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【 ORIGINAL ARTICLE 】

Early Combination Therapy with Corticosteroid and Nucleoside Analogue Induces Rapid Resolution of Inflammation in Acute Liver Failure due to Transient Hepatitis B Virus Infection

Keiichi Fujiwara[1], Shin Yasui[1], Yuuki Haga[1], Masato Nakamura[1], Yutaka Yonemitsu[1], Makoto Arai[1], Tatsuo Kanda[1], Shigeto Oda[2], Osamu Yokosuka[1] and Naoya Kato[1]

Abstract:

Objective Patients with acute hepatitis B sometimes develop acute liver failure (ALF), which has a poor prognosis. The efficacy of nucleoside analogue (NA) monotherapy for ALF due to transient hepatitis B virus infection (HBV-ALF) remains controversial. Further investigations are necessary in nations with a shortage of donor livers for liver transplantation. In the present study, we aimed to clarify the efficacy of combination therapy with corticosteroid (CS) and NA in the treatment HBV-ALF.

Patients We examined the clinical and biochemical features of 19 patients with HBV-ALF who were treated in the early stage of the disease between 2000 and 2015.

Results Fourteen patients received CS and NA (CS + NA group) and 5 received NA monotherapy (NA group). Eleven patients (58%) survived and 8 (42%) died. The survival rates in the CS + NA and NA groups were 64% and 40%, respectively (p=0.60). The mean alanine aminotransferase (ALT) levels declined significantly at week 2 in both groups. The mean PT activities improved significantly at weeks 1 and 2 in the CS + NA group ($p<0.05$) but not in the NA group. None of the surviving patients developed persistent infection.

Conclusion Combination therapy with CS and NA induces the rapid resolution of inflammation leading to a rapid recovery of the liver function. When it is administered at a sufficiently early stage, it would have a survival benefit and prevent persistent infection in HBV-ALF.

Key words: acute hepatitis B, acute liver failure, combination therapy, corticosteroid, nucleoside analogue

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Introduction

It is estimated that more than 2 billion people worldwide have been infected with hepatitis B virus (HBV) (1). Acute hepatitis B (AHB), which is caused by transient HBV infection, sometimes leads to acute liver failure (ALF), which has a poor prognosis (2-4). Mathematical modeling for the year 2,000 estimated that 600,000 deaths from HBV-related disease occurred worldwide, 40,000 were attributed to AHB (5). In contrast to Western countries, AHB accounts for a large proportion of ALF cases in Eastern countries and developing nations (4, 6-9). In Japan, where the government does not provide universal vaccination, it is estimated that 2,100-2,400 people develop AHB per year (17-19 per 1 million population per year); 6% of these patients develop fulminant hepatitis (FH) and 4% die of the disease (10). A Japanese nationwide survey also revealed that FH caused by transient HBV infection was associated with a poor prognosis in patients who did not receive liver transplantation (LT) (11). LT, which is the only established treatment for ALF, is often difficult to perform in Japan because of a shortage of donor livers. Thus, treatments other than LT must be further investigated.

[1]Department of Gastroenterology, Graduate School of Medicine, Chiba University, Japan and [2]Department of Emergency and Critical Care Medicine, Graduate School of Medicine, Chiba University, Japan
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Correspondence to Dr. Keiichi Fujiwara, fujiwara-cib@umin.ac.jp

There have been limited studies on the treatment of ALF due to transient HBV infection (HBV-ALF). Nucleoside analogues (NAs) have been shown to markedly suppress HBV replication via the suppression of HBV-polymerase activity; however, the efficacy of these agents in improving the survival of HBV-ALF patients is controversial (3, 4, 12).

In the United States and Europe, randomized clinical trials in 1970s concluded that corticosteroid (CS) treatment did not enhance the survival of ALF patients, and CS use in ALF has been almost denied (13-15). However, a Japanese nationwide survey revealed that in Japan, where there is a shortage of donor livers, CS treatment was introduced in more than 70% of ALF cases between 1998 and 2010 for the purpose of suppressing pro-inflammatory cytokines in the early stage of ALF (7, 8, 16, 17).

We recently reported the efficacy of high-dose CS treatment for suppressing the destruction of hepatocytes in patients with viral ALF, when used in the early stage (18), and also reported the efficacy of high-dose CS in combination with NA for treating severe acute exacerbations in HBV carriers by suppressing HBV DNA rapidly and reversing deterioration, when used in the early stage and for more than a few weeks (16, 19-21). However, the efficacy of combination therapy with CS and NA for HBV-ALF is unknown.

In the present study, we aimed to clarify the clinical efficacy of combination therapy with CS and NA for HBV-ALF in comparison to NA monotherapy.

