

## Transient Exacerbation After Infections in Patients With Autoimmune Hepatitis

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**Conflict-of-interest statement:** The authors declare that there is no conflict of interest regarding the publication of this paper.

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Received: July 16, 2018

Revised: October 2, 2018

Accepted: October 5, 2018

Published online: October 21, 2018

### ABSTRACT

**AIMS:** Although the pathogenesis of autoimmune hepatitis (AIH) is unknown, many recent studies have demonstrated that infection can act as a trigger for the onset of AIH. The existence of a pathogenetic link between AIH and infections has not been confirmed. If AIH is triggered by infections, it is possible that infections may transiently worsen liver function in patients with AIH. We investigated the association between the effects of infections and the exacerbation of liver dysfunction in patients with AIH.

**METHODS:** We determined the changes in liver function before

and after infections in 20 patients with definite AIH, 33 with probable AIH, 24 with primary biliary cholangitis (PBC), 30 with chronic hepatitis C [CH(C)], and 23 control subjects.

**RESULTS:** During the study period, 19 of the 20 patients (95%) with AIH experienced one or more signs of liver dysfunction after infection. Seventy-three (59%) out of the 124 total occurrences of infections in 19 patients met the criteria for transient exacerbation of liver dysfunction. The incidence of liver dysfunction and the serum IgG levels after infection were significantly higher in the patients with definite AIH than in the patients with probable AIH, PBC and CH(C), and in the control subjects. Serum IgG level was a significant independent predictor of liver dysfunction.

**CONCLUSION:** The present study results suggested that infection was one cause of exacerbation of liver dysfunction in patients with AIH, and that serum IgG level was a significant independent predictor of exacerbation of liver dysfunction after infection.

**Key words:** Liver dysfunction; Autoimmune hepatitis; Exacerbation; IgG

#### A list of abbreviations

autoimmune hepatitis: AIH

primary biliary cholangitis: PBC

chronic hepatitis C: CH(C)

anti-nuclear antibody: ANA

immunoglobulin G: IgG

prednisolone: PSL

ursodeoxycholic acid: UDCA

alanine aminotransferase: ALT

antimitochondrial antibody: AMA

alkaline phosphatase: ALP

immunoglobulin M: IgM

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Maruyama S, Koda M. Transient Exacerbation After Infections in Patients With Autoimmune Hepatitis. *Journal of Gastroenterology and Hepatology Research* 2018; **7(5)**: 2696-2701 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2383>

## INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic active hepatitis characterized serologically by positive anti-nuclear antibody (ANA) and selective elevation of serum immunoglobulin G (IgG), and histologically by portal inflammatory cell infiltration and interface hepatitis. Although the exact mechanisms of onset have not been elucidated, it is postulated that the pathogenesis of AIH requires unknown external triggers to set off a sequence of events leading to AIH in a susceptible host. Susceptibility develops according to a predetermined genetic background and is probably influenced by multiple environmental agents such as infections. In particular, viruses, bacteria and other infectious pathogens are the major postulated environmental triggers of AIH<sup>1,2,3</sup>. If AIH is triggered by infection, it is possible that infection may transiently worsen liver function in a patient with AIH whose aminotransferases are sustained at normal levels by medical treatment. We aimed to demonstrate the effects of infection on liver function, determine the changes in liver function before and after infections in patients with AIH, and compare these factors with other liver diseases.

## PATIENTS AND METHODS

Twenty-seven patients who were diagnosed with definite AIH (all patients with type 1 AIH) between November 2000 and April 2015 at boarded-certified special hospitals including our hospital and who could be observed between April 2005 and May 2016 at our hospital were enrolled. A diagnosis of AIH was made according to the revised scoring system proposed by the International Autoimmune Hepatitis Group (IAIHG)<sup>4</sup>, in which a definite diagnosis of AIH requires a pretreatment score exceeding 15. Seven of the 27 AIH patients who were still receiving treatment with prednisolone (PSL) monotherapy, were excluded from our study (although their data were adopted later in our additional study) because they had not achieved sustained remission and were susceptible to infection as a result of their PSL therapy. The remaining 20 AIH patients (3 men, 17 women; mean age  $51 \pm 12$  years; age range 28-71 years), who were treated with ursodeoxycholic acid (UDCA) monotherapy and achieved normalization of serum alanine aminotransferase (ALT) levels, were consecutively enrolled in this study.

