Published in final edited form as:

Dig Dis Sci. 2012 May ; 57(5): 1349–1357. doi:10.1007/s10620-011-2013-3.

Use of Nucleoside (Tide) Analogues in Patients with Hepatitis B-Related Acute Liver Failure

Doan Y Dao¹, Emmanuel Seremba², Veeral Ajmera¹, Corron Sanders¹, Linda S. Hynan³, William M. Lee¹, and the Acute Liver Failure Study Group

¹Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas

²Makerere University Medical School, Kampala, Uganda ³Departments of Clinical Sciences (Biostatistics), Psychiatry, University of Texas Southwestern Medical Center at Dallas

Abstract

Background & Aims—The efficacy of nucleoside(tide) analogues (NA) in the treatment of acute liver failure due to hepatitis B virus (HBV-ALF) remains controversial. We determined retrospectively the impact of NAs in a large cohort of patients with HBV-ALF.

Methods—The US Acute Liver Failure Study Group, a 23-site registry prospectively enrolled 1,413 patients with ALF with different etiologies between 1998 and 2008. Of those, 105 patients were identified as HBV-ALF patients, of whom we excluded those without data on NA use or with co-infection with hepatitis C, leaving 85 patients, 43 of whom had received NA treatment. HBV-DNA on admission was quantified by real time polymerase chain reaction.

Results—The treated and untreated groups were similar in most respects but differed significantly in regard to higher aminotransferase and bilirubin levels and hepatic coma grades, all being observed in the untreated group. Median duration of NA treatment was 6 (range: 1-21) days. Overall survival in the NA treated and untreated groups were 61% and 64% respectively (p=0.72). Rates of transplant-free survival were 21% and 36% in the treated and untreated groups respectively, p=0.42. Multivariate analysis revealed that not using a NA [odds ratio (OR) 4.4, 95% CI 1.1-18.1, p=0.041], hepatic coma grade I or II [OR 14.4, 95% CI 3.3-62.8, p<0.001], prolonged prothrombin time (PT) [OR 0.59, 95% CI 0.39-0.89, p=0.012] were predictors of improved transplant-free survival.

Conclusions—Patients who are admitted with established HBV-ALF do not appear to benefit from viral suppression using nucleoside(tide) analogues presumably because of rapid disease evolution and short treatment duration. Despite the lack of benefit, NAs should still be given to transplantation candidates since viral suppression prevents recurrence after grafting.

Keywords

Liver transplantation; severe viral hepatitis

Introduction

Acute liver failure (ALF) is characterized by a sudden deterioration of liver function with hepatic encephalopathy and coagulopathy (1). Patients with ALF exhibit massive necrosis of

hepatocytes; in many cases, more than 60% of total liver mass is lost (2). Hepatitis B virus (HBV) infection comprises a major portion of adult ALF (HBV-ALF) ranging from 8-19% in Western countries to 38% in Japan and 21% in Korea (3,4). Survival in patients with HBV-ALF who do not undergo orthotopic liver transplantation (OLT) ranges from 19-33% (4). The efficacy of nucleoside(tide) analogues (NAs) for patients with HBV-ALF is uncertain (5).

NA treatment in chronic HBV infection results in suppression of HBV-DNA replication and increased sero-conversion rates (6). Favorable clinical outcomes including improved liver histology or survival in this setting are seen but evolve slowly in months or years (6). By contrast, therapy for acute hepatitis B does not clearly alter the course of disease. A recent randomized clinical trial demonstrated that 3 months of lamivudine use decreased HBV-DNA concentrations faster only for the first 4 weeks of therapy in the lamivudine treated group as opposed to the placebo control. Clinical and biochemical outcomes in this study were comparable between the two groups after one year of follow-up (7). Compared to those with more typical chronic or acute HBV infection, patients with HBV-ALF represent a more extreme condition with rapid evolution from diagnosis to fatal outcome within a matter of days to weeks. Patients exhibiting a fulminant course have been thought to have a more vigorous immune response than is seen in self-limited acute hepatitis B infection (8,9). In support of the concept of an overactive immune response, undetectable HBV-DNA on presentation, rapid HBsAg clearance and early anti-HBs appearance is observed in 20% of HBV-ALF patients (8). NAs have been proposed as treatment for this rapidly fatal condition.

Few studies evaluating the efficacy of NA use specifically in HBV-ALF patients have been performed, most series having included patients with milder disease, without encephalopathy (3). In this retrospective study we determined whether NA use in patients with HBV-ALF was associated with improvement in short-term patient survival.