Materials and Methods

Study design and patients

This study was a retrospective cohort study in a Japanese tertiary medical facility (Chiba University Hospital). A total of 110 consecutive Japanese adult patients with ALF, who were treated between 2000 and 2015 were enrolled. We analyzed the patients with HBV-ALF who were treated in the early stage. The early stage was defined as a period of ≤14 days after the clinical onset. We divided the patients into two groups according to the treatments: NA and a sufficient dose of CS (combination therapy, CS + NA group) and NA only (monotherapy, NA group). We assessed survival as the primary endpoint and the biochemical response, virological response and complications as secondary endpoints. Patients who had co-infection with hepatitis A virus (HAV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) were excluded.

The work described in this manuscript was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all patients or appropriate family members. This study was approved by an institutional review board (2153).

Diagnosis

The diagnosis of hepatitis B was made based on the positivity for hepatitis B surface antigen (HBsAg), IgM anti-hepatitis B core antibodies (IgM-HBc), or HBV DNA. A diagnosis of acute hepatitis B was made based on either negative test result for HBsAg preceding the onset of liver injury in the absence of immunosuppressive and/or anticancer therapies in the previous 12 months, or a positive test for high levels of IgM-HBc and negative or low levels of IgG anti-hepatitis B core antibodies (22).

The diagnosis of ALF was made based on the diagnostic criteria for ALF in Japan (2011), as follows: a prothrombin time (PT) of ≤40% the standardized value, or an international normalization ratio (INR) of ≥1.5 due to severe liver damage within 8 weeks after the onset of disease symptoms, where the liver function prior to the current onset of liver damage was estimated to have been normal based on blood laboratory data and imaging examinations. ALF is classified into ALF without hepatic coma and ALF with hepatic coma; patients with the former type present no or grade I hepatic encephalopathy, while patients with the latter type show grade ≥II hepatic encephalopathy. ALF with hepatic coma is further subclassified into 2 disease types: the "acute type" and the "subacute type". In the acute type, grade ≥II hepatic encephalopathy develops within 10 days after the onset of disease symptoms; in the subacute type, it develops after 11-56 days after the onset of disease symptoms (23).

Virological analysis

Patients were examined for viral markers including IgM-hepatitis A antibodies, IgM-HBc, HBsAg, HBV DNA, HBeAg, anti-HBe antibodies (HBeAb), hepatitis D virus (HDV) RNA, anti-HCV antibodies, HCV RNA, hepatitis E virus (HEV) RNA, IgM anti- Epstein-Barr virus antibodies, IgM anti-Herpes simplex virus antibodies and IgM anti-cytomegalovirus antibodies. None of the patients had clinical or laboratory evidence of AIDS.

Treatment

High-dose CS therapy with 1,000 mg of methylprednisolone (MPSL) or 60 mg of prednisolone (PSL), daily (as the initial dose) was administered. The dose was reduced doses according to the treatment response. NA (lamivudine before 2007, entecavir after 2007) and/or interferon was administered as antiviral therapy, and was stopped after HBsAg clearance. Patients received intravenous glycyrrhizin, an aqueous extract of licorice root, at a daily use of 60-100 mL. This agent is reported to have anti-inflammatory activity and has been used for the treatment of acute and chronic liver injury in Japan (24, 25). All patients received comprehensive supportive care, including artificial liver support (plasma exchange and hemodiafiltration) for comatose patients (26).

Assessment

A biochemical response was defined as the improvement of alanine aminotransferase (ALT), PT activity and total bilirubin (T-BIL) at 1 and 2 weeks after the start of treat-

Table 1. Clinical Features of All and Each Treatment Groups at Admission.

	Overall (n=19)	CS+NA Group (n=14)	NA Group (n=5)	p (CS+NA vs. NA)
Female sex*	8 (42)	5 (36)	3 (60)	0.60‡
Age† (yr)	45.0±14.2	50.0±9.5	32.0±18.0	0.06§
Type of disease*				
ALF without coma	6 (32)	5 (36)	1 (20)	1.00‡
ALF with coma	13 (68)	9 (64)	4 (80)	–
Acute type	11 (58)	8 (57)	3 (60)	1.00‡
Subacute type	2 (10)	1 (7)	1 (20)	–
Laboratory values†				
AST (IU/L)	7,145±7,651	7,532±8,183	6,060±6,618	0.58§
ALT (IU/L)	6,309±4,136	6,625±4,217	5,424±4,226	0.55§
LDH (IU/L)	5,143±8,603	5,683±9,768	3,631±4,367	0.52§
T-BIL (mg/dL)	8.6±4.8	7.5±3.0	11.7±7.5	0.13§
D-BIL (mg/dL)	5.5±4.3	4.9±2.0	7.3±6.2	0.49§
PT (%)	18±16	20±17	14±13	0.46§
PLT (×10,000/μL)	13.3±8.7	12.4±8.2	15.9±10.4	0.49§
Cre (mg/dL)	1.5±1.3	1.5±1.3	1.6±1.6	0.40§
AFP (ng/mL)	117±274	113±306	128±177	0.31§
HGF (ng/mL)	5.8±7.1	5.1±7.3	7.8±7.0	0.40§

CS: corticosteroid, NA: nucleoside analogue, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, T-BIL: total bilirubin, D-BIL: direct bilirubin, PT: prothrombin time, PLT: platelet, Cre: creatinine, AFP: alpha-fetoprotein, HGF: hepatocyte growth factor

* No. (%), †mean±SD, ‡ Fisher's exact probability test, §Wilcoxon rank sum test

ment. A virological response was defined as the decline of HBV DNA at 2 weeks after treatment and HBsAg seroconversion. HBsAg seroconversion was defined as serum HBsAg clearance and the presence of anti-HBs antibodies (HBsAb).

