“Entecavir in Severe Acute Hepatitis B”

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Introduction

An estimated 350 million persons worldwide are chronically infected with HBV [1]. The average estimated carrier rate of Hepatitis B Virus (HBV) in India is 4%, with a total pool of approximately 36 million carriers.

Most of India’s carrier pool is established in early childhood, predominantly by horizontal spread due to crowded living conditions and poor hygiene. Acute and subacute liver failure is common complications of viral hepatitis in India and HBV is reckoned to be the etiological agent in 42% and 45% of adult cases, respectively. In conclusion, hepatitis B is a major public health problem in India and will continue to be until appropriate nationwide vaccination programmes and other control measures are established.

Carriers of HBV are at increased risk of developing cirrhosis, hepatic decompensation, and Hepatocellular Carcinoma (HCC) [2]. The prevalence of HBeAg among asymptomatic HBsAg Positive persons varies from 9-20%.

HBV is transmitted by perinatal, percutaneous, and sexual exposure, as well as by close person-to-person contact presumably by open cuts and sores, especially among children in hyperendemic areas [3]. HBV can survive outside the body for prolonged period [4,5].

The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers to 25% to 30% in infants and children under 5 and to less than 5% in adults [6-9]. In addition, immune suppressed persons are more likely to develop chronic HBV infection after acute infection.

HBV Genotypes

Eight genotypes of HBV have been identified labeled A-H [10,11]. The prevalence of HBV genotypes varies depending on the geographical location. (Genotype C progresses to chronic hepatitis faster than B and D faster than A). In India, genotype D had been the predominant genotype both in North and Eastern India.

About 1/3 rd of patients of acute hepatitis is related to hepatitis B. Clinical presentation varies from asymptomatic infection to cholestasis and rarely to liver failure. After an icteric period of 4-6 wks the adult patient most of time (90%) makes an uninterrupted recovery. Clinical and biochemical recovery is usual within six months of onset. Few patients can go to prolonged cholestasis and most of them have benign course and recover. About 10% of patients undergo unusual course.

Acute Hepatic Failure (AHF) in India almost always presents with encephalopathy within 4 weeks of the onset of acute hepatitis. In India, Hepatitis E (HEV) and Hepatitis B (HBV) viruses are the most important causes of AHF; approximately 60% of cases are caused by these viruses. Hepatitis B virus core mutants are very important agents in cases where hepatitis results in AHF in this country.

Acute Liver Failure (ALF) is a syndrome where patients develop encephalopathy within 4 wks of onset of jaundice and carry high mortality [12]. The clinical course is progressive deterioration leading to death in 70-80% of patients. Continued viral replication with extensive hepatocyte necrosis on an autoimmune basis has been suggested to be a possible mechanism for the progressive liver damage [13]. Viral hepatitis is the commonest cause of acute and subacute hepatic failure and among viruses Non-A, Non-B is considered to be the major cause followed by hepatitis B virus [13].

Hepatitis B Virus (HBV) is successfully cleared in more than 95% of adult patients with acute infection. Acute HBV infection can cause severe acute hepatitis B that can progress to liver failure. Death may result in up to 80% of people who develop severe acute hepatitis B [14]. Thus it becomes important to find out if any available therapy can play a role in preventing the progression of severe acute hepatitis B to liver failure. The pathogenesis of severe acute hepatitis B is still unclear. Maybe it is related to HBV replication and enhanced immune response.

The treatment of complicated acute hepatitis B is mainly supportive. Patients of acute and subacute hepatic failure carry high mortality (60-80%) despite intensive medical support and last option for these patients remains liver transplantation. However the option for liver transplantation in Asian population is almost nil due to poor economic status and lack of donor liver. Further even after liver transplant, there is high incidence of recurrence of hepatitis B virus infection of the allograft, which reduces patient and graft survival.

There are various drugs which have been tried in acute hepatitis B, various polyherbal drugs which include phyllanthusnururi, rheum imodi, sylmarin and ursodeoxycholic acid. There are many clinical studies which found lamivudine causes rapid clinical, biochemical, serological and virological recovery in severe acute hepatitis B and significantly decreases the incidence of hepatic failure and mortality of these patients and a rapid decline of HBV DNA load. Lamivudine has also been found to effective in patients of severe acute hepatitis B with rapid clinical and biochemical recovery in department of gastroenterology skims.

In vitro studies have found Entacavir as a better antiviral drug in hepatitis B with rapid and sustained clinical and virological response.

Entecavir, approved by the FDA in March 2005, is the newest antiviral agent among the hepatitis B treatment options [15].

Entecavir, a cyclopentylanalogue of 2-deoxyguanosine analog with activity against HBV polymerase, is a produg efficiently phosphorylated intracellularly to the active triphosphate form [16]. This active triphosphate form has an intracellular half-life of approximately 15 hours. By actively competing with the natural substrate deoxyguanosine triphosphate, Entecavir triphosphate inhibits HBV replication by three different mechanisms:

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Retention of HBV DNA polymerase (distinctive to entecavir),
The reverse transcription of the negative-strand DNA from the Messenger RNA,
Synthesis of the positive-strand DNA.

In vitro studies comparing Entecavir with other nucleoside analogs (lamivudine, lobucavir, ganciclovir, acyclovir, and penciclovir) demonstrated that Entecavir was the most potent inhibitor of HBV replication [15]. Entecavir is active against both wild-type and lamivudine-resistant HBV.

In vitro studies showed that Entecavir is more potent than lamivudine and adefovir and is effective against lamivudine-resistant HBV mutants. After oral administration in healthy subjects, Entecavir concentration (C_{trough}) was 0.5 ng/ml. Both the oral tablet and the oral solution are 100% bioavailable. Entecavir should be administered on an empty stomach.

Entecavir is predominantly eliminated by the kidneys unchanged, undergoes both glomerular filtration and tubular secretion. However, no significant alterations in the pharmacokinetics of Entecavir were noted when a single 10-mg dose was given to patients with moderate-to-severe hepatic impairment.

Entecavir is classified as a pregnancy category C drug. Entecavir should be administered to this population only if the benefit clearly outweighs the risk. No studies have assessed pharmacokinetic parameters in the pediatric population.

Efficacy in various categories of patients

1) HBeAg-positive patients: - Entecavir resulted in significantly higher rates of histologic (72% vs. 62%), virologic [HBV DNA undetectable by PCR] (67% vs. 36%) and biochemical (68% vs. 60%) responses compared to lamivudine. Serum HBV DNA was undetectable by PCR in 81% vs. 39%, and normalization of ALT occurred in 79% vs. 68% of patients who continued Entecavir and lamivudine treatment, respectively [17].

