The Combination of Nucleotide Analog Therapy and Steroid Pulse Therapy for Acute HBV Infection Effectively Promotes HBV Clearance

合谷, 孟

gastroenterology insights

MDPI

Article

The Combination of Nucleotide Analog Therapy and Steroid Pulse Therapy for Acute HBV Infection Effectively Promotes HBV Clearance

Takeshi Goya [1,†], Tomoyuki Kurashige [1,†], Miho Kurokawa [1], Masatake Tanaka [1], Tomomi Aoyagi [1], Motoi Takahashi [1], Koji Imoto [1], Shigeki Tashiro [1], Hideo Suzuki [1], Masaki Kato [1,2], Motoyuki Kohjima [1,*] and Yoshihiro Ogawa [1]

[1] Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan; goya.takeshi.120@m.kyushu-u.ac.jp (T.G.); tomo7381@med.kyushu-u.ac.jp (T.K.); kurom@med.kyushu-u.ac.jp (M.K.); masa-t@med.kyushu-u.ac.jp (M.T.); aoyagi.tomomi.414@m.kyushu-u.ac.jp (T.A.); takam@med.kyushu-u.ac.jp (M.T.); imok@med.kyushu-u.ac.jp (K.I.); tashiro.shigeki.675@m.kyushu-u.ac.jp (S.T.); hides@med.kyushu-u.ac.jp (H.S.); mkato11@med.kyushu-u.ac.jp (M.K.); ogawa.yoshihiro.828@m.kyushu-u.ac.jp (Y.O.)

[2] Graduate School of Nutritional Sciences, Nakamura Gakuen University, 5-7-1 Befu, Jounan-ku, Fukuoka 814-0198, Japan

* Correspondence: kohjima@med.kyushu-u.ac.jp; Tel.: +81-92-642-5282; Fax: +81-92-642-5287

† These two authors contributed equally to this work.

Abstract: Acute hepatitis B virus (HBV) infection occasionally progresses to acute liver failure, often with poor prognosis. The appropriate pharmacological approach is yet to be established. Although nucleotide analogs (NA) and corticosteroids are candidates for the treatment of acute HBV infection, their therapeutic effects, especially their effect on HBV clearance, remain unclear. To clarify effects on the HBV clearance of combination therapy of NA and steroid pulse therapy (SPT) for acute HBV infection, we first analyze the effectiveness of this therapy in patients with HBV infection compared with NA monotherapy (NAM). Of the 57 consecutive patients with acute hepatitis B infection from May 2007 to December 2018, we have included 25 patients for this study, whom we followed up until HBV clearance. According to the administration of NA and SPT, we divided patients into two groups (NAM group and NA + SPT group) and compared their results. Of the 25 patients, 10 received NAM, whereas 15 received NA + SPT. There were no appreciable adverse effects related to SPT. The time required for the clearance of HBsAg (76 (43–116) days vs. 26 (14–51) days, $p = 0.0418$) and HBV-DNA (NAM group vs. NA + SPT group: 180 (83.5–220) vs. 69 (43–136) days, $p = 0.0420$) was significantly shorter in the NA + SPT group than in the NAM group. The hazard ratio of NA + SPT for the clearance of HBsAg and HBV-DNA were 0.45 (0.19–1.09) and 0.35 (0.14–0.89), respectively. In conclusion, we showed that NA + SPT promoted HBV elimination. These findings support the use of the NA + SPT combination for acute HBV infection without the concern of persistent HBV infection.

Keywords: HBV; acute liver failure; acute hepatitis; steroids; nucleotide analog

Citation: Goya, T.; Kurashige, T.; Kurokawa, M.; Tanaka, M.; Aoyagi, T.; Takahashi, M.; Imoto, K.; Tashiro, S.; Suzuki, H.; Kato, M.; et al. The Combination of Nucleotide Analog Therapy and Steroid Pulse Therapy for Acute HBV Infection Effectively Promotes HBV Clearance. *Gastroenterol. Insights* **2022**, *13*, 1–8. https://doi.org/10.3390/gastroent13010001

Academic Editor: David A. Gerber

Received: 9 December 2021
Accepted: 30 December 2021
Published: 31 December 2021

1. Introduction

Acute hepatitis B virus (HBV) is a partially double-stranded DNA virus that belongs to the *Hepadnaviridae* family. Worldwide, it is estimated that 296 million people are chronically infected with HBV, with 1.5 million new infections occurring each year [1]. Acute HBV infection can occasionally progress into acute liver failure (ALF), often with poor prognosis. In Japan, 12.4% of acute liver disease cases and 20.3% of ALF or acute-on-chronic liver failure cases are reportedly caused by HBV [2]. Therefore, acute HBV infection is considered a major health problem, and an appropriate pharmacological approach to solving this

problem is needed. Although nucleotide analogs (NA) and corticosteroids are candidates for the therapy of acute HBV infection, the therapeutic effects of these drugs remain unclear.