Statistical analysis

We analyzed the differences in variables between groups and the differences in of HBV DNA changes by Fisher's exact probability test, Pearson's chi-squared test, the Wilcoxon rank sum test or Student's *t*-test using the SPSS software program (version 22, IBM, New York, USA), and analyzed differences in the changes in the ALT level, PT activity and T-BIL level by the Friedman test and Dunn's multiple comparison test using the GraphPad Prism 5 software program (version 5.0a, GraphPad software, La Jolla, USA). p values of <0.05 were considered to indicate statistical significance.

Results

Patients and treatment

Among the 110 patients, 23 patients with HBV-ALF were admitted to our unit during the study period. Four patients were excluded because the period from the onset of clinical symptoms was >14 days or because they were not treated sufficiently; thus, 19 patients were included in this study. None of the patients had co-infection with HAV, HCV or HIV. The mean age of the 19 patients was 45.0±14.2 years, and 8 patients were female. Fourteen patients received combination therapy with CS and NA (CS + NA group) and 5 received NA monotherapy (NA group) (Table 1).

As the initial CS treatment, PSL (60 mg) was administered to the first patient in 2002; MPSL (1,000 mg) was administered to the 13 subsequent patients. The mean duration between the onset and the introduction of CS was 4.6±2.4 days, the mean period of CS therapy was 7.3±5.5 (mean ± SD) days and the mean total dose of CS was 4.1±1.0 g. NA was administered to all patients; entecavir (ETV) to 9 patients in the CS + NA group, lamivdine (LMV) to 5 patients in the CS + NA group and 5 patients in the NA group. Interferon was administered to 2 patients in the CS + NA group and to 1 patient in the NA group. The mean duration between the onset and the introduction of NA was 5.5±3.1 days and the mean period of NA therapy was 51.7±39.6 days.

The clinical and virological features at admission

Table 1 shows the clinical features of patients at admission. There were no differences in the age, sex, type of disease or laboratory values between the CS + NA group and the NA group at admission. There were no statistically significant differences between the two groups.

Table 2 shows the virological features (HBV DNA, the HBV genotypes, precore mutations, core promoter mutations, and the number of cases that were positive for HBsAg, HBsAb, HBeAg and HBeAb) at admission. There were no statistically significant differences between the two groups.

Table 2. Virological Features of All and Each Treatment Groups at Admission.

	Overall (n=19)	CS+NA Group (n=14)	NA Group (n=5)	p (CS+NA vs. NA)
HBV DNA† (log copies/mL)	5.3±1.3	5.3±1.5	5.2±0.8	0.63‡
Genotype of HBV*				
A	2 (11)	0 (0)	2 (40)	0.053§
B	2 (11)	2 (14)	0 (0)	
C	4 (21)	4 (29)	0 (0)	
Not determined	3 (16)	3 (21)	0 (0)	
No data	8 (42)	5 (36)	3 (60)	
Precore mutation*				0.07§
Wild	3 (16)	1 (7)	2 (20)	
Mutant	7 (37)	7 (50)	0 (0)	
No data	9 (47)	6 (43)	3 (60)	
Core promoter mutation*				0.52§
Wild	7 (37)	5 (36)	2 (40)	
Mutant	3 (16)	3 (21)	0 (0)	
No data	9 (47)	6 (43)	3 (60)	
HBs antigen/antibody*				0.34§
positive/negative	13 (68)	9 (64)	4 (80)	
positive/positive	4 (21)	4 (29)	0 (0)	
negative/positive	2 (11)	1 (7)	1 (20)	
HBe antigen/antibody*				0.92§
positive/negative	4 (21)	3 (21)	1 (20)	
positive/positive	5 (26)	4 (29)	1 (20)	
negative/positive	10 (53)	7 (50)	3 (60)	

CS: corticosteroid, NA: nucleoside analogue, HBs antigen/antibody: hepatitis B surface antigen/antibody, HBe antigen/antibody: hepatitis B envelope antigen/antibody

* No. (%), † mean±SD, ‡ Wilcoxon rank sum test, § Pearson's chi-square test

Outcome

Eleven of the 19 (58%) patients survived and 8 (42%) died due to liver failure. None of the patients received liver transplantation. The overall survival rates were 64% in the CS + NA group and 40% in the NA group (p=0.60). The survival rates in patients with acute-type ALF with coma were 44% in the CS + NA group and 25% in the NA group (p=1.00).