Patients and methods

Between January 1998 and December 2008, the US ALF Study Group enrolled 1,413 patients with acute liver failure (ALF) comprising all etiologies from 23 sites around the nation, to study in prospective fashion their clinical characteristics and outcomes. The definition of ALF used by the group included severe acute liver injury without known cirrhosis, with onset of illness within 26 weeks of onset of encephalopathy with coagulopathy (prothrombin time ≥ 15 seconds or international normalized ratio (INR) ≥ 1.5) (1). During this period, 105 patients with ALF secondary to hepatitis B infection (HBV-ALF) who exhibited at least one marker of HBV (HBsAg and/or anti-HBc immunoglobulin M [anti-HBc IgM]) were enrolled (Figure 1). Within the cohort, 2 patients with HBV+HCV co-infection were excluded. No patient was found to be co-infected with hepatitis A, hepatitis D or hepatitis E.

Using data on the remaining 103 HBV patients, we performed a retrospective review of case report forms (CRFs) and medical charts for NA use. In cases where the CRFs did not reveal use of NA or its denial, we queried the study site for relevant additional information, excluding 10 patients lacking such information regarding NA use as well as 4 whose NA had been given >3 weeks before admission to study and 4 whose NA was started >3 weeks after admission to study. Full information on NA use *within* 3 weeks prior to or post study admission was available for 85 patients. Among these, 9 were considered immunosuppressed, either due to prednisone therapy largely for inflammatory bowel disease (n=7) or HIV co-infection (n=2, neither patient was on anti-retroviral therapy at time of study). We recognized that there were two groups within this cohort: those with new acute

HBV infection leading to ALF (AHBV-ALF) and those with ALF occurring in the setting of chronic HBV (CHBV-ALF). These two categories of either AHBV-ALF or CHBV-ALF have recently been described in detail (10). AHBV-ALF (n=61) was defined by patient history of apparent *recent* HBV infection (i.e., no history of chronic hepatitis B infection and/or a recent exposure to a likely carrier). By contrast, CHBV-ALFs (n=24) were defined by a history of prior HBV infection.

Since all patients experienced some degree of encephalopathy, informed consent was obtained from next of kin prior to study enrollment after approval by the local Institutional Review Board. Detailed clinical and demographic data were available on all patients.

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, Illinois). Groups were divided into those with NA use (n=43) and those without NA use (n=42). Primary outcome of HBV-ALF patients was defined by spontaneous (transplant free) survival (SS) vs. Non-SS (Death or orthotopic liver transplantation [OLT]) within 3 weeks after admission to the study. Secondary outcomes were OLT vs. non-OLT and overall survival with or without OLT. Hepatic coma grade was grouped into mild (grades I and II) vs. severe hepatic encephalopathy (grades III and IV). Admission HBV-DNA levels were measured on 69 patients. Chi-square or Fisher's Exact Test (when appropriate) were employed to compare dichotomous variables between the groups (NA use vs. Non-NA use or SS vs. non-SS). Mann-Whitney U Test was used to determine the difference between groups (NA use vs. Non-NA use or SS vs. non-SS) based on measures of continuous variables. Logistic regression analysis was employed to independently predict the primary outcome (SS vs. Non-SS) using admission hepatic coma grade, prothrombin time/INR, creatinine, age and the two groups (NA use vs. No NA use) as covariates; the predictions from the multivariate model were used in an ROC analysis. For all statistical tests, a p value ≤ 0.05 was considered statistically significant. Values of continuous variables were expressed as median (range), unless otherwise stated.

Results

Overall demographics and outcomes

For the 85 HBV ALF patients included in the study, overall survival was 62% (53/85), spontaneous survival was 28% (27/85), and 38% (32/85) underwent transplantation. The group included 45% (38/85) self-identified as Caucasian, 32% (27/85) African Americans, 15% (13/85) Asian, and 8% (7/85) other ethnicities. The median age was 42 years old and 47% (40/85) were female.

Within the NA treatment group, 11/43 (26%) began therapy within 3 weeks before admission while the remaining 32/43 (74%) began NA therapy only after hospital admission (Figure 1). Among patients in this group, 31/43 (72%) were given lamivudine, 8/43 (19%) received entecavir, one (2%) tenofovir and 3/43 (7%) received both lamivudine and adefovir. The NA treatment group included significantly more Asian patients 27% (10/43) vs. 7% (3/42) in the untreated group ($p = 0.04$). The median ALT was significantly higher in the untreated group 2,475 IU/L (range: 166-10,965) vs. 1,395 IU/L (range: 87-7,960) in the treated group ($p < 0.01$). The untreated group more often had higher hepatic coma grades: 24/42 (67%) demonstrated coma grade III or IV, compared to 19/43 (44%) with advanced coma grades among the NA treated patients ($p=0.037$). The treated group had higher median serum bilirubin levels and lower median AST values; these differences were not statistically significant (Table 1). Viral loads were available on admission on 69 of 85 patients, equally balanced between the two groups and were similar (Table 1). Spontaneous survival was not

different between the treated group 9/43 (21%) and the untreated group 15/42 (36%, $p=0.13$). The rate of overall survival was also similar at 26/43 (61%) and 27/64 (64%, $p=0.72$) respectively for the treated and untreated groups.

