

# Use of entecavir for the treatment of complex forms of Hepatitis B

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**Abstract.** – **INTRODUCTION:** Although most HBV infections are effectively managed by the available therapies, the treatment of the most complex cases of hepatitis B still represents an unmet medical need. Entecavir is considered a first-line therapeutic option for hepatitis B, due to its demonstrated efficacy in rapidly suppressing the viral load. Its activity is also characterized by a high genetic barrier and an overall favorable safety profile.

**AIM:** This review provides an overview of the most recent evidence related to the use of entecavir in the management of the most complex forms of hepatitis B.

**MATERIALS AND METHODS:** Original articles for inclusion in this review were retrieved from online databases such as PubMed/Medline and EMBASE; their reference list was browsed to find other relevant papers. The identified papers were selected for inclusion in the present manuscript according to their relevance for the topic. The search was last updated on December 2013.

**RESULTS:** Several studies have proven the efficacy and safety of entecavir in the treatment of patients affected by complex forms of hepatitis B, as those with decompensated cirrhosis, exacerbations of HBV infection and fulminant hepatic failure or in transplanted subjects.

**CONCLUSIONS:** Overall, entecavir seems a powerful therapeutic strategy for the treatment of HBV infection, even in patients affected by the most complex forms of hepatitis. The high efficacy of entecavir, associated with its safety profile, its high genetic barrier to resistance and its cost-effectiveness, allowed this molecule to become one of the preferred first-line options of treatment to manage HBV infections. However, further researches and trials are still needed to definitively elucidate its effectiveness in the daily clinical practice.

*Key Words:*

Entecavir, HBV, Hepatitis B, complex forms.

## Introduction

Hepatitis B virus (HBV) infection represents a major cause of acute and chronic hepatitis. The

estimates indicate that over 350 millions of people worldwide are currently infected with chronic hepatitis B, and 600,000 of these die every year for long-term complications such as decompensated cirrhosis and hepatocellular carcinoma<sup>1-3</sup>. In Europe, HBV prevalence ranges between 0.1% and 7%, with an increase from North to South and from West to East<sup>4,5</sup>. Due to its wide prevalence, HBV heavily impacts on the health care system and costs<sup>2</sup>.

Both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) developed specific guidelines to manage HBV infection in clinical practice<sup>6,7</sup>. Although most cases of HBV can be effectively managed, many problems still exist when facing a complex form of hepatitis B, as those occurring in patients with decompensated cirrhosis, in transplanted subjects, and in patients with exacerbations of HBV infection<sup>8</sup>.

The final aim of HBV therapy is to prevent disease progression and prolong patients' survival. Guidelines recommend that therapy should be initiated with a potent drug with maximal activity and a low rate of resistance in order to maximize the chances of achieving treatment goals.

At present, seven therapies have been approved to treat chronic hepatitis B: interferon alfa, pegylated interferon- $\alpha$ 2a (IFN- $\alpha$ 2a) and a group of five nucleos(t)ide analogues (NA). These include two L-nucleosides (lamivudine and telbivudine), the oral deoxyguanosine nucleoside analogue (entecavir), and two acyclic nucleotide phosphonates (tenofovir disoproxil fumarate and adefovir dipivoxil)<sup>2</sup>. Recently combination strategies have also been proposed and investigated by clinicians<sup>9,10</sup>.

Among the available options entecavir is an oral nucleoside analog able to inhibit the activity of the viral DNA polymerase: this action results in a rapid and sustained suppression of the viral load in HBV-infected patients<sup>11</sup>.

Guidelines consider entecavir and tenofovir as the first line therapy to treat HBV infection due to their specific activity, the high genetic barrier to resistance and the low incidence of associated complications<sup>6,7,12,13</sup>. In particular, a systematic review highlights that these agents are cost-effective interventions in the management of HBV infected patients<sup>14</sup>.

Despite its wide use against HBV infections, few data are available on the use of entecavir in the most complex forms of hepatitis B. This paper reviews the most recent evidence on the topic in order to provide a comprehensive overview of the activity of entecavir in terms of safety, efficacy and management of the complex forms of hepatitis B. The focus of this review is on entecavir only – and not on other anti-viral agents – in order to enhance clarity and to present the results in a short, easy-to-grasp fashion.

### **Methods Followed to Retrieve Evidence**

Original articles for inclusion in this review were retrieved from online databases such as PubMed/Medline and EMBASE. Databases were searched using the search terms “entecavir” AND (“HBV” OR “hepatitis B”). The identified papers were selected for inclusion in the present manuscript according to their relevance for the topic; the reference list of each article was browsed in order to find other relevant papers. Other articles and information were also identified in author’s personal archive. The search was last updated on December 2013.