Biochemical responses

Fig. 1a, b and c show the changes in the ALT levels, PT activities and T-BIL levels after the start of treatment, respectively. The mean ALT levels declined significantly at week 1 in the CS + NA group and at week 2 in both groups. The mean PT activities showed a significant improvement at week 1 and 2 in the CS + NA group but not in the NA group. The mean T-BIL levels showed no significant changes at weeks 1 or 2 in either group.

Virological responses

Fig. 1d shows the change in HBV DNA load. The Mean HBV DNA levels declined significantly at week 2 in the CS + NA group. In the NA group, HBV DNA was only measured in 2 patients at week 2; thus, it was not possible to conduct a statistical analysis.

Regarding HBV DNA and HBsAg clearance after the start of treatment, 8 of the 9 surviving patients in the CS + NA group had been positive for HBsAg before treatment; 6 patients (2 were lost to follow-up) achieved HBsAg seroconversion without HBV DNA. All of the surviving patients in the NA group were positive for HBsAg before treatment, and all patients achieved HBsAg seroconversion without HBV DNA. NA use was stopped after HBsAg clearance, and no patients developed HBV reactivation during the follow-up period: the median interquartile range (IQR) was 715 days (112-1,824) in the CS + NA group, and 85 and 503 days in the NA group. The mean HBsAb titer at the time of stopping NA was 71.6±89.5 mIU/mL.

Complications

The complications at admission in the CS + NA group included acute renal failure (n=2), acute pancreatitis (n=1), and hyperamylasemia (n=1). The complications after admission included gastrointestinal hemorrhage (n=2), hemorrhage of the iliopsoas and rectus abdominis muscle (n=1), catheter-related blood stream infection (n=1), and aspergillus pneumonia (n=1). In the NA group, 1 patient had acute renal failure and was pregnant (third trimester) at admission. No patients had complications after admission. There were no differences in the incidence of complications at admission (p=1.00) or after admission (p=0.24).