2) HBeAg-negative patients: - Entecavir resulted in significantly higher rates of histologic (70% vs. 61%), virologic (90% vs. 72%) and biochemical (78% vs. 71%) responses compared to lamivudine [18].

3) Decompensated cirrhosis/recurrent hepatitis B after liver transplantation: - Studies on the safety and efficacy of Entecavir in patients with decompensated Cirrhosis is ongoing.

4) Lamivudine-refractory HBV: - Entecavir was shown to be effective in suppressing Lamivudine-resistant HBV but a higher dose 1.0 mg was required [19]. Entecavir resulted in significantly higher rates of histologic (55% vs. 28%), virologic (21% vs. 1%) and biochemical (75% vs. 23%) responses compared to lamivudine [20].

5) Adefovir-resistant HBV: - In vitro studies showed that Entecavir is effective in suppressing adefovir-resistant HBV mutants. There is one case report on the efficacy of Entecavir in patients with adefovir-resistant HBV. Lamivudine should be discontinued when patients are switched to Entecavir to decrease the risk of Entecavir resistance.

Dose regimen

The approved dose of Entecavir for nucleoside-naive patients is 0.5 mg daily p.o. and for lamivudine-refractory/resistant patients is 1.0 mg daily p.o. Doses should be adjusted for patients with estimated creatinine clearance <50 ml/min.

<table>
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<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Entecavir naïve</th>
<th>Lamivudine Refractory/resistant</th>
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<tr>
<td>≥ 50</td>
<td>0.5 mg qd</td>
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<td>Peritoneal ambulatory</td>
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Predictors of response

Entecavir appears to be equally effective in decreasing serum HBV DNA levels and in inducing histologic improvement in Asians and Caucasians, and across HBV genotypes A-D and a wide range of pretreatment HBV DNA and ALT levels. However, HBeAg seroconversion rates were lower in patients with normal ALT, being 12%, 23%, and 39% among those with pretreatment ALT <2, 2-5, and >5 times normal, respectively [21,22].

Adverse events

Entecavir had a similar safety profile as lamivudine in clinical trials [23,24]. The Entecavir package insert contains a black-box warning regarding the possibility of lactic acidosis and severe hepatomegaly with steatosis secondary to mitochondrial toxicity. Although this has occurred with other nucleoside analogs, Entecavir has not caused these reactions and is well tolerated at 0.5-1.0 mg/day [19-21]. Most adverse events in the phase III studies were mild and consisted of headache, upper respiratory tract infections, cough, fatigue, pharyngitis, upper abdominal pain, and gastrointestinal upset [25-29]. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including Entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy.

Entecavir reduces viral load, clears the virus, reduce the antigenic challenge and may alter immunological response against hepatocytes thereby preventing ongoing liver injury in acute hepatic failure, thereby improving outcome. Besides Entacavir is safe and can be given orally to such group of patients where liver is failing and where prospects of liver transplantation are nil.

Review of Literature

Hepatitis B is considered as one of the most serious infectious diseases in the world, about 100 times more infectious than even AIDS. Hepatitis B Virus (HBV) infection is an important global health problem and may cause both acute and chronic infection in man [30]. It is estimated that 400 million people worldwide are chronic HBV carriers [31]. It is the leading cause of primary hepatocellular carcinoma. Persons having chronic hepatitis B infection are at 100 times' greater risk of liver cancer than non-infected ones. Every year approximately 30-40 million people will become infected with deadly
The chronic phase [32]. Approximately 15% to 40% of people who are HBsAg carrier state, chronic hepatitis of various degree of the elevation of aminotransferases. Necroinflammation at histology (HBeAg positive chronic hepatitis) or adult acquired infection and chronic hepatitis B usually present in low rates of spontaneous HBeAg clearance. Patients with childhood normal levels of aminotransferases, minimal liver damage and very high HBsAg and HBeAg. Both these are translated from a common gene. HBeAg is derived from HBCAg. HBeAg is essential for viral replication and is an integral part of nucleocapsid. It is not detectable in serum but can be detected in liver tissue in patients with acute or chronic HBV infection. HBeAg is a soluble protein that can be detected in serum of patients with high virus titres though not essential for viral replication its presence indicates greater infectivity. The viral core is surrounded by an envelope of surface proteins. Hepatitis B surface antigen is a part of surface envelope of the virus. It is a glycoprotein and is produced in excess amount required for viral synthesis and can be detected in the blood as 22nm spherical and tubular particles. The viral envelope also has two other proteins closely associated with HBsAg. They are pre s1 and pre s2 proteins. These two proteins are supposed to play an important role in attachment of the virus to the hepatocytes.

Hepatitis B Virus (HBV) infection can cause acute, fulminant or chronic hepatitis, liver cirrhosis and Hepatocellular Carcinoma (HCC). Perinatally or childhood acquired HBV infection usually causes subclinical or anicteric acute hepatitis and is associated with a high risk of chronicity (30 to 90% of cases), whereas adult acquired infection may cause acute symptomatic hepatitis (approximately 30% of patients) and is associated with a low risk of chronicity (less than 5%). Fulminant hepatic failure is unusual (0.1 to 0.5% of patients), but acute co-infection with other hepatitis viruses increases the risk of fulminant hepatitis. Chronic HBV infection is a dynamic process with an early replicative phase and active liver disease and a late low or non-replicative phase with remission of liver disease. Perinatally acquired HBV infection is characterized by a prolonged “immunotolerant” phase with hepatitis B e antigen (HBeAg) positivity, high levels of serum HBVDNA, and normal levels of aminotransferases, minimal liver damage and very low rates of spontaneous HBeAg clearance. Patients with childhood or adult acquired infection and chronic hepatitis B usually present in the “immunoreactive” phase with elevated aminotransferases and liver necroinflammation at histology (HBeAg positive chronic hepatitis) and approximately 50% will clear HBeAg within 5 years. The rate of spontaneous HBeAg seroconversion may vary in relation to the degree of the elevation of aminotransferases.

The clinical spectrum of HBV infection ranges from sub clinical to acute symptomatic hepatitis or, rarely, fulminant hepatitis during the acute phase and from the inactive hepatitis B surface antigen (HBsAg) carrier state, chronic hepatitis of various degree of histological severity to cirrhosis and its complications during the chronic phase [32]. Approximately 15% to 40% of people who develop chronic hepatitis B are expected to progress to cirrhosis and end stage liver disease [30].

Perinatal infection from infected mothers to their infants or horizontal infection early in childhood from exposure to HBsAg positive family members are the main routes of HBV transmission in high endemic area, such as South-East Asia, most Africa, Pacific Islands and the Arctic, whereas in low endemic regions, such as Western countries, hepatitis B is primarily a disease of adolescents and adults as a result of high risk sexual activity and injection drug use.

