Table 4. Variables and points for simplified diagnostic criteria

Variable	Points non-severe ($n = 29$)	Severe ($n = 14$)	Fulminant ($n = 12$)
Autoantibodies[1]	1.2 ± 0.8	1.1 ± 0.8	1.6 ± 0.7
IgG[2]	1.0 ± 0.9	1.4 ± 0.9	1.8 ± 0.6
Liver histology[3]	0.6 ± 0.7	0.2 ± 0.4	0.1 ± 0.3
Absence of viral hepatitis[4]	1.8 ± 0.6	1.9 ± 0.5	2.0 ± 0.0

Values are mean ± SD or number.
[1]No statistical significance among the three groups.
[2]Significant difference ($P = 0.002$) between non-severe and fulminant by Welch's t-test.
[3]Significant difference between non-severe and severe by Welch's t-test ($P = 0.04$), and between non-severe and fulminant by Welch's t-test ($I = 0.003$).
[4]No statistical significance among the three groups.

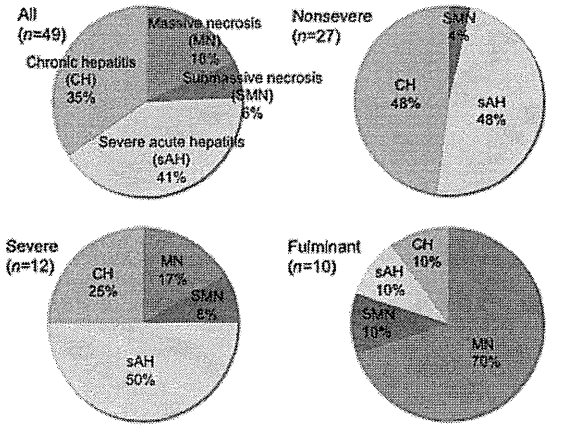

Fig. 1. Pathological characteristics of acute-onset autoimmune hepatitis patients.

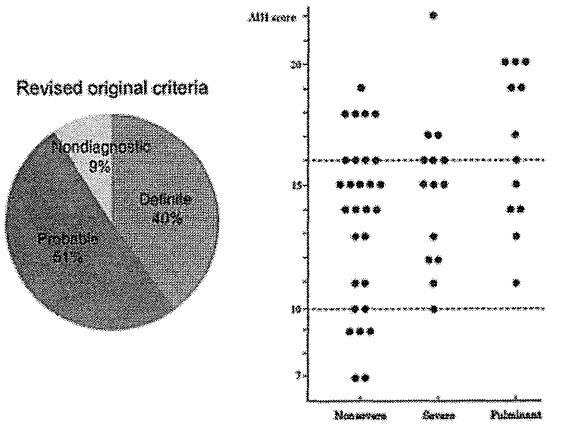

Fig. 2. Discrimination of acute-onset autoimmune hepatitis patients using the revised original scoring system.

The absence of viral hepatitis did not differ among non-severe, severe and fulminant patients (Table 4).

As described above, 32 patients showed acute hepatitis (14 of 27 non-severe patients, 9 of 12 severe ones and 9 of 10 fulminant ones). In these real acute-onset patients, the simplified score before treatment was 4.1 ± 1.5 and 3.6 ± 1.4 in non-severe ones, 3.8 ± 1.5 in severe ones and 5.2 ± 1.1 in fulminant ones respectively. None of the patients was diagnosed as 'definite' AIH, nine (28%) as 'probable' and 23 (72%) as 'non-diagnostic' (Tables 2 and 3).

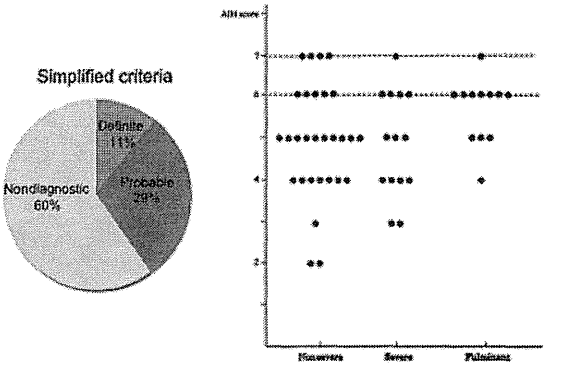

Fig. 3. Discrimination of acute-onset autoimmune hepatitis patients using the simplified scoring system.

We analysed 21 high-score patients whose scores were > 15 and diagnosed as 'definite' in revised original criteria. Six patients showed chronic hepatitis (acute on chronic) and 15 showed acute hepatitis (real acute onset: severe acute hepatitis, massive necrosis or submassive necrosis). In the simplified criteria, four (19%) were diagnosed as 'definite', seven (33%) as 'probable' and 10 (48%) as 'non-diagnostic'. In six acute on chronic patients, four (67%) were diagnosed as 'definite, one (17%) as 'probable and one (17%) as 'non-diagnostic'. In 15 real acute-onset patients, none was diagnosed as 'definite', six (40%) 'probable' and six (60%) 'non-diagnostic' (Fig. 4).

Regarding the specificity of the criteria, we cannot show it because we analysed only AIH patients and did not include non-AIH patients in this study.

Model of end-stage liver disease scores

The MELD scores at admission were 18.5 ± 7.9 (10–42) in severe and 26.3 ± 6.6 (18–37) in fulminant patients. The difference was significant ($P = 0.01$).

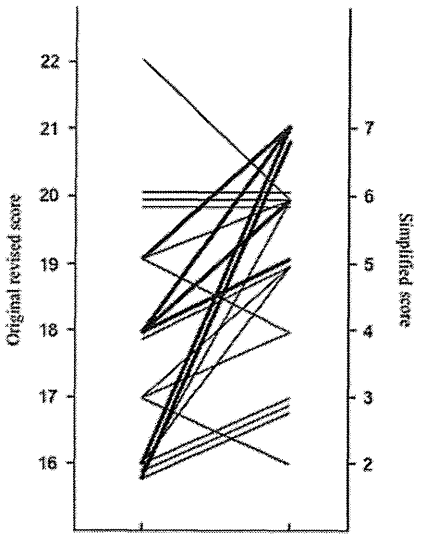

Fig. 4. Comparison of the scores by revised original criteria and simplified criteria in 21 patients whose scores were > 15 and diagnosed as 'definite' in revised original criteria. Thin solid and thick solid lines denote patients with histologically acute hepatitis and chronic hepatitits respectively.

Discussion

After the establishment of the criteria of the International AIH Group (8) and the recognition of acute-onset AIH (17), the diagnosis of acute-onset AIH was made. However, the diagnosis of AIH is challenging, and the diagnosis of acute-onset AIH is even more of a challenge. In the present study, we could diagnose > 90% of acute-onset AIH using the original scoring system, but only 40% by the simplified scoring system.

Acute-onset AIH patients often lack the typical features of AIH, and some patients have no autoantibodies and/or no hypergammaglobulinaemia. At present, they are being diagnosed as cryptogenic hepatitis. It was reported that severe acute and chronic cryptogenic hepatitis was similar to AIH in clinical, biochemical and histological features as well as responsiveness to immunosuppressive therapy, and that severe cryptogenic hepatitis patients might have an autoimmune liver disease with no identified immunoserological marker (18, 19). On the other hand, it was reported that autoantibodies were present in 30% of patients with acute liver failure, and that significantly higher international AIH scores were found in patients with cryptogenic disease as compared with those with other aetiologies, suggesting that it is difficult to evaluate whether primary autoimmune processes are responsible for the condition, although cryptogenic cases have features of autoimmune pathogenesis (20).

Thus, acute-onset AIH patients are at a risk of not being diagnosed and losing the timing for the initiation of immunosuppressive therapy. We have had 14 severe and 12 fulminant AIH patients between 2000 and 2009. Severe AIH patients were often resistant to immunosuppressive therapy in liver regeneration, and fulminant AIH patients were usually resistant to the therapy and showed a poor prognosis, with < 20% survival without liver transplantation (6, 11).

It was reported that severe and fulminant patients had higher titres of ANA and higher levels of IgG than non-severe patients (21, 22). In our present study, ANA negativity (< 1:40) was 11% in all patients, 31% in non-severe, 29% in severe and 8% in fulminant. The IgG level was normal in 31% of all patients, 41% of non-severe, 29% of severe and 8% of fulminant. Thus, our fulminant patients also had relatively higher titres of ANA ($P = 0.13$) and higher levels of IgG ($P = 0.01$) than non-severe patients, as described in previous reports. These findings suggested that the period of initial symptoms to the diagnosis of severe and fulminant hepatitis was occasionally longer than that of non-severe hepatitis (21, 22), but we observed that the duration from onset to admission to our unit was 43 days in all patients, with no statistically significant difference among non-severe, severe and fulminant patients. Patients with acute-onset AIH did not have severe disease at onset, progressing to severe and fulminant during the subacute clinical course without precise diagnosis and treatment. We speculate that this shows the heterogeneous nature of the progression of AIH, and that ANA titre and IgG level do not depend on the time duration but rather on the disease severity, based on our histological observation.

Our recent study of 28 severe and fulminant AIH showed that AIH with low PT activity had very severe and advanced histology (submassive to massive necrosis) and presented impaired hepatocellular regeneration that might be associated with resistance to immunosuppressive therapy, and that the difference in histological findings (massive necrosis, submassive necrosis, severe acute hepatitis and chronic hepatitis) did not depend on the timing of the histological examination (11).

In our previous study of 18 non-severe acute-onset AIH, liver histology showed severe activity with centrilobular necrosis in 95% of the patients, despite PT activity being maintained (10). The duration from onset to admission to our unit of these 18 patients was 32 days, while it was 43 days in the present study of 29 non-severe patients, with the differences not being significant among non-severe, severe and fulminant patients.

Regarding the scoring systems, Czaja (23) reported that the revised original system is useful for diagnosing patients with atypical features of AIH and that the simplified scoring system has superior specificity and predictability and can exclude diagnosis in diseases with concurrent immune manifestations, concluding that each system can support but not supercede the clinical diagnosis. Yeoman *et al.* (24) reported that the simplified criteria retain high specificity but exhibit lower sensitivity and that only 24% of fulminant AIH patients were

Liver International (2011)

diagnostic based on the simplified criteria, but 40% on the revised original criteria. Miyake *et al.* (25) reported that 77% of patients with acute presentation and 50% of those with histologically acute hepatitis were diagnostic based on the simplified criteria.

In our present study, 91% of acute-onset patients were diagnostic based on the revised original criteria, all of severe and fulminant, and 83% of non-severe patients. In contrast, only 40% of patients were diagnostic based on the simplified criteria, 67% fulminant, 36% severe and 31% non-severe. The simplified criteria include the titre of autoantibodies, level of IgG, liver histology and absence of viral hepatitis as variables. In acute-onset AIH patients, especially non-severe, the titre of autoantibodies and level of IgG were lower than those in chronic AIH, and liver histology often showed acute hepatitis, with the total points becoming lower as a result. Only 28% of patients with histologically acute hepatitis were diagnostic, 56% fulminant, 22% severe and 14% non-severe respectively. The revised original scoring system was found to perform better than the simplified scoring system in our patients with acute-onset AIH, as described in other reports.