NA are drugs that inhibit viral replication in infected cells. The efficacy of NAs for chronic HBV infection has been well established. These antiviral drugs can reduce plasma levels of HBV-DNA, decrease liver inflammation, prevent liver carcinogenesis, and consequently improve the prognosis of chronic HBV infection. Similarly, the safety and efficacy of lamivudine in patients with ALF have been reported [3,4]. Moreover, it is reported that early NA initiation in patients with acute HBV infection might enhance HBV clearance [5]. Meanwhile, corticosteroids, which are known to inhibit an excessive immune response and inflammatory reactions [6], are widely used for multiple diseases. However, several clinical studies on the efficacy of corticosteroids for ALF demonstrated no improvement in survival associated with their use [7,8]. In Japan, because liver transplantation (LT) was limited due to the shortage of liver donors, other therapies, including corticosteroid therapy, have been investigated for ALF. Recently, several reports have indicated the possibility of the therapeutic effect of corticosteroids on ALF [9,10]. Regarding acute HBV infection, Fujiwara et al. reported that combination therapy with NA and corticosteroids induced the rapid resolution of inflammation in HBV ALF [11]. However, because this study focused on the short-term effect of combination therapy, the long-term effect on acute HBV infection remains unclear.

Thus, in this study, we aimed to clarify the long-term effect of NA + SPT for acute HBV infection.

2. Materials and Methods

2.1. Patients

We conducted a single-center retrospective study to evaluate the effectiveness of NA and SPT in patients with acute hepatitis B infection admitted to Kyushu University Hospital between May 2007 and December 2018. Acute hepatitis B infection was diagnosed based on positivity for HBsAg, IgM anti-hepatitis B core antibodies (IgM-HBc), or HBV-DNA. We excluded the possibility of acute exacerbation of HBV based on negative HBsAg tests preceding the onset of liver injury or a positive test for high levels of IgM-HBc and negative or low levels of IgG anti-hepatitis B core antibodies. ALF was diagnosed using the criteria established by the Intractable Hepato-Biliary Diseases Study Group in Japan. Patients with previously normal liver functions having prothrombin activity percentages of 40% or less of the standardized values or international normalized ratios of 1.5 or more caused by severe liver damage within eight weeks of the onset of symptoms were diagnosed with ALF, and they were further classified into ALF with or without hepatic coma. In the former, hepatic encephalopathy grade II or more severe hepatic coma develops within eight weeks [12]. When obvious liver atrophy and hepatic coma were observed on admission, the patient was immediately prepared for LT. There were 57 consecutive patients with acute hepatitis B infection. However, we excluded one patient who had a malignant tumor, two patients with HIV, and one patient who consulted more than 56 days after the onset of disease symptoms. To evaluate the long-term effect, we further excluded 6 patients who underwent liver transplants, 6 patients who died, and 10 patients who were lost to follow up. Finally, 6 patients received neither NA nor SPT, 10 patients received NAM, and 15 patients received NA + SPT; we then compared the NAM group and the NA + SPT group (Figure 1).