HBV infection is a dynamic process characterized by replicative and non-replicative phases based on virus host interaction, which are present in some form in all infected patients. The presence of circulating HBsAg, hepatitis B e antigen (HBeAg) and high levels of serum HBV-DNA identifies the first immunotolerant phase. In adult acquired infection this phase marks the incubation period of acute HBV infection and lasts about two to four weeks, in contrast with perinatal infection this phase often lasts for decades. During this phase patients have no symptoms, normal or slightly increased serum Alanine Aminotransferases (ALT) levels and minimal histological activities, which imply that there is a lack or very weak immune response against the infected hepatocytes. Experimental results in transgenic mice have suggested an immune regulatory function for HBeAg in neonates, which are believed to induce a state of immunological tolerance to HBV [33]. During the course of HBV infection, for unknown reasons, the tolerogenic effect is lost and patients may enter the second immune active phase which is associated with a decrease in HBV-DNA concentrations and increased ALT levels and histological activity, reflecting the host immune mediated lysis of infected hepatocytes. In acute HBV infection this phase is the period of clinical symptoms and jaundice and usually lasts for three to four weeks, whereas in patients with chronic HBV infection has a variable duration from months to years.

The third low or non-replicative phase involves serocconversion from HBeAg to antibody to HBeAg (anti-HBe) usually preceded by a marked reduction of serum HBV-DNA levels below 105 copies per ml, that are not detectable by hybridization techniques, and followed by normalization of ALT levels and resolution of liver necroinflammation. Serum HBV-DNA remains detectable only by ultrasensitive technique of polymerase chain reaction (PCR) in many patients. In chronic HBV infection this phase is also referred as the inactive HBsAg carrier state [32]. The inactive carrier state may last for lifetime, but a proportion of patients may undergo subsequent spontaneous or immune suppression induced reactivation of HBV replication with reappearance of high levels of HBV-DNA with or without HBeAg seroreversion and rise in ALT levels [32]. For reasons that are not yet known during HBeAg clearance or later on after HBeAg serocconversion replication–competent HBV variants with mutations in the precore or core promoter regions preventing HBeAg production may be selected [34]. Patients who become HBsAg negative and develop antibody to HBsAg (anti-HBs) are diagnosed as having resolved hepatitis B [32]. This is an uncommon phenomenon in chronic HBV infection. During this stage HBVDNA may still be detectable by PCR assay both in serum and liver [35]. In rare cases of severe immune suppression, such as cancer chemotherapy or after organ transplantation HBV can reactivate in patients with resolved hepatitis B [36].

Acute HBV infection is generally sub-clinical and anicteric in neonates and children, whereas in approximately 30 to 50% of adults may cause icteric hepatitis [37]. Patients who recover from acute hepatitis B acquire protective levels of anti-HBs and gain lifelong immunity. However a proportion of patients may become chronically infected and develop chronic hepatitis B. Cirrhosis develops in 10% to 20% of people who persistently infected with HBsAg.
infected and approximately 0.1 to 0.5% of patients develop fulminant hepatitis. Acute HBV and Hepatitis Delta Virus (HDV) co-infection is associated with high rate of fulminant hepatitis [38]. Acute HBV and Hepatitis C Virus (HCV) co-infection has also been reported to increase the risk of fulminant hepatitis [39]. It is generally believed that fulminant hepatitis is the consequence of an enhanced immune response of the host inhibiting viral replication and causing massive lysis of infected hepatocytes, thus explaining the absence of serological markers of HBV infection in many patients [40]. Persistence of HBsAg, HBeAg and HBV-DNA in high titer for more than 6 months implies progression to chronic HBV infection [41]. Age at the time of primary HBV infection is the best established determinant of chronicity. Up to 90% of infants of highly infectious HBsAg and HBeAg positive mothers become chronic HBV carriers as compared with approximately 30% of children infected after the neonatal period but before the age of 5 years [37,42]. In contrast only 1% to 5% of adults become persistently infected after clinically overt acute hepatitis [43]. In addition to age at infection also the maternal HBeAg/anti-HBe status is an important determinant of the outcome of HBV infection. Indeed less than 10% of babies born to HBeAg negative/anti-HBe positive mothers become persistently infected, although small proportions (approximately 5%) develop acute symptomatic or fulminant hepatitis within the first 3 to 4 months of life [42]. High maternal viral load appears to increase the risk of persistently infected infant; on the other hand HBV mutants not producing HBeAg were detected both in babies with benign and fulminant hepatitis and their mothers, indicating that HBV genomic heterogeneity does not play a major role in the clinical outcome of perinatal HBV infection [44,45].

Majority of patients of acute Hepatitis B recover however about 10% of patients develop complications in the form of acute liver failure, sub-acute hepatic failure, prolonged cholestasis, chronic carrier state or may lead to Chronic Liver Disease (CLD).

Host response to HBV infection varies widely. The frequency of development of clinical manifestations of infection is highly age dependent most newborns do not display any sign or symptom. About 5-15% of infants between 1-5 yrs of age develop symptoms of the disease, where as 30-50% of infected adults and older children develop symptomatic disease [46-48].

About 90% of adults infected with HBV will develop antibodies against the disease and clear the virus from their body. About 5-10% of infected adults never develops antibodies to the virus and become chronic hepatitis B carriers. The risk of developing chronic infection varies inversely with age and is highest (90%) for infants infected in the perinatal period. 20-50% of children infected between age of 1-5 yrs develop chronic infection [48].

The usual signs and symptoms include fatigue fever muscle or joint pain, loss of appetite nausea vomiting jaundice dark urine and clay colored stools. About 10% of symptomatic patients may develop extra hepatic manifestations such as arthralgia, arthritis vasculitis etc. About 1-2% infected patients present with severe fulminant hepatitis the mortality in this group ranges between 60-90% [48]. Various signs and symptoms and biochemical parameters which predict unusual course includes persistent deep jaundice with itching development of ascites, bleeding tendency, hypoalbuminemia, coagulopathy, encephalopathy and persistent transaminitis.

Severe acute hepatitis B [46a/46b] is defined as persons who fulfill any two of the three criteria;
1) Hepatic encephalopathy
2) Bilirubin more than or equal to 10 mg/dl
3) International normalized ratio of equal to or more than 1.6

Pts developing encephalopathy within seven days of onset of jaundice are termed to have hyper-acute liver failure and those developing encephalopathy within 4 wks of onset of jaundice an acute liver failure and beyond 4 wks as sub-acute hepatic failure [47]. Viral hepatitis is the commonest cause of ALF /SAHF and hepatitis B constitutes one of the major causes. Signs and symptoms of liver disease with persistent HBsAg positivity beyond 6 months are defined as Chronic Liver Disease (CLD). ALF and SAHF carry high mortality and ultimately need liver transplant despite intensive medical support [12,13].