In conclusion, it is very difficult to diagnose acute-onset AIH because of the lack of a gold standard. When we diagnose patients with acute-onset AIH, we should use the scoring system properly, the revised original scoring system rather than the simplified scoring system, after excluding other causes systematically. Multicentre studies are also needed to clarify the features of acute onset, especially severe and fulminant AIH, and to clearly define the standard for diagnosis.

Acknowledgments

We are indebted to all our colleagues at the liver unit of our hospital who cared for the patients described herein. This study was supported in part by a Health Labour Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan as a project by the Intractable Hepato-Biliary Disease Study Group of Japan.

Disclosures: All authors have nothing to disclose.

No conflicts of interest exist.

References

1. Czaja AJ. Autoimmune hepatitis: evolving concepts and treatment strategies. *Dig Dis Sci* 1995; **40**: 435–56.
2. Czaja AJ, Carpenter HA. Sensitivity, specificity and predictability of biopsy interpretations in chronic hepatitis. *Gastroenterology* 1993; **105**: 1824–32.
3. Fujiwara K, Mochida S, *et al.* Intractable Liver Diseases Study Group of Japan. Fulminant hepatitis and late onset hepatic failure in Japan. *Hepatol Res* 2008; **38**: 646–57.
4. Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. *Liver Transpl* 2008; **14**: S67–79.
5. Lee WM, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. *Hepatology* 2008; **47**: 1401–15.
6. Fujiwara K, Yasui S, Tawada A, *et al.* Autoimmune fulminant liver failure in adults. Experience in a Japanese center. *Hepatol Res* 2011; **41**: 133–41.
7. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. *Hepatology* 1993; **18**: 998–1005.
8. Alvarez F, Berg PA, Bianchi FB, *et al.* International Autoimmune Hepatitis Group report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; **31**: 929–38.
9. Hennes EM, Zeniya M, Czaja AJ, *et al.* Simplified diagnostic criteria for autoimmune hepatitis. *Hepatology* 2008; **48**: 169–76.
10. Fujiwara K, Fukuda Y, Yokosuka O. Precise histological evaluation of liver biopsy specimen is indispensable for diagnosis and treatment of acute onset autoimmune hepatitis. *J Gastroenterol* 2008; **43**: 951–8.
11. Yasui S, Fujiwara K, Yonemitsu Y, *et al.* Clinicopathological features of severe and fulminant forms of autoimmune hepatitis. *J Gastroenterol* 2011; **43**: 378–90.
12. Fujiwara K, Nakano M, Yasui S, *et al.* Advanced histology and impaired liver regeneration are associated with disease severity in acute onset autoimmune hepatitis. *Histopathology* 2011; **58**: 693–704.
13. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; **19**: 1513–20.
14. Kamath PS, Kim WR. The model of end-stage liver disease (MELD). *Hepatology* 2007; **45**: 797–805.
15. Dienes HP. Viral and autoimmune hepatitis. Morphologic and pathogenetic aspects of cell damage in hepatitis with potential chronicity. *Veroff Pathol* 1989; **132**: 1–107.
16. Meyer zum Büschenfelde KH, Dienes HP. Autoimmune hepatitis. Definition–classification–histopathology–immunopathogenesis. *Virchows Arch* 1996; **429**: 1–12.
17. Nikias GA, Batts KP, Czaja AJ. The nature and prognostic implications of autoimmune hepatitis with an acute presentation. *J Hepatol* 1994; **21**: 866–71.
18. Kaymakoglu S, Cakaloglu Y, Demir K, *et al.* Is severe cryptogenic chronic hepatitis similar to autoimmune hepatitis? *J Hepatol* 1998; **28**: 78–83.
19. Potthoff A, Deterding K, Trautwein C, *et al.* Steroid treatment for severe acute cryptogenic hepatitis. *Z Gastroenterol* 2007; **45**: 15–9.
20. Bernal W, Ma Y, Smith HM, *et al.* The significance of autoantibodies and immunoglobulins in acute liver failure: a cohort study. *J Hepatol* 2007; **47**: 664–70.
21. Tokumoto Y, Onji M. Acute-onset autoimmune hepatitis. *Intern Med* 2007; **46**: 1–2.
22. Singh R, Nair S, Farr G, Mason A, Perrillo R. Acute autoimmune hepatitis presenting with centrizonal liver disease: case report and review of the literature. *Am J Gastroenterol* 2002; **97**: 2670–3.
23. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. *Hepatology* 2008; **48**: 1540–8.

24. Yeoman AD, Westbrook RH, Al-Chalabi T, *et al.* Diagnostic value and utility of the simplified International Autoimmune Hepatitis Group (IAIHG) criteria in acute and chronic liver disease. *Hepatology* 2009; **50**: 538–45.

25. Miyake Y, Iwasaki Y, Kobashi H, *et al.* Clinical features of autoimmune hepatitis diagnosed based on simplified criteria of the International Autoimmune Hepatitis Group. *Dig Liver Dis* 2010; **42**: 210–5.

Liver International (2011)

staging the histological lesions. Am J Gastroenterol 1999;94: 2467-2474.
2. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al.; Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. HEPATOLOGY 2005;41:1313-1321.
3. Brunt E, Kleiner D, Wilson L, Belt P, Neuschwander-Tetri BA; NASH Clinical Research Network. The NAS and the histopathologic diagnosis in nonalcoholic steatohepatitis: Distinct clinicopathologic meanings. HEPATOLOGY 2011;53:810-820.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.24380
Potential conflict of interest: Nothing to report.

Efforts at Making the Diagnosis of Acute-Onset Autoimmune Hepatitis

To the Editor:

We read with great interest the article by Stravitz et al.,[1] who report that patients with indeterminate acute liver failure (ALF) often have features of autoimmune hepatitis (AIH) according to histological, serological, and clinical analyses. Fifty-eight percent of their patients with indeterminate ALF were diagnosed with probable AIH-ALF on the basis of pathological features, and they had higher serum globulin levels and higher levels of anti-nuclear antibodies, anti–smooth muscle antibodies, or both in comparison with patients without histological findings suggestive of probable AIH-ALF.

As hepatologists struggling against intractable liver diseases in Japan, we applaud their efforts at making the diagnosis of acute-onset AIH.

In past Japanese surveys of ALF, a specific etiology could not be identified in 30% to 40% of adult patients.[2] Since the establishment of the criteria of the International Autoimmune Hepatitis Group[3] and the recognition of acute-onset AIH, patients with autoimmune ALF have begun to be diagnosed.[4] However, in the early stages of their illness, they often demonstrate a histological pattern atypical for AIH that consists of centrilobular necrosis with or without portal changes.[5-7]

Recently, we have also reported that AIH is not a rare cause of ALF in our unit, and the number of patients with unknown causes could decrease according to the precise diagnosis of AIH, which is based on a combination of the aforementioned pathological features and the original revised criteria.[8] In our unit, AIH has been involved in 29% of ALF cases, and unknown causes have been involved in 12%; this means that in comparison with the results of a national survey, approximately half of our patients with unknown causes have been diagnosed with AIH-ALF.

In our recent studies,[7-10] the severity of acute-onset AIH was not high at its onset in most patients, but some of them advanced to severe diseases without a precise diagnosis or treatment. For an early diagnosis, it is most important to exclude other causes systematically, to remember acute-onset AIH in the differential diagnosis, and then to apply the scoring system; comprehensive evaluations of clinical, biochemical, radiological, and histological features are necessary. In particular, a precise pathological evaluation plays an important role in the differential diagnosis, as the authors describe. However, this is complicated by the fact that there is still no gold standard for making the diagnosis of acute-onset AIH, as the authors repeatedly note.

We believe that one of the pathological characteristics of acute-onset AIH is its histological heterogeneity, especially in severe and fulminant AIH. Histological heterogeneity leads to radiological heterogeneity. Unenhanced computed tomography often shows hypoattenuated and hyperattenuated areas, with the former reflecting massive hepatic necrosis and the latter reflecting regenerative islands. Ultrasound shows similar heterogeneity. Histological heterogeneity also leads to clinical heterogeneity. The time from onset to admission to our unit did not differ with the clinical severity (nonsevere, severe, or fulminant), and the time from onset to histological examination did not differ with the histological features (chronic hepatitis, severe acute hepatitis, or massive/submassive necrosis; Fig. 1).

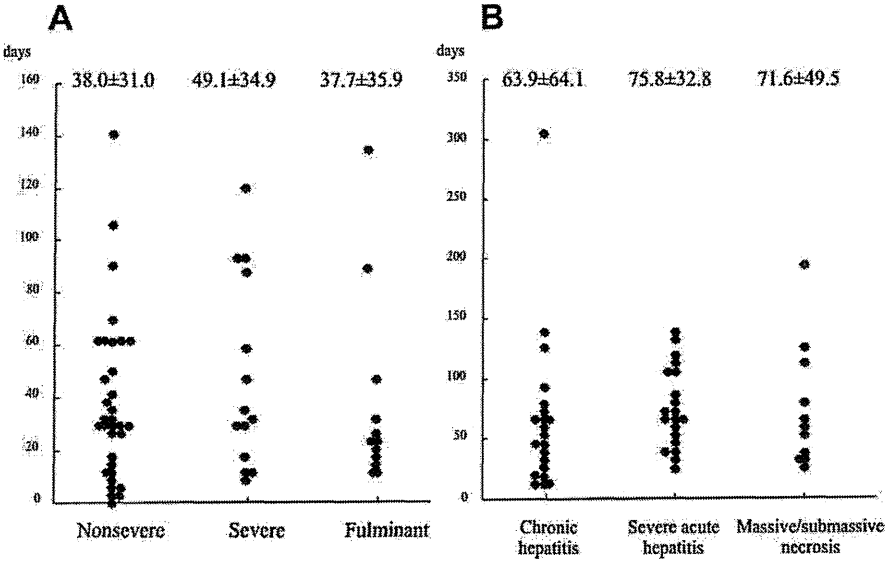

Fig. 1. Associations between (A) the clinical severity and the time from onset to admission and (B) the histological features and the time from onset to histological examination.

Characteristic morphological patterns of liver necrosis and regeneration should exist in patients with acute-onset AIH, and a better understanding of these patterns would be helpful in making the diagnosis.

KEIICHI FUJIWARA, M.D.
SHIN YASUI, M.D.
OSAMU YOKOSUKA, M.D.
Department of Medicine and Clinical Oncology
Graduate School of Medicine, Chiba University, Chiba, Japan

References

1. Stravitz RT, Lefkowitch JH, Fontana RJ, Gershwin ME, Leung PS, Sterling RK, et al., for Acute Liver Failure Study Group. Autoimmune acute liver failure: proposed clinical and histological criteria. HEPATOLOGY 2011;53:517-526.
2. Fujiwara K, Mochida S, Matsui A, Nakayama N, Nagoshi S, Toda G, for Intractable Liver Diseases Study Group of Japan. Fulminant hepatitis and late onset hepatic failure in Japan. Hepatol Res 2008;38:646-657.
3. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-938.
4. Kessler WR, Cummings OW, Eckert G, Chalasani N, Lumeng L, Kwo PY. Fulminant hepatic failure as the initial presentation of acute autoimmune hepatitis. Clin Gastroenterol Hepatol 2004;2: 625-631.
5. Misdraji J, Thiim M, Graeme-Cook FM. Autoimmune hepatitis with centrilobular necrosis. Am J Surg Pathol 2004;28:471-478.
6. Abe M, Onji M, Kawai-Ninomiya K, Michitaka K, Matsuura B, Hiasa Y, et al. Clinicopathologic features of the severe form of acute type 1 autoimmune hepatitis. Clin Gastroenterol Hepatol 2007;5:255-258.
7. Fujiwara K, Fukuda Y, Yokosuka O. Precise histological evaluation of liver biopsy specimen is indispensable for diagnosis and treatment of acute-onset autoimmune hepatitis. J Gastroenterol 2008;43:951-958.
8. Fujiwara K, Yasui S, Tawada A, Okitsu K, Yonemitsu Y, Chiba T, et al. Autoimmune fulminant liver failure in adults: experience in a Japanese center. Hepatol Res 2011;41:133-141.
9. Fujiwara K, Nakano M, Yasui S, Okitsu K, Yonemitsu Y, Yokosuka O. Advanced histology and impaired liver regeneration are associated with disease severity in acute onset autoimmune hepatitis. Histopathology; doi:10.1111/j.1365–2559.2011.03790.x.
10. Yasui S, Fujiwara K, Yonemitsu Y, Oda S, Nakano M, Yokosuka O. Clinicopathological features of severe and fulminant forms of autoimmune hepatitis. J Gastroenterol 2011;46:378-390.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.24331
Potential conflict of interest: Nothing to report.