Eight of the 20 patients began treatment with PSL (30-40 mg daily) monotherapy, which was continued until normalization of ALT levels. After the normalization of ALT levels, PSL was tapered by 1-5 mg every 1-2 weeks to a maintenance dose of  $\leq 5$  mg/day and UDCA was added. After combination therapy with PSL and UDCA, the PSL was stopped when the normal levels of serum ALT continued at a maintenance dose of PSL for more than one year. These patients were finally treated with UDCA alone and showed normalization of ALT at a dose of 600 mg/day. The remaining 12 patients—all of whom had histological low-grade inflammatory activity, and of whom 2 patients were comparatively elderly patients, 5 patients had co-morbid diseases such as peptic ulcers, glaucoma, hypertension, osteoporosis and diabetes, and 5 patients had relatively low serum ALT levels ( $< 100$  IU/L)—were treated with UDCA alone from the beginning and achieved normalization of serum ALT levels. All of the above patients achieved sustained remission for at least one year before the initiation of our study and had no evidence of biochemical relapse during the observation period, although they had small changes in ALT levels (less than 2 times of the previous data) for which no added medication was needed. Relapse occurred in four of the 20 patients. When relapse was observed, the patients were subsequently treated

with PSL and then we stopped their further observation; however, the data until the relapse were adopted in our study. Concerning relapse, it occurred probably after infection in one patient; in the remaining three patients, it occurred irrelevantly to infection.

All patients were seronegative for hepatitis B surface antigen, anti-hepatitis C virus antibody, hepatitis C virus RNA, and antimitochondrial antibody (AMA). Patients with other causes of chronic liver diseases such as nonalcoholic fatty liver, alcohol abuse (alcohol consumption  $> 20$  g per day for  $> 5$  years), and drug use were excluded from the study.

Thirty-three patients (33 women, mean age  $57 \pm 10$  years; age range 35-72 years) were considered to have probable AIH according to the IAIHG scoring system (a score between 10 and 15). Although 9 of the patients with probable AIH underwent liver biopsy, the remaining 24 patients had AIH based on clinical data alone. All 33 patients were treated with UDCA alone from the beginning and achieved normalization of serum ALT levels. All patients were negative for hepatitis B and C viruses and patients with other causes of chronic liver diseases such as nonalcoholic fatty liver, alcohol abuse and drug use were excluded.

Twenty-four patients (5 men, 19 women; mean age  $59 \pm 10$  years; age range 43-78 years) had primary biliary cholangitis (PBC), which was diagnosed based on elevation of alkaline phosphatase (ALP), presence of AMA, selective elevation of serum immunoglobulin M (IgM) and specific bile duct pathology. All patients were seronegative for ANA. [ANA-positive patients ( $n = 12$ ) with PBC were excluded from the present study, although their data were adopted later in our additional study]. Twenty of the patients with PBC were treated with UDCA (600 mg/day) alone and 4 of the patients were treated with UDCA in combination with bezafibrate (200 mg/day). All of the patients showed normalization of ALT and decreased levels of ALP.

Thirty patients (5 men, 25 women; mean age  $63 \pm 8$ ; age range 49-79 years) had chronic hepatitis C [CH(C)], which was diagnosed based on positivity for serum hepatitis C virus (HCV) RNA, and which was measured quantitatively by polymerase chain reaction (PCR). All patients were seronegative for ANA. (ANA-positive patients ( $n = 16$ ) with CH(C) were excluded from the present study, although their data were adopted later in our additional study.) Seven patients with CH(C) were treated with UDCA alone, 9 with a combination of UDCA and monoammonium glycyrrhizinate, and 14 were followed without any treatment. None of the CH(C) patients had received anti-viral treatment before or during the observation period. When anti-viral treatment was started, we stopped their further observation and they were excluded from further study.

Control subjects (23 women; mean age;  $59 \pm 15$  years; age range 36-80 years) showed normal liver function according to an annual routine medical checkup and were negative for hepatitis B and C virus antibody and ANA. (ANA-positive subjects ( $n = 24$ ) were excluded from the present study, although their data were adopted later in our additional study.)