### **A brief overview of the Pharmacology, Efficacy and Safety of Entecavir**

#### **Pharmacology**

Entecavir is a member of the class of nucleos(t)ide analogs. In detail, it is a cyclopentyl-guanosine analogue, an orally derivative with potent and selective inhibition of the priming, DNA-dependent synthesis and reverse transcription functions of HBV polymerase<sup>9,15,16</sup>.

Like all the other nucleotide analogs, once entered in the cell it undergoes phosphorylation, to be converted in the active triphosphate form<sup>17</sup>. The active form resembles the structure of the physiological substrate deoxyguanosine, thus preventing the activity of the polymerase by affecting all the steps necessary for viral replication.

*In vitro* assays showed that entecavir has a greater potency (defined as IC<sub>50</sub>) than lamivudine and adefovir in inhibiting HBV polymerase<sup>18,19</sup>.

#### **Genetic Barrier**

Acquired resistance to NAs is one of the major issues affecting long-term NAs treatment. Patients who develop virological breakthrough due to resistance-inducing mutations often experience acute disease exacerbations and a more rapid progression to liver failure, liver transplantation, HCC or death<sup>20</sup>.

Entecavir is characterized by a high genetic barrier to resistance, as it is active against mutants resistant to other molecules<sup>18,19</sup> and can be used as a second-line treatment for previously treated patients who have developed resistance or with insufficient virologic suppression<sup>20</sup>.

According to available evidence, entecavir seems to have a high genetic barrier to resistance. Three different mutations are required to develop resistance against entecavir, while only a single mutation is necessary to confer complete resistance to lamivudine, telbivudine or adefovir treatment<sup>21-23</sup>. Lamivudine resistance occurs at a very high frequency: it emerges in 14 to 32% of patients within the first 12 months of therapy, and increases to 40% within 2 years of treatment and to 57% by year 3<sup>19</sup>. More in detail, prolonged use of lamivudine has been associated with amino-acid substitutions in the B domain (L528M) – involved in the positioning of the viral template – and in the YMDD motif of the C domain (M552I and M552V) – which is involved in nucleotide binding – of the viral DNA polymerase<sup>18</sup>. On the other hand, long-term studies with entecavir report a 1-2% of resistance rate over 6 years of therapy<sup>23</sup>. Important differences between entecavir and lamivudine were observed in a woodchuck (WHV) model<sup>19</sup>: entecavir therapy suppressed the levels of WHV DNA in blood by up to 8 log<sub>10</sub> units and reduced hepatic closed circular DNA levels by about to 4 log<sub>10</sub> units. After 14-36 months of entecavir therapy, no drug-resistant WHV was observed. Conversely, lamivudine therapy failed to reduce intrahepatic covalently closed circular DNA levels and led to the emergence of drug-resistant variants with mutations in WHV polymerase.

However, the pre-existence of minor population of partially resistant viral strains and treatment non-compliance probably contributed to the development of the few reported cases of primary entecavir resistance<sup>24</sup>.

#### **Virological Response**

Two large scale pivotal studies showed that the rates of virological response, biochemical re-

sponse and histological improvement were higher at 48 weeks with entecavir than with lamivudine, while the safety profiles of the two molecules were similar<sup>25,26</sup>. Other studies have further confirmed the safety and the efficacy of entecavir in different populations of patients<sup>27,28</sup>.

A virological response to entecavir in cirrhotic patients has been associated with a better clinical outcome and the prevention of liver disease progression<sup>29</sup>. Long-term treatment with entecavir a marked and durable virological suppression, in an improved liver histology and function<sup>30</sup>.