Acute liver failure or sub acute liver failure is considered to be immunologically mediated by cytotoxic T lymphocytes (CTL, CD8) Continued viral replication with extensive hepatocyte necrosis on an autoimmune basis has been suggested to be a possible mechanism for the progressive liver damage [13].

Acute liver or sub-acute liver failure is considered to be immunologically mediated by Cytotoxic T-Lymphocytes (CTL, CD8). Clinical observations suggest that immune response of the host is more important than viral factors in the pathogenesis of liver injury this is substantiated by chronic carriers with normal liver enzymes and normal histology despite very high levels of viral replication. Significant liver injury would be predicted, if the virus were directly cytopathic. However it is the immunological attack against virally infected cells which causes hepatocytes injury and viral clearance. It has been widely accepted that CTL are responsible for destruction of virally infected hepatocytes with viral clearance, however the number of CTLs involved are generally much fewer than number of virally infected hepatocytes thus secondary non–antigen specific immune responses such as those mediated by inflammatory cytokines may in fact be more important for viral clearance than a CTL mediated necrosis. Theoretically the continued hepatic injury or ongoing hepatic injury could be halted or reduced if the viral load or active viral replication is stopped by anti-viral drugs like entecavir, Lamivudine or interferon which may secondarily reduce the immunological attack against the hepatocytes which are cleared of virus by Entecavir or Lamivudine or interferon alpha

Hepatitis B Virus (HBV) is successfully cleared in more than 95% of adult patients with acute infection. Acute HBV infection can cause severe acute hepatitis B that can progress to liver failure. Death may result in up to 80% of people who develop severe acute hepatitis B [14]. Thus it becomes important to find out if any available therapy can play a role in preventing the progression of severe acute hepatitis B to liver failure.

Despite the introduction of several new therapies and the involvement of critical care personnel and procedures, survival rates for ALF with medical therapy alone in cases that progress to stage 3 or 4 encephalopathy are poor varying between 10-40%. With the introduction of Orthotopic Liver Transplantation (OLT) as a therapeutic option for patients with ALF survival rates have increased to 60-80%. Thus the current goal of medical management has become not only to support the patient and allow the native liver to regenerate but also to improve the patient’s condition for possible OLT.

Few drugs have been tried in severe acute hepatitis B like sylmarin, phyllanthusniruri, rheum emodi, new livfit and ursodeoxycholicacid for cholestasis with promising results. Suppression of HBV replication is principal goal of long term hepatitis B therapy [48,49].
Nucleoside analogues reduce the viral load by clearing HBV DNA and prevent the remaining hepatocytes from getting damaged by altering the immunological response. Although liver transplantation is the ultimate treatment in a failing liver, there is no access to it by the majority of Asian population.

Torri et al. [50] conducted a study in the year 2002, titled “Effectiveness and long term outcome of Lamivudine therapy for acute hepatitis B”. He concluded that Lamivudine might prevent the progression of severe acute hepatitis B to fulminant liver failure and it appears to modify the clinical course of disease.

Nucleoside analogue has shown to be effective in prevention and treatment of hepatitis exacerbation. Lamivudine, an L-nucleoside analogue, at a daily dose of 100 mg, is effective in suppressing HBV DNA with Alanine Aminotransferase (ALT) normalization and histological improvement in both hepatitis B e antigens (HBeAg)-positive and HBeAg-negative patients [50]. However, with regard to Lamivudine treatment of patients with severe acute hepatitis B, studies with a limited number of patients and case reports are encouraging [51-54].

Tillman et al. [55] reported that Lamivudine may prevent the progression of severe hepatitis B to liver failure by decreasing HBV DNA load, reducing inflammatory reaction and improving liver function when administered early enough.

Lisotti et al. [56] have found that early antiviral treatment attenuates the clinical and biochemical impairment can lead to fast healing and prompt complete recovery. The pathogenesis of severe acute hepatitis B remains unclear, although host- and virus-specific factors are considered to have a great impact on the clinical course. For HBV infection, it has been reported that precore mutation, core promoter mutation, HBV genotype, and pretreatment HBV load are associated with the development of fulminant hepatitis [56]. Previous studies have proven that serum level of Total Bilirubin (TBil), ratio of total to direct bilirubin, white blood cell count; hepatic coma grade, prothrombin time and age are important prognostic factors for patients with fulminant hepatic failure [57,58].

Yu et al. [59] studied the efficacy of lamivudine in patients with severe acute hepatitis B and concluded that early treatment with lamivudine leads to a greater decrease in HBV DNA level, better clinical improvement and mortality improvement in patients with severe acute hepatitis B and also decreases the progression to hepatic failure.

Also a study by Dr Jaswinder Singh in the dept. of gastroenterology SKIMS in 2002-2005 titled “role of Lamivudine in severe acute hepatitis B” concluded to have rapid clinical and biochemical recovery with Lamivudine in patients with severe acute hepatitis B and found it may prevent the progression of severe acute hepatitis B to chronic liver disease.

More potent antiviral drugs such as Entecavir and tenofovir are now available. It is conceivable that these drugs might even be better, especially in reaching a rapid decrease in viral load and a faster recovery for the patients who cannot achieve a 2 log10 HBV DNA decline at week 2. It is conceivable that these new drugs for the treatment of hepatitis B (i.e. Entecavir and telbivudine) might be even better in reaching a rapid decrease in viral load and a faster recovery in patients with fulminant or severe acute hepatitis B [55].

Entecavir has been tried in many case reports and case series of severe acute hepatitis B with excellent results [59-61]. Dienstag et al. [62] conducted a study regarding comparison of the efficacy of oral antiviral drugs and concluded Over a 12-month treatment period, the antiviral efficacy of Entecavir would be superior to that of Lamivudine, which in turn would be superior to that of Adeovir, in nucleoside-naive patients with chronic HBV infection.

Entecavir up-regulates dendritic cell function in patients with chronic hepatitis B. Dendritic Cells (DCs) are crucial antigen-presenting cells responsible for initiating antiviral immune Responses.

Preclinical and phase-II studies suggested ETV is a novel hepatitis B antiviral agent with potent antiviral activity against the HBV and LVD-resistant HBV [62-64]. The safety profile of the Lamivudine and entecavir is similar, and there is no evidence of viral resistance to Entecavir [65].