Patient demographics and outcomes for the acute HBV ALF patients

Of the 85 patients, 61 (72%) were identified as AHBV-ALF as opposed to CHBV-ALF (Table 2). Among them, 20/61 (33%) were spontaneous survivors, 23/61 (38%) were transplanted, yielding an overall survival of 42/61 (69%). Within the cohort, the patients receiving NA comprised 44% (27/61). Characteristics between these two subgroups did not differ; however, there appeared to be more Asian-Americans in the CHBV-ALF group, probably because this group would be more likely to be assumed to have chronic rather than acute infection (10). More Asian-American patients were received NA treatment (85%) compared to Caucasians or African-Americans (37 and 50% respectively), possibly reflecting this same trend. As observed for the overall study cohort, the NA use group with presumed acute hepatitis B was associated with lower ALT and AST levels compared to the untreated group but these differences were not statistically significant (Table 3). Survival was similar but slightly better for the group that had not received NA treatment.

Factors impacting spontaneous survival

Univariate analysis of SS versus those dying or requiring liver transplantation, revealed that three factors were statistically significant: prothrombin time (PT/INR), hepatic coma grade and serum creatinine level (Table 3). Median INR among spontaneous survivors was 2.3 (range: 1-7) vs. 3.7 (range: 1-20) in those in the non-SS group, ($p=0.001$). Higher hepatic coma grade was also associated with decreased spontaneous survival: 41/61 (67%) of those who died or required transplantation were listed initially as having a coma grade of III or IV as compared to only 6/24 (25%) of spontaneous survivors, ($p<0.001$). Also, spontaneous survivors had a somewhat lower median serum creatinine level: 0.95 mg/dL (range: 0-7) compared to 1.2 mg/dL (range: 0-11) among those without spontaneous survival, ($p=0.03$). Younger age also showed a trend with the spontaneous survival group having a median age of 41 (range: 17-71) compared to a median age of 43 (range: 18-65) among those without spontaneous survival, ($p=0.056$).

Multivariate analysis

The factors determined to significantly impact spontaneous survival on univariate analysis; PT/INR, creatinine and hepatic coma grade (I-II vs. III-IV), were used in a multivariate logistic regression analysis along with NA use and age (Table 4). The model was found to fit the data well (Hosmer-Lemeshow 2-sided $p=0.974$). Multivariate analysis revealed that the untreated NA group had an increase in spontaneous survival with an odds ratio of 4.4 (95% CI: 1.06-18.12, $p=0.041$). Furthermore, lower hepatic coma grades (I or II) were associated with a significantly higher rate of spontaneous survival OR 14.45, (95% CI: 3.33-62.79, $p<0.001$). A higher PT/INR was associated with a lower rate of spontaneous survival: OR 0.59, 95% CI: 0.39-0.89, $p=0.012$. The associations between creatinine and age and spontaneous survival were not statistically significant on multivariate analysis. The predictions from the logistic regression model were used in a ROC analysis; the area under the curve (AUC) was high and significantly different from the diagonal (AUC=.891, $p<0.0001$; Figure 2).

Discussion

In this retrospective series of US patients with acute liver failure due to hepatitis B, we did not find any significant survival benefit related to NA use. The study was not randomized and thus the patients receiving NA therapy were not randomly selected. Nevertheless, the

groups were reasonably well matched for most measures of severity. Both the NA treated and untreated groups demonstrated similar numbers of patients; gender balance, age, HBsAg negativity, HBeAg negativity, HBV DNA levels and laboratory parameters on admission to the study were also similar between groups. Significant differences between the two groups existed for race, aminotransferases and hepatic coma grade. Among those differences, higher hepatic coma grade on admission was associated with poorer overall outcome. Importantly, the burden of higher coma grades, associated with decreased spontaneous survival, was on the untreated group, 67% coma grade III or IV vs. 44% coma grade III or IV in the NA treated group, but this did not appear to result in poorer spontaneous or overall survival when compared to those receiving nucleoside analogues. Multivariate analysis revealed that mild hepatic coma grade (I or II) and, to a lesser extent, lower INR values were independently associated with better spontaneous survival (Table 4), as has been recognized in previous studies (11). The group where NA had not been used had a significantly higher odds ratio for spontaneous survival but their actual overall outcomes were not improved as might be expected.