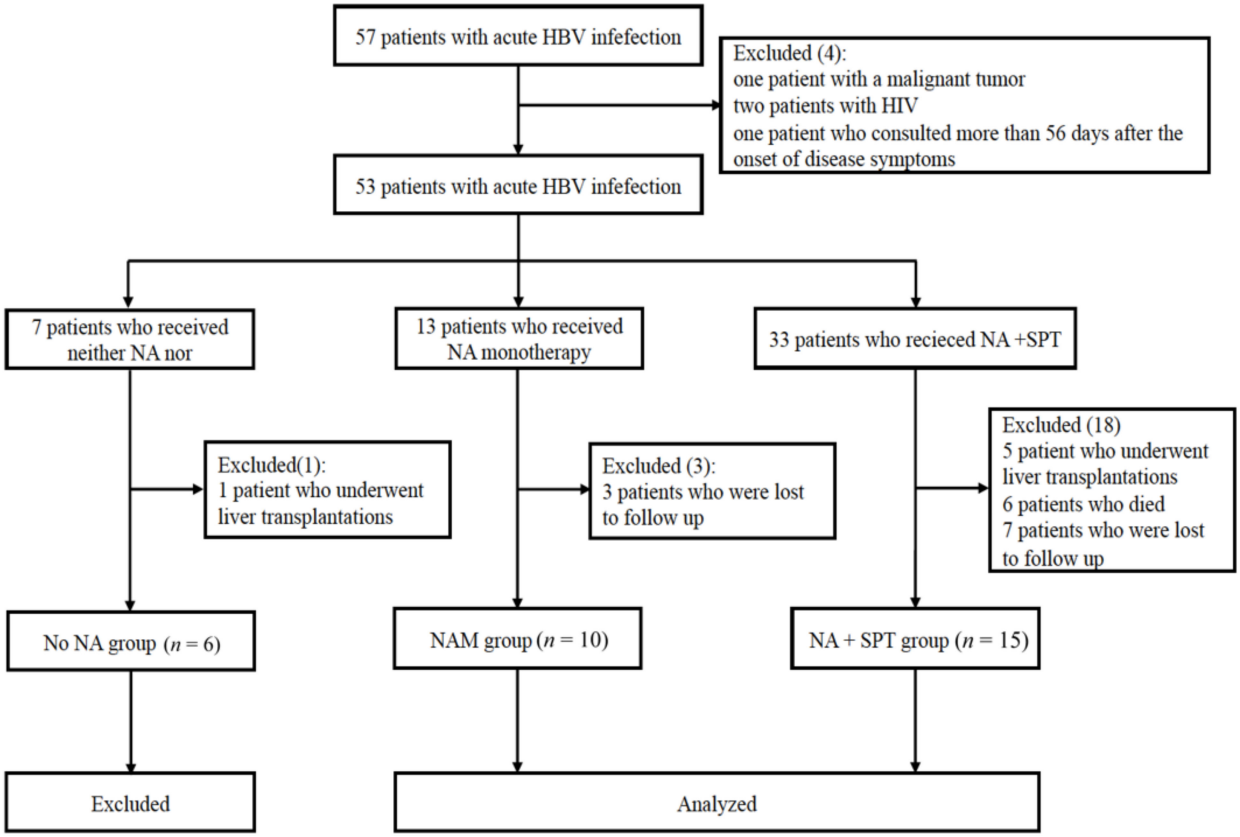

Figure 1. The flow diagram of the study.

2.2. Therapy

As antiviral therapy, lamivudine (LMV) or entecavir (ETV) was administered. As SPT, 1000 mg of methylprednisolone was administered for three days. As necessary, the patients received comprehensive supportive care, including plasma exchange, continuous hemodiafiltration (CHDF), and/or anticoagulant therapy, including recombinant thrombomodulin and anti-thrombin III (AT III).

2.3. Statistical Analysis

Data were analyzed using the JMP software package (version 15.1.0; SAS Institute, Inc., Cary, NC, USA). Continuous variables are expressed as median and interquartile range. Significant differences between groups were assessed using the unpaired Student's *t*-test, Fisher's exact test, the χ^2 test, or Cox proportional hazard model. A *p*-value of <0.05 was considered to be statistically significant, and a *p*-value of <0.10 was considered marginally significant.

3. Result

3.1. Subject Characteristics

Of the 53 patients with acute HBV infection, seven received neither NA nor SPT due to patient disagreement (no NA group), 13 received NAM (NAM group), and 33 received NA + SPT (NA+ SPT group). The proportion of patients who survived without LT in the no NA, NAM, and NA + SPT groups were 86% (6/7), 100% (13/13), and 66% (22/33), respectively (patients' profiles and characteristics are shown in Supplementary Table S1). Three patients in the NA + SPT group developed infectious complications. However, the infection was considered a consequence of ALF development and not an adverse effect of steroids because these patients presented severe ALF states before intervention. Because the severity differed in each group, we did not evaluate the therapeutic effect on survival in this study. To evaluate the effect on the HBV clearance of NA and SPT, we studied

25 patients who received NAM or NA + SPT and were followed up for a long time. Of the 25 patients, 10 received NAM and 15 received NA + SPT. Patients in the NA + SPT group presented more severe states of liver failure than those in the NAM group. Patients in the NA + SPT group showed higher proportions of ALF and levels of AST, ALT, and LDH compared to patients in the NAM group (Table 1).

Table 1. Characteristics of patients in the NAM and NA + SPT groups.