This study was approved by Tottori University (No. 1606A030), and informed consent was obtained from all subjects.

Routine laboratory tests were performed using automated methods and included tests for ALT and ALP. The normal upper limits of ALT and ALP were 45 IU/mL and 340 IU/mL, respectively. White blood cell count and analysis were measured with an automated hematology analyzer (CELL-DYN Sapphire Hematology Analyzer; Abbott Diagnostics, Tokyo, Japan) and C-reactive protein was measured with latex coagulating nephelometric analysis (N-Assay LA CRP-S Nittobo D-type; Nittobo Medical Co. Ltd., Tokyo, Japan). The serum concentration of IgG was determined by single diffusion in agar gel

using the Oudin tube method. The normal upper limit of IgG was 1700 mg/dl. ANA was detected by indirect immunofluorescence analysis of rat liver and kidney sections. Serum samples with a titer of at least 40 were considered positive.

Infections are caused by various infectious pathogens, mainly viruses and bacteria. Hematologically leukocytosis (leukocyte count  $> 11000/\mu\text{l}$ ) with neutrophilia [more than 60% increase in the number of neutrophils by leukogram or an increase in the absolute number of mature neutrophils greater than  $7000/\mu\text{l}$ ] and left shift [an increase in the amount of immature neutrophils (myelocytes, metamyelocytes, and band neutrophils) in the peripheral blood] is characteristic of bacterial infection as laboratory diagnosis, while comparative lymphocytosis (more than 40% increase in lymphocytes by leukogram or an increase in the absolute count greater than  $4500/\mu\text{l}$ ) indicates viral infection<sup>[5,6]</sup>. Directly bacterial culture of excretory substance or serum virus-IgM antibody determined by enzyme immunoassay was used to reveal bacteria or viruses in some patients. Accordingly, we simply divided two infectious pathogens into two groups - bacterial and viral. Infections were defined as acute infectious diseases in the respiratory, urinary or gastrointestinal tracts and we diagnosed infections based on the symptoms accompanied by each tract infections, inflammatory signs (abnormal white blood cell counts and positivity of C-reactive protein) and the special examinations for each organ. A diagnosis of the respiratory infection was made based on the symptoms of fever, cough and sputum, an abnormality on a chest radiograph, or both. The urinary tract infection was defined when white blood cells or bacteria which could be classified as bacilli and cocci were detected in the urine. A diagnosis of the gastrointestinal infection was made according to the symptoms of fever and any or all of diarrhea, abdominal pain, nausea and vomiting and the abdominal findings detected by ultrasonography.

The frequency of infection indicates the total number of infections during an observation period. The frequency of liver dysfunction indicates the total number of instances of liver dysfunction after infections. The rate of infection means the ratio of the frequency of infection versus the observation period. The rate of liver dysfunction means the ratio of the total occurrences of liver dysfunction versus the total occurrences of infections during an observation period. In the present study, the criteria for liver dysfunction were defined as ALT or ALP over the upper limits of normal and greater than 2 times the previous data, and the elevated levels of ALT or ALP rapidly and spontaneously normalized for short times without any additional therapy. Follow-up clinical visits and liver function tests in each patient group were routinely obtained at one-month intervals and when patients experienced infection. The control subjects visited our hospital for the purpose of an annual routine medical checkup and when they experienced infection. The medical record was reviewed on a retrospective basis from April 2005 from March 2016, and all events that constituted liver dysfunction during that period were recorded.

#### Statistical analysis

All measurements are expressed as mean  $\pm$  SD. Standard statistical methods were employed using Student's *t*-test. Differences among the five groups were determined using analysis of variance (ANOVA). Correlation analysis was performed by univariate linear regression analysis. Multivariate forward stepwise regression analysis to identify independent factors of frequency of liver dysfunction was conducted with StatFlex version 6.0 (Artech Co., Ltd., Osaka, Japan). *P* values  $< 0.05$  were considered statistically significant.