This study reflects clinical practice at academic centers over more than a decade, during the initial evolution of NA use in the US. Despite this fact, only a modest increase in usage was observed over the duration of the study, possibly reflecting slow clinician acceptance of a new treatment of uncertain value in the acute or ALF setting. The poorer outcomes in the treated group may reflect that, on average, patients considered to have more advanced disease might be considered for NA use more frequently or in the context of transplantation listing. As evidence of this, the NA group experienced a higher rate of transplantation than the untreated group (42% vs. 33%), which partially accounts for their lower spontaneous survival. This may also have reflected a bias towards beginning prophylactic treatment with nucleoside analogues for those expected to undergo liver grafting. An additional possible contributing factor to the poorer outcome was that patients not receiving NA treatment exhibited a much higher, approximately 2-fold increase, in ALT and AST levels compared to NA treated group (Table 1). This, coupled with lower bilirubin levels, might indicate a more acute and therefore self-limited, rather than chronic disease. Nonetheless, higher aminotransferases are generally considered to indicate more severe liver injury and higher coma grades were indeed observed in the group that did not receive NA treatment. These differences were maintained when the group considered to have acute hepatitis B were compared separately for NA use to the group with presumed chronic infection (10). Overall survival rates between the treated and untreated group were similar at 61% (26/43) and 64% (27/42) respectively.

Previous studies evaluating the efficacy of NAs in ameliorating severe acute hepatitis B have yielded mixed results; some studies have included only a few true ALF cases (with encephalopathy). A case report described a 74-year old woman with severe acute hepatitis B with encephalopathy who recovered completely after four months of lamivudine therapy (12). Another study of severe acute hepatitis B suggested that treatment with lamivudine yielded a positive clinical response in 13 of 15 patients. However, only 5 patients in this study had encephalopathy and there were no untreated controls (13). A study of 17 consecutive NA-treated patients with severe acute hepatitis B, when compared to historic controls, demonstrated significant improvement in overall survival. However, of the 7 patients who had hepatic encephalopathy in this study, 6 patients had only hepatic coma grade I (14). A retrospective Japanese study evaluated survival outcomes in 33 patients with ALF defined by the presence of encephalopathy and coagulopathy; 29/33 (88%) patients in this study underwent plasma exchange. In this report, nucleoside analogue use in 10 patients was associated with significant survival benefit (15).

Our study differs from previous reports in that it included exclusively patients with encephalopathy and coagulopathy. With these advanced disease patients, the average duration from jaundice to coma was short, averaging 6 days. The brief period of NA use reflects that patients with HBV-ALF resemble those with apparent fulminant autoimmune hepatitis—more chronic forms of the disease exist but in these very acute and severe cases acuity no rescue is possible. As in autoimmune patients where corticosteroids rescue most but not all patients, improvement is seldom seen in very acute, severe cases.

It is generally agreed that HBV is a non-cytopathic virus (16). Thus, liver injury is caused by the host immune reaction and the immune response is most vigorous in patients that eventually experience ALF (9, 17). It is unclear what the effect of a nucleoside analogue would be in the setting of massive hepatocyte necrosis or what a short duration of NA therapy could provide in this setting. To date, NA has been shown to be ineffective in improving biochemical parameters and survival in patients without prolonged treatment; at least a month's therapy is required to lower viral load effectively (6,7). Since the median duration of treatment in our study was six days (range: 1-21 days), it seems unlikely, from first principles, that any benefit on survival or prevention of transplantation could accrue in this setting. While there have been few studies of viral load in recent years with sensitive assays, it appears that patients with HBV-ALF have similar viral levels to those with acute hepatitis B, in the range of 1,000 to 2,000,000 IU/L. Lower VLs might be more amenable to treatment and more rapid clearance—we were unable to demonstrate any association of low VL with improved survival (data not shown).

The study included 61 'new' acute hepatitis B related ALF patients as well as 24 patients with CHBV ALF (Figure 1). Analysis of the chronic subgroup did not reveal any significant differences in clinical or biochemical parameters from the AHBV-ALF group, but the patient number was too small to make definitive conclusions (Table 3). NA use did not show a survival benefit in any subgroup of HBV-ALF patients. A somewhat similar study evaluating severe acute exacerbations of chronic hepatitis B infection revealed no decrease in the progression to HBV ALF in patients treated with lamivudine (18).

While our study did not reveal a survival benefit with NA treatment, practice guidelines and the recent consensus statement of an NIH panel on treatment of HBV infection has recommended NA for patients with HBV-ALF (5, 19). Patients with HBV ALF are thought to have higher likelihood of viral clearance post OLT, but this can be compromised by immunosuppression, so that viral suppression in the immediate post-OLT period and use of HBIG still are considered standard of care (5). NAs effectively reduce HBV DNA over months of treatment and have a favorable histological impact in patients with chronic HBV (20, 21). They have also proven useful in preventing reactivation of HBV and decreasing HBV related morbidity and mortality in patients with chronic HBV who are placed on immunosuppressive therapies (22, 23). Treatment with NAs is indicated for patients listed to undergo liver transplantation, which represents, in selected patients, the only definitive treatment for HBV ALF (24). Information concerning long term follow up visits were available on 19 of 32 patients who had undergone OLT; there had been 3 late deaths at 1, 2, and 3 months after study admission; two had been transplanted. Our study was limited by the fact that data was obtained retrospectively and treated and untreated groups were not matched although their characteristics were similar. The duration of treatment varied in the NA treatment group, but was generally quite short. As in any study of ALF, overall survival is influenced by transplantation, a rescue therapy, which itself depends on availability of a donor organ, graft quality, stage and severity of the underlying liver disease as well as complications. A prospective trial might be of value to determine NA efficacy. However, it is unlikely to be undertaken since patients under consideration for transplantation should be given nucleoside analogues as prophylaxis to reduce the likelihood of post-transplant HBV