Factor	NAM Group (n = 10)	NA + SPT Group (n = 15)	p Value
Age (y.o.)	44.5 (32–58.5)	43 (36–54)	0.57
Gender (M/F)	7/3	7/8	0.41
WBC (/mL)	6035 (5397.5–9507.5)	5200 (4260–9170)	0.17
Hb (g/dL)	14.95 (13.2–15.5)	14.8 (12.3–15.8)	0.62
Plt (/μL)	16.7 (11–19.4)	11.3 (9.4–17.2)	0.24
Alb (g/dL)	3.6 (3.0–4.0)	3.7 (3.3–4.0)	0.71
T-Bil (mg/dL)	6.0 (1.3–10.9)	5.6 (3.6–7.8)	1
AST (IU/L)	1188 (547–4438)	3261 (1802–5080)	0.07
ALT (IU/L)	1562 (1014–7700)	3868 (2981–5421)	0.07
LDH (IU/L)	560 (407–1753)	1512 (825–3180)	0.049
γ-GTP (IU/L)	181 (119–279.5)	146 (82–273)	0.7
ALP (IU/L)	609 (371–685))	466 (393–790)	0.88
BUN (mg/dL)	8 (7–17)	9 (5–14)	0.63
Cre (mg/dL)	0.71 (0.58–0.86)	0.63 (0.46–0.77)	0.45
CRP (mg/dL)	0.74 (0.4–2.2)	2.1 (0.5–6.6)	0.13
PT%	45 (31.8–90.2)	40 (25–49)	0.28
APTT	38.8 (34.4–47.1)	41.3 (37.2–43.4)	0.85
ATIII	66 (43–101)	67 (45–74)	0.95
NH3	51 (35–60)	69 (35–166)	0.17
Ferrtin	2388 (1028–6371)	8813 (384–13545)	0.33
AFP	5 (3.0–14.3)	2.8 (1.7–3.6)	0.078
MELD score	20 (11–24)	19 (16–26)	0.37
Type of disease			
ALI	5	1	
ALF without coma	5	11	
ALF with coma	0	3	
Proportion of ALF	50%	93%	0.023
Therapy			
Plasma exchange (Y/N)	6/4 (60%)	13/2 (87%)	0.17
CHDF (Y/N)	1/9 (10%)	2/13 (13%)	1
Anticoagulant (Y/N)	5/5 (50%)	12/3 (80%)	0.19

Data are expressed as median and interquartile range. WBC: white blood cell, Hb: hemoglobin, Plt: platelet, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ-GTP: gamma-glutamyl transpeptidase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein, PT%: prothrombin activity percentage, APTT: activated partial thromboplastin time, ATIII: antithrombin III, AFP: alpha-fetoprotein, MELD: model for end-stage liver disease, ALI: acute liver injury, ALF: acute liver failure, CHDF: continuous hemodiafiltration.

3.2. The Short-Term Effect of NA + SPT

In both the NAM and the NA + SPT groups, a significant decrease in alanine aminotransferase (ALT) levels and an increase in prothrombin activity percentage (PT%) were observed over time (Figure 2A,B). In the NA + SPT group, the decrease in ALT levels and the increase in PT% tended to be greater than in the NAM group; however, the differences were not statistically significant (decrease in ALT levels: NAM group vs. NA + SPT group: 533 (81–4036) IU/L vs. 2970 (1770–4429) IU/L, p = 0.24, increase of PT%: NAM group vs. NA + SPT group: 23 (1–46)% vs. 39 (31–45)%, p = 0.2888, Figure 2C,D).

