months

<table>
<thead>
<tr>
<th>Months of treatment</th>
<th>Virological response</th>
<th>Virological response</th>
<th>Virological response</th>
<th>Virological response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 (n = 11)</td>
<td>12 (n = 11)</td>
<td>24 (n = 9)</td>
<td>36 (n = 6)</td>
</tr>
<tr>
<td>HBV DNA undetectablea</td>
<td>3 (28%)</td>
<td>6 (55%)</td>
<td>5 (56%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>HBV DNA &gt; 2000 IU/mL</td>
<td>4 (36%)</td>
<td>2 (18%)</td>
<td>4 (44%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Virological breakthroughb</td>
<td>4 (36%)</td>
<td>3 (27%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALT &gt; 1.5 UNLc</td>
<td>1 (9%)</td>
<td>1 (9%)</td>
<td>1 (9%)</td>
<td>1 (17%)</td>
</tr>
</tbody>
</table>

aLower limit of quantification of real time PCR <12 IU/mL.

bGreater than 1 log increase of serum HBV DNA compared to on-treatment nadir, confirmed in two occasions. One patient showed a virological breakthrough at month 45 (#2, Figure 2a).

cAmong the three patients with baseline ALT > 1.5 UNL. One patient maintained ALT > 1.5 UNL (ALT = 60 IU/L) despite a virological response.

rtA181A/T mutation at baseline (Figure 2, patient #6), HBV DNA progressively declined to become undetectable.

ALT became normal in two of three patients with baseline ALT > 1.5 UNL (Table 2) but no patient seroconverted to anti-HBe or cleared HBsAg. Among the three HCV co-infected patients, two achieved undetectable HBV-DNA, while serum HCV-RNA levels remained unchanged.
Fig. 2. Continued
Fanconi syndrome or tubular dysfunction as assessed by blood phosphate, proteinuria and glycosuria measurements or required haemodialysis. Chronic allograft and/or calcineurin inhibitor-related nephropathy may have contributed to the worsening of renal function, although minimal tubular dysfunction could not be completely ruled out, since more sensitive tests like urinary pH, bicarbonaturia, urinary excretion of H⁺, phosphaturia and phosphorus index of excretion were not performed [24–26]. The risk of ADV-related renal worsening in kidney transplants is controversial, the unfavourable results from one study [14] not being confirmed by others [13,16,27].

In conclusion, LMV-R renal transplant recipients with chronic hepatitis B can be safely and effectively treated with add-on therapy with ADV, provided that ADV dose is timely adapted according to CLcr.

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Pietro Lampertico: Advisory Board/Speaker Bureau for BRISTOL-MEYERS-SQUIBB, ROCHE, NOVARTIS, GILEAD, GSK.

References


Fig. 2. Individual patterns of HBV DNA dynamics and RT polymerase resistance patterns during combination therapy with LMV plus ADV. The vertical arrow indicates the time points of ADV dose reduction in patients with renal impairment. HBV genotype is indicated within brackets.

Fig. 3. Median CLcr levels by CG and MDRD during combination therapy with LMV plus ADV and in the preceding 12 months of LMV monotherapy. Vertical line corresponds to the start of ADV + LMV therapy.


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