recurrence. Withholding NA's in the ALF population would be considered unethical and we found no evidence that they were harmful. Still, it is unlikely that NA use in the setting of HBV ALF has direct benefit. Patients presenting with ALF due to HBV have a low likelihood (< 25%) of survival without grafting.

In conclusion, while NAs are thought to be indicated for the treatment of HBV ALF they do not appear to improve immediate survival. Liver transplantation remains the definitive treatment. To lower VL prior to transplant, HBV ALF patients should receive NAs. The effect during the brief period preceding transplant may be minimal; however the drugs are well tolerated and pose little risk.

Acknowledgments

We gratefully acknowledge the support provided by the members of The Acute Liver Failure Study Group 1998-2008. This study was funded by NIH grant DK U-01 58369 for the Acute Liver Failure Study Group provided by the National Institute of Diabetes, Digestive and Kidney Disease. Additional funding provided by the Tips Fund of Northwestern Medical Foundation and the Jeanne Roberts and Rollin and Mary Ella King Funds of the Southwestern Medical Foundation, and T-32 DK007745-12 to DD. *Members and institutions participating in the Acute Liver Failure Study Group 1998-2006: W.M. Lee, MD (Principal Investigator), George A. Ostapowicz, MD, Frank V. Schiødt, MD, Julie Polson, MD, University of Texas Southwestern, Dallas, TX; Anne M. Larson, MD, University of Washington, Seattle, WA; Timothy Davern, MD, University of California, San Francisco, CA; Michael Schilsky, MD, Mount Sinai School of Medicine, NY, NY; Timothy McCashland, MD, University of Nebraska, Omaha, NE; J. Eileen Hay, MBBS, Mayo Clinic, Rochester, MN; Natalie Murray, MD, Baylor University Medical Center, Dallas, TX; A. Obaid S. Shaikh, MD, University of Pittsburgh, Pittsburgh, PA; Andres Blei, MD, Northwestern University, Chicago, IL; Atif Zaman, MD, University of Oregon, Portland, OR; Steven H.B. Han, MD, University of California, Los Angeles, CA; Robert Fontana, MD, University of Michigan, Ann Arbor, MI; Brendan McGuire, MD, University of Alabama, Birmingham, AL; Raymond T. Chung, MD, Massachusetts General Hospital, Boston, MA; Alastair Smith, MB, ChB, Duke University Medical Center, Durham, NC; Robert Brown, MD, Cornell/Columbia University, NY, NY; Jeffrey Crippin, MD, Washington University, St Louis, MO; Edwin Harrison, Mayo Clinic, Scottsdale, AZ; Adrian Reuben, MBBS, Medical University of South Carolina, Charleston, SC; Santiago Munoz, MD, Albert Einstein Medical Center, Philadelphia, PA; Rajender Reddy, MD, University of Pennsylvania, Philadelphia, PA; R. Todd Stravitz, MD, Virginia Commonwealth University, Richmond, VA; Lorenzo Rossaro, MD, University of California Davis, Sacramento, CA; Raj Satyanarayana, MD, Mayo Clinic, Jacksonville, FL; and Tarek Hassanein, MD, University of California, San Diego, CA. The University of Texas Southwestern Administrative Group included Grace Samuel, Ezmina Lalani, Carla Pezzia, and Corron Sanders, PhD and the Statistics and Data Management Group included, Joan Reisch, PhD, Linda Hynan, PhD, Janet P. Smith, Joe W. Webster, and Mechelle Murray. We further acknowledge all the coordinators from the study sites as well as the patients and their families who participated in this study.

Grand Support: We gratefully acknowledge the support provided by the members of The Acute Liver Failure Study Group 1998-2008. This study was funded by NIH grant DK U-01 58369 for the Acute Liver Failure Study Group provided by the National Institute of Diabetes, Digestive and Kidney Disease; DD was supported by a medical student training grant T-32 DK007745-12. ES was supported by a grant from the Jim and Alinda Wikert Fund of the Southwestern Medical Foundation. Additional funding provided by the Tips Fund of Northwestern Medical Foundation and the Jeanne Roberts and Rollin and Mary Ella King Funds of the Southwestern Medical Foundation.