Autoimmune Acute Liver Failure

To the Editor:

We read with great interest the article entitled "Autoimmune Acute Liver Failure: Proposed Clinical and Histological Criteria" by Stravitz et al.[1]

Our reading of this article has given rise to several comments. It is necessary to be very cautious when one is ranking histological features first in the diagnosis and management of severe forms of autoimmune disease; during their study, Stravitz et al.[1] examined liver biopsy samples from 72 of 204 patients (i.e., 35% of the total cohort). However, the use of different liver biopsy techniques, such as transjugular liver biopsy, native liver biopsy, and postmortem biopsy, may have induced variations in the histological patterns. Centrilobular necrosis (CN), which corresponds to massive hepatic necrosis type 1 in this study, is an important but infrequent histopathological pattern of autoimmune hepatitis; centrilobular necrosis with sparing of the portal tracts was present in 3.5% of the cases reported by Hofer et al.[2] This particular pattern is of crucial importance because it may be indicative of an early stage of the disease. For the series described by Stravitz et al., it would be interesting to have a description of the phenotype and, more specifically, the prognosis of the patients with isolated centrilobular necrosis. The fact that the centrilobular zone is damaged during an early stage by the immune process is intriguing and suggests that specific autoantigens in this area could be presented to the immune system early during the course of liver disease. Clearly, the identification of these potential targets during an initial phase of the disease would be of considerable interest. In addition, it is unfortunate that the identification of a pattern typical of severe autoimmune hepatitis (AIH) is based only on this experience; in several reports, researchers have attempted to describe this entity, and experiences besides those of the US Acute Liver Failure Study Group should be cited.[3-6] In particular, the characteristics of the patients may differ between the studies. In our cohort, 8 of 16 patients (50%) suffered from grade 3/4 encephalopathy,[3] whereas 26 of 72 patients (39%) in Stravitz et al.'s study did.

The most important and problematic issue in the management of severe autoimmune liver disease is corticosteroid therapy. Of course, if a response to corticosteroid therapy is an important argument in favor of an autoimmune process, it is important that any decision to administer this therapy be balanced against the high potential risk of sepsis; infections occurred in 5 of 12 patients (42%) during steroid therapy in our study.[3] If treatment failure seems to be predicted by changes in the Model for End-Stage Liver Disease–Sodium score and the UK Model for End-Stage Liver Disease score on day 7,[7] specific scores on entry must be defined for making decisions about the administration of steroid therapy.

JEAN-CHARLES DUCLOS-VALLÉE, M.D., PH.D.[1,2,3]
PHILIPPE ICHAI, M.D.[1,2,3]
DIDIER SAMUEL, M.D., PH.D.[1,2,3]
[1]*Centre Hépato-Biliaire*
Hôpital Paul Brousse
Assistance Publique–Hôpitaux de Paris
Villejuif, France
[2]*Unité Mixte de Recherche en Santé 785*
Université Paris-Sud
Villejuif, France
[3]*Unité 785*
Institut National de la Santé et de la Recherche Médicale
Villejuif, France

References

1. Stravitz RT, Lefkowitch JH, Fontana RJ, Gershwin ME, Leung PSC, Sterling RK, et al. Autoimmune acute liver failure: proposed clinical and histological criteria. HEPATOLOGY 2011;53:517-526.
2. Hofer H, Oesterreicher C, Wrba F, Ferenci, Penner E. Centrilobular necrosis in autoimmune hepatitis: a histological feature associated with acute clinical presentation. J Clin Pathol 2006;59:246-249.

Dig Dis Sci (2011) 56:3638–3647
DOI 10.1007/s10620-011-1789-5

ORIGINAL ARTICLE

Efficacy of Intravenous Glycyrrhizin in the Early Stage of Acute Onset Autoimmune Hepatitis

Shin Yasui · Keiichi Fujiwara · Akinobu Tawada · Yoshihiro Fukuda · Masayuki Nakano · Osamu Yokosuka

Received: 22 April 2011 / Accepted: 2 June 2011 / Published online: 17 June 2011

Abstract
Background Acute onset autoimmune hepatitis (AIH) shows acute presentation like acute hepatitis and does not have typical clinicopathological features of AIH. There is no gold standard for making the diagnosis. Therefore, losing the timing of starting immunosuppressive therapy, some of the cases develop into severe or fulminant form and have poor prognosis.
Aims Our aim was to elucidate the efficacy of intravenous glycyrrhizin in decreasing alanine aminotransferase (ALT) level in the early stage of acute onset AIH.
Methods Thirty-one patients were defined as acute onset AIH based on our uniform criteria, and were enrolled in this study. We prospectively treated 17 patients with sufficient doses (100 ml/day) of intravenous glycyrrhizin (SNMC) at an early stage (SNMC group), and treated 14 patients of severe disease with intravenous glycyrrhizin and corticosteroids (CS) (SNMC + CS group). We examined their clinical and biochemical features and treatment responses.
Results The ALT level could be controlled at an early stage using SNMC with no significant difference compared with SNMC + CS, and responsiveness to the therapy was determined by the disease severity at the time of starting therapy rather than the time duration from onset to therapy. Recovery rate was higher in the SNMC group than in the SNMC + CS group ($P = 0.035$).
Conclusions The early introduction of sufficient doses of SNMC might prevent disease progression in patients with acute onset AIH. SNMC can be used safely and be useful for patients with difficult-to-diagnose acute liver disease as an 'initial' treatment tool to improve liver inflammation before starting disease-specific treatments.

Keywords Autoimmune hepatitis · Acute onset · Intravenous glycyrrhizin · Disease severity

Abbreviations

AIH	Autoimmune hepatitis
SNMC	Stronger Neo-Minophagen C
CS	Corticosteroid

Introduction

Autoimmune hepatitis (AIH) is an unresolving inflammation of the liver of unknown cause, and is characterized by the presence of interface hepatitis and plasma cell infiltration on histological examination, hypergammaglobulinemia and autoantibodies. A prospective study has indicated that as many as 40% of patients with untreated severe disease die within 6 months of diagnosis [1]. Cirrhosis develops in at least 40% of survivors [2]. An acute onset of illness and fulminant presentation is possible [3–7].

An AIH scoring system based on the clinicopathological features was proposed by the international AIH group in 1999 [8]. Although this scoring system has been used as a diagnostic tool, there have been unusual patients who do not

Shin Yasui and Keiichi Fujiwara have contributed equally to the study.

S. Yasui · K. Fujiwara (✉) · A. Tawada · Y. Fukuda · O. Yokosuka
Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
e-mail: fujiwara-cib@umin.ac.jp

M. Nakano
Department of Pathology, Tokyo Women's Medical University Yachiyo Medical Center, Chiba 276-8524, Japan

show typical features and do not fulfill the criteria. AIH with clinical features of acute hepatitis (acute onset AIH) is one of these conditions. The diagnosis of acute onset AIH has been difficult in that patients show acute presentation like acute hepatitis and may not have typical clinicopathological features of AIH. Some of them develop into severe or fulminant form, are at risk of losing the timing of starting immunosuppressive therapy, and are sometimes resistant to immunosuppressive therapy and have poor prognosis.

Glycyrrhizin, an aqueous extract of licorice root, has been used for more than 50 years in Japan as a treatment for various liver diseases, mainly chronic viral hepatitis [9, 10]. Intravenous glycyrrhizin significantly lowered alanine aminotransferase (ALT), and improved liver histology in chronic active hepatitis [11]. The efficacy of glycyrrhizin for chronic hepatitis is established in Japan, although its mechanism of action in hepatocytes has yet to be fully elucidated. On the other hand, its efficacy for acute liver diseases has not been well documented. The expected side effects associated with pseudoaldosteronism are usually minor and reversible. Therefore, intravenous glycyrrhizin will be of help for patients with difficult-to-diagnose acute liver disease whose ALT levels remain high if it is found to be effective for them.

In the present study, we prospectively treated patients with acute onset AIH with early administration of sufficient doses (100 ml/day) of intravenous glycyrrhizin in order to clarify the benefits and limitations of the effect of decreasing ALT level as an initial treatment tool for acute onset AIH, which is one of the acute liver diseases difficult to diagnose and therefore difficult to treat.

Patients and Methods

Patients

Thirty-one consecutive Japanese patients with acute onset AIH were admitted to our liver unit (Chiba University Hospital and related hospitals) between 2000 and 2009 and were studied prospectively.

A diagnosis of AIH was made based on the criteria defined by the International Autoimmune Hepatitis Group reaching the score for probable or definite AIH [8] with exclusion of other causes systematically. Eligibility criteria of acute onset AIH were as follows: (1) acute onset liver injury, (2) negativity for active viral markers such as hepatitis A, B and C viruses, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and herpes simplex virus (HSV) and drug-induced liver injury, toxic and metabolic disorders, and (3) no signs of chronicity on the basis of physical examination, laboratory data and abdominal ultrasound findings. Eligibility criteria of severe disease, in addition to the criteria described above, were as follows: prothrombin time (PT) activity less than 50% of control or total bilirubin level more than 20 mg/dl, and patients with a PT activity less than 40% of control and hepatic encephalopathy were defined as fulminant hepatitis (FH). Informed consent was obtained from all patients or appropriate family members. The work described in this manuscript have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Clinical, Biochemical, and Immunoserological Analysis

Data obtained from patients were as follows: sex; age at diagnosis; time of onset, severe disease and fulminant disease; complications; serum levels of alanine aminotransferase (ALT), total bilirubin (T-Bil), prothrombin time (PT) activity, immunoglobulin G (IgG), ANA, ASMA, liver kidney microsomal antibody-1 (LKM-1) and anti-mitochondrial antibody (AMA); types of therapy, and response to therapy; and outcome. They were also examined for any histories of recent exposure to drugs and chemical agents as well as heavy alcohol consumption (>50 g/day for >5 years). In acute onset AIH, early symptoms including fever, general malaise, fatigue, nausea, vomiting and right upper quadrant discomfort are frequently observed, so we defined the beginning of these symptoms as clinical onset.