The analysis of the viral kinetics upon entecavir administration shows a rapid reduction of HBV DNA in the serum of chronic HBV-infected patients<sup>27,31,32</sup>. In addition entecavir seems to be associated to HBsAg seroconversion in a short period of time in both HBeAg-positive and HBeAg-negative patients<sup>33</sup>. In a retrospective study on 190 nucleos(t)ide-naïve chronic hepatitis B patients treated with entecavir (30% HBeAg positive), 83% of the patients (61% HBeAg-positive; 92% HBeAg-negative) achieved a virological response, defined as HBV DNA <50 IU/ml by PCR, at week 48, and 82% (78% HBeAg-positive; 83% HBeAg-negative) of those with elevated baseline alanine aminotransferase showed a biochemical response (alanine aminotransferase  $\leq 1 \times$  upper limit of normal)<sup>27</sup>. Twenty-two per cent of patients achieved seroconversion to anti-HBe. Noteworthy, a significant correlation was observed between virological response at week 12 and the rate of seroconversion to anti-HBe at week 48 ( $p = 0.039$ ); this correlation was also observed at weeks 24, 36 and 48 ( $p = 0.003$ , 0.002 and 0.017, respectively). In a randomized study, 69 nucleoside-naïve patients with baseline HBV DNA of  $10^8$  copies/mL or more were randomized to entecavir 0.5 mg/day or adefovir 10 mg/day for a minimum of 52 weeks<sup>32</sup>. Overall, entecavir was superior to adefovir in terms of mean change from baseline in HBV DNA at week 12 ( $-6.23 \log_{10}$  copies/mL vs  $-4.42 \log_{10}$  copies/mL; mean difference  $-1.58 \log_{10}$  copies/mL;  $p < 0.0001$ ). Both drugs demonstrated a biphasic viral kinetics, with a first phase of rapid decline which lasted 10 days. However, a significant difference in favor of entecavir was reached at day 10 (day 10 ETV-ADV difference estimate:  $-0.66 \log_{10}$  copies/mL; 95% CI  $[-0.30, -0.01]$ ). Early virological response was found to be predictive of subsequent virological response, and there was considerably less variability in the extent of HBV DNA reductions in patients treat-

ed with entecavir versus adefovir. Both the mean decrease in serum HBV DNA and the proportion of patients achieving virological response (HBV DNA < 300 copies/mL) were greater in entecavir-treated than adefovir-treated patients at weeks 2, 4, 8, 12, 24, and 48, and at week 48, one (3%) ETV-treated versus 15 (47%) ADV-treated patients had HBV DNA  $\geq 10^5$  copies/mL. These data allowed to extrapolate the mean half-life of circulating HBV particles in patients undergoing pharmacological antiviral treatment. Half-lives range from 14-16 hours for entecavir to 30 hours with adefovir<sup>11,31,32</sup>. The reduction rate and the overall clearance of HBV DNA from serum are now considered two basic parameters for the evaluation of treatment efficacy; in addition, they are considered the primary goal of anti-HBV therapy, since they may be correlated with a diminished risk of progressive liver-related mortality and the development of resistance to other antiviral drugs<sup>11</sup>. A very recent paper by Ono et al<sup>34</sup> assessed the effect of entecavir on 474 NA-naïve patients who were continuously exposed to entecavir for 4 years. Results showed that continuous treatment over 4 years was associated with 96% likelihood of achieving undetectable HBV DNA levels, regardless of HBeAg status and genotype. Moreover, the drug showed a favourable safety profile and rarely (0.4%) led to the development of entecavir-resistant mutations.

### ***Entecavir in Patients with Decompensated Cirrhosis***

Hepatic decompensation is one of the most frequent clinical complications in HBV-infected patients. The 5-year survival rate for patients with chronic hepatitis B and decompensated cirrhosis ranges from 14 to 35%, depending from the studies. This value is three to five fold lower than that reported in subjects with compensated cirrhosis (range 80-86%)<sup>6</sup>.

The use of interferon- $\alpha$  for the treatment of this particular class of patients has been recently questioned because of its sub-optimal efficacy and the possible exacerbation of liver disease that can occur even at low doses<sup>35</sup>. Current guidelines recommend the early initiation of NAs treatment as the best approach to effectively manage HBV infection in these patients<sup>6</sup>. Lamivudine treatment has been correlated with the development of resistant forms of HBV<sup>36,37</sup>, while adefovir is characterized by sub-optimal potency and renal toxicity<sup>38,39</sup>, a major adverse event considering

that decompensated cirrhotic patients are more likely to undergo kidney dysfunction *per se*.

Entecavir treatment results in an almost complete virological response in patients regardless of their pathological status, as shown in Figure 1<sup>29</sup>.