## RESULTS

Table 1 shows the clinical characteristics of the 20 patients with definite AIH with respect to infection. The mean frequency of infection was  $6.3 \pm 4.0$  times (range 1-14) in the 20 patients during the total observation period, and the rate of infection [frequency of infection (times)/observation periods (years)] was  $1.0 \pm 0.9$  (range 0.1-3.0) in each patient. With respect to liver dysfunction after infection, the mean frequency of liver dysfunction in the 20 patients was  $3.7 \pm 2.8$  times (range 0-9) during the observation period, and the rate of liver dysfunction [frequency of liver dysfunction (times)/frequency of infection (times)] was  $0.6 \pm 0.3$  (range 0-1.0) in each patient. Nineteen of the 20 patients (95%) with AIH experienced one or more (range 1-9) occurrences of liver dysfunction during the study period, and a total of 73 events met the criteria for acute exacerbation. The total number of occurrences of infection and of liver dysfunction in all 20 patients with AIH were 124 and 73, respectively; therefore, the rate of liver dysfunction after infection was estimated as 59% (73/124).

Among the 73 instances of infections coexistent with liver dysfunction, the mean ALT values before and after infections were  $27 \pm 10$  IU/L (range 10-43) and  $89 \pm 59$  IU/L (range 46-332), respectively. The levels of ALT after infections were significantly higher than before infections ( $p < 0.0001$ ) and elevated 3.6 times higher than before. The changes in ALP values before and after infections were almost the same as those of ALT. These elevated levels of ALT or ALP spontaneously normalized for short times ( $27 \pm 9$  days; range 8-43 days) without any additional therapy (data not shown).

Meanwhile the frequency of liver dysfunction without infections was 9 times in total number of occurrences in 8 out of the 20 patients with AIH. The mean ALT values before and after liver dysfunction were  $27 \pm 12$  IU/L (range; 13-45) and  $84 \pm 6$  IU/L (range; 74-92), respectively. The levels of ALT after liver dysfunction were significantly higher than before liver dysfunction ( $p < 0.0001$ ) and elevated 3.1 times as compared with before. The changes in ALP values were almost the same as those in ALT. These elevated levels of ALT or ALP were spontaneously normalized for about two months ( $62 \pm 6$  days; range 54-70 days) without any additional therapy (date not shown). Although the mean values of ALT and ALP after dysfunction were not different between both groups of after and without infection, the time necessary for the improvement of liver dysfunction without infection (mean  $62 \pm 6$  days; range 54-70 days) was longer than after infection (mean  $27 \pm 9$  days; range 8-43 days).

According to our criteria, bacterial infections were seen in 33 cases, viral infections in 31 and unknown pathogens in 9 among the 73 infections. Infections were defined as acute infectious diseases in the respiratory, urinary or gastrointestinal tracts. The origins of the infections were the upper respiratory tract ( $n = 25$ ), respiratory tract ( $n = 25$ ), urinary tract ( $n = 1$ ) and gastrointestinal tract ( $n = 6$ ), respectively. Eight patients had fever of unknown origin and 8 had influenza. There were no significant differences in biochemical data among the different kinds of infectious pathogens or origins.

Table 2 shows the clinical characteristics of the 20 patients with definite AIH, the 33 patients with probable AIH, the 24 patients with PBC, the 30 patients with CH(C), and the 23 control subjects. All of the clinical data were those values determined at the start of observation (not at diagnosis). The sex distribution was similar in all groups, but the mean age in the definite AIH group was significantly lower than in the other groups ( $p < 0.001$ ). Although the observation periods and the rates of infection were similar in all groups, the rate of patients with liver dysfunction and the rate of liver dysfunction in

the patients with definite AIH were significantly higher than in the other groups (both;  $p < 0.0001$ ). Meanwhile, the rate of patients with liver dysfunction and the rate of liver dysfunction without infection in CH(C) group were significantly higher than in other groups and there were not significant difference among definite AIH, probable AIH and PBC groups (data not shown). The serum ALT values were significantly higher in the definite AIH group than in the other groups ( $p < 0.0001$ ) except for the CH(C) group, whereas the serum IgG levels in the definite AIH group were significantly higher than in the other groups ( $p < 0.0001$ ). Although white blood cell count and analysis (percentage of lymphocytes or granulocytes) were similar in all groups, ESR/h in AIH and PBC groups were significantly higher than in CH(C) and control groups ( $p < 0.0001$ ).