References

1. Lee WM. Acute liver failure. *N Engl J Med*. 1993; 329:1862–1872. [PubMed: 8305063]
2. Scotto J, Opolon P, Eteve J, Vergoz D, Thomas M, Caroli J. Liver biopsy and prognosis in acute liver failure. *Gut*. 1973; 14:927–933. [PubMed: 4785282]
3. Lee HC. Acute liver failure related to hepatitis B virus. *Hepatol Res*. 2008; 38:S9–S13. [PubMed: 19125959]
4. Wai CT, Fontana RJ, Polson J, Hussain M, Shakil AO, Han SH, Davern TJ, et al. Clinical outcome and virological characteristics of hepatitis B-related acute liver failure in the United States. *J Viral Hepat*. 2005; 12:192–198. [PubMed: 15720535]
5. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009; 50:661–662. [PubMed: 19714720]

6. Dienstag JL. Hepatitis B virus infection. *N Engl J Med*. 2008; 359:1486–1500. [PubMed: 18832247]
7. Kumar M, Satapathy S, Monga R, Das K, Hissar S, Pande C, Sharma BC, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. *Hepatology*. 2007; 45:97–101. [PubMed: 17187417]
8. Bernuau J, Goudeau A, Poynard T, Dubois F, Lesage G, Yvonnet B, Degott C, et al. Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology*. 1986; 6:648–651. [PubMed: 3732998]
9. Woolf IL, El Sheikh N, Cullens H, Lee WM, Eddleston AL, Williams R, Zuckerman AJ. Enhanced HBsAb production in pathogenesis of fulminant viral hepatitis type B. *Br Med J*. 1976; 2:669–671. [PubMed: 974529]
10. Dao DY, Hynan LS, Yuan HJ, Sanders C, Balko J, Attar N, Lok ASF, Word RA, Lee WM. Two distinct subtypes of hepatitis B virus-related acute liver failure are separable by quantitative serum IgM anti-HBc and HBV DNA levels. *Hepatology*. 2011 Oct 10. Epub ahead of print.
11. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, Davern TL III, Murray NG, McCashland T, Reisch J, Robuck PR, the ALFSG. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology*. 2009; 137:856–864. [PubMed: 19524577]
12. Reshef R, Sbeit W, Tur-Kaspa R. Lamivudine in the treatment of acute hepatitis B. *N Engl J Med*. 2000; 343:1123–1124. [PubMed: 11032526]
13. Schmilovitz-Weiss H, Ben-Ari Z, Sikuler E, Zuckerman E, Sbeit W, Ackerman Z, Safadi R, et al. Lamivudine treatment for acute severe hepatitis B: a pilot study. *Liver Int*. 2004; 24:547–551. [PubMed: 15566503]
14. Tillmann HL, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, Graziadei I, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. *J Viral Hepat*. 2006; 13:256–263. [PubMed: 16611192]
15. Miyake Y, Iwasaki Y, Takaki A, Fujioka S, Takaguchi K, Ikeda H, Kobashi H, et al. Lamivudine treatment improves the prognosis of fulminant hepatitis B. *Intern Med*. 2008; 47:1293–1299. [PubMed: 18628576]
16. Chisari FV. Rous-Whipple Award Lecture. Viruses, immunity, and cancer: lessons from hepatitis B. *Am J Pathol*. 2000; 156:1117–1132. [PubMed: 10751335]
17. Webster GJ, Reignat S, Maini MK, Whalley SA, Ogg GS, King A, Brown D, et al. Incubation phase of acute hepatitis B in man: dynamic of cellular immune mechanisms. *Hepatology*. 2000; 32:1117–1124. [PubMed: 11050064]
18. Tsubota A, Arase Y, Suzuki Y, Suzuki F, Sezaki H, Hosaka T, Akuta N, et al. Lamivudine monotherapy for spontaneous severe acute exacerbation of chronic hepatitis B. *J Gastroenterol Hepatol*. 2005; 20:426–432. [PubMed: 15740488]
19. Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, Kern ER, et al. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. *Ann Intern Med*. 2009; 150:104–110. [PubMed: 19124811]
20. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, Crowther L, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med*. 1999; 341:1256–1263. [PubMed: 10528035]
21. Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M. A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med*. 1995; 333:1657–1661. [PubMed: 7477217]
22. Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, Csako G. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med*. 2008; 148:519–528. [PubMed: 18378948]
23. Lee WC, Wu MJ, Cheng CH, Chen CH, Shu KH, Lian JD. Lamivudine is effective for the treatment of reactivation of hepatitis B virus and fulminant hepatic failure in renal transplant recipients. *Am J Kidney Dis*. 2001; 38:1074–1081. [PubMed: 11684562]
24. Angus PW, Patterson SJ. Liver transplantation for hepatitis B: what is the best hepatitis B immune globulin/antiviral regimen? *Liver Transpl*. 2008; 14(2):S15–22. [PubMed: 18825721]

Figure 1.