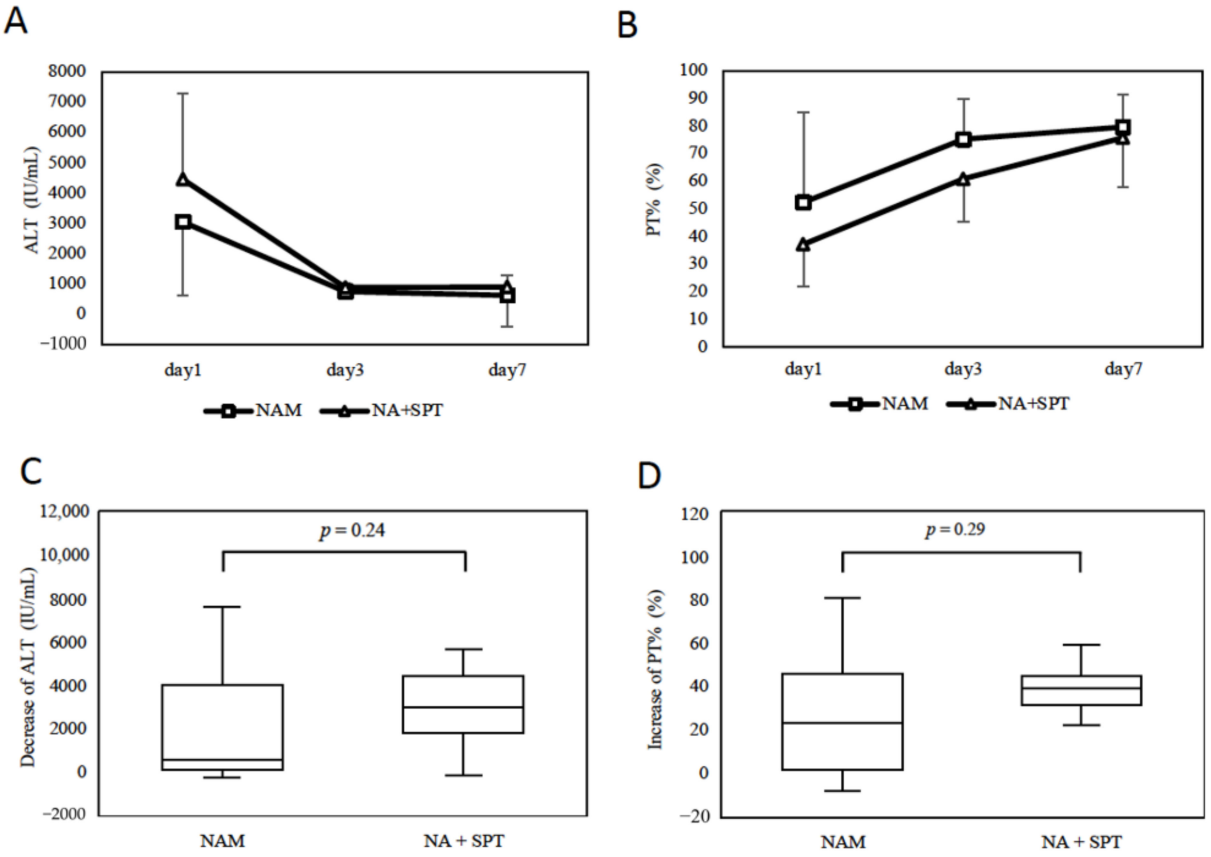

Figure 2. The short-term effect of NA +SPT. (**A**) Changes in ALT values in patients of the NAM and NA + SPT groups. (**B**) Changes in PT% in patients in the NAM and NA + SPT groups. (**C**) Comparison of the decrease in ALT values between the NAM and NA + SPT groups. (**D**) Comparison of the increase in PT% between the NAM and NA + SPT groups.

3.3. NA + SPT Efficiently Accelerates HBV Elimination

To evaluate the effect on HBV clearance, we evaluated the hepatitis B surface antigen (HBsAg) and HBV-DNA. HBV-DNA decreased over time in both groups (Figure 3A). In the NA + SPT group, the decline in HBV-DNA at eight weeks after the start of treatment was significantly greater than that in the NAM group (NAM group vs. NA + SPT group: 3.66 (1.86–5.65) logIU/mL vs. 5.04 (4.53–6.78) logIU/mL, $p = 0.0412$, Figure 3B). Moreover, the time required for the clearance of HBsAg and HBV-DNA was significantly shorter in the NA + SPT group than in the NAM group (HBsAg: NAM group vs. NA + SPT group: 76 (43–116) days vs. 26 (14–51) days, $p = 0.0418$, HBV-DNA: NAM group vs. NA + SPT group: 180 (83.5–220) days vs. 69 (43–136) days, $p = 0.0420$, Figure 3C,D). The hazard ratio of NA + SPT for the clearance of HBsAg and HBV-DNA were 0.45 (0.19–1.09) and 0.35 (0.14–0.89), respectively. Intention-to-treat analysis, including the eliminated patients, revealed that the clearance of HBsAg and HBV-DNA was significantly shorter in the NA + SPT group than in the NAM group ($p = 0.0468$ and 0.0418, respectively). Because it is possible for the severity of liver damage to affect HBV elimination, we performed the same comparison only in the patients with ALF without hepatic coma. In these cases, 5 patients received NAM whereas 11 patients received NA + SPT. No significant differences in profile and baseline characteristics were found between these two groups except for activated partial thromboplastin time (APTT) (Supplementary Table S2). Although the differences we found were not statistically significant due to the small sample size, the time required for the clearance of HBsAg and HBV-DNA tended to be shorter in the NA + SPT group than in the NAM group (HBsAg: NAM group vs. NA + SPT group: 72 (13–86) days vs.