The rate of liver dysfunction in the 20 patients with definite AIH treated with UDCA alone ( $0.59 \pm 0.26$ ) was significantly higher than

in the 7 patients treated with PSL alone ( $0.03 \pm 0.05$ ) ( $p < 0.0001$ ); while the serum IgG levels in the UDCA group ( $2213 \pm 201$ ) were significantly higher than in the PSL group ( $1924 \pm 280$ ) ( $p < 0.01$ ) (data not shown). In the PBC, CH(C), and control groups, ANA-positive cases consisted of 12 patients in the PBC group, 15 in the CH(C) group, and 24 in the control group. There were no significant differences between the ANA-positive and ANA-negative patients in each group with respect to the rate of liver dysfunction and serum IgG levels (data not shown).

Table 3 shows the correlations between the rate of liver dysfunction and clinical biochemical parameters. The rate of liver dysfunction was significantly correlated with serum IgG, lymphocytes (%) and granulocytes (%). Multivariate analysis showed that serum IgG was a significant independent predictor of the rate of liver dysfunction.

**Table 1** Clinical characteristics of patients with definite AIH in relation to infection.

No. of patients	gender	age	A: Observation periods (years)	B: Frequency of infection (times)	C: Frequency of liver dysfunction (times)	Rate of infection (= B/A)	Rate of liver dysfunction (= C/B)	Frequency of liver dysfunction (times) without infections
1	F	55	11	9	4	0.82	0.44	2
2	F	61	11	4	2	0.36	0.5	1
3	F	52	11	4	3	0.36	0.75	0
4	F	65	10	1	0	0.1	0	0
5	F	53	10	3	1	0.3	0.33	0
6	F	65	10	3	2	0.3	0.67	0
7	F	38	10	14	5	1.4	0.36	0
8	M	28	4	12	9	3	0.75	0
9	F	29	9.5	7	5	0.74	0.71	1
10	F	51	7.5	12	9	1.6	0.75	1
11	F	56	4	1	1	0.25	1	0
12	M	37	5	12	9	2.4	0.75	1
13	M	40	2	5	3	2.5	0.6	0
14	F	49	6.5	5	3	0.77	0.6	1
15	F	68	7	1	1	0.14	1	0
16	F	52	7	6	1	0.86	0.17	1
17	F	41	7	9	4	1.29	0.44	0
18	F	47	6.5	7	6	1.08	0.86	1
19	F	53	9	3	2	0.33	0.67	0
20	F	71	10	6	3	0.3	0.5	0

**Table 2** Clinical characteristics of patients with AIH, PBC, CH(C) and control subjects.

	AIH (definite) (n = 20)	AIH (probable) (n = 33)	PBC (n = 24)	CH(C) (n = 30)	Control (n = 23)	p value
Gender (M/F)	3/17	0/33	5/19	5/25	0/23	NS
Age(yr)	50.6 ± 11.9	57.0 ± 9.7	59.1 ± 9.5	63.2 ± 7.7*	59.1 ± 14.7	<0.001
Observation periods (years)	7.9 ± 2.7	7.2 ± 2.6	6.1 ± 2.5	8.3 ± 2.3	8.2 ± 2.0	NS
Rate of infection (times/years)	0.93 ± 0.82	0.70 ± 0.79	0.75 ± 0.76	0.63 ± 0.48	1.16 ± 0.74	NS
Rate of patients with liver dysfunction	19/20(95%)	12/33(36%)*	6/24(25%)*	0/30(0%)*	1/23(4%)*	<0.0001
Rate of liver dysfunction	0.59 ± 0.26	0.12 ± 0.17*	0.05 ± 0.11*	0*	0.01 ± 0.04*	<0.0001
ALT(IU/L)	37.7 ± 8.8	23.9 ± 8.7*	22.9 ± 9.3*	34.9 ± 19.2	17.0 ± 6.2*	<0.0001
ALP(IU/L)	325 ± 88	274 ± 70	364 ± 166	299 ± 76	234 ± 64*	<0.0001
ANA	440 ± 448	121 ± 238*	0*	0*	0*	<0.0001
IgG(mg/dL)	2213 ± 201	1437 ± 229*	1377 ± 317	1564 ± 348*	1285 ± 219*	<0.0001
WBC(/μL)	5095 ± 1002	5785 ± 1784	5121 ± 1066	4863 ± 1004	5209 ± 1227	NS
Lymphocytes(%)	37.9 ± 6.7	40.2 ± 10.2	42.8 ± 14.6	39.5 ± 10.3	37.3 ± 7.5	NS
Granulocytes(%)	50.1 ± 7.5	54.1 ± 10.1	52.6 ± 14.3	55.9 ± 10.6	56.0 ± 14.3	NS
ESR/h	28.5 ± 12.6	21.3 ± 10.8	25.0 ± 8.3	18.6 ± 14.1*	8.4 ± 4.4*	<0.0001