In clinical studies, Entecavir revealed excellent suppression of hepatitis B virus replication without significant side effects or evidence of mitochondrial toxicity. Until now, no Entecavir-resistant viral mutants have been described. Prolonged therapy as well as prophylactic therapy, for example, in liver transplant recipients, is feasible and not limited by breakthrough infections. Data on Entecavir therapy for treatment of nucleoside-naive, wild-type hepatitis B virus is being generated in Phase III clinical trials worldwide for both hepatitis B envelope antigen-positive and -negative subpopulations, as well as in Lamivudine-resistant patients [66].

In 2009 Mayra J. Sanchez, Maria Buti, Maria Homs, Andres Palacios, Francisco Rodriguez-Frias, Rafael Esteban presented a case of a HBsAg-negative patient diagnosed with chronic lymphocytic leukemia who received a Chemotherapeutic regimen that included rituximab, who subsequently presented with severe HBV reactivation with asites, jaundice and coagulopathy and was treated with Entecavir. Entecavir produced a rapid and sustained suppression of HBV that was associated with rapid clinical improvement without any side effects. They Concluded Entecavir is an efficacious and safe treatment for severe HBV reactivation. In summary, this case demonstrated the usefulness and safety of Entecavir in the treatment and reversal of severe HBV reactivation and provides evidence for the use of this drug in HBV reactivation associated with a high viral load, as suggested by European guidelines [55].

Christoph Jochum et al. [61] studied Entecavir in acute liver failure due to hepatitis B in 6 patients and concluded that immediate treatment of HBV induced liver failure with Entecavir is well tolerated and beneficially affects the course of the disease and avoids the need for liver transplantation.

Similarly Giuseppe Vittorio L, de Socio, Alessandra Mercuri, Francesco di Candilo & Franco Baldelli [59] from the Department of Infectious Diseases, ‘Santa Maria Della Misericordia’ Hospital, University of Perugia, Perugia, Italy in 2009, may published a case report on successful treatment of severe acute hepatitis B with Entecavir.

They found that early antiviral treatment and supporting therapy improved the symptomatic phase of infection, reducing the risk of fatal outcome. Antiviral therapy was administered together with other general medical measures, so it was impossible to draw indisputable conclusions about the specific contribution of Entecavir. Acute liver failure is a very serious event that can lead to death or necessitate liver transplantation. Case reports and small series in severe or prolonged acute B hepatitis suggest the potential benefits of early antiviral therapy [55,67,68]. On the other hand, in a randomized controlled clinical trial to treat acute hepatitis B, Lamivudine compared to placebo showed
greater decreases in HBV levels but not significant difference in clinical improvement [69]. More potent antiviral drugs such as Entecavir and tenofovir are now available. The limited toxicity characteristic of nucleos(t)ide analogue therapy justifies its use in patients who demonstrate impending or definite serious liver damage. In addition, for patients in need of liver transplantation nucleoside analogue therapy is utilized as prophylaxis with the aim of preventing recurrence of HBV infection [70]. They believed that Entecavir monotherapy may be effective in patients with acute severe HBV infection. Clinical trials are needed to confirm this hypothesis.

**Aims and Objectives**

To use Entecavir in severe acute hepatitis B infection, in a randomized Double blind placebo controlled study and to ascertain its therapeutic efficacy in terms of clinical, biochemical and serological outcome and survival.

**Materials and Method**

11 patients with acute hepatitis like illness were screened for hepatotropic viruses which included

- Hepatitis A virus.
- Hepatitis B virus.
- Hepatitis C virus.
- Hepatitis E virus.
- Hepatitis D virus.

**Diagnosis of acute hepatitis B**

Patients were diagnosed as hepatitis B infection on the basis of:

1. Clinical profile
2. Biochemical profile
3. Serological profile
   a) HBsAg +ve
   b) IgMantiCore +ve

Patients were considered to have severe acute hepatitis B if they had:

- The recent onset of jaundice (bilirubin>10 mg/dl) and coagulopathy (INR: 1.40-1.60)
- Acute hepatitis B with prolonged cholestasis beyond 6 wks up to 6 months
- Acute liver failure; if patient developed encephalopathy within 4 wks of the onset of jaundice without any preceding history of illness

**Exclusion criteria:**

- Pregnant patients
- Super infection or co infection with other viruses
- Other liver diseases
- Previous use of interferon, thymosin or other antiviral agents
- Prior lamivudine therapy >12 wks
- Previous treatment with Entecavir/Adefovir
- Age<16 yrs
- Seropositivity for IgGHBCab
- Any sign of CLD (liver palm and spider angiomas) or USG or endoscopy documented CLD (splenomegaly, atrophy of the right lobe of liver with enlargement of left lobe and varices or collaterals)

**End points of treatment:**

- Survival or death
- Complete or partial clinical recovery
- Complete or partial biochemical recovery
- Serological recovery

**Study protocol:** All patients with complicated acute hepatitis B were be admitted in the ward and given appropriate medical treatment and then randomized into two groups:

- E- group: - who received Entacavir 0.5 mg/d orally or through Ryle's tube
- P- group: - who received equivalent placebo

Entecavir and placebo were given in a randomized double blind manner.

**Methods:** Blood Samples were drawn at admission (baseline) and subsequently on follow up for haematological, biochemical and serological assay.

**Viral markers:**

- HBsAg: - Enzyme immuno assay
- IgMantiHBC: - Enzyme immuno assay
- HBeAg: - Enzyme immuno assay
- IgMantiHEV: - Enzyme immuno assay (EIA) (AmarDiagnostics)
- IgMantiHAV: Enzyme immunoassay (EIA) (Amar Diagnostics)
- HBV DNA (quantitative):- measured by Roche Amplicor polymerase-chain reaction (PCR) assay in DNA copies/ml, detection limit was 100 copies/ml

**Follow up:**

Clinical assessment was done by assessing

- Level of Jaundice
- Grade of Encephalopathy
- Serial Liver Span
- Development of ascites
- Serial wt/abdominal girth

**Biochemical assessment:**

- Serial LFT: - Twice weekly
- Serial coagulogram (PT, PTI, PTTK) twice weekly

**Serological assessment:**

HBV DNA estimated at baseline and then subsequently at recovery or death.
Other viral markers:
- HBsAg
- HBeAg
- antiHBe and antiHBs was done at baseline and then subsequently at recovery or death

Statistical Methods

The statistical analysis of the data was done by using chi square test and fisher’s exact test for nominal data and Mann-Whitney’s test for differences of means for quantitative data. These tests were two sided and were referred for values for their significance. Any p-value < 0.05 was taken to be statistically significant. Logistic regression analysis for independent variables which could affect the survival.

The analysis of the data was performed by using statistical package (SPSS version 11.3) Chicago, USA for windows.

Observations and Results

A total of 33 patients of severe acute hepatitis B were enrolled for the study in the department of Gastroenterology at SKIMS, over a period of 2 yrs from the year 2008 - 2010.