40 (18–67) days, $p = 0.66$, HBV-DNA: NAM group vs. NA + SPT group: 146 (73–235) vs. 83 (59–156), $p = 0.2213$, Supplementary Figure S1A,B).

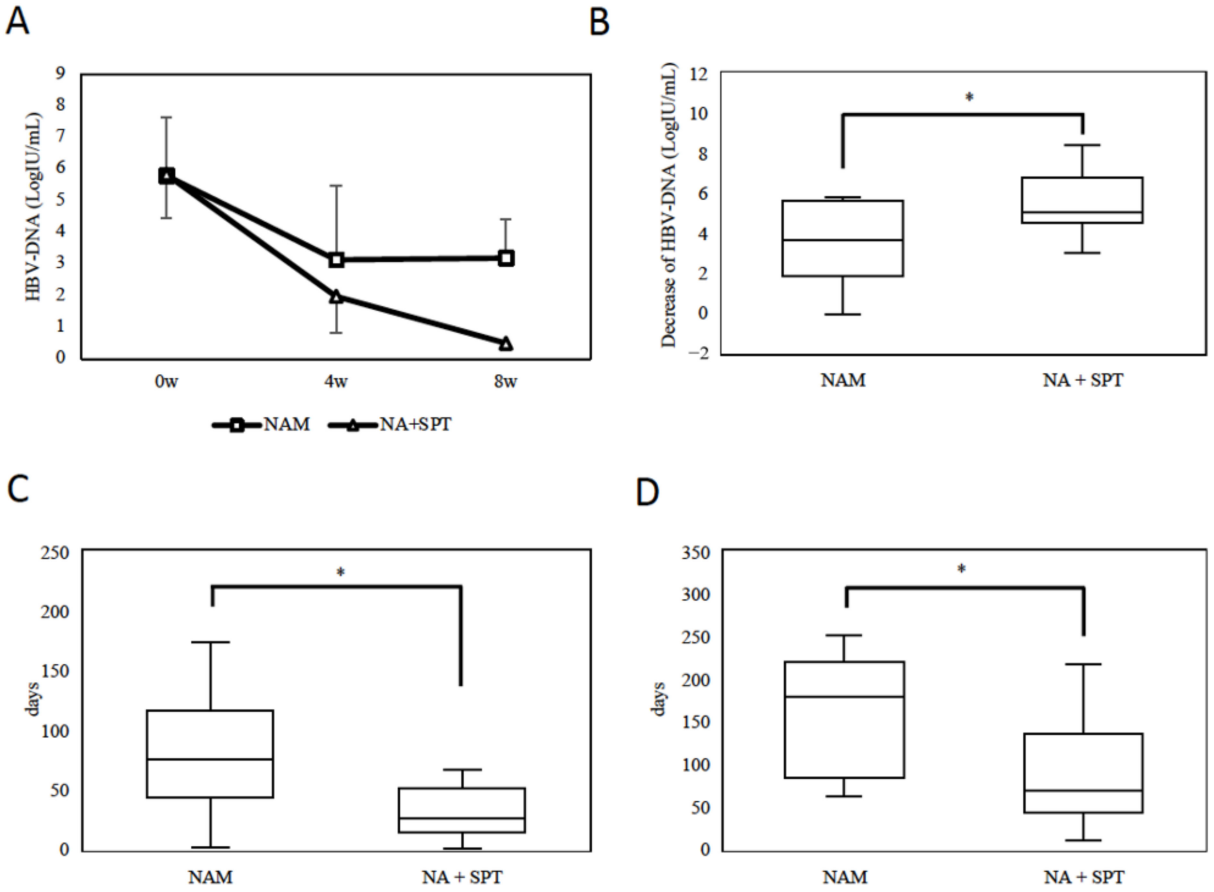

Figure 3. The antiviral effect of NA +SPT. (**A**) Changes in HBV-DNA levels in the NAM and NA + SPT groups. (**B**) Comparison of the decrease in HBV-DNA over 8 weeks. (**C**) Comparison of the time until clearance of HBsAg between the NAM and NA + SPT groups. (**D**) Comparison of the time until clearance of HBV-DNA between the NAM and NA + SPT groups. *: $p < 0.05$.