Study schema of NA use in HBV-ALF indicating patient groups and outcomes. Of the 105 patients with HBV-ALF enrolled, 12 were excluded because of either co-infection with hepatitis C (2) or lack of NA data (10). Eight additional patients were excluded because treatment had been started either >3 weeks prior to study admission or >3 weeks after study admission.

NA: Nucleoside (tide) analogues; SS: Spontaneous Survival; OLTx: Transplantation; OS: overall survival; CG: coma grade

Figure 2. Receiver operator characteristic (ROC) curve for a logistic regression model using admission hepatic coma grade, prothrombin time/INR, creatinine, age and the two groups (NA use vs. No NA use) as covariates. The area under the curve was 0.891 which was highly significant.

Table 1
Baseline Characteristics of the Study Patients With and Without NA Use

Characteristics	Total HBV-ALF (n=85)	NA Use (n=43)	Non-NA Use (n=42)	Univariate <i>P</i> value ^a
Age [median (range)] yr	42 (17-71)	45 (20-69)	41 (17-71)	0.25
Race-no. (%)				
African American	27 (32)	13 (35)	14 (34)	0.04
Asian	13 (15)	10 (27)	3 (7)	
Caucasian	38 (45)	14 (38)	24 (59)	
Other [‡]	7 (8)			
Female-no. (%)	40 (47)	20 (47)	20 (48)	0.92
HBV-DNA [n, median(range)] (IU/mL) [#]	69, 9.88×10 ³ (0-4.96×10 ⁸)	33, 8.68×10 ³ (0-4.96×10 ³)	36, 1.5×10 ⁴ (0-8.48×10 ⁷)	0.55
ALT [median(range)] (IU/L)	1906 (87-10956)	1395 (87-7960)	2474.5 (166-10965)	0.006
AST [median(range)] (IU/L)	1056 (66-9901)	750 (66-9901)	1334.5 (76-8615)	0.06
Bilirubin [median(range)] (mg/dL)	18.3 (4-40)	19.2 (4-30)	15.9 (4-40)	0.06
Albumin [median(range)] (g/dL)	2.8 (2-4)	2.7 (2-4)	2.8 (2-4)	0.34
INR [median(range)]	2.9 (1-20)	2.8 (1-16)	3 (2-20)	0.72
Hepatic Coma Grade-no. (%)				
I & II	38 (45)	24 (56)	14 (33)	0.037
III & IV	47 (55)	19 (44)	24 (67)	
Creatinine [median(range)] (mg/dL)	1.1 (0-11)	1 (1-11)	1.1 (0-9)	0.62
Days from Jaundice Onset of Hepatic Coma [median (range)]	5 (0-48)	8 (0-48)	4 (0-46)	0.11
HBsAg Negativity (%)	10 (12)	4 (9)	6 (14)	0.52
HBeAg Positivity (%)	19 (22)	9 (22)	10 (24)	0.79
Anti-HBc Immunoglobulin Positivity-no./no. total available (%)	63/75 (74)	31/38 (82)	32 (86)	0.56
N-Acetylcysteine Treatment-no. (%)	37 (44)	18 (42)	19 (45)	0.75
Alcohol Use-no. (%)	29 (34)	10 (24)	19 (46)	0.038
Spontaneous Survival-no. (%)	24 (28)	9 (21)	15 (36)	0.13
Transplanted-no. (%)	32 (38)	18 (42)	14 (33)	0.42
Overall Survival-no. (%)	53 (62)	26 (61)	27 (64)	0.72

^a comparison between NA Use vs. Non-NA Use groups

[‡] not included in the analysis due to small sample size

[#] not all patients have HBV-DNA available

Table 2
Baseline Characteristics of the patients with new acute HBV-ALF (AHBV-ALF)