The baseline Clinical, biochemical, and virologic characteristics of patients between Entecavir and the control group are summarized in Table 1 (a,b).

Their mean follow up was 12 ± 3 months. 16 patients (8M, 8F) mean age 41 ± 12.5 years were in P-group and 17 patients (6M, 11F) mean age 39.1 ± 13 years were in E-group. In P and E group (11,12) and (5,5) patients were in acute liver failure(ALF) and Severe Hepatitis (SH) subgroup respectively. All the patients in the subgroups were fulfilling diagnostic criteria of severe acute hepatitis B [46a/46b].

Similarly the baseline characteristics among subgroups (ALF and SH) were comparable as shown in Table 2.

The normalization of serum TBil levels was more common in the Entecavir group than the control group (at 4 weeks: 84.6% 11/13 versus 14.3% 1/7, p=0.002) which was significant (Bar 1a).

The mean serum ALT levels of patients in the Entecavir group at weeks 1,2,4,12 & 24 after treatment were (740 ± 620), (420 ± 110), (52 ± 22.61), (34 ± 11.6), (30 ± 14.1); while they were (730 ± 614), (610 ± 226), (432 ± 310) in the control group (Bar 1b).

The normalization of serum ALT was more common in the Entecavir group than the control group at 4 weeks (76.9% 10/13 versus 14.3% 1/7, p=0.007) (Bar 1a).

The mean INR level of patients in the Entecavir group at weeks 1,2,4,12 & 24 after treatment were (1.84 ± 0.31), (1.43 ± 0.81), (1.10 ± 0.13), (1.05 ± 0.160), (1.03 ± 0.15) which were lower than those of patients in the control group (1.71 ± 0.62), (1.65 ± 0.91), (1.24 ± 0.27), (1.15 ± 0.150), (1.08 ± 0.63) (Bar 2b and 2c).

In the Entecavir group 13/17 (76.5%) patients survived as compared to placebo, 7/16 (43.8%). More patients survived in the Entecavir group Bar 3. Survival in the study group was 4.2 times more than the control group but the difference was not statistically significant. There was a trend towards survival but this did not reach to significant level (p=0.055) as the number of patients were small as shown in Table 3.

Complete clinical and biochemical recovery was more in Entecavir group (70.6%) as compared to placebo group (31.3%) which was significant (p = 0.024) with odds ratio of 4.8 shown in bar 4. The rate of clinical and biochemical recovery was faster in Entecavir group (6.6 ± 2
In sub-group (severe hepatitis) of acute hepatitis B there was no difference in survival between Entecavir and placebo group but the rate of clinical (6 ± 3.7 wks) and biochemical recovery (10.9 ± 4 wks) in Entecavir group was more, as compared to placebo group (15 ± 4.2 wks) and (18.4 ± 6 wks) respectively (Table 4).

In subgroup ALF (Acute Liver Failure) in the placebo group mortality was 72.7% (8/11) while in Entecavir group it was 33.3% (4/12) with odds ratio of 5.3 but this was not statistically significant as the sample size was small (p=0.06). The rate of complete clinical recovery (8.2 ± 2.3 wks) and biochemical recovery (12.8 ± 4.7) in Entecavir group was more as compared to placebo group (15.4 ± 3.6 wks) and (20.4 ± 4.4 wks) respectively (p=0.04) as shown in Table 5.

In subgroup acute liver failure (ALF), 4/12 (33.3%) patients on Entecavir died while no patient died in subgroup severe hepatitis and there was 5 times more likelihood of dying in subgroup acute liver failure but it was not statistically significant (p=0.14).

Also the rate of clinical and biochemical recovery in the two subgroups was not statistically significant as shown in Table 6 with more likelihood of quick recovery in severe hepatitis.

There was increased mortality in the subgroup acute liver failure as shown in Table 7 (Bar 5a).

The mean serum HBV DNA levels of patients in Entecavir group at
baseline were \((1.04 \pm 0.99) \times 10^5\) copies/ml with 7 patients having DNA levels \(>1 \times 10^5\) copies/ml and 10 patients in \(10^4-10^5\) copies/ml range (Table 1b) (Bar 5b).

In the control group mean serum HBV DNA levels were \((1.01 \pm 0.98) \times 10^5\) copies/ml at baseline with 6 patients having DNA levels \(>1 \times 10^5\) copies/ml and 10 patients having DNA levels in \(10^4-10^5\) copies/ml range.

At 4 wks after Entecavir treatment in study group 11/13 (84.6%) patients had undetectable DNA levels (< 100 copies/ml) in serum while two patients had detectable HBV DNA levels mean \((0.0211 \pm 0.0143) \times 10^5\) copies/ml but both these patients had >2 log decrease in HBV DNA levels as compared to baseline levels as shown in Table 3.

In the placebo group 2/7 (28.6%) patients had undetectable DNA levels in the serum at 4 wks. The remaining 5 patients had mean HBV DNA level of \((0.0299 \pm 0.0188) \times 10^5\) copies/ml with 2 patients having >2 log decrease in HBV DNA levels as shown in Table 8.

The serum HBV DNA undetected (<100 copies/ml) could be seen more in Entecavir group versus the control group at 4 weeks (84.6%, 11/13 versus 28.6%, 2/7, \((\chi^2=6.282), p=0.02\)) which was significant as shown in Table 8 (Bar 6).

At 24 wks in the Entecavir group, 12/13 (92.3%) patients who survived had DNA levels <100 copies/ml (undetectable), while 6/7 (85.7%) patients had undetectable HBV DNA levels in the placebo group as shown in Table 9 (Bar 7) which was not statistically significant \((\chi^2=0.220)\) \((p=0.63)\).

**Bar 3:** Comparison of survival between P & E-group at 4 wks after treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-group (n=16)</th>
<th>E-group (n=17)</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>7/16(43.8%)</td>
<td>13/17(76.5%)</td>
<td>4.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Complete clinical recovery</td>
<td>5/16(31.3%)</td>
<td>12/17(70.6%)</td>
<td>4.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Biochemical Recovery</td>
<td>5/16(31.3%)</td>
<td>12/17(70.6%)</td>
<td>4.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Progression To CHB</td>
<td>2/16(12.5%)</td>
<td>1/17(6.9%)</td>
<td>0.43</td>
<td>0.42</td>
</tr>
</tbody>
</table>

**Bar 4:** Comparison of complete clinical and biochemical recovery at 4 wks between P & E-group.

**Table 3:** Outcome of Entecavir Therapy as compared to Placebo.

**Table 4:** Subgroup analysis at recovery in patients of severe hepatitis.

**Table 5:** Subgroup analysis at recovery in patients of acute hepatic failure.

**Table 6:** Comparison of outcome between subgroup ALF vs Severe Hepatitis in Patients on Entecavir.

**Table 7:** Comparison of Mortality between E-group and P-group in patients of ALF and Severe Hepatitis.
On follow up at 3 months (12/13, 92.3%) patients in the Entecavir group lost HBsAg as shown in Table 10 (Bar 8). HBsAg was positive in one patient who was followed at 6 months when he persisted with +veHbsAg (with negative HBeAg, and +veHBeAb). HBsAg seroconversion rate in the Entecavir group was (61.5%, 8/13) and in the control group (71.4%, 5/7).