4. Discussion

In this study, we investigated the efficacy of the combination of NA and SPT for acute HBV infection. Because of the difference in severity, we could not evaluate the effect of NA + SPT on survival benefits. Serum ALT level is a surrogate marker of hepatocyte damage because it is markedly elevated during hepatocyte destruction [13]. PT% is a sensitive marker of hepatic synthetic ability and is used to determine the severity of coagulopathy in patients with ALF [14]. Although the differences were not statistically significant, the greater decrease in ALT and increase in PT in the NA + SPT group than in the NAM group might suggest the therapeutic effect of NA + SPT on the inhibition of liver inflammation and the improvement of liver function. Because the negative studies of steroids for ALF were carried out in the 1970s, it is possible that the appropriate management for the adverse effects of corticosteroids such as the use of proton pump inhibitors and antibacterial agents was not provided, the etiology of ALF was variable, and the corticosteroids were administered in a non-uniform fashion, e.g., variable doses, time, periods, and timing, in these previous studies. Recent studies have indicated that the use of corticosteroids may have therapeutic effects on viral ALF in the early stages [9,10]. However, particularly in HBV infection, because it is reported that corticosteroids stimulate HBV gene expression [15,16], there is serious concern that the use of corticosteroids prolongs the duration of HBV infection and promotes progression to chronic HBV infection. In fact, anti-inflammatory

treatment, including steroids for acute HBV infection, was reported to promote persistent HBV infection [17]. Recently, Fujiwara et al. reported that the combination of NA and corticosteroids induced rapid resolution of inflammation in HBV ALF [11]. They showed that all patients receiving NA + corticosteroid therapy achieved HBsAg seroconversion and also highlighted the possibility that corticosteroids did not affect HBV clearance. Nevertheless, because they examined only six patients whom they could follow up for a long time, it remains unclear whether corticosteroid therapy affects HBV clearance. Here, although our study had some limitations (e.g., retrospective, observational study, small sample size, unbalanced groups, massive loss of follow-up from the intervention group), we showed that the NA + SPT combination significantly shortened the time required for HBsAg and HBV-DNA clearance. NA alone was considered to have mild HBV elimination power. However, especially in the presence of corticosteroids, NA might play an important role in the control of HBV replication. We have considered that NA inhibition of HBV replication and SPT-induced resolution of innate immune system in the liver synergistically led to rapid HBV elimination.

Taken together, the NA + SPT combination could shorten the time to clearance without any adverse effects of SPT. These findings support the use of the NA + SPT combination for acute HBV infection without the concern of persistent HBV infection. However, we need more valid studies, including randomized controlled trials with larger samples, in order to demonstrate the effect of NA + SPT on acute HBV infection.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/gastroent13010001/s1, Table S1: Characteristics of patients in the no NA, NAM, and NA + SPT groups.; Table S2: Characteristics of non-comatose ALF patients in the NAM and NA + SPT groups. Figure S1: The antiviral effect of NA +SPT on non-comatose ALF patients.

Author Contributions: T.G., T.K., M.K. (Motoyuki Kohjima), M.T. (Masatake Tanaka), M.K. (Masaki Kato), and Y.O. designed this study. M.K. (Motoyuki Kohjima), M.K. (Miho Kurokawa), T.A., M.T. (Motoi Takahashi), K.I., S.T. and H.S. conducted the data analyses. M.K. (Motoyuki Kohjima), M.T. (Masatake Tanaka) and Y.O. contributed to the analysis and interpretation of the data. M.K. (Motoyuki Kohjima), M.T. (Masatake Tanaka) and Y.O. assisted in the preparation of the manuscript and critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported in part by the Takeda Science Foundation, Smoking Research Foundation, and JSPS KAKENHI (Grant Numbers: JP17K09430, JP18H05039, JP19H01054, JP19K17496, JP20K22877, and JP20H04949).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Kyushu University Hospital (No.27-377 and 28-432).

Informed Consent Statement: This study was approved by the Ethics Committee of Kyushu University Hospital and the requirement for written informed consent was waived because of the retrospective study design.

Data Availability Statement: The data collected and/or analyzed during this current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. World Health Organization. Hepatitis, B. 2021. Available online: http://www.who.int/news-room/fact-sheets/detail/hepatitis-b (accessed on 9 December 2021).
2. Sato, M.; Tateishi, R.; Yasunaga, H.; Horiguchi, H.; Yoshida, H.; Matsuda, S.; Fushimi, K.; Koike, K. Acute liver disease in Japan: A nationwide analysis of the Japanese Diagnosis Procedure Combination database. *J. Gastroenterol.* **2014**, *49*, 547–554. [CrossRef] [PubMed]