A randomized, open-label comparative study investigated the efficacy of a daily treatment with either entecavir 1.0 mg or adefovir 10 mg daily for up to 96 weeks in 191 adult subjects, HBV-infected with decompensated cirrhosis (Child-Turcotte-Pugh score  $\geq 7$ ), positive or negative for HBeAg and either experienced or naïve for treatment with nucleos(t)ide analogues<sup>40</sup>. Entecavir exerted a superior activity than adefovir for the primary efficacy endpoint, i.e. the mean reduction in serum HBV DNA at week 24 adjusted for baseline HBV DNA and lamivudine resistance status (treatment difference 1.74  $\log_{(10)}$  copies/mL [95% confidence interval (CI) -2.30, -1.18];  $p < 0.0001$ ). In addition, entecavir treatment led to a greater reduction from baseline in HBV DNA at all considered time points. This resulted in a higher frequency of patients achieving the threshold of HBV DNA  $< 300$  copies/mL both at week 24 (entecavir 49%; adefovir 16%;  $p < 0.0001$ ) and week 48 (entecavir 57%; adefovir 20%;  $p < 0.0001$ ; Figure 2). Progression to HCC was observed in 12% of patients treated with entecavir and 20% with adefovir, while cumulative death rates were 23% and 33% for entecavir and adefovir, respectively<sup>40</sup>. The two treatment arms showed a comparable safety profile. The frequency of severe adverse events directly related to the decompensated cirrhotic patho-

logical status, such as hepatic flares, renal failure and lactic acidosis, was in line to expectations. The safety profile of entecavir reported in this study is also similar to that documented in another phase II, double-blind randomized clinical trial published by the same group<sup>41</sup>.

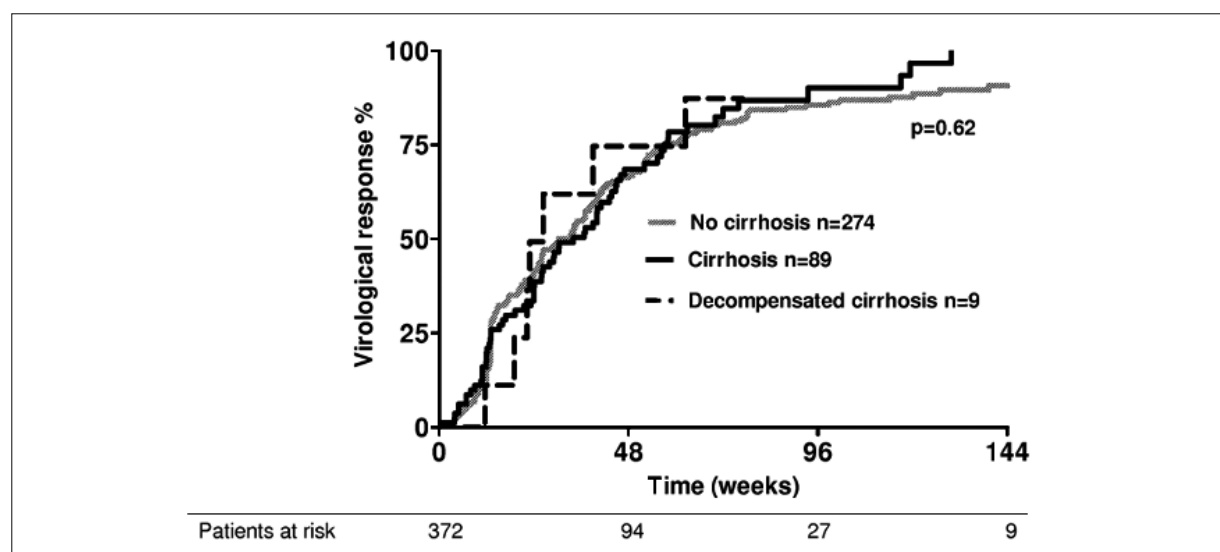
In addition, a recent meta-analysis has shown that entecavir therapy in patients with decompensated cirrhosis is associated with improved virological, biochemical and clinical parameters at 1-year follow-up, with no cases of resistance<sup>42</sup>.

Taken together, the above-mentioned results indicate that entecavir may be effective and well-tolerated in patients with chronic hepatitis B with decompensated cirrhosis.