Virological Analysis

Patients were examined for viral markers such as IgM anti-hepatitis A virus antibody (IgM-HA), IgM anti-HBc antibody (IgM-HBc), HBsAg, anti-HCV antibody, HCV RNA, IgM anti-EBV antibody (IgM-EBV), IgM anti-HSV antibody (IgM-HSV) and IgM anti-CMV antibody (IgM-CMV). None of the patients had clinical or laboratory evidence of acquired immune deficiency syndrome.

Histological Examinations

Histological examination was performed before the administration of corticosteroids, in the convalescent phase, or post-mortem. Three specialists reviewed the histopathological changes by evaluating the degrees of portal and lobular changes and plasma cell infiltrations on hematoxylin-eosin stained sections. In histologically chronic hepatitis, staging and grading were evaluated based on the classification of Desmet et al. [12].

Glycyrrhizin Therapy

The glycyrrhizin-containing herbal medicine Stronger Neo-Minophagen C (SNMC; Minophagen Pharmaceutical,

Tokyo, Japan) is used in the form of an i.v. solution and contains 0.2% glycyrrhizin, 0.1% cysteine and 2% glycine in physiological solution. It is made by dissolving glycyrrhizin (200 mg), cysteine (100 mg) and glycine (2 g) in 100 ml of physiological saline. A sufficient dose of SNMC was introduced at 100 ml daily [13], with the dosage and frequency being reduced gradually according to the improvement of ALT level, and finally tapered off.

Protocols for Treatment

Acute onset AIH patients were treated by the following protocols prospectively. Non-severe patients who did not fulfill eligibility criteria of severe disease "on admission to our unit" were administered glycyrrhizin injection monotherapy, and then corticosteroid (CS) was added after the histological diagnosis of AIH (SNMC-initiated group; Fig. 1a, b). This group includes those with severe disease who had been administered glycyrrhizin injection monotherapy for more than 2 weeks before they were referred to our unit, and CS was added on admission to our unit. Patients presenting with severe disease on admission to our unit received combination therapy with intravenous glycyrrhizin and CS (SNMC + CS-initiated group; Fig. 1c).

An initial dose of 20–60 mg prednisolone daily was administered. Patients with marked prolongation of PT were treated with 1,000 mg of methylprednisolone daily for 3 days followed by the prednisolone therapy.

Assessments of Outcome

The primary response parameter was the improvement of ALT during 4 weeks of the observation period. The secondary response parameters were clinical outcome (recovery or death) and the improvement of T-Bil, PT activity and IgG. Tolerability and side effects were also monitored.

Statistical Analysis

Differences in proportions among the groups were compared by Fisher's exact probability test, Student's *t* test and Welch's *t* test.

Results

Characteristics of Patients

Of the 31 patients, 8 were men and 23 women. Mean age at the time of diagnosis was 54.2 ± 13.7 years (Tables 1 and 2). Nineteen patients (61%) had primary complications and histories of medications, 6 with hypertension, 5 with diabetes mellitus, 3 with hyperlipidemia, 2 with hyperthyroidism, 2 with ischemic heart disease, 2 with bronchial asthma, 1 with rheumatoid arthritis, 1 with Hashimoto disease, 1 with manic depressive illness, 1 with multiple sclerosis, 1 with Sjögren syndrome, 1 with hypoventilation syndrome, 1 with hyperuricemia and 1 with glioma.

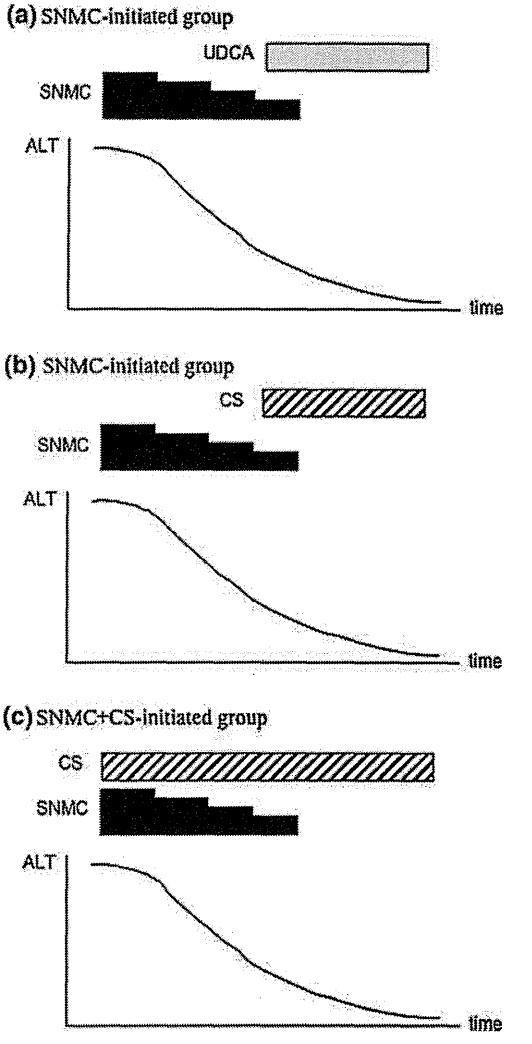

Fig. 1 Schemas of treatments. **a** *Intravenous glycirrhizin (SNMC)-initiated group*: in 4 patients, ALT levels remained normal with UDCA and without CS after SNMC was tapered off. **b** *SNMC-initiated group*: in 13 patients, CS was administered after the histological examinations, while SNMC was tapered off. **c** *SNMC + CS-initiated group*: in 14 patients, SNMC and CS were administered. *ALT* alanine aminotransferase, *SNMC* Stronger Neo-Minophagen C, *UDCA* ursodeoxycholic acid, *CS* corticosteroid

The clinical and biochemical features of all patients before initiating treatment were as follows. Mean ALT was 664 ± 488 IU/l, mean T-Bil 11.8 ± 10.3 mg/dl, and mean PT activity 59 ± 33%. Mean IgG was 2,350 ± 1,230 mg/dl. Yhe IgG level was normal (<1.0× upper normal value: UNV)

Table 1 Laboratory data of patients of SNMC group before initiating treatment

Patient	Age/sex	ALT (IU/l)	T-BIL (mg/dl)	PT (%)	IgG (mg/dl)	ANA (fold)	ASMA (fold)
1	65/M	628	0.9	90	4,980	320	40
2	51/F	255	0.7	91	1,480	160	<40
3	68/F	760	1.4	79	1,020	40	<40
4	54/F	942	4.3	77	1,510	<40	40
5	64/F	198	0.5	97	1,820	640	40
6	62/F	329	0.9	106	2,101	320	40
7	70/F	956	0.6	109	1,546	<40	<40
8	45/F	565	2.0	95	1,713	160	<40
9	68/M	1,080	11.5	48	1,880	80	ND
10	37/F	498	11.2	49	6,424	1,280	160
11	72/F	700	0.5	126	1,760	80	<40
12	33/F	597	0.7	83	1,300	80	40
13	56/F	132	13.4	54	1,960	40	ND
14	58/F	230	29.2	16	1,957	80	ND
15	45/F	1,398	8.1	91	5,870	320	160
16	54/F	744	10.1	112	1,789	320	<40
17	26/F	183	5.8	48	1,515	80	<40

ALT alanine aminotransferase, *T-Bil* total bilirubin, *PT* prothrombin time, *IgG* immunoglobulin G, *ANA* anti-nuclear antibody, *ASMA* anti-smooth muscle antibody

Table 2 Laboratory data of patients of SNMC + CS group before initiating treatment

Patient	Age/sex	ALT (IU/l)	T-BIL (mg/dl)	PT (%)	IgG (mg/dl)	ANA (fold)	ASMA (fold)
C1	64/M	1,998	19.4	40	2,377	640	<40
C2	71/F	1,530	14.8	25	1,990	40	<40
C3	72/F	964	21.9	45	2,295	80	<40
C4	33/F	751	13.2	55	1,522	80	<40
C5	23/F	508	7.8	33	5,427	160	<40
C6	52/M	329	32.6	34	1,274	80	<40
C7	49/F	1,865	23.6	29	2,868	1,280	40
C8	70/F	402	27.6	20	4,178	1,280	<40
C9	61/M	333	12.0	36	2,662	640	<40
C10	56/M	49	30.2	15	3,053	1,280	80
C11	51/M	513	2.0	48	1,870	80	40
C12	55/F	395	25.5	18	4,322	640	40
C13	39/F	424	16.7	49	1,249	40	<40
C14	56/M	355	17.7	28	2,123	80	<40

ALT alanine aminotransferase, *T-Bil* total bilirubin, *PT* prothrombin time, *IgG* immunoglobulin G, *ANA* anti-nuclear antibody, *ASMA* anti-smooth muscle antibody

in 9 of 31 (29%), 1.0–1.5× UNV in 13 (42%), 1.5–2.0× UNV in 5 (16%), and > 2.0× UNV in 4 (13%). ANA was positive (≥1:40) in 28 of 31 (90%) patients; <1: 40 in 2 (6%), 1: 40 in 4 (13%), 1: 80 in 10 (32%), and >1: 80 in 15 (48%). ASMA was positive (≥1:40) in 11 of 31 (35%). None was positive for LKM-1. One patient (#7) in the SNMC-initiated group was negative for both ANA and ASMA.

No patient was positive for HBs Ag and HCV Ab. In one patient (#4) with multiple sclerosis, onset was subsequent to the withdrawal of steroid pulse therapy. Although 61% of the patients had primary complications and histories of medications as described above, any possible hepatotoxic drugs were excluded on the basis of the drug-induced liver injury diagnostic scale of Maria and Victorino [14].

Table 3 Histological findings, treatment and outcome of SNMC group

Patient	Histology	AIH score (before treatment)	Duration from onset to SNMC (days)	Duration of SNMC Monotherapy (weeks)	Duration from SNMC to CS (days)	Loading dose of CS (PSL) (mg)	Outcome
1	CH (F2, severe)	16	8	>4			Recovery
2	CH (F3, severe)	10	10	>4			Recovery
3	CH (F2, severe)	15	5	>4			Recovery
4	CH (F3, severe)	15	1	>4			Recovery
5	CH (F2, severe)	18	1	>4	121	40	Recovery
6	AH, severe	14	90	>4	150	40	Recovery
7	AH, severe	10	25	>4	85	40	Recovery
8	AH, severe	18	2	>4	62	40	Recovery
9	CH (F4, severe)	12	9	>4	62	20	Recovery
10	AH, severe	16	35	>4	65	40	Recovery
11	AH, severe	13	2	4	30	30	Recovery
12	CH (F2, severe)	11	66	4	94	40	Recovery
13	CH (F3, severe)	10	150	4	176	40	Recovery
14	Massive necrosis	17	29	4			Death
15	CH (Fl, severe)	16	7	2	21	60	Recovery
16	AH, severe	18	28	2	42	40	Recovery
17	Massive necrosis	15	37	2	45	40	Recovery

CH chronic hepatitis, *AH* acute hepatitis, *AIH* autoimmune hepatitis, *SNMC* Stronger Neo-Minophagen C, *CS* corticosteroid, *PSL* prednisolone

Pathological Features

The pathological characteristics of the patients are summarized in Tables 3 and 4. Centrilobular necrosis and plasma cell accumulation in portal and centrilobular areas were characteristic for acute onset AIH.

In the SNMC-initiated group, all 17 patients showed severe activity, with 6 (35%) showing severe acute hepatitis, 2 (12%) massive necrosis, and 9 (53%) severe activity with fibrosis stage 2–4.