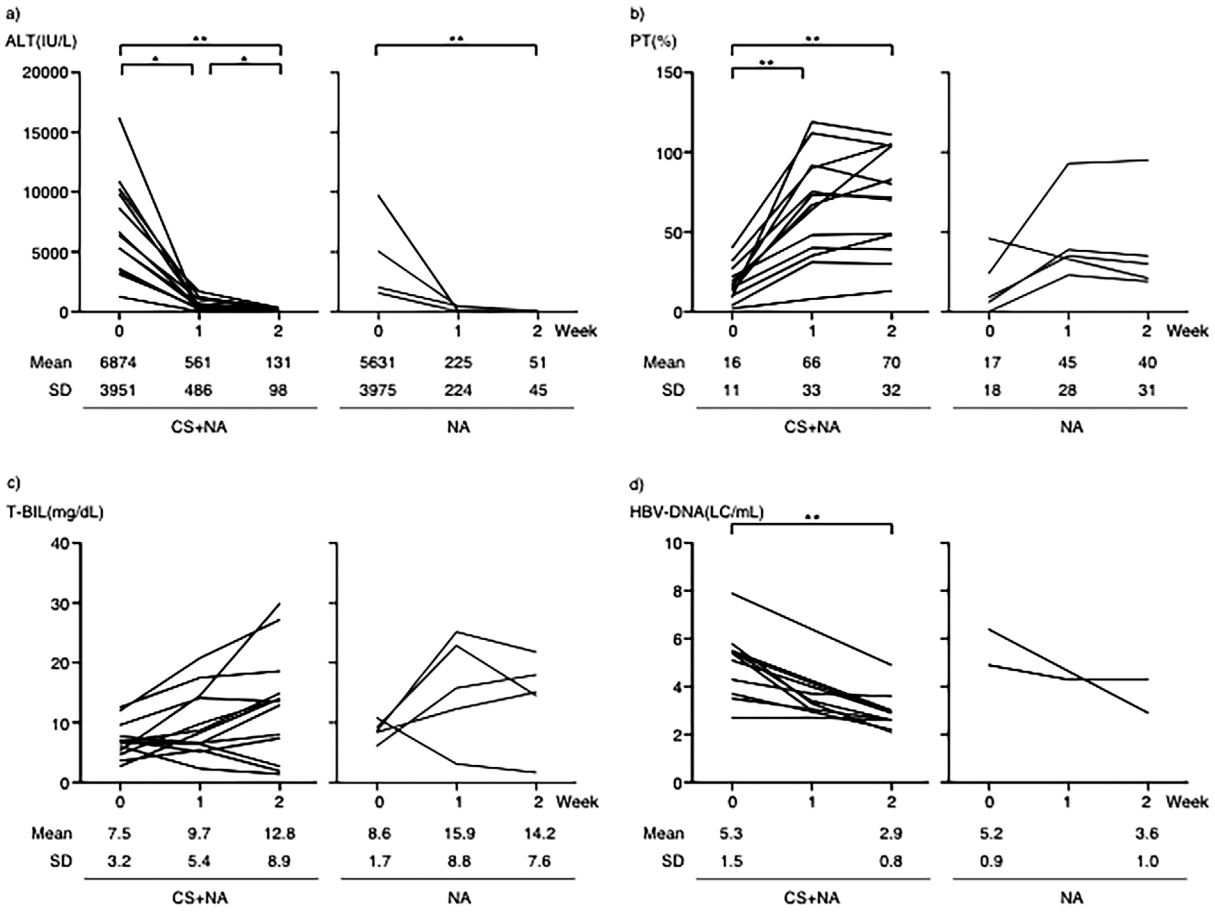

Figure 1. **Changes in alanine aminotransferase (ALT) (a), prothrombin time (PT) (b), total bilirubin (T-BIL) (c), and HBV DNA level (d) in the CS+NA and NA group; *p<0.05, **p<0.01.**

Comparison between the survivors and the non-survivors

There were no statistically significant differences in sex, or the mean levels of aspartate aminotransferase (AST), ALT, lactate dehydrogenase (LDH), D-BIL, platelet (PLT), alpha-fetoprotein (AFP), hepatocyte growth factor (HGF) or HBV DNA between the survivors and the non-survivors. The non-survivors had a higher proportion of patients with ALF with coma (p=0.01). The mean age, T-BIL level and Cre level were higher (p=0.03, 0.03 and 0.02, respectively), and mean PT activity was lower (p=0.03) in the non-survivors (Table 3).

Fig. 2 show changes in the ALT level, PT activity, T-BIL level and HBV DNA load after the start of treatment in both groups, respectively. The mean ALT level declined significantly at week 2 in both groups (p<0.001, respectively). The mean PT activity showed a significant improvement at weeks 1 and 2 in the survivors (p<0.001 and p<0.01, respectively). The mean T-BIL level was significantly elevated at weeks 1 and 2 in non-survivors (p<0.05 and p<0.01, respectively). The mean HBV DNA level showed a significant decline at week 2 in the survivors (p<0.01).

Discussion

The present study showed two important clinical observations. First, although the result did not reach statistical significance, combination therapy with NA and CS led to the rapid recovery of the liver function, and as a result, a higher survival rate than NA monotherapy in patients with HBV-ALF. Second, combination therapy achieved HBsAg seroconversion with HBV DNA negativity, and NA could be stopped safely without the reactivation of HBV DNA in survivors. The clinical course of a recovered patient is shown in Fig. 3.

The efficacy of NA monotherapy in the treatment of HBV-ALF remains controversial. Earlier studies reported a survival benefit (12, 27, 28). In contrast, a recent large cohort study reported that NA therapy did not show a survival benefit in patients with HBV-related ALF, including acute HBV-ALF, because patients did not benefit from viral suppression using NA due to the rapid evolution of the disease and the short duration of treatment (4).

In the present study, the spontaneous survival rate (survival rate without LT) of HBV-ALF patients was 58% (11/19). According to the type of therapy, the survival rate in the CS + NA group was 64% (9/14), while that in the NA

Table 3. Clinical Features of Survived and Dead Patients at Admission.

	Survived (n=11)	Dead (n=8)	p
Female sex*	7 (64)	1 (13)	0.63‡
Age† (yr)	±	46.9±13.2	0.03§
Type of disease*			
ALF without coma	6 (55)	0 (0)	0.01‡
ALF with coma	5 (45)	8 (100)	
Acute type	5 (45)	6 (75)	0.35‡
Subacute type	0 (0)	2 (25)	
Laboratory values†			
AST (IU/L)	5,361±4,778	9,598±10,297	0.24§
ALT (IU/L)	5,252±3,541	7,763±4,681	0.20§
LDH (IU/L)	2,902±2,906	8,224±12,629	0.19§
T-BIL (mg/dL)	6.6±1.9	11.4±6.2	0.03§
D-BIL (mg/dL)	4.4±1.5	7.1±4.9	0.11§
PT (%)	25±16	9±10	0.03§
PLT (×10,000/μL)	14.9±8.8	11.2±8.6	0.38§
Cre (mg/dL)	0.9±0.8	2.4±1.6	0.02§
AFP (ng/mL)	180±347	30±73	0.19§
HGF (ng/mL)	5.3±7.7	6.4±6.8	0.78§
HBV DNA (log copies/mL)	5.3±1.6	5.3±1.0	0.97§

AST: aspartate aminotransferase, ALT: alanine aminotranferase, LDH: lactate dehydrogenase, T-BIL: total bilirubin, D-BIL: direct bilirubin, PT: prothrombin time, PLT: platelet, Cre: creatinine, AFP: alpha-fetoprotein, HGF: hepatocyte growth factor

* No. (%), †mean±SD, ‡ Fisher's exact probability test, §Student's t test

group was 40% (2/5).