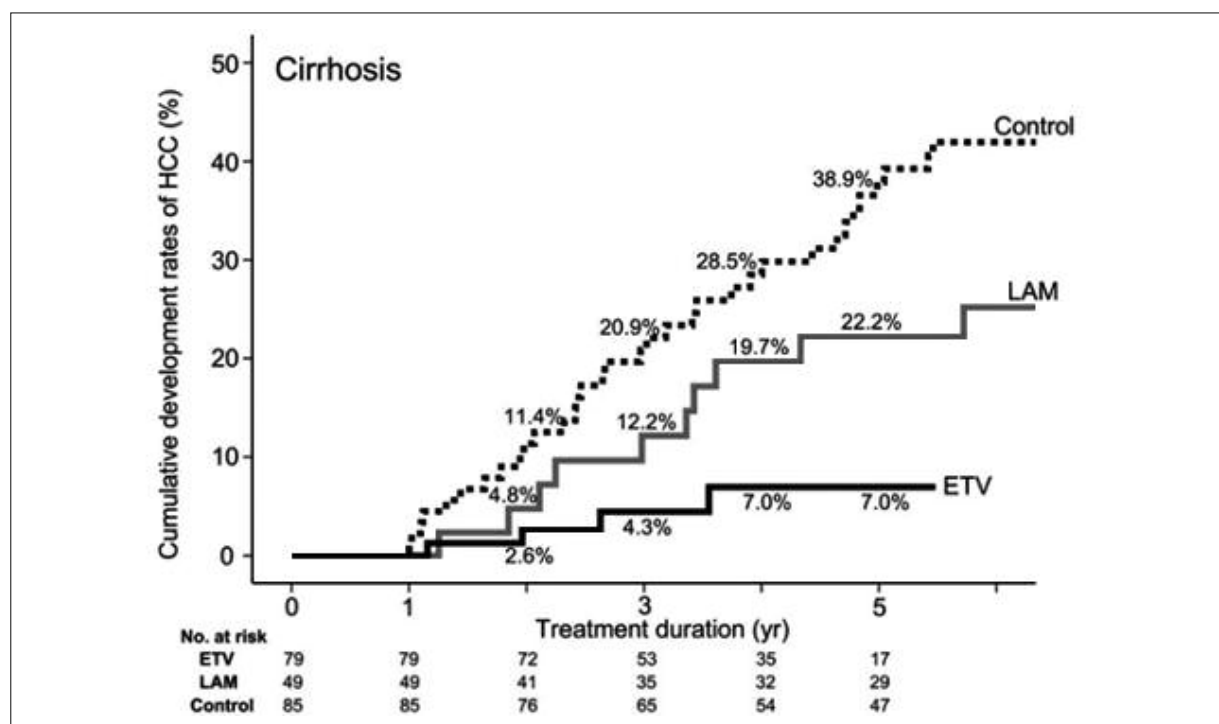
### Entecavir in Patients with Exacerbations of HBV Infections

Acute exacerbations of chronic HBV infection represent a major clinical issue since they may result in severe or potentially life-threatening consequences, in particular when associated with jaundice and coagulopathy<sup>43,44</sup>. Every year acute exacerbations affect 10-30% of HBV-infected patients<sup>45</sup>. Lamivudine monotherapy was shown not to be effective in protecting against rapid progression of severe exacerbations of hepatitis B to hepatic failure<sup>44</sup>.

To our knowledge, two different reports have documented the efficacy of entecavir in this specific setting. In the former, two patients experiencing severe exacerbation of chronic hepatitis B with jaundice and coagulopathy were successful-



**Figure 1.** Kaplan-Meier analysis of the probability to achieve a virological response by using entecavir in patients with different levels of cirrhosis. Reproduced from Zoutendijk et al<sup>29</sup>.



**Figure 2.** Kaplan-Meier curve analysis of the cumulative probability to develop HCC in cirrhotic patients treated with lamivudine (LAM), entecavir (ETV) or untreated. Reproduced from Hosaka et al<sup>61</sup>.

ly treated with a combination of entecavir 0.5 mg/day and prednisolone (30 or 50 mg/day)<sup>44</sup>. For both drugs, the combined treatment induced a rapid reduction in serum HBV DNA level, and the clearance of viral load under undetectable levels was reached after 12-15 weeks of treatment. After the clearance of viral infection, only the treatment with entecavir as single agent was maintained, while corticosteroids administration was stopped. This benefit lasted for one year from the beginning of treatment. The Authors of this study concluded that the combination of entecavir and prednisolone could improve the prognosis in patients with severe exacerbations of chronic hepatitis B but a higher sample size is necessary to confirm these evidences.