In the SNMC + CS-initiated group, liver histology was examined in 11 of 14 patients. Ten patients showed severe activity, with 3 (27%) showing severe acute hepatitis, 1 (9%) recovery phase from fulminant hepatitis, 5 (45%) massive necrosis, and 1 (9%) submassive necrosis. One (9%) showed moderate activity with fibrosis stage 2.

AIH Scoring System

The original revised scoring system (AIH score) proposed by the International Autoimmune Hepatitis Group [8] was used for all patients (Tables 3 and 4). Recently, the simplified scoring system were proposed by the same group [15], but the revised original scoring system performed better in patients with acute onset AIH than the simplified scoring system [16], therefore we used the former in this study.

The AIH score ranged from 10 to 22 (15.4 ± 3.2) before treatment. Fifteen (48%) of 31 were diagnosed as definite AIH, and 16 (52%) as probable. In the SNMC-initiated group, the AIH score ranged from 10 to 18 (14.4 ± 2.9) before treatment. Seven (41%) of 17 were diagnosed as definite AIH, and 10 (59%) as probable (Table 3). In the SNMC + CS-initiated group, the AIH score ranged from 11 to 22 (16.6 ± 3.3) before treatment. Eight of 14 (57%) were diagnosed as definite AIH and 6 (43%) as probable (Table 4).

Treatment and Response in SNMC-Initiated Group

Thirty-one patients with acute onset AIH were examined. All patients were treated with SNMC safely and side-effects associated with pseudoaldosteronism were minor and reversible. Among them, 17 patients underwent glycyrrhizin injection monotherapy for more than 2 weeks from the early stage of illness (SNMC-initiated group) (Table 3).

Four severe patients (#9, 10, 14, 17) were exceptionally included in the SNMC-initiated group. Patient #14 had fulminant hepatitis with marked prolonged PT and hyperbilirubinemia, and living donor-related liver transplantation was being considered. The other 3 had severe hepatitis with a difficulty of diagnosis of AIH without liver histology.

Duration from onset to the administration of SNMC was 30 ± 40 days. Fourteen patients received SNMC

Table 4 Histological findings, treatment and outcome of SNMC + CS group

Patient	Histology	AIH score (before treatment)	Duration from onset to SNMC + CS (days)	Type of CS	Loading dose of CS (mg)	Outcome
C1	CH (F2, moderate)	14	15	PSL	50	Recovery
C2	Massive necrosis	19	17	mPSL	1,000	Death
C3	AH, severe	18	18	mPSL	1,000	Recovery
C4	AH, severe	16	25	PSL	60	Recovery
C5	AH, severe	22	26	mPSL	1,000	Recovery
C6	Massive necrosis	13	30	mPSL	1,000	Death
C7	FH, recovery	20	35	mPSL	1,000	Recovery
C8	Massive necrosis	20	44	mPSL	500	Death
C9	ND	13	60	PSL	60	Recovery
C10	ND	11	60	PSL	60	Death
C11	ND	15	85	PSL	60	Recovery
C12	Massive necrosis	20	90	mPSL	1,000	Death
C13	Massive necrosis	16	121	PSL	60	Recovery
C14	Submassive necrosis	15	135	mPSL	1,000	Death

CH chronic hepatitis, *AH* acute hepatitis, *FH* fulminant hepatitis, *ND* not done, *AIH* autoimmune hepatitis, *SNMC* Stronger Neo-Minophagen C, *CS* corticosteroid, *PSL* prednisolone, *mPSL* methylprednisolone

monotherapy for more than 4 weeks, and 3 for 2 weeks. In 4 (24%) of the 17 patients, ALT levels remained normal with ursodeoxycholic acid (UDCA) and without CS after SNMC was tapered off (Fig. 1a). In the other 12 patients (except 1 with fulminant hepatitis waiting for liver transplantation), CS was administered after histological examinations, with SNMC being tapered off, and all showed a complete response (Fig. 1b). Duration from the start of administration of SNMC to that of CS was 79 ± 48 days.

Changes in ALT levels, T-Bil levels, PT activities and IgG levels during the first 4 weeks after the start of treatment are shown in Figs. 2a, b and 3a, b. ALT levels fell in all 17 patients during the course with statistical significance (Fig. 2a). In 7 (50%) of 14 patients receiving SNMC monotherapy for more than 4 weeks, ALT decreased to normal (<40 IU/l) within 4 weeks. The improvements of T-Bil levels, PT activities and IgG levels were not significant during 4 weeks (Figs. 2b and 3a, b). One with fulminant hepatitis died of hepatic failure and the others recovered.

Treatment and Response in SNMC + CS-Initiated Group

Of 31 patients, 14 presenting with advanced disease on admission to our unit received glycyrrhizin therapy in combination with corticosteroids (CS) (SNMC + CS-initiated group) (Table 4). Eight had fulminant hepatitis and 6 severe hepatitis.

Changes in ALT levels, T-Bil levels, PT activities and IgG levels during 4 weeks after the start of treatment are shown in Figs. 2c, d and 3c, d. ALT levels fell with statistical significance in all 14 patients between week 0 and week 2, and week 0 and week 4 (Fig. 2c). The improvements in T-Bil levels and PT activities were not significant during 4 weeks (Figs. 2d and 3c). IgG levels improved with statistical significance between week 0 and week 4, in contrast to the SNMC group (Fig. 3d).

Six of 8 fulminant hepatitis patients died of hepatic failure and the others recovered.

Comparison of Characteristics of Patients Between SNMC Monotherapy and SNMC and CS Combination Therapy

Differences in mean age, sex, mean ALT level, mean IgG level, ANA titer, AIH score and the duration from onset to the administration of SNMC were not statistically significant. Mean T-Bil level was higher and mean PT activity was lower in the SNMC + CS group than in the SNMC group ($P < 0.001$).

Liver histology showed 8 acute hepatitis and 9 chronic hepatitis in the SNMC group, and 10 acute hepatitis and 1 chronic hepatitis in the SNMC + CS group. The proportion of acute hepatitis was not different between the groups. Recovery rate was higher in the SNMC group than in the SNMC + CS group ($P = 0.035$) (Table 5).

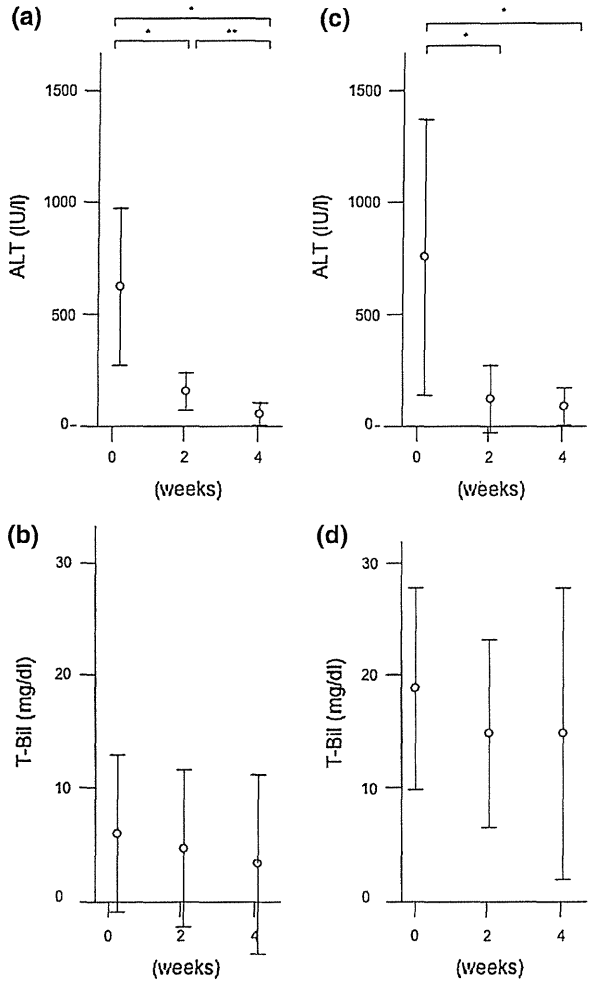

Fig. 2 **a** Alanine aminotransferase (*ALT*) levels and **b** total bilirubin (*T-Bil*) levels before, 2 weeks after and 4 weeks after the administration of Stronger Neo-Minophagen C (SNMC) in 17 patients of SNMC-initiated group. **c** *ALT* levels and **d** *T-Bil* levels before, 2 weeks after and 4 weeks after the administration of SNMC and CS in 14 patients of SNMC + CS-initiated group. **a** The mean level at each time point was 600 ± 359, 130 ± 120 and 62 ± 43 IU/l, respectively; $*P < 0.005$, $**P < 0.05$. **b** The mean level at each time point was 6.0 ± 7.5, 4.7 ± 7.2 and 3.6 ± 8.3 mg/dl, respectively; the differences were not statistically significant. **c** The mean level at each time point was 744 ± 615, 125 ± 148 and 79 ± 67 IU/l, respectively; $*P < 0.005$. **d** The mean level at each time point was 18.9 ± 8.7, 13.7 ± 8.9 and 14.1 ± 13.6 mg/dl, respectively; the differences were not statistically significant

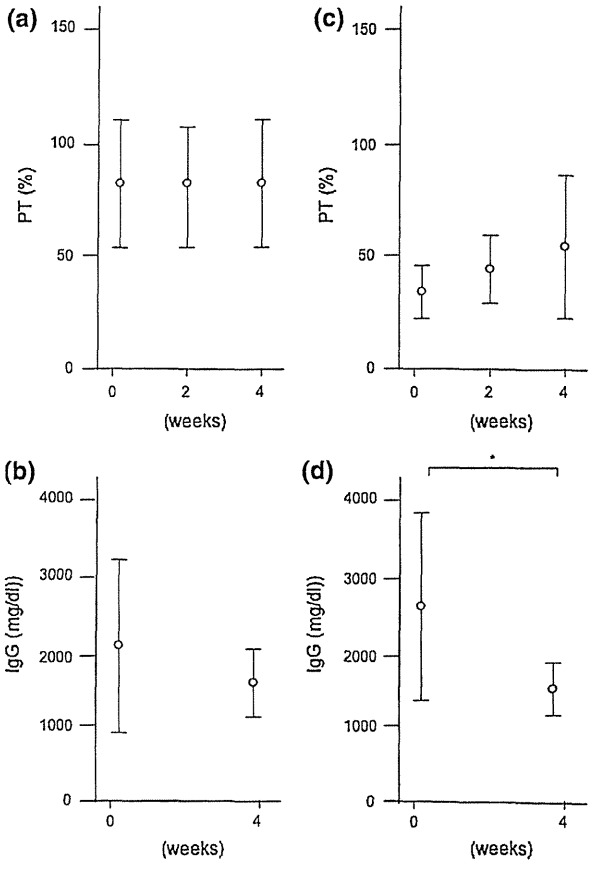

Fig. 3 **a** Prothrombin time (*PT*) activities before, 2 weeks after and 4 weeks after the administration of Stronger Neo-Minophagen C (SNMC), and **b** immunoglobulin G (*IgG*) levels before and 4 weeks after the administration of SNMC in 17 patients of SNMC-initiated group. **c** PT activities before, 2 weeks after and 4 weeks after the administration of SNMC and CS, and **d** *IgG* levels before and 4 weeks after the administration of SNMC and CS in 14 patients of SNMC + CS-initiated group. **a** The mean activity at each time point was 81 ± 29, 78 ± 26 and 83 ± 30%, respectively; the differences were not statistically significant. **b** The mean level at each time point was 2,096 ± 1,205 and 1,635 ± 463 mg/dl, respectively; the differences were not statistically significant. **c** The mean activity at each time point was 34 ± 13, 45 ± 17 and 52 ± 30%, respectively; the differences were not statistically significant. **d** The mean level at each time point was 2,658 ± 1,231 and 1,561 ± 385 mg/dl, respectively; $*P < 0.005$

Comparison of ALT Levels During 4 weeks Among Non-treatment Historical Controls, SNMC-Initiated, and SNMC + CS-Initiated Groups

We selected 8 patients (4 non-severe and 4 severe) who had ALT data without SNMC and/or CS therapies for 4 weeks as historical controls, and compared ALT levels during 4 weeks with SNMC and SNMC + CS groups. Changes in ALT levels during 4 weeks were not statistically significant in historical controls ($P = 0.10$) (Fig. 4). ALT levels at week 0 were not different among 3 groups. Those at week 4 were lower in SNMC and SNMC ± CS groups than in historical controls ($P = 0.009$ and $P = 0.01$, respectively). Therefore, SNMC was thought to be effective in decreasing ALT levels.