The published studies on the efficacy of NA in HBV-ALF in studies that involve ≥10 patients are summarized in Table 4. Dao and the US-Acute Liver Failure (ALF) Study Group reported that the rate of spontaneous survival of HBV-ALF patients treated with NA was 22% (6/27) (4), which was inferior to the survival rate of our overall population and the CS + NA group (p=0.015 and p=0.011, respectively). Yu et al. evaluated the efficacy of LMV in patients with fulminant hepatitis B (3). They also performed pulse steroid treatment with MPSL (500-1,000 mg/day) for 3 days in order to suppress the activity of liver injury according to the description of their treatment protocol, and showed that the spontaneous survival of Chinese fulminant hepatitis patients treated with LMV and CS was 37% (14/38); this result was not significantly different from the survival rate of our CS + NA-treated fulminant hepatitis patients (p=0.48).

Tillmann et al. (12) and Kumar et al. (29) reported high survival rates, probably because the proportions of fulminant hepatitis patients were much smaller than in other studies. Miyake et al. also reported a survival rate of 70% (7/10) in fulminant hepatitis patients (30), probably because their patients had less advanced disease: 70% had coma grade II, and some had received pulse steroid treatment. A Japanese nationwide survey conducted between 1998 and 2009 revealed that the spontaneous survival rate of HBV-ALF patients was 49.8% (8, 11).

Webster et al. observed that the initial and maximal reduction in HBV DNA occurred before the peak of ALT, and that adaptive immune mechanisms are present during the incubation phase (31). The incubation phase, including the early clinical phase before the ALT peak could be considered as the critical period for the interaction between the host and HBV. Thus, we believe that rapid immunosuppression in the early clinical phase, especially before the ALT peak, is important for the cessation of the massive destruction of hepatocytes, which leads to recovery from liver failure.

The use of CS in ALF was denied in the US and European countries in the 1970s, as describe above. However, the results that led to this position were premature because CS was not administered in a uniform fashion, especially with regard to the timing of administration. Subsequently, the mechanisms of ALF came to be understood: massive hepatic necrosis triggers an innate immune response, which is followed by inflammatory cell recruitment, which exacerbates the initial liver injury, and pro-inflammatory cytokines predominate at an early phase. CSs are known to suppress pro-inflammatory genes and induce anti-inflammatory genes. Thus, CS treatment might be beneficial during the early phase of ALF (32). Now that effective agents against the complications that occur due to CS treatment (i.e., antibacterial, anti-fungal, and anti-viral agents, H_2-blockers/proton pump inhibitors) have become available, the efficacy of CS treatment for ALF should be re-evaluated.