The latter study, with an observational design, evaluated 153 patients with hepatitis B and severe exacerbation of disease, treated either with entecavir ( $n = 36$ ) or lamivudine ( $n = 117$ )<sup>46</sup>. By week 48, 7 (19%) patients in the entecavir-treated group and 5 (4%) in the lamivudine-treated group had died (adjusted hazard ratio [HR] 5.1, 95% CI 1.5-17.2,  $p = 0.010$ ). Moreover, a higher liver-related mortality was reported in the entecavir group (adjusted HR 4.0, 95% CI 1.0-15.7,  $p = 0.044$ ) and, despite a lower prevalence of cir-

rhotic cases, a higher number of patients belonging to this group developed prolonged jaundice, ascites or hepatic encephalopathy. Conversely, entecavir exerted a more rapid and sustained viral suppression than lamivudine: 71% of entecavir-treated patients achieved an undetectable HBV DNA level at week 48, while the percentage in the lamivudine group was only 40% ( $p = 0.007$ ). These data convey a two-faced result, with a marked difference between the short-term outcome and the overall efficacy of treatments. Entecavir might be associated with a slightly increased short-term mortality than lamivudine in patients with severe acute exacerbation of chronic hepatitis B, but also with a higher incidence of virological response over a long term. Further studies are thus necessary to shed new lights on the potential role and the optimal therapeutic schemes of entecavir administration for the treatment of hepatitis B patients who experience severe exacerbations of disease.

#### **Entecavir in Patients with Fulminant Hepatic Failure**

Patients with fulminant hepatic failure have an extremely poor prognosis. The use of entecavir to treat these patients is still controversial due to the

lack of reported evidence. An anecdotal report described the case of an 82-year asymptomatic HBV-infected man treated with entecavir and corticosteroids who died from fulminant hepatic failure without proximate cause<sup>47</sup>. Autopsy revealed a submassive hepatic necrosis with faint regeneration.

Conversely, a patient with decompensated cirrhosis who experienced virological breakthrough and hepatic failure after lamivudine withdrawal, was successfully treated with entecavir therapy<sup>48</sup>. This case report was published within a more complete meta-analysis on the treatment of HBV-associated hepatic failure. Authors suggested that entecavir can effectively manage this kind of critical clinical events, but also pointed up the need for additional evidence to reach definite conclusions.

### ***Entecavir in Patients with Liver Transplant***

Liver transplantation is the last therapeutic option for patients with advanced irreversible liver failure<sup>49</sup>. At present, the recurrence rate of HBV is less than 1% post-transplant<sup>50</sup>. The risk of post-transplant HBV recurrence can be reduced by a preoperative suppression of HBV viral load followed by the maintenance of antiviral therapy after transplantation.

The extended use of hepatitis B immunoglobulin (HBIG) has markedly reduced the recurrence of HBV in liver-transplanted patients and the protection rate has been further increased by combining HBIG with lamivudine<sup>51</sup>.

Disappointingly, lamivudine treatment is invariably associated with the development of resistance in liver-transplanted patients, with a rate of resistance that could reach up to 50% after 3 years of therapy<sup>52</sup>. In order to limit the incidence of recurrences of hepatitis B after liver transplantation, other molecules less prone to induce resistance have been tested in this therapeutic setting.

Xi et al<sup>49</sup> have reported the results of an observational study with a 3-year follow-up on 120 patients who underwent liver transplantation. Thirty patients were randomly assigned to receive entecavir (0.5 mg/day) while the 90 remaining were treated with lamivudine (100 mg/day); all of them received long-term HBIG at a low dosage as concurrent complementary therapy. Before transplantation, HBV DNA was positive in 18 patients in the entecavir group and 52 patients in the lamivudine group; the mean levels of HBV

DNA before liver transplantation were  $1.21 \times 10^7$  copies/mL and  $1.39 \times 10^7$  copies/mL, respectively. Patients in the entecavir group achieved undetectable HBsAg earlier than those in the LAM group (median values: 3 days vs 5 days;  $p = 0.003$ ). The HBV-DNA of those who had positive HBV DNA before transplantation were undetectable within 1 week in both groups. The average HBeAg time of seroconversion was 4 days (range, 1-9 days) with entecavir and 3 days with lamivudine. Treatment with entecavir was associated with a significantly lower rate of recurrence of hepatitis B when compared with lamivudine ( $p < 0.05$ ). One patient died for liver failure due to HBV reinfection in the lamivudine group. Moreover, undetectable HBsAg was achieved earlier by entecavir-treated patients than those in the lamivudine group, while the survival rate was similar in the two groups. Of note, no adverse events related to entecavir administration were reported.

Perrillo et al<sup>53</sup> reported safety and efficacy data for entecavir on patients eligible for liver transplant due to end-stage liver disease associated with HBV. In this phase IIIb open-label study, both NAs-naïve and NAs-experienced patients (all with HBV DNA  $< 10$  IU/mL) were concurrently treated with 1 mg/day entecavir and a variable dosage of HBIG depending on the study site. At 72 weeks after transplant, virological and serological efficacy was assessed (Table I). All patients experienced HBV virological recurrence and HBsAg recurrence was observed only in two patients.