Table 5 Comparison of findings of patients between SNMC group and SNMC + CS group

	SNMC group	SNMC + CS group	*P* value
n	17	14	
Age[a]	54.6 ± 13.6[1]	53.7 ± 14.4[1]	0.85[1]
Sex (M/F)	2/15[2]	6/8[2]	0.058[2]
ALT (IU/l)[a]	600 ± 359[3]	744 ± 615[3]	0.48[3]
T-BIL (mg/dl)[a]	6.0 ± 7.5[4]	18.9 ± 8.7[4]	<0.001[4,*]
PT activity (%)[a]	81 ± 29[5]	34 ± 13[5]	<0.001[5,*]
IgG (mg/dl)[a]	2,096 ± 1,205[6]	2,658 ± 1231[6]	0.21[6]
ANA ≥ ×40	15[7]	14[7]	0.29[7]
AIH score*	14.4 ± 2.9[8]	16.6 ± 3.3[8]	0.058[8]
Duration from onset to treatment (days)[a]	30.0 ± 39.6[9]	54.1 ± 39.8[9]	0.10[9]
Histologically acute hepatitis	8[10]	10[10]	0.16[10]
Recovery	16[11]	8[11]	0.035[11,*]

1, 4, 6, 8, 9 by Student's *t* test

3, 5 by Welch's *t* test

2, 7, 10, 11 by Fisher's exact probability test

[a] Mean ± SD

* $P < 0.05$ was considered significant

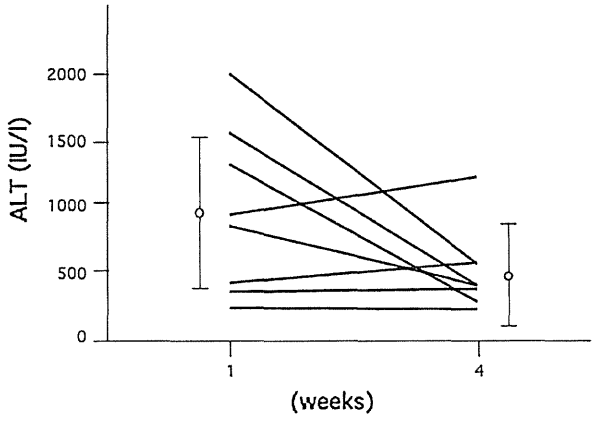

Fig. 4 Changes in alanine aminotransferase (*ALT*) levels during 4 weeks in 8 non-treatment historical controls. The mean level at week 0 and week 4 was 907 ± 625 and 455 ± 312 IU/l, respectively ($P = 0.10$)

Discussion

In this study, we showed that we could control the ALT level at an early stage of acute onset AIH by sufficient dose of intravenous glycyrrhizin without significant difference compared to combination therapy with intravenous glycyrrhizin and corticosteroid, and with significant difference compared to historical controls.

Glycyrrhizin is an aqueous extract of licorice root. Anti-inflammatory, anti-ulcerous and anti-viral effects of glycyrrhizin and glycyrrhizinic acid were reported from 1950s [17–19]. Experimental evidence has demonstrated that glycyrrhizin is hepatoprotective in vitro, probably by preventing changes in cell membrane permeability and providing membrane stabilization [20, 21]. It is suggested that glycyrrhizin possibly acts as a radical scavenger in the cytoplasm of hepatocytes, decreases cell membrane permeability and prevents membrane penetration of viral particles, although the precise mechanism is still to be elucidated [21].

Recently, the protective effects of glycyrrhizin have been investigated in animal models. Yang et al. reported that pre-treatment of intravenous glycyrrhizin (Stronger Neo-Minophagen C, SNMC) can effectively protect liver against fulminant hepatic failure induced by lipopolysaccharide (LPS)/D-galactosamine (D-Gal N) in mice, and that SNMC prevents hepatocyte apoptosis by inhibiting inflammatory reaction and stabilizing mitochondria membrane to suppress the release of cytochrome C and sequential activation of caspase-3 [22]. Ikeda et al. reported that glycyrrhizin inhibited the apoptosis of liver cells through the prevention of an IL-18-mediated inflammatory response in a caspase-independent manner in LPS/D-GalN-induced mouse liver injury [23].

In the clinical setting, SNMC has been used for the treatment of chronic viral hepatitis for more than 50 years in Japan. Yamamoto et al. first reported the efficacy of SNMC in patients with chronic hepatitis in 1958 [9], and Suzuki et al. confirmed the effect in a randomized, double-blind controlled trial [10]. It was reported that combined treatment with ursodeoxycholic acid and SNMC was effective for patients with chronic hepatitis C in improving liver-specific enzyme abnormalities in a Japanese prospective randomized controlled trial [24]. In a Chinese

prospective study of chronic hepatitis B, SNMC proved to be effective and safe [25]. In European patients with chronic hepatitis C, short-term administration of SNMC induced a significant ALT decrease and was effective [26].

From the viewpoint of acute liver disease, a nationwide survey of fulminant hepatitis and late onset hepatic failure between 1998 and 2003 in Japan revealed that prognosis was especially poor in AIH patients, whose survival rate was 17.1% without liver transplantation [27]. The diagnosis of acute onset AIH has been difficult because patients show acute presentation like acute hepatitis and may not have typical clinicopathological features of AIH. Therefore, they are at risk of losing the best timing of initiating immunosuppressive therapy, and are sometimes resistant to immunosuppressive therapy and have poor prognosis.

In our experience, most acute onset AIH patients had conserved PT activities at clinical onset and high levels of continuous liver injury for more than a few weeks, after which liver failure gradually progressed in a subacute clinical course [28–33]. Acute type of fulminant hepatitis is rare in AIH. Therefore, at the beginning of the present prospective study, we supposed that we could reduce the number of severe and fulminant AIH patients and improve the poor prognosis of fulminant AIH if we could control the ALT level and suppress inflammation at an early stage of illness, before progressing to liver failure. The primary end point of this study was the improvement of ALT during 4 weeks of the observation period. In fact, in this study, we were able to control the ALT level at an early stage by SNMC monotherapy, showing no significant difference compared to combination therapy with SNMC and CS.

We examined clinical outcomes as one of secondary end points. SNMC + CS group consisted of 14 patients, 6 severe and 8 fulminant, and 6 of 8 fulminant patients died. The survival rate was equal to other reports around the world [27, 34, 35]. Regarding the effects for outcomes of combination therapy with SNMC and CS compared to CS monotherapy in severe patients, we do not have enough data for discussion. However, we suppose that SNMC would have favorable and addictive effect, considering the fact that SNMC has the effect of decreasing ALT level in various liver diseases described above; on the other hand, the side effects are usually minor and reversible.

In a study of patients with subacute liver failure, Acharya et al. reported that survival was better in the glycyrrhizin-treated group than the historical control group [36]. Tandon et al. reported that intravenous glycyrrhizin was effective for moderate or severe hepatitis E patients in India [37]. But, in general, the efficacy for acute liver diseases has not been well documented. Taken together, intravenous glycyrrhizin should be of help for patients with acute liver disease, especially for those difficult to diagnose and treat, if it is found to be effective for them.

In the present study, patients in the SNMC + CS-initiated group had relatively longer duration from onset to treatment than those in the SNMC-initiated group ($P = 0.10$), but the proportion of histologically acute hepatitis was relatively greater in the former than in the latter ($P = 0.16$). In AIH, on the one hand, some patients present with severe diseases with a short time-duration, while on the other hand, some present with non-severe diseases with a long time-duration. The disease severity is not always parallel to the time duration from clinical onset in AIH-related liver failure, although it is usually parallel in viral or drug allergy-induced acute liver failure. Also, responsiveness to therapy is determined by the disease severity at the time of its initiation rather than the time duration from onset to therapy.

In summary, we showed that intravenous glycyrrhizin could improve ALT at least transiently and prevent the progression to severe and fulminant disease in acute onset AIH, if it is administered in the early stage of illness. However, delay in starting treatment may result in fatal liver failure, suggesting that an early diagnosis of such patients is urgently required. Intravenous glycyrrhizin can also be expected to be used safely and have a favorable effect for patients with acute liver disease difficult to diagnose and treat, like cryptogenic hepatitis and acute onset AIH, as an 'initial' treatment tool to improve liver inflammation before starting disease-specific treatments. Our study is not a controlled trial and the number of patients is small. We were unable to include placebo-controlled patients, considering the current knowledge of the poor prognosis of severe and fulminant patients. But controlled and multicenter studies are needed in order to confirm the effectiveness of intravenous glycyrrhizin for acute onset AIH.

Acknowledgments We are indebted to all our colleagues at the liver units of our hospitals who cared for the patients described here. This study was supported in part by a Health Labour Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan as a project by the Intractable Hepato-Biliary Disease Study Group of Japan.

Conflicts of interest None.

References

1. Soloway RD, Summerskill WHJ, Baggenstoss AH, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. *Gastroenterology*. 1972;63:820–833.
2. Mistilis SP, Skyring AP, Blackburn CRB. Natural history of active chronic hepatitis. I. Clinical features, course, diagnostic criteria, morbidity, mortality, and survival. *Australas Ann Med*. 1968;17:214–223.