In Entecavir group (13/13,100%) patients became HBeAg negative and 6/7(85.7%) patient in the control group (N=7) lost HbeAg at 3 months. Over a 12 month follow up period 6/7(85.7%) patients who survived in placebo group seroconverted ( HBeAb +ve) while as in Entecavir group 8/13 patients (61.5%) who survived seroconverted as shown in Table 11 (Bar 9).

Seroconversion rate was higher in the control group (p=0.848)

Non survivors had higher grades of encephalopathy, ascites, and ALT, AST and serum urea levels. Higher survival rate was found in patients on Entecavir treatment compared to those of placebo. As shown in Table 12.
In binary logistic regression encephalopathy (p=0.01), ascites (p=0.01), high TLC (p=0.04), urea (p=0.04), ALT (p=0.04) were associated with the mortality (Table 13).

**Discussion**

Most symptomatic patients with acute hepatitis B recover, and treatment is not necessary. Severe acute hepatitis B will cause a rapid destruction of hepatic parenchyma, leading to liver failure, death, or a need of liver transplant in more than 80% of these patients. Though both viral factors and the host's immune response may play important roles [71], the precise mechanisms of liver injury from severe acute hepatitis B and the factors contributing to the progression of liver failure remain unknown. Viral factors are emphasized in the pathogenesis of HBV-associated severe hepatitis, which has been demonstrated by the efficacy of antiviral therapy using nucleoside analogues [72]. The opportunity for patients with severe acute hepatitis B to progress to liver failure is quite high, once severe deterioration of clotting function becomes obvious. The experience with antiviral treatment of patients with severe acute hepatitis B is limited and controversial. There are ethical problems to conducting a randomized, double blind, placebo-controlled trial in such a serious disease condition, because the previous encouraging results of lamivudine have been reported [51-53]. However, the possibility that severe acute hepatitis B might naturally subside without treatment cannot be completely excluded, and whether nucleoside analogues efficiently prevents the rapid progression to hepatic failure could not be confirmed.

Ours was the first randomized double blind placebo controlled study, where we used Entecavir as a therapeutic drug in severe acute hepatitis B which included patients of acute hepatic failure and those of acute hepatitis B (prolonged and severe illness of >6 wks duration). There have been earlier case reports of Entecavir being used in severe acute hepatitis B, complicated by hepatic failure with success. Entecavir has also been successfully used in a case series in patients of acute hepatic failure due to hepatitis B [60]. There have also been case reports of Entecavir being used in reactivation of hepatitis B causing hepatic

<table>
<thead>
<tr>
<th>S.No.</th>
<th>VARIABLE</th>
<th>SURVIVORS (N=20)</th>
<th>NON - SURVIVORS (N=13)</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>AGE</td>
<td>39.6 ± 13.3</td>
<td>40.6 ± 12</td>
<td>0.9</td>
</tr>
<tr>
<td>2)</td>
<td>GENDER(M/F)</td>
<td>10/10 (50%)</td>
<td>4/9 (30.8%)</td>
<td>0.3</td>
</tr>
<tr>
<td>3)</td>
<td>ENCEPHALOPATHY</td>
<td>10/10 (50%)</td>
<td>12/13 (82.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>4)</td>
<td>ASCITIS</td>
<td>10/10 (50%)</td>
<td>12/13 (82.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>5)</td>
<td>HB</td>
<td>12.2 ± 1.8</td>
<td>11.7 ± 2.03</td>
<td>0.5</td>
</tr>
<tr>
<td>6)</td>
<td>TLC</td>
<td>6.5 ± 2.21</td>
<td>8.4 ± 4.8</td>
<td>0.05</td>
</tr>
<tr>
<td>7)</td>
<td>TBIL</td>
<td>17.4 ± 11</td>
<td>23.2 ± 9.3</td>
<td>0.2</td>
</tr>
<tr>
<td>8)</td>
<td>AST</td>
<td>462 ± 410</td>
<td>1092 ± 662</td>
<td>0.004</td>
</tr>
<tr>
<td>9)</td>
<td>ALT</td>
<td>452 ± 408</td>
<td>1157 ± 630</td>
<td>0.003</td>
</tr>
<tr>
<td>10)</td>
<td>INR</td>
<td>1.6 ± 1.2</td>
<td>2.06 ± 1.08</td>
<td>0.3</td>
</tr>
<tr>
<td>11)</td>
<td>TP</td>
<td>7.2 ± 0.7</td>
<td>6.6 ± 1.1</td>
<td>0.05</td>
</tr>
<tr>
<td>12)</td>
<td>ALBUMIN</td>
<td>3.0 ± 0.6</td>
<td>3.5 ± 0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>13)</td>
<td>UREA</td>
<td>25 ± 16</td>
<td>38.3 ± 20.8</td>
<td>0.04</td>
</tr>
<tr>
<td>14)</td>
<td>BLOOD SUGAR</td>
<td>79 ± 9.9</td>
<td>101 ± 39</td>
<td>0.2</td>
</tr>
<tr>
<td>15)</td>
<td>TREATMENT METHOD (E/P)</td>
<td>13/7</td>
<td>4/9</td>
<td>0.04</td>
</tr>
</tbody>
</table>

In binary logistic regression encephalopathy (p=0.01), ascites (p=0.01), high TLC (p=0.04), urea (p=0.04), ALT (p=0.04) were associated with the mortality (Table 13).
failure with success [73]. Also there have been studies of lamivudine being used in severe acute hepatitis B with great success and mortality benefit.

We gave Entecavir to 17 patients and other 16 received placebo. In this study, we found that the improvement of serum HBV DNA, TBiL, ALT and INR levels of patients in the Entecavir group were significantly greater than those in the control; and the HBV DNA-negative rates and the TBiL normalization rates of the Entecavir group were significantly higher than those of the control group (p=0.02).

Number of patients who survived in Entecavir group was more as compared to placebo. There was a trend towards more survival in Entecavir group but since the number of patients was small it could not reach to significant levels (p=0.05).

The number of patients who had complete clinical and biochemical recovery (normalization of liver enzymes) were more in Entecavir group as compared to placebo group (p=0.03) and similarly the rate of clinical and biochemical recovery was more in Entecavir group than placebo group and this was statistically significant (p=0.02).