Taken together, these studies suggest that the concurrent combination of entecavir with low dosages of HBIG might be an effective and well-tolerated option to prevent the recurrences of hepatitis B in patients who underwent liver transplant, but the long-term effects of the combination are still to be explored.

A recent study shows that entecavir monotherapy exerts comparable results to HBIG plus lamivudine in terms of antiviral profilaxis<sup>54</sup>. Entecavir was also evaluated in monotherapy as prophylaxis prior to liver transplantation<sup>55</sup>. This study showed the outcome of 80 patients receiving prophylaxis with entecavir monotherapy (0.5 mg/day) prior to liver transplant for hepatitis B-related disease. None of the patients received HBIG; the median follow-up was 26 months. Before transplantation, only 21 patients (26%) presented undetectable levels of HBV DNA. Despite this, the cumulative rate of

**Table I.** Efficacy of entecavir associated with hepatitis B immunoglobulin for the prevention of HBV recurrence in liver-transplanted patients. Reproduced from Perrillo et al<sup>53</sup>.

	n/N (%)	95% CI
Virological recurrence (HBV DNA $\geq$ 50 IU/mL)	0/61 (0)*	0.0, 5.9
HBeAg serology <sup>†</sup>		
HBeAg loss	7/7 (100)	59.0, 100.0
HBeAg seroconversion	0/7 (0)	0.0, 41.0
HBsAg serology		
HBsAg loss	59/61 (96.7)	88.7, 99.6
anti-HBs (+)	49/61 (80.3)	68.2, 89.4
HBsAg recurrence <sup>‡</sup>	2/61 (3.3) <sup>§</sup>	0.4, 11.3

CI: confidence interval; HBV: hepatitis B virus. \*0/49 (0%) in non-completer = missing analysis. <sup>†</sup>Among those HBeAg(+) at baseline. <sup>‡</sup>Defined as HBsAg-positivity after on-treatment HBsAg loss. <sup>§</sup>1/54 (1.9%) in non-completer = missing analysis.

HBsAg loss was 86% after 1 year and 91% after 2 years, respectively. In total, 18 patients (22.5%) were HBsAg positive at the time of last examination: among these, 17 had undetectable levels of HBV DNA, and the remaining one presented a very low level of HBV DNA (217 copies/mL). Overall, seroclearance at week 52 since transplantation was achieved by 100% of patients with HBV DNA level  $< 5 \log_{10}$  copies/mL and HBsAg level  $< 3 \log$  IU/mL at baseline versus 78% in those without. Importantly, no mutations in the active site of the HBV polymerase able to confer resistance to entecavir were detected.

Another recent study<sup>56</sup> evaluated the effects of lamivudine and entecavir administration as monotherapy in preventing HBV re-infection after liver transplantation. Two hundred and fifty-two patients were enrolled in the study. The average duration of follow-up was about 3 years. Both compounds were active on HBV infection, but entecavir showed a higher efficacy in reducing serum concentration of HBV DNA: the HBV DNA level decreased from  $3.89 \times 10^6$  to  $5.31 \times 10^5$  copies/mL in the lamivudine group, and from  $8.74 \times 10^6$  to  $5.49 \times 10^4$  copies/mL in patients treated with entecavir ( $p < 0.05$ ). Notably, eighteen patients in the lamivudine-treated group developed HBV re-infection while no case occurred in the entecavir group. Once again, entecavir showed a superior profile than lamivudine in preventing HBV re-infection following liver transplantation<sup>56</sup>.

Overall, these studies seem to suggest that entecavir monotherapy, either with or without HBIG-complementary regimen, can effectively prevent the recurrence of hepatitis B after liver transplantation.

### Entecavir in Immuno-Compromised Patients

The incidence of HBV infection is frequent in patients with autoimmune conditions and in particular in those with Crohn's disease, due to the increased requirement for high-risk procedures like surgery and endoscopy<sup>57</sup>. Moreover, immunosuppressive drugs used to treat Crohn's disease may negatively influence the ratio between host immune response and viral replication, leading to hepatic flare. Recent data support the use of entecavir in immunocompromised patients<sup>58</sup>.

To our knowledge, we described for the first time<sup>57</sup> the successful management of two cases of hepatic flare attributable to systemic corticosteroids and/or azathioprine used to treat acute Crohn's disease. Both subjects had impaired hepatic function, and one had experienced jaundice and liver decompensation with ascites. Entecavir treatment (0.5 mg/day) allowed the reduction of both HBV-DNA and hepatic enzyme levels within 4-7 days. HBV-DNA levels became undetectable after 1 and 5 months, respectively. No adverse events were reported.