3. Czaja AJ, Davis GL, Ludwig J, et al. Autoimmune features as determinants of prognosis in steroid-treated chronic active hepatitis of uncertain etiology. *Gastroenterology*. 1983;85:713–717.
4. Crapper RM, Bhathal PS, Mackay IR, et al. "Acute" autoimmune hepatitis. *Digestion*. 1986;34:216–225.
5. Amontree JS, Stuart TD, Bredfeldt JE. Autoimmune chronic active hepatitis masquerading as acute hepatitis. *J Clin Gastroenterol*. 1989;11:303–307.
6. Nikias GA, Batts KP, Czaja AJ. The nature and prognostic implications of autoimmune hepatitis with an acute presentation. *J Hepatol*. 1994;21:866–871.
7. Porta G, Da Costa Gayotto LC, Alvarez F. Anti-liver-kidney microsome antibody-positive autoimmune hepatitis presenting as fulminant liver failure. *J Ped Gastroenterol Nutrition*. 1990;11:138–140.
8. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol*. 1999;31:929–938.
9. Yamamoto S, Maekawa Y, Imamura M, et al. Treatment of hepatitis with antiallergic drug, Stronger Neo-Minophagen C. *Clin Med Pediatr*. 1958;13:73.
10. Suzuki H, Ohta T, Takino T, et al. Effects of glycyrrhizin on biochemical tests in patients with chronic hepatitis. Double-blind trial. *Asian Med J*. 1983;26:423–438.
11. Hino K, Miyakawa H, Kondo T, et al. Effects of glycyrrhizin therapy on liver histology in chronic aggressive hepatitis. In: Shikata T, Porcell RH, Uchida T, eds. *Viral hepatitis C, D and E*. Amsterdam: Excerpta Medica; 1987:295–303.
12. Desmet VJ, Gerber M, Hoofnagle JH, et al. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology*. 1994;19:1513–1520.
13. Iino S, Tango T, Matsushima T, et al. Therapeutic effects of stronger neo-minophagen C at different doses on chronic hepatitis and liver cirrhosis. *Hepatol Res*. 2001;19:31–40.
14. Maria VAJ, Victorino RMM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology*. 1997;26:664–669.
15. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified diagnostic criteria for autoimmune hepatitis. *Hepatology*. 2008;48:169–176.
16. Fujiwara K, Yasui S, Tawada A, et al. Diagnostic value and utility of the simplified International Autoimmune Hepatitis Group criteria in acute onset autoimmune hepatitis. *Liver Int*. (Epub ahead of print). doi:10.1111/j.1478-3231.2011.02524.x
17. Finney RS, Somers GF. The antiinflammatory activity of glycyrrhetinic acid and derivatives. *J Pharm Pharmacol*. 1958;10:613–620.
18. Doll R, Hill ID, Hutton C, et al. Clinical trial of a triterpenoid liquorice compound in gastric and duodenal ulcer. *Lancet II*. 1962;793–796.
19. Pompei R, Flore O, Marccialis MA, et al. Glycyrrhizic acid inhibits virus growth and inactivates virus particles. *Nature*. 1979;281:689–690.
20. Crance JM, Lévêque F, Biziagos E, et al. Studies on the mechanism of action of glycyrrhizin against hepatitis A virus replication in vitro. *Antiviral Res*. 1994;23:63–76.
21. van Rossum TG, Vulto AG, de Man RA, et al. Review article: glycyrrhizin as a potential treatment for chronic hepatitis C. *Aliment Pharmacol Ther*. 1998;12:199–205.
22. Yang BS, Ma YJ, Wang Y, et al. Protective effect and mechanism of stronger neo-minophagen C against fulminant hepatic failure. *World J Gastroenterol*. 2007;13:462–466.
23. Ikeda T, Abe K, Kuroda N, et al. The inhibition of apoptosis by glycyrrhizin in hepatic injury induced by injection of lipopolysaccharide/D-galactosamine in mice. *Arch Histol Cytol*. 2008;71:163–178.
24. Tsubota A, Kumada H, Arase Y, et al. Combined ursodeoxycholic acid and glycyrrhizin therapy for chronic hepatitis C virus infection: a randomized controlled trial in 170 patients. *Eur J Gastroenterol Hepatol*. 1999;11:1077–1083.
25. Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. *Hepatol Res*. 2002;24:220.
26. van Rossum TG, Vulto AG, Hop WC, et al. Glycyrrhizin-induced reduction of ALT in European patients with chronic hepatitis C. *Am J Gastroenterol*. 2001;96:2432–2437.
27. Fujiwara K, Mochida S, Matsui A, et al. Fulminant hepatitis and late onset hepatic failure in Japan. *Hepatol Res*. 2008;38:646–657.
28. Fujiwara K, Fukuda Y, Yokosuka O. Precise histological evaluation of liver biopsy specimen is indispensable for diagnosis and treatment of acute onset autoimmune hepatitis. *J Gastroenterol*. 2008;43:951–958.
29. Yasui S, Fujiwara K, Yonemitsu Y, et al. Clinicopathological features of severe and fulminant forms of autoimmune hepatitis. *J Gastroenterol*. 2011;46:378–390.
30. Fujiwara K, Nakano M, Yasui S, et al. Advanced histology and impaired liver regeneration are associated with disease severity in acute onset autoimmune hepatitis. *Histopathology*. 2011;58:693–704.
31. Fujiwara K, Yasui S, Tawada A, et al. Autoimmune fulminant liver failure in adults. A single Japanese center experience. *Hepatol Res*. 2011;41:133–141.
32. Yasui S, Fujiwara K, Yokosuka O. Autoimmune fulminant hepatic failure in chronic hepatitis C during peg-interferon-alfa 2b plus ribavirin treatment showing histological heterogeneity. *Dig Liver Dis*. (Epub ahead of print). doi:10.1016/j.dld.2011.02.014
33. Fujiwara K, Yasui S, Yokosuka O. Efforts at making the diagnosis of acute onset AIH. *Hepatology*. (Epub ahead of print). doi:10.1002/hep.24331
34. Lee WM, Squires RH Jr, Nyberg SL, et al. Acute liver failure: summary of a workshop. *Hepatology*. 2008;47:1401–1415.
35. Williams R, Wendon J. Indications for orthotopic liver transplantation in fulminant liver failure. *Hepatology*. 1994;20:S5–S10.
36. Acharya SK, Dasarathy S, Tandon A, et al. A preliminary open trial on interferon stimulator (SNMC) derived from Glycyrrhiza glabra in the treatment of subacute hepatic failure. *Indian J Med Res*. 1993;98:69–74.
37. Tandon A, Tandon BN, Bhujwala RA. Clinical spectrum of acute sporadic hepatitis E and possible benefit of glycyrrhizin therapy. *Hepatol Res*. 2002;23:55–61.

Hepatology Research

Hepatology Research 2012; 42: 42–50 doi: 10.1111/j.1872-034X.2011.00892.x

Original Article

Importance of computed tomography imaging features for the diagnosis of autoimmune acute liver failure

Shin Yasui,[1] Keiichi Fujiwara,[1] Koichiro Okitsu,[1] Yutaka Yonemitsu,[1] Hisao Ito[2] and Osamu Yokosuka[2]

[1]*Departments of Medicine and Clinical Oncology and* [2]*Radiology, Graduate School of Medicine, Chiba University, Chiba, Japan*

Aim: The diagnosis of acute liver failure due to autoimmune hepatitis is often difficult because of atypical clinicopathological features. Patients with autoimmune acute liver failure are sometimes resistant to immunosuppressive therapy and have poor prognosis. Although their survival rates are especially poor (5–20%) without liver transplantation in Japan, their clinicopathological features have remained uncertain. A major problem is that there is no gold standard for making the diagnosis of acute onset autoimmune hepatitis. If there are diagnosing tools supporting clinicopathological features, they are of benefit to the patients. We examined computed tomography (CT) imaging features of autoimmune acute liver failure to clarify the usefulness of imaging for the diagnosis.

Methods: A retrospective analysis of 129 unenhanced CT scans of 68 patients with acute hepatitis, consisting of 23 with autoimmune acute liver failure (ALF) (group 1), 25 with early admission-viral ALF (group 2) and 20 with late admission-viral ALF (group 3), was performed.

Results: Autoimmune acute liver failure showed heterogeneous hypoattenuating areas and viral ALF diffuse ones ($P < 0.001$). The diffuse hypoattenuating areas were present in none of group 1, 15 (60%) of group 2, and 7 (30%) of group 3. The heterogeneous hypoattenuating areas were present in 15 (65%) of group 1, none of group 2 and 1 (5%) of group 3.

Conclusions: Heterogeneous hypoattenuation on unenhanced CT was a characteristic CT imaging feature of autoimmune acute liver failure compared with viral ALF. This finding could be one of the tools for diagnosing autoimmune acute liver failure in combination with clinicopathological features.

Key words: acute liver failure, autoimmune hepatitis, computed tomography, hypoattenuation, massive necrosis

INTRODUCTION

AUTOIMMUNE HEPATITIS (AIH) is regarded as a chronic hepatitis, characterized by the presence of interface hepatitis and plasma cell infiltration on histological examination, hypergammaglobulinemia, and autoantibodies.[1,2] An acute presentation of AIH is common,[3,4] and severe or fulminant hepatitis is possible.[5] Acute onset AIH sometimes does not show typical clinicopathological features and is difficult to diagnose.[6] A major problem is that there is no gold standard for making the diagnosis of acute onset AIH.

Recently, we reported the importance of a precise histological examination for the early diagnosis of acute onset AIH.[7] In our analysis of clinicopathological features of patients with autoimmune acute liver failure (ALF), most of them showed severe activity including massive or submassive necrosis on liver histology.[8–10] Thus, histological examination is useful for the diagnosis of acute onset AIH, but it is sometimes difficult to perform liver biopsy due to the complicated coagulopathy and ascites in patients with ALF. Therefore, other tools contributing to the diagnosis are required.

The computed tomography (CT) findings of fulminant liver failure are reduced liver size, diffuse or localized areas of hypoattenuation in the liver, dilatation of the portal vein, and narrow or non-depicted hepatic veins.[11] An area of hypoattenuation on unenhanced CT

Correspondence: Dr Keiichi Fujiwara, Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan. Email: fujiwara-cib@umin.ac.jp

This study was supported in part by a Health Labor Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan as a project by the Intractable Hepato-Biliary Disease Study Group of Japan.

Disclosures: All authors have nothing to disclose.

No conflicts of interest exist.

Received 4 April 2011; revision 1 August 2011; accepted 16 August 2011.

is associated with massive necrosis of hepatocytes. CT plays an important role in predicting the prognosis of fulminant liver failure,[12–16] whereas little has been reported regarding the usefulness of imaging to differentiate causes of ALF.

Therefore, in the present study we examined clinical and imaging features of autoimmune ALF and viral ALF to clarify the utility of CT imaging to diagnose and evaluate autoimmune ALF.

METHODS

Patients

THE ACUTE HEPATITIS (AH) database at our institution from March 1990 to February 2011 was reviewed to identify all patients with acute onset AIH, hepatitis A, acute hepatitis B and acute exacerbation of hepatitis B viral (HBV) carrier who had undergone abdominal ultrasound and CT with prothrombin time (PT) activity less than 60% of control.

A diagnosis of AIH was made based on the presence of anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (ASMA), as well as on the criteria defined by the International Autoimmune Hepatitis Group.[17] Eligibility criteria of acute onset AIH were as follows: (i) acute onset liver injury with no history of chronic liver injury; (ii) negative for possibility of drug-induced liver injury and active viral markers such as hepatitis A, B and C viruses, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and herpes simplex virus (HSV); (iii) liver histologic findings compatible with AIH, consisting of interface hepatitis, centrilobular necrosis and plasma cell infiltration in those undergoing liver histologic examination; and (iv) no signs of chronicity on the basis of physical examination, laboratory data and abdominal ultrasound findings. A diagnosis of hepatitis A was made based on positive IgM anti-hepatitis A virus antibody (IgM-HA), acute hepatitis B based on positive HBsAg, and high titer of IgM anti-hepatitis B core antibody (IgM-HBc) in conjunction with compatible symptoms and laboratory findings. The diagnosis of HBV carrier was made based on either the positivity of HBsAg for at least 6 months before entry or, in patients with follow-up periods less than 6 months before entry, it was based on the positivity of HBsAg, anti-hepatitis B core antibody (HBcAb) at high titer, and negativity or low titer IgM-HBc. Patients with a prothrombin time less than 40% of control and hepatic encephalopathy were defined as fulminant hepatitis (FH). Informed consent was obtained from all patients or appropriate family members. The work described in this manuscript has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Clinical, biochemical and immunological analysis

Data obtained from patients were as follows: age at diagnosis; sex; time of onset; serum levels of alanine aminotransferase (ALT), total bilirubin (T-Bil), prothrombin time (PT) activity. Additional data obtained from AIH patients were as follows: immunoglobulin G (IgG) and ANA.