Characteristics	AHBV-ALF (n=61)	NA Use (n=27)	Non-NA Use (n=34)	Univariate P value [€]
Age [median (range)] yr	39 (17-69)	36 (20-69)	41 (17-68)	0.98
Race-no. (%)				
African American	23 (38)	10 (37)	13 (38)	
Asian**	5 (8)	4 (15)	1 (3)	
Caucasian	28 (46)	9 (33)	19 (56)	0.41
Other**	5(8)	4 (15)	1 (3)	
Female-no. (%)	30 (49)	15 (56)	15 (44)	0.38
HBV-DNA [n, median(range)] (IU/mL) [#]	50, 7.27×10 ³ (0-8.48×10 ⁷)	21, 6.65×10 ³ (0-1.36×10 ⁶)	29, 8.52×10 ³ (0-8.48×10 ⁷)	0.29
ALT [median(range)] (IU/L)	2087 (87-7960)	1415 (87-7960)	2479 (166-7865)	0.10
AST [median(range)] (IU/L)	1044 (66-9901)	798 (66-9901)	1345 (76-8615)	0.18
Bilirubin [median(range)] (mg/dL)	18.3 (4-40)	22 (4-30)	17 (4-40)	0.10
Albumin [median(range)] (g/dL)	2.9 (2-4)	3 (2-4)	2.8 (2-4)	0.46
INR [median(range)]	2.9 (1-20)	3.4 (1-16)	2.9 (2-20)	0.84
Hepatic Coma Grade-no. (%)				
I & II	28 (46)	15(56)	13(38)	
III & IV	33 (54)	12 (44)	21 (62)	0.18
Creatinine[median(range)] (mg/dL)	1 (0-9)	1 (-7)	1.1 (0-9)	0.93
Days from Jaundice to Onset of Hepatic Coma [median(range)]	4.5 (0-48)	7 (0-48)	4 (0-46)	0.17
HBsAg Negativity (%)	10 (16)	4 (15)	6 (18)	0.77
HBeAg Positivity (%)	15 (25)	7 (26)	8 (24)	0.81
Anti-HBc ImmunoglobulinPositivity-no. (%)	55 (90)	25 (93)	30 (88)	0.22
N-Acetyl Cysteine Treatment-no. (%)	31(51)	15(56)	18(53)	0.51
Alcohol Use-no. (%)	21 (34)	5 (19)	16 (47)	0.02
Spontaneous Survival-no. (%)	20 (33)	6 (22)	14 (41)	0.12
Transplanted-no. (%)	23 (38)	13 (48)	10 (29)	0.13
Overall Survival-no. (%)	42 (69)	18 (67)	24 (71)	0.74

[€] Comparisons between NA Use group vs. Non-NA Use group

** Did not enter into the analysis

[#] not all patients have HBV-DNA available

Table 3
Baseline Characteristics of the study Patients With and Without Spontaneous Survival

Characteristics	Total HBV-ALF (n=85)	Spontaneous Survival (n=24)	Non-SS (Death/OLT) (n=61)	Univariate <i>P</i> value ^β
Age [median (range)] yr	42 (17-71)	41 (18-56)	43 (17-71)	0.056
Race-no. (%)				
African American	27 (32)	9 (43)	18 (32)	
Asian	13 (15)	2 (9) **	11 (19)	
Caucasian	38 (45)	10 (48)	28 (49)	0.48
Other ***	7 (8)			
Female-no. (%)	40 (47)	13 (54)	32 (53)	0.89
HBV-DNA[n,median(range)] (IU/mL) [#]	69, 9.88×10 ³ (0-4.96×10 ⁸)	20, 1.27×10 ⁴ (0-2.0×10 ⁷)	42, 9.83×10 ³ (0-4.96×10 ⁸)	0.69
ALT [median(range)] (IU/L)	1906 (87-10956)	1863 (94-6666)	2021 (87-10965)	0.97
AST [median(range)] (IU/L)	1056 (66-9901)	1056 (76-6631)	1100 (66-9901)	0.23
Bilirubin [median(range)] (mg/dL)	18.3 (4-40)	16.25 (6-40)	18.4 (4-30)	0.72
Albumin [median(range)] (g/dL)	2.8 (2-4)	2.85 (2-4)	2.7 (2-4)	0.40
INR [median(range)]	2.9 (1-20)	2.3 (1-7)	3.7 (1-20)	0.001
Hepatic Coma Grade-no. (%)				
I&II	38 (45)	18 (75)	20 (33)	
III & IV	47 (55)	6 (25)	41 (67)	<0.001
Creatinine[median(range)] (mg/dL)	1.10 (0-11)	0.95 (0-7)	1.20 (0-11)	0.03
Days from Jaundice Onset of Hepatic Coma [median (range)]	5 (0-48)	6 (0-45)	5 (0-48)	0.42
HBsAg Negativity (%)	10 (12)	3 (13)	7 (12)	>0.99
HBeAg Positivity (%)	19 (22)	4 (18)	15 (26)	0.40
Anti-HBc Immunoglobulin Positivity-no. (%)	63 (74)	22 (92)	41 (67)	0.15
N-Acetylcysteine Treatment-no.(%)	37 (44)	14 (58)	23 (38)	0.08
Alcohol Use-no. (%)	29 (34)	13 (57)	40 (68)	0.40

^β Comparisons between NA Use group vs. Non-NA Use groups

**
n<5

not included in the analysis due to small sample size

Table 4
Multivariate Analysis- Predictors of Spontaneous Survival (SS) vs. Non-SS

Variable	<i>O.R (95% CI)</i>	<i>P value</i>
Non-NA Use	4.39 (1.06-18.12)	0.041
Lower Hepatic Coma Grade (I+II vs. III+IV)	14.45 (3.33-62.89)	<0.001
Age	0.96 (0.91-1.01)	0.099
Prothrombin Time/INR	0.59 (0.39-0.89)	0.012
Creatinine	0.78 (0.53-1.15)	0.204