### Conclusions and Future Perspectives

At present, entecavir is recommended by the EASL and the AASLD, together with tenofovir, as the first-line option of treatment to face HBV infection<sup>6,7</sup>. This result can be attributed to its safety and efficacy as assessed in several clinical trials, and also to its high genetic barrier to resistance<sup>6</sup>.

First-line therapies able to prevent the development of resistant HBV strains offer the greatest chance to achieve successful long-term suppression of viral replication and thus the highest probability to reach a positive outcome.

Mounting evidence supporting entecavir use in patients affected by complex forms of hepatitis B, as those with decompensated cirrhosis, exacerbations of HBV infection and fulminant hepatic failure are now available. Entecavir in monotherapy or in combination may play a fundamental role in preventing re-infection in liver-transplanted patients. Entecavir could also be effective in treating immunocompromised subjects, as those affected by Crohn's disease or, potentially, even in subjects undergoing immunosuppressive therapies.

One of the primary aims in the treatment of HBV infection is the prevention of progression towards HCC. Some studies have investigated the use of entecavir in this context. Kobashi et al<sup>59</sup> reported the results of a long-term (4.25 years) study in patients with either chronic hepatitis B (n = 194) or cirrhosis (n = 62) naïve for treatment with nucleos(t)ide analogues treated with either entecavir or lamivudine. At the end of the study 24 subjects treated with lamivudine and 11 treated with entecavir developed a hepatocellular carcinoma. The difference was not statistically significant *per se*, but a significantly higher incidence of HCC was registered for patients who developed resistance to lamivudine (n = 60) when compared with those without lamivudine resistance (n = 67;  $p = 0.03$ ). This could be associated with the development of resistance already observed after lamivudine, but not with entecavir treatment.

The possible positive effect of entecavir on hepatocellular carcinoma, as observed by Kobashi et al, received further support in other studies. The study of Jin et al. enrolled 231 nucleoside-naïve patients with chronic hepatitis B treated with entecavir; of these, 71 had HCC at the beginning of entecavir treatment<sup>60</sup>. Patients with HCC showed similar cumulative rates of HBV-DNA negativization, alanine aminotransferase normalization, and hepatitis 'e' antigen loss when compared with those without HCC (100% vs 95.4%, 94.7% vs 97.3%, and 40.8% vs 41.8%, respectively). Another study compared the incidence of HCC in patients treated with either lamivudine or entecavir (Figure 2)<sup>61</sup>.

These findings can indicate that entecavir is effective both on patients at risk of HCC and on those who have already developed the neoplasia. In addition, the recent commentary by D'Angelo et al<sup>62</sup> proposed that HBV monotherapy with entecavir, when performed on patients affected by HCC, should be used to reduce the initial viral

load and preserve liver function, in order to allow a more efficacious follow-up treatment with sofosbuvir. In their opinion, the initial viral clearance by entecavir should improve the efficacy of chemotherapy. Unfortunately, the low number of investigated subjects makes it difficult to draw any conclusion. These interesting results deserve, in our opinion, further evaluations, given the high mortality rate associated with HCC. A deeper analysis of the relation between entecavir and HCC seems, therefore, a promising line of research. We advocate that further trials on the topic should be conducted, also in Western Countries, to confirm this tendency.

Another topic that should be investigated more in detail in our opinion is the onset frequency of lactic acidosis in subjects treated with nucleos(t)ide analogues. In a small case series reported by Marzano et al<sup>63</sup> on 12 HBV- or HCV-infected patients with decompensated cirrhosis and high Model for End-Stage Liver Disease score, only one of six patients with HBV infection developed lactic acidosis during entecavir treatment. This positive indication that correlates entecavir treatment with a reduced number of lactic acidosis events should be confirmed by trials characterized by a sufficient sample size or by retrospective analysis.

On the basis of the evidences previously described, entecavir seems a powerful therapeutic strategy for the treatment of HBV infection, even in patients affected by the most complex forms of hepatitis.

The high efficacy of entecavir, associated with its safety profile, its high genetic barrier to resistance and its cost-effectiveness, allowed this molecule to become one of the preferred first-line options of treatment to manage HBV infections. However, further researches and trials are still needed to definitively elucidate its effectiveness in the daily clinical practice.

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#### Conflict of Interest

The Authors declare that there are no conflicts of interest.



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