In acute hepatitis, early symptoms including fever, general malaise, fatigue, nausea, vomiting and right upper quadrant discomfort are frequently observed, so we defined the beginning of these symptoms as clinical onset.

CT imaging examination

Computed tomography scans were performed over a 21-year period. Patients were scanned with either a single-slice spiral CT scanner or a multi-slice (16-detector row) CT scanner (General Electric Company, Fairfield, CT, USA), or a multi-slice (four-detector row) CT scanner (Siemens Medical Solutions, Forchheim, Germany).

Initial CT scans for each patient were reviewed. These patients' CT scans were evaluated to describe the CT features of acute onset AIH, hepatitis A, acute hepatitis B and acute exacerbation of HBV carrier with low PT activity.

Twenty-two of 68 patients (13 female and nine male; age range 17–71; mean age: 50.5 years) had serial CT scans during their clinical courses. A total of 83 imaging studies were available in this subgroup of patients. The mean duration of follow-up was 3.6 months (range: 1–20 months). These patients' imaging studies were evaluated to describe changes associated with treatment.

Imaging feature analysis

Two hepatologists and one radiologist with more than 10 years of specialist experience in abdominal imaging independently performed a consensus review of all CT images. For CT scans, the presence and the patterns of hypoattenuating areas were assessed subjectively. An area of hypoattenuation was identified on CT when liver attenuation was less than spleen attenuation on unenhanced scans. Fatty liver was ruled out by ultrasound; an area of hypoattenuation on CT reflecting

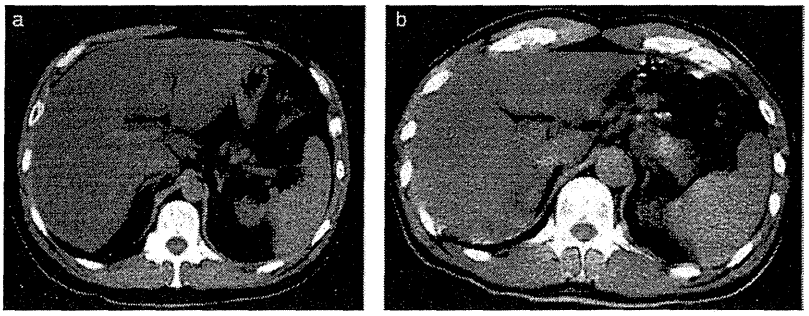

Figure 1 Computed tomography (CT) findings of a 39-year-old male patient with severe hepatitis A (a) and a 54-year-old male patient with fulminant hepatitis B (b). CT scans showed diffuse hypoattenuating areas at admission.

massive necrosis was detected as hypoechoic area on ultrasound. If an area of hypoattenuation was present, it was assessed as diffuse (Fig. 1) or heterogeneous (Figs 2–4). In the cohort of patients with serial CT scans, changes in hypoattenuating areas were examined.

Statistical analysis

Differences in proportions among the groups were compared by Fisher's exact probability test and Student's *t*-test ($P < 0.05$ was considered significant).

RESULTS

Clinical and biochemical features

A TOTAL OF 68 patients (34 female and 34 male; age range 17–71; mean age: 47.1 years) were identified. Twenty-three were patients (16 female and seven male; age range 17–71; mean age: 48.8 years) with acute onset AIH, 13 (5 female and eight male; age range 26–69; mean age: 47.0 years) with hepatitis A, 19 (10 female and nine male; age range 17–62; mean age: 44.2 years) with acute hepatitis B and 13 (three female and 10 male; age range 33–66; mean age: 48.5 years) with acute exacerbation of HBV carrier.

Mean ALT was 2914 ± 3616 IU/L, mean T-Bil 13.3 ± 10.3 mg/dL, and mean PT activity 31 ± 15%. The duration from initial symptoms to the admission to our unit was 21.6 ± 22.5 days (range: 3–124 days).

Immunological and pathological features of AIH patients

Mean IgG was 2382 ± 855 mg/dL. ANA was ≤ 1:40 in three (13%), 1:40 in three (13%), 1:80 in six (26%), and ≥ 1:80 in 11 (48%). Mean AIH score was 15.7 ± 2.6. Histological examination was performed in 18 of 23 patients and all were performed before the administration of corticosteroids, in the convalescent phase, or post mortem. Seventeen of 18 showed acute hepatitis, exhibiting zonal, submassive and massive necrosis with or without plasma cell accumulation in portal and centrilobular areas. One showed chronic hepatitis. There were no differences in imaging findings between patients with histological acute and chronic hepatitis.

CT features of all patients

Areas of hypoattenuation were present in 38 (56%) of 68 patients. Diffuse hypoattenuating areas were present in 22 (58%) of 38 patients, and heterogeneous hypoattenuating areas in 16 (42%). There were no significant differences in hypoattenuation appearance between single-slice spiral and multi-slice CT scanner.

Comparison of backgrounds between patients with autoimmune ALF and viral ALF

In Japan, fulminant hepatitis is classified into two subtypes: the acute type and subacute type in which the encephalopathy occurs within 10 days and later than 11 days from onset, respectively. Fulminant AIH patients usually present subacute type and all of our autoimmune ALF patients in this study were subacute type. Liver regeneration of subacute type is more impaired than acute type; therefore we divided viral ALF into two groups.

Patients were divided into three groups: group 1 (autoimmune ALF) comprised patients diagnosed as acute onset AIH; group 2 (early admission-viral ALF) comprised patients diagnosed as hepatitis A or acute hepatitis B or acute exacerbation of HBV carrier with 10 or fewer days of duration from onset to admission; group 3 (late admission-viral ALF) comprised patients diagnosed as hepatitis A or acute hepatitis B or acute

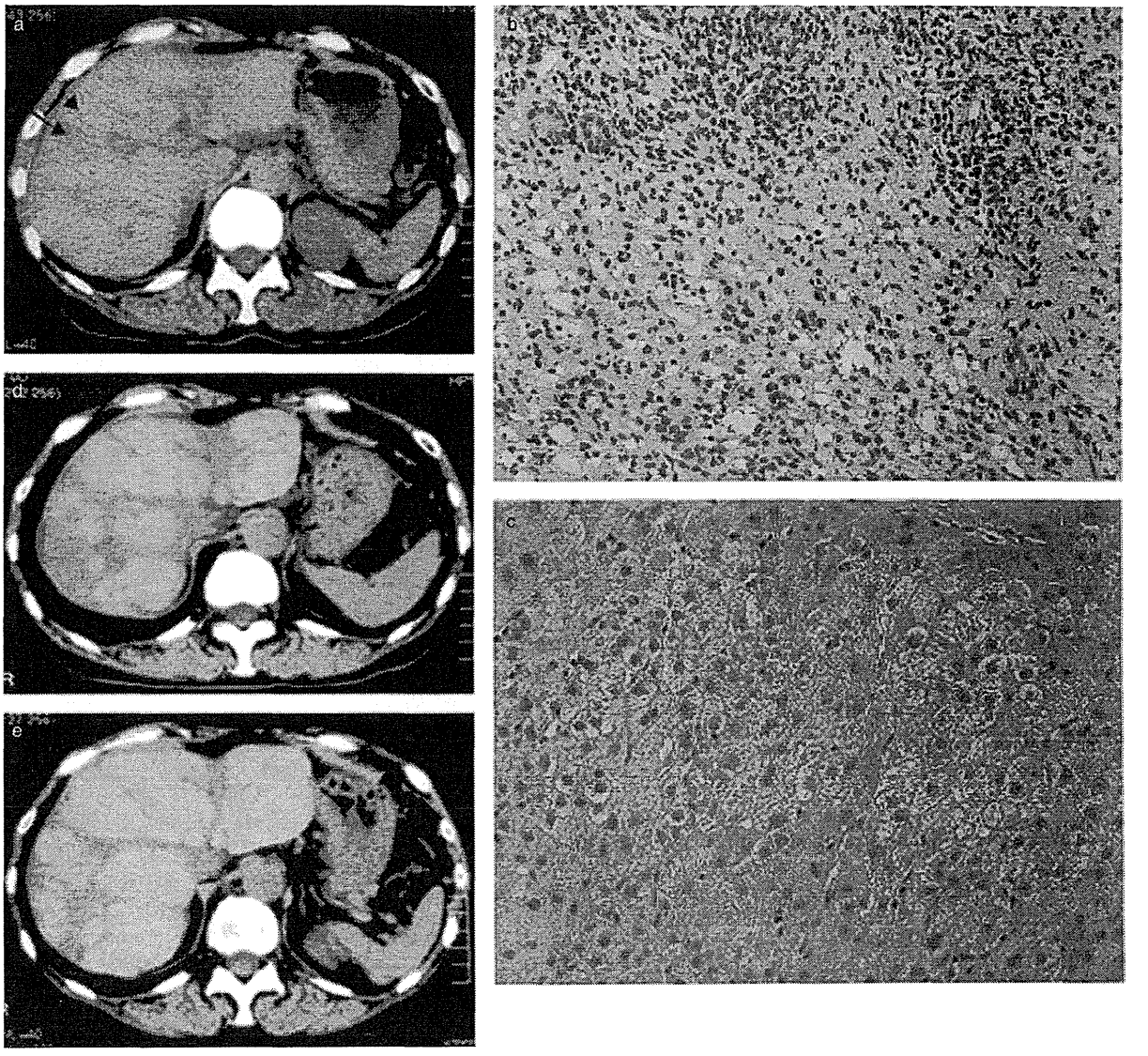

Figure 2 Computed tomography (CT) and histological findings of a 62-year-old female patient with severe autoimmune hepatitis. (a) CT scan showed heterogeneous hypoattenuating areas at admission. (b) Liver histology showed massive necrosis with plasma cell accumulation in a hypoattenuating area (arrow area), and (c) liver regeneration in a non-hypoattenuating area (arrow head area). (d) One month after the administration of corticosteroid, heterogeneous hypoattenuating areas and hyperattenuating islands became prominent in response to the therapy. (e) Seven months after, CT scan showed enlargement of hyperattenuating islands and a decrease in the hypoattenuating areas.

exacerbation of HBV carrier with 11 or more days of duration from onset to admission. The clinical, biochemical and imaging features of the groups were compared to discover imaging features of acute onset AIH.

The clinical and biochemical features of each group are shown in Table 1. The differences in mean age were not statistically significant among the three groups. Female sex was more dominant in group 1 than in group 3 ($P = 0.015$). Duration from onset to admission was longer in group 1 than in groups 2 and 3 ($P \leq 0.001$, $P = 0.006$, respectively). Mean ALT was higher in group 2 than in group 1 ($P < 0.001$), and the difference between groups 1 and 3 was not significant. Mean T-Bil