\*  $p < 0.01$  compared to AIH (definite) group.



**Table 3** Correlation between rates of liver dysfunction and clinical biochemical parameters.

parameter	r	p-value
Age(yr)	-0.078	NS
ALT(IU/L)	-0.239	NS
ALP(IU/L)	-0.13	NS
ANA	-0.220	NS
IgG(mg/dL)	0.932	<0.0001
WBC(/ $\mu$ L)	0.245	NS
Lymphocytes(%)	0.670	<0.001
Granulocytes(%)	-0.575	<0.001
ESR/h	0.213	NS
Histology	-0.416	NS
AIH score	-0.354	NS

## DISCUSSION

The exact mechanisms leading to AIH are still incompletely explained. Viruses, bacteria and other infectious pathogens are the major postulated environmental triggers of AIH. Several case studies have revealed associations between pathogenic infections and the occurrence of AIH<sup>[2,3,7]</sup>. The presence of cross-reactive autoantibodies and the existence of structural similarities between AIH autoantigens and pathogens (i.e., molecular mimicry) provide a plausible explanation of how tolerance to liver autoantigens might be broken by infectious pathogens<sup>[8]</sup>. Experimental designs of AIH have clearly demonstrated that viral and bacterial superantigens can induce relapse and exacerbations of a T cell-mediated autoimmune process<sup>[9]</sup>. Although the liver may not be the primary target organ of viral or bacterial infections, it can be collaterally damaged. Hepatic dysfunction may be a consequence of the immune response to viral and bacterial antigens, with a close topographic association between the presence of viral and bacterial antigens and the associated inflammatory infiltrates in the liver<sup>[10-12]</sup>. From our various investigations, we ruled out other etiologies such as other environmental factors or the medication and elucidated that infection was one cause of exacerbation of liver dysfunction in patients with AIH. The present study demonstrated that the AIH patients experienced liver dysfunction more frequently than the patients with other liver diseases after infections. From these results, it can also be presumed that pathogenic infections in patients with AIH promote a more intense systemic immune response than in patients with other liver diseases; and liver dysfunction occurred more frequently in the AIH patients.

Although the values of liver dysfunction after infection was not different from being irrelevant to infection, the time necessary for the improvement of liver dysfunction after infection was shorter than without infection. We speculated that by a consequence of the immune response to viral and bacterial antigens under the activated autoimmune reactions, liver dysfunction after infection in patients with AIH was improved for short times in cooperation with the immunosuppressive effect of UDCA to accelerated autoimmune reaction to exogenous pathogens.

We examined independent factors among the clinicopathological parameters for frequency of liver dysfunction and found that serum IgG was the most important independent factor. IgG is known to be locally produced by B lymphocytes and transported from the blood in the form of immune complexes<sup>[13-15]</sup>. Serum IgG levels is elevated in patients with chronic infection, chronic hepatitis, liver cirrhosis<sup>[16]</sup>, collagen diseases, autoimmune diseases, and more. AIH

is characterized by a striking increase in serum IgG. Increased IgG implies a lasting stimulation of antigens and abnormal activation of immune systems, and these conditions induce self-perpetuating autoimmune reactions in susceptible individuals. In AIH patients with increased IgG, immune responses to liver autoantigens could be easily triggered by molecular mimicry; and immune responses to exogenous pathogens cross-react with structurally similar self-components. We presume that transient exacerbation after infections in patients with AIH may be a consequence of their immune response to viral and bacterial antigens under the activated autoimmune reactions by increased IgG.