In this study we found survival in Entecavir group (13/17, 76.5%), was 4.2 times more as compared to the placebo group (43.8%, odds ratio 4.2). Similarly rate of clinical and biochemical recovery was significantly more in the study group as compared to placebo (p=0.02).

In ALF subgroup there was (33.3%) mortality in patients on Entecavir as compared to placebo (72.7%). The rate of recovery was faster in Entecavir group as compared to placebo (p=0.03).

We clearly observe in the study that there is a rapid fall in HBV DNA at 4 wks (p=0.02) and ALT and the rate of clinical biochemical recovery is faster in Entecavir group (p=0.02) but the effect on survival and development of CLD needs to be seen in larger multicentre trials.

These findings may indicate that the rapid reduction in HBV DNA levels through the use of Entecavir can result in a less intense host response against HBV, shorten and improve the symptomatic phase of infection and allow a ready clinical and biochemical improvement, and thus partially prevent the progression to liver failure, and decrease the mortality of these patients [60].

Sainokami et al. [57] reported that in patients with fulminant hepatitis B, serum level of HBV DNA on admission was higher in patients who died than those who recovered. They further found that the rapid decrease in viral load in the early phase of acute HBV infection was associated with the severity of the disease if the patients did not receive antiviral therapy.

In another study by Jian-Wu et al. [59] they proved that a rapid decline of HBV DNA load during antiviral therapy was a good predictor for the outcome, while the pretreatment HBV DNA load was not associated with the mortality. They speculated that as a result of enhanced immune reaction in severe acute hepatitis B, decline of HBV DNA load during therapy may affect the prognosis more strongly compared to pretreatment HBV DNA load. They also found that the incidence of liver failure of patients receiving treatment within a week was lower. This emphasizes that for patients with severe acute hepatitis B, the timing of antiviral administration is crucial. So these patients should be given antiviral therapy as early as possible.

The value of lamivudine therapy has been demonstrated in patients with HBeAg -ve CHB, Entecavir had a significantly higher response rate than lamivudine in patients with HBeAg –positive CHB who had not previously received a nucleoside analogue; Entecavir can effectively inhibit the replication of HBV DNA and normalize the levels of ALT in refractory CHB patients treated with lamivudine [74]. Entecavir is also effective in treating HBeAg-ve patients with CHB. Molecular analysis has revealed that Entecavir also affects HBV DNA that has mutated in either the core promoter or pre-core regions. Although we did not analyze the resistance of HBV to Entecavir but the cases of resistance in initial 6 months of Entecavir therapy are quite low.

In our study, the rates of HBSAg and HBeAg seroconversion of patients in Entecavir group were lower than those of the control group, which may be attributable to too-early administration of Entecavir. Receiving Entecavir too early may inhibit the production of neutralizing antibody in the early phase of the disease. We observed that rate of seroconversion was higher in placebo 6/8(75.0%) as compared to Entecavir group 8/13 (61.5%). In Entecavir group, 4 patients who had complete clinical / biochemical recovery did not seroconvert to HBsAb during the 1 year follow up.

In the course of acute self limited hepatitis HBsAb usually appears about 6 months after the onset of hepatitis, but in approximately 10% AHB patients HBsAb never appears. It has been seen that chronic hepatitis develops in 5- 10% of adult infected with HBV. Based on these findings we conclude that the rate of seroconversion to antiHBs in our patients who were on Entecavir was lower than usual rate among HBV self limited infections. None of our patients had any suspicion of HIV infection or any disorder associated with immune suppression.

A neutralizing antiHBsAb response has been detected during the early phase of acute hepatitis. Virus specific anti antibody producing B-cell, induced by the T cells are enriched early after acute viral infection. Therefore the host immune system should be exposed to antigen during the early phase in order to eliminate infected hepatocytes and induce production of neutralizing antibody. Although levels of serum HBV DNA and infected hepatocytes significantly decline during Entecavir, levels of CCC-DNA which can be replaced by DNA also decline, but persist in hepatocytes. These findings indicate that lack of production of HBsAb in our patients may have been the result of starting Entecavir during the early phase of acute hepatitis. Another possible explanation for the lack of HBsAb is the interruptions of host immune clearance. Nakamura et al. demonstrated that a temporal deficiency in the acute intrahepatic effective mechanism mediated by IFN-γ and TNF-α leads to chronicity. Entecavir may inhibit the naturally occurring inter- hepatic effector mechanisms by artificially decreasing the viral load. Decreased induction of inflammatory cytokines due to decreased viral antigen presentation may have occurred and resulted in the lack of HBsAb. Given this possibly changes in immune status in patients undergoing Entecavir therapy should be closely monitored.

The prognostic factors for severe acute hepatitis B have not been fully examined. Various previous studies have suggested that age, prothrombin time, serum level of total bilirubin, ratio of total to direct bilirubin, white blood cell count, and hepatic coma grade are associated with the treatment outcomes of patients with fulminant hepatitis B [75]. In our study we found ascites, encephalopathy, high ALT, high urea, high TLC count, and low total protein at presentation were associated with mortality.

This study indicates that early treatment with Entecavir could induce a prompt clinical, biochemical, serological, and virological response in patients with severe acute hepatitis B, and this could significantly decrease the incidence of liver failure and mortality of these patients, and a rapid decline of HBV DNA load is a good predictor for the outcome of the treatment. However, too early Entecavir administration hinders
seroconversion. The number of our study population was limited. Thus, a further prospective study with a larger number of patients is needed.

Further, more clinical trials and investigation of treatment of AHB with Entecavir and other agents are needed. In conclusion Entecavir is a powerful tool with which to treat severe acute hepatitis B. It reduces dramatically viral load with the rapid clinical and biochemical recovery with negligible side effects. The drug is cost effective and can be given orally. It may modify the immune status of patients and further multicentre trials are needed to see its effect on immune status and on overall survival benefits and whether it prevents the progression to CLD.

Conclusion

- Viral hepatitis B is one of the leading causes of acute hepatitis
- Entecavir is an oral nucleoside analogue which inhibits reverse transcriptase of HBV. It can be given orally and is cost effective with minimal side effects
- 0.5 mg of Entecavir rapidly decreases HBV DNA to below detectable levels in <4 weeks
- Early treatment with Entecavir induces a prompt clinical, biochemical, serological, and virological response in patients with severe acute hepatitis B and may improve survival
- However it may alter the immune system as it may delay the seroconversion in severe acute hepatitis B for which further trials are needed
- Entecavir may decrease the incidence of liver failure and mortality in severe acute hepatitis B
- We recommend use of Entecavir in severe acute hepatitis B

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References