We have previously reported the benefit of combination

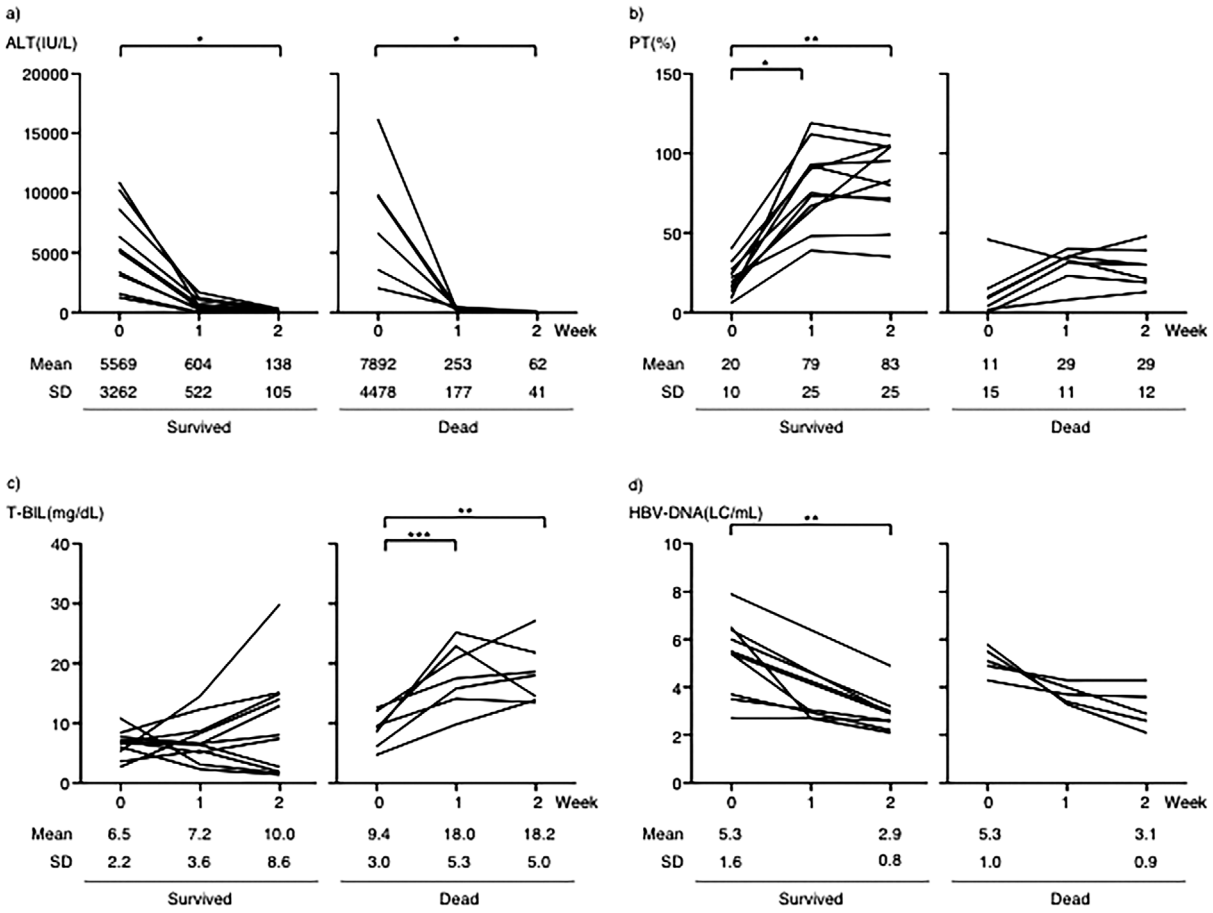

Figure 2. **Changes in alanine aminotransferase (ALT) (a), prothrombin time (PT) (b), total bilirubin (T-BIL) (c), and HBV DNA level (d) in survivors and non-survivors; *p<0.001, **p<0.01, ***p<0.05.**

therapy with high-dose CS and NA in HBV-related ALF (16, 18-21). In the present study, the PT activity of the CS + NA group recovered more rapidly in comparison to the NA group, which indicates that rapid immunosuppression with high-dose CS induced rapid liver regeneration. The high transaminase level and low PT activity of our patients at admission suggest that the massive destruction of hepatocytes in the whole liver was ongoing; thus, the administration of high-dose CS in the early clinical stage would be reasonable for controlling the liver enzyme levels, and suppressing liver inflammation and the progression of liver failure.

Combination therapy with CS and NA achieved the clearance of HBsAg with HBV DNA negativity. CS therapy is generally considered to be associated with a risk of progression to persistent HBV infection; however, none of our patients who were treated with CS showed this progression. NA in combination with CS might contribute to the prevention of persistent infection. However, recent Japanese studies revealed that 4.2-9.8% of AHB patients developed chronic infection and that NA treatment did not prevent progression to chronic infection (33, 34). Patients starting NA treatment within 8 weeks from the onset of disease never progressed to chronicity (33). In the present study, the rapid initiation of NA (the median duration from the onset to initiation was 5 days), might lead to the prevention of persistent infection. Additionally, our data suggest that NA can be stopped safely in the presence of HBsAb without future reactivation.

In the present study, there were no differences in the incidence of complications between the CS + NA and NA groups. However, fungal infection occurred in one patient in the CS + NA group. We previously reported that CS use did not significantly increase the incidence of infection in acute liver failure of various etiologies (35). In that report, fungal infection only occurred in patients treated with CS; however, the difference between the patients with and without CS did not reach statistical significance. Physicians should take care of the possible development of fungal infection, which may occur as a complication of CS. Although peptic ulcer is a major complication of CS, none of the gastrointestinal hemorrhage events that occurred in the present study were due to peptic ulcer.

The present study is associated with some limitations. First, although this is one of the largest case series reported from a single center to date, the number of patients in our study was limited (Table 4). Second, this was not a randomized study because ethical issues obviously prevent a randomized control study due to the life-threatening nature of