The basic treatment strategy for AIH in Japan is PSL administered alone or in combination with UDCA, because azathioprine is not covered by the Japanese national health insurance<sup>[17]</sup>. It has become clear that UDCA produces some favorable effects in certain AIH patients, most of whom show milder elevation of serum transaminases or histological low-grade inflammatory activity at onset<sup>[18]</sup>. Although the mechanism of the action of UDCA on AIH is still unknown, UDCA has been reported to exert some degree of immunomodulating effects<sup>[17-21]</sup>. Experiments have demonstrated that UDCA suppresses the secretion of several cytokines from activated T lymphocytes and acts directly on B cells to reduce the production of IgG<sup>[19]</sup>. In the present study, the exacerbation of signs of liver dysfunction after infection in patients with AIH treated with UDCA spontaneously normalized for comparatively short times without any additional therapy, and none of the patients developed relapse. UDCA prevents relapse by its immunosuppressive effect on accelerated autoimmune reaction in AIH to exogenous pathogens.

This is the first study in patients with AIH to elucidate the association of infection with the exacerbation of liver dysfunction and demonstrate that higher IgG level is an important factor associated with this exacerbation. Although further research is required to pinpoint the exact relationship between infection and the exacerbation of liver dysfunction in patients with AIH, the present study suggests that infection may play an important causal role in the exacerbation.

### Conflict of interest

The authors who have taken part in this study declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. All authors certify that this article is not under consideration for publication elsewhere. Publication is approved by all authors and by the responsible authorities where the work was carried out.

### Authors' contributions

study concepts/study design, Shigeo Maruyama, Masahiko Koda; Clinical data collection, Shigeo Maruyama; statistical analysis, Masahiko Koda; manuscript drafting or manuscript revision for important intellectual content, Shigeo Maruyama, Masahiko Koda; approval of final version of submitted manuscript, Shigeo Maruyama, Masahiko Koda; and manuscript editing, Masahiko Koda.

## REFERENCES

1. Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 2006; **354**: 54-66. [PMID: 16394302]; [DOI: 10.1056/NEJMr050408]
2. Vento S, Cainelli F. Is there a role for viruses in triggering autoimmune hepatitis? *Autoimmun Rev* 2003; **3**: 61-69. [PMID: 14871651]; [DOI: 10.1016/S1568-9972(03)00053-3]
3. Ercolini AM, Miller SD. The role of infections in autoimmune disease. *Clin Exp Immunol* 2008; **155**: 1-15.

4. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooksley WG, Czaja AJ, Desmet VJ, Donaldson PT, Eddleston AL, Fainboim L, Heathcote J, Homberg JC, Hoofnagle JH, Kakumu S, Krawitt EL, Mackay IR, MacSween RN, Maddrey WC, Manns MP, McFarlane IG, Meyer zum Büschenfelde KH, Zeniya M, et al. International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; **31**: 929-938. [PMID: 10580593]
5. Lyrad KR, Jedda R. Evaluation of patients with leukocytosis. *Am Fam Physician* 2015; **92**: 1004-11. [PMID: 26760415]
6. Honda T, Uehara T, Matsumoto G, Arai S, Sugano M. Neutrophil left shift and white blood cell count as markers of bacterial infection. *Clin Chim Acta* 2016; **457**: 46-53. [PMID: 27034055]; [DOI: 10.1016/j.cca.2016.03.017]
7. Rehmann B, Michitaka K, Durazzo M, Mergener K, Velev P, Manns MP. Viruses and auto-immune hepatitis. *Eur J Clin Invest* 1994; **24**: 11-19. [PMID: 8187802]
8. Christen U, Hintermann E. Pathogen infection as a possible cause for autoimmune hepatitis. *Inter Rev Immunol* 2014; **33**: 296-313. [PMID: 24911790]; [DOI: 10.3109/08830185.2014.921162]
9. Wucherfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. *J Clin Invest* 2001; **108**: 1097-1104. [PMID: 11602615]; [PMCID: PMC209539]; [DOI: 10.1172/JCI14235]
10. Papic N, Pangercic A, Vargovic M, Barsic B, Vince A, Kuzman I. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. *Influenza Other Resp Viruses* 2012; **6**: e2-e5. [PMID: 21951624]; [PMCID: PMC4941665]; [DOI: 10.1111/j.1750-2659.2011.00287.x]
11. Adams DH, Hubscher SG. Systemic viral infections and collateral damage in the liver. *Am J Pathol* 2006; **168**: 1057-1059. [PMID: 16565481]; [PMCID: PMC1606546]; [DOI: 10.2353/ajpath.2006.051296]
12. Shimizu Y. Liver in systemic disease. *World J Gastroenterol* 2008; **14**: 4111-4119. [PMID: 18636653]; [PMCID: PMC2725369]
13. Lui Y, Huang T, Su M, Li J, Chen Z, Qiu Y, Liu X, Yan M, Wang Y, Gu J. Expression and distribution of immunoglobulin G in the normal liver, hepatocarcinoma and postpartial hepatectomy liver. *Lab Invest* 2014; **94**: 1283-1295. [PMID: 25264708]; [DOI: 10.1038/labinvest.2014.114]
14. Migliaccio G, Migliaccio AR, Petti S, Mavilio F, Russo G, Lazaro D, Testa U, Marinucci M, Peschle C. Human embryonic hemopoiesis: kinetics of progenitors and precursors underlying the yolk sac--- liver transition. *J Clin Invest* 1986; **78**: 51-60. [PMID: 3722384]; [PMCID: PMC329530]; [DOI: 10.1172/JCI112572]
15. Gurevich P, Elhayany A, Ben-Hur H, Moldavsky M, Szvalb S, Zandbank J, Schneider DF, Zusman I. Secretory component, J chain, and immunoglobulins in human embryos and fetuses of the first trimester of pregnancy: immunohistochemical study. *Pediatr Dev Pathol* 2002; **6**: 35-42.
16. Maruyama S, Hirayama C, Horie Y, Yorozu K, Maeda K, Inoue M, Fujii Y, Umeki K, Koda M. Serum immunoglobulins in patients with chronic hepatitis: a surrogate marker of disease severity and treatment outcome. *Hepato-Gastroenterol* 2007; **54**: 493-498.
17. Ohira H, Takahashi A. Current trends in the diagnosis and treatment of autoimmune hepatitis in Japan. *Hepatol Res* 2012; **42**: 131-138. [PMID: 22044759]; [DOI: 10.1111/j.1872-034X.2011.00904.x]
18. Toda G, Zeniya M, Watanabe F, Imawari M, Kiyosawa K, Nishioka M, Tsuji T, Omata M. Present status of autoimmune hepatitis in Japan – correlating the characteristics with international criteria in an area with a high rate of HCV infection. *J Hepatol* 1997; **26**: 1207-1212. [PMID: 9210605]
19. Yoshikawa M, Tsuji T, Matsumura K, Yamao J, Matsumura Y, Kubo R, Fukui H, Ishizaka S. Immunomodulatory effects of ursodeoxycholic acid on immune responses. *Hepatology* 1992; **16**: 358-364. [PMID: 1639344]
20. Nakamura K, Yoneda M, Yokohama S, Tamori K, Sato Y, Aso K, Aoshima M, Hasegawa T, Makino I. Efficacy of ursodeoxycholic acid in Japanese patients with type 1 autoimmune hepatitis. *J Gastroenterol Hepatol* 1998; **13**: 490-495. [PMID: 9641646]
21. Miyake Y, Iwasaki Y, Kobayashi H, Yasunaka T, Ikeda F, Takaki A, Okamoto R, Takaguchi K, Ikeda H, Makino Y, Ando M, Sakaguchi K, Yamamoto K. Efficacy of ursodeoxycholic acid for Japanese patients with autoimmune hepatitis. *Hepatol Int* 2009; **3**: 556-562. [PMID: 19847577]; [PMCID: PMC2790591]; [DOI: 10.1007/s12072-009-9155-9]

Peer Reviewers: Hee Bok Chae; Bulent Baran