3. Tillmann, H.L.; Hadem, J.; Leifeld, L.; Zachou, K.; Canbay, A.; Eisenbach, C.; Graziadei, I.; Encke, J.; Schmidt, H.; Vogel, W.; 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. [CrossRef] [PubMed]
4. Yu, J.-W.; Sun, L.-J.; Zhao, Y.-H.; Kang, P.; Li, S.-C. The Study of Efficacy of Lamivudine in Patients with Severe Acute Hepatitis, B. *Dig. Dis. Sci.* **2010**, *55*, 775–783. [CrossRef] [PubMed]
5. Ito, K.; Yotsuyanagi, H.; Yatsuhashi, H.; Karino, Y.; Takikawa, Y.; Saito, T.; Arase, Y.; Imazeki, F.; Kurosaki, M.; Umemura, T.; et al. Risk factors for long-term persistence of serum hepatitis B surface antigen following acute hepatitis B virus infection in Japanese adults. *Hepatology* **2014**, *59*, 89–97. [CrossRef] [PubMed]
6. Coutinho, A.E.; Chapman, K.E. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol. Cell. Endocrinol.* **2011**, *335*, 2–13. [CrossRef] [PubMed]
7. Gregory, P.B.; Knauer, C.M.; Kempson, R.L.; Miller, R. Steroid therapy in severe viral hepatitis. A double-blind, randomized trial of methyl-prednisolone versus placebo. *N. Engl. J. Med.* **1976**, *294*, 681–687. [CrossRef] [PubMed]
8. European Association for the Study of the Liver. Randomized trial of steroid therapy in acute liver failure: A report from the European Association for the Study of the Liver. *Gut* **1979**, *20*, 620–623. [CrossRef] [PubMed]
9. Zhao, B.; Zhang, H.-Y.; Xie, G.-J.; Liu, H.-M.; Chen, Q.; Li, R.-F.; You, J.-P.; Yang, S.; Mao, Q.; Zhang, X.-Q. Evaluation of the efficacy of steroid therapy on acute liver failure. *Exp. Ther. Med.* **2016**, *12*, 3121–3129. [CrossRef] [PubMed]
10. Fujiwara, K.; Yasui, S.; Yonemitsu, Y.; Mikata, R.; Arai, M.; Kanda, T.; Imazeki, F.; Oda, S.; Yokosuka, O. Efficacy of high-dose corticosteroid in the early stage of viral acute liver failure. *Hepatol. Res.* **2014**, *44*, 491–501. [CrossRef] [PubMed]
11. Fujiwara, K.; Yasui, S.; Haga, Y.; Haga, Y.; Nakamura, M.; Yonemitsu, Y.; Arai, M.; Kanda, T.; Oda, S.; Yokosuka, O.; et al. Early combination therapy with corticosteroid and nucleoside analog induces rapid resolution of inflammation in acute liver failure due to transient hepatitis B virus Infection. *Intern. Med.* **2018**, *57*, 1543–1552. [CrossRef] [PubMed]
12. Mochida, S.; Takikawa, Y.; Nakayama, N.; Oketani, M.; Naiki, T.; Yamagishi, Y.; Ichida, T.; Tsubouchi, H. Diagnostic criteria of acute liver failure: A report by the intractable hepato-biliary diseases study group of Japan. *Hepatol. Res.* **2011**, *41*, 805–812. [CrossRef] [PubMed]
13. Rueff, B.; Benhamou, J.P. Acute hepatic necrosis and fulminant hepatic failure. *Gut* **1973**, *14*, 805–815. [CrossRef] [PubMed]
14. Robert, A.; Chazouilleres, O. Prothrombin time in liver failure: Time, ratio, activity percentage, or international normalized ratio. *Hepatology* **1996**, *24*, 1392–1394. [CrossRef] [PubMed]
15. Tur-Kaspa, R.; Burk, R.D.; Shaul, Y.; Shafritz, D.A. Hepatitis B virus DNA contains a glucocorticoid-responsive element. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 1627–1631. [CrossRef] [PubMed]
16. Chou, C.-K.; Wang, L.-H.; Lin, H.-M.; Chi, C.-W. Glucocorticoid stimulates hepatitis B viral gene expression in cultured human hepatoma cells. *Hepatology* **1992**, *16*, 13–18. [CrossRef] [PubMed]
17. Kobayashi, M.; Arase, Y.; Ikeda, K.; Tsubota, A.; Suzuki, Y.; Saitoh, S.; Kobayashi, M.; Suzuki, F.; Akuta, N.; Someya, T.; et al. Viral genotypes and response to interferon in patients with acute prolonged hepatitis B virus infection of adulthood in Japan. *J. Med. Virol.* **2002**, *68*, 522–528. [CrossRef] [PubMed]