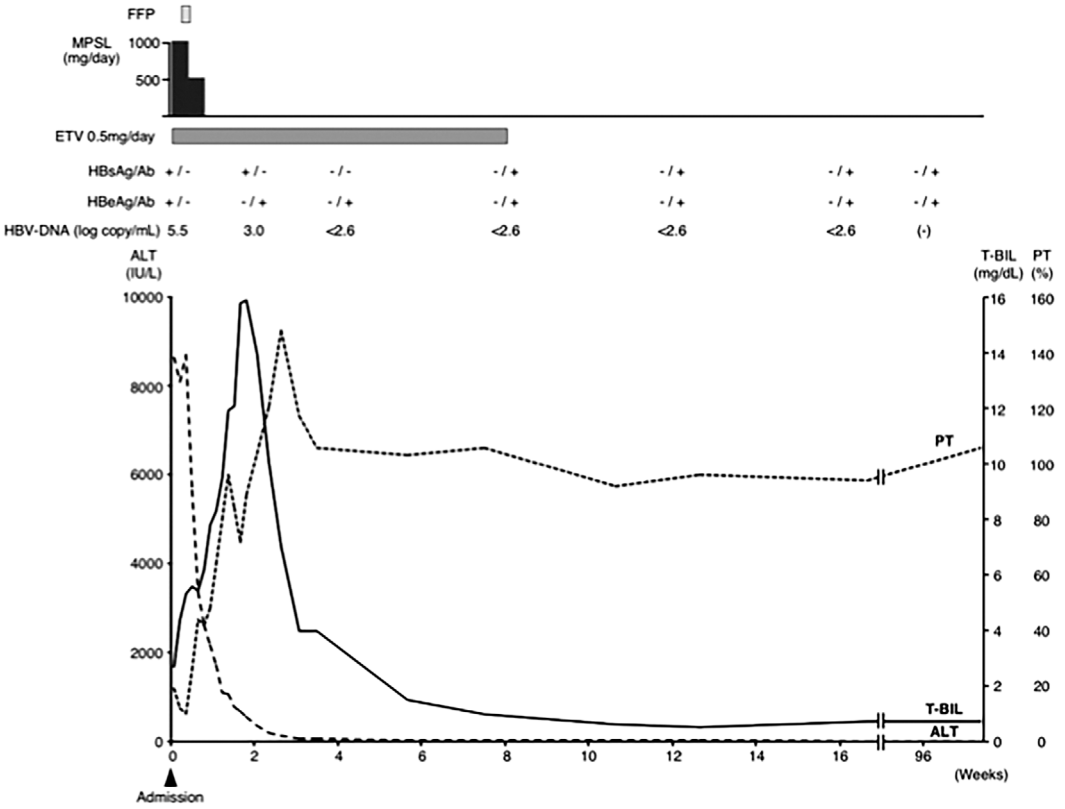

Figure 3. **The clinical course of a 37-year-old female patient. She was admitted to our unit at four days after the onset of disease. Corticosteroid was administered in combination with nucleoside analogue. Her ALT levels rapidly decreased, and her PT improved. Her T-BIL levels gradually improved. Nucleoside analogue was administered for 8 weeks until HBs Ag clearance. Liver function tests continued to be normal without HBV reactivation during the follow-up period of 24 months. FFP: fresh frozen plasma, MPSL: methylpredonisolone, ETV: entecavir, ALT: alanine aminotranferase, T-BIL: total bilirubin, PT: prothrombin time**

Table 4. **Publications about the Efficacy of NA in HBV-ALF.**

Reference	4	3	12	29	30	Present study
Inclusion criteria	ALF · INR ≥ 1.5 · HE	FHF · PT ≤ 40% · HE ≥ grade II	SH, FH · INR>2.0 · HE*	SH** · INR ≥ 1.6 · HE · T-BIL ≥ 10.0 mg/dL	FH · PT ≤ 40% · HE ≥ grade II	ALF · PT ≤ 40% or INR ≥ 1.5
Number of patients treated with NA (FH/SH)	27	38 (38/0)	17 (7/10)	22 (2/20)	10 (10/0)	19 (13/6)
Type of NA	Not described	LMV 38	LMV 17	LMV 22	LMV 10	LMV 10 ETV 9
Number of patients treated with CS	-	38	-	-	+	14
Transplant-free survival rate	22%	37%	82%	100%	70%	58%
Country	United States	China	Germany	India	Japan	Japan
Year	2012	2011	2006	2007	2008	
Type of trial	Multicenter	Single center	Multicenter	Single center	Multicenter	Single center

ALF: acute liver failure, FHF: fulminant hepatic failure, SH: severe hepatitis, FH: fulminant hepatitis, HE: hepatic encephalopathy, NA: nucleoside analogue, HBV-ALF: acute liver failure due to transient HBV infection, LMV: lamivudine, ETV: entecavir, CS: corticosteroid

*Only in case of fulminant hepatitis, **patients fulfilled any 2 of 3 criteria

HBV-ALF.

In summary, the present study showed that combination therapy with CS and NA, when administered at a sufficiently early stage, induces the rapid resolution of inflammation and leads to a rapid recovery of the liver function and the prevention of persistent infection in patients with HBV-ALF. The survival rate of the patients who received our combination therapy was superior to that of patients who received NA monotherapy in a recent report by the US-ALF Study Group (4).

We should realize the fact that treatments other than LT must be further investigated for patients in Japan where a shortage of donor livers remains a serious problem. We are convinced that combination therapy in the early stage has a potential survival benefit in HBV-ALF. Further multicenter studies with uniform criteria and treatment protocols are necessary to validate the benefits of the therapy.

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