Medical Science Monitor
eISSN: 1643-3750
PUBLISHER: ISI

Med Sci Monit. 2017; 23: 4028–4033.
Published online 2017 Aug 20. doi: 10.12659/MSM.902576
PMCID: PMC5574375
PMID: 28822993

Seropositivity and Titers of Anti-Smooth Muscle Actin Antibody Are Associated with Relapse of Type 1 Autoimmune Hepatitis

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Received 2016 Nov 28; Accepted 2017 Feb 13.

Abstract

Background

It is important to avoid relapse in autoimmune hepatitis (AIH) because repeated multiple relapses have been associated with a worse prognosis. However, risk factors for relapse before initiation of treatment are not fully understood. The aim of this study was to find predictive markers for relapse of type 1 AIH.

Material/Methods

We reviewed the records of 53 patients diagnosed with type 1 AIH based on the revised scoring system proposed by the International Autoimmune Hepatitis Group (IAIHG) between 2009 and 2014 at 4 hospitals belonging to the Saga Study Group of Liver Diseases (SASLD). We analyzed the differences in background characteristics between patients with or without relapse.

Results

All patients achieved remission after treatment, and 9 (17%) subsequently relapsed. The relapsed patients were significantly younger and had a higher positive rate of anti-smooth muscle antibody (ASMA) than the non-relapsed patients (100% *vs.* 25%, *P*=0.0012). Moreover, relapse rate increased with titer of ASMA, while titer of antinuclear antibody was not associated with relapse rate.

Conclusions

ASMA is a useful predictive marker for relapse of type 1 AIH during or after withdrawal of medical therapy. More careful attention should be paid to immunosuppressive therapy in patients with high titers of ASMA.

MeSH Keywords: Autoantibodies, Hepatitis, Autoimmune, Recurrence

Background

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown etiology that typically affects women, and is characterized by elevated liver enzymes and serum immunoglobulins, and autoantibodies. Some studies have reported the importance of achieving normalization of alanine aminotransferase (ALT) levels and a good response to immunosuppressive therapy to attain good prognosis [1,2]. Most patients attain normalization of ALT within 6 months after the introduction of immunosuppressive therapy [3]; therefore, the prognosis of AIH is generally good. However, it has been reported that multiple relapses, compared with single relapse or sustained remission, are associated with a worse prognosis. Patients who had relapsed repeatedly and required retreatment have high risk of several steroid-related complications, including diabetes, stomach ulcer, and osteoporosis, as well as high risk of developing cirrhosis and hepatic death or need for liver transplantation [4,5].

A previous study showed that the duration and the tapering rate of corticosteroid administration until ALT normalization were associated with relapse [6]. However, there are, in fact, some patients who relapse in spite of continuous and sufficient immunosuppressive therapy. Although another study demonstrated that patient characteristics such as age, ALT, or IgG level were related to relapse, it is still unclear whether this is true [7]. Accordingly, finding factors associated with relapse is very important to management of AIH patients and would help improve their outcomes.

AIH is classified into types 1 and 2, based on autoantibody profile. Anti-smooth muscle antibody (ASMA) and antinuclear antibody (ANA) have been used to define type 1 AIH, and antibodies to liver–kidney microsome (anti-LKM) type 1 have been used to define type 2 AIH [8]. According to a Japanese nationwide survey, approximately 90% of AIH cases were positive for ANA, and ASMA was seen in 42.5% [3], whereas anti-LKM1 is rarely found in Japan [9]. Some recent studies have demonstrated that these autoantibodies might be associated with disease activity of AIH.

Therefore, the aim of this study was to find risk factors for relapse of type 1 AIH, including autoantibody status, disease severity, mode of disease onset, and liver histology before treatment.

Material and Methods

Study population

We reviewed the records of patients diagnosed with type 1 AIH between 2009 and 2014 at 4 hospitals associated with the Saga Study Group of Liver Diseases (SASLD). Seventy-six patients were diagnosed with AIH based on the revised scoring system proposed by the IAIHG [10] and the profile of autoantibodies. Patients with hepatic failure at diagnosis, hepatitis B or C virus infection, evidence of alcohol- or drug-induced liver injury, or incomplete medical records were excluded from this study.

Finally, we enrolled 53 patients and analyzed their clinical and laboratory data retrospectively. All the patients satisfied the IAIHG diagnostic criteria for probable or definite AIH. The median observation period was 46.2 months. For eligible patients, the following clinical characteristics were examined: sex, age, body mass index (BMI), blood counts, biochemical tests, IgG levels, autoantibodies (including ANA and ASMA), concomitant autoimmune diseases, disease severity, type of disease presentation, treatment method, and liver histology. The Institutional Review Board or Ethics Committee of each institution approved the study protocol.

Remission was defined as improvement of serum ALT levels within the upper limit of normal (ULN) after medical treatment. Relapse was defined as serum ALT levels ≥2 times ULN after remission [11]. Acute AIH was defined as acute presentation of symptoms with serum total bilirubin levels >5 mg/dl and/or serum ALT levels ≥10 times ULN, and no history of liver disease [12]. Disease severity was classified as described previously [13].

Detection of ANA and ASMA was carried out by indirect immunofluorescence using HEp-2 cells or frozen sections of rat kidney. A serum titer of 1: 40 or more was defined as positive for ANA and ASMA.

All but 1 case underwent liver biopsy to evaluate pathological characteristics before or just after initiation of treatment. Percutaneous liver biopsy was performed with a 16-gauge needle using an ultrasound-guided technique. Fibrotic staging ranged from 0 to 4 [14].

Statistical analysis

Differences in patient characteristics and laboratory data between those with and without relapse were assessed using the χ^2 test for categorical data and *t* test for continuous variables. $P<0.05$ was considered statistically significant. Statistical analyses were conducted with R version 3.0.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

All 53 patients achieved remission once after initial treatment, and 9 (17%) subsequently relapsed. Table 1 shows the differences in clinical characteristics at the time of diagnosis according to patients with/without relapse.

Table 1

Comparison of patients characteristics between with and without relapse.

Characteristic	Relapse (n=9)	Non-relapse (n=44)	P
Age (years)	50.7±13.0	63.5±10.8	0.0028
Female	9 (100)	38 (86.4)	0.2394
Body mass index (kg/m^2)	20.6±7.6	22.6±3.8	0.2378
Platelet (×10^4/mm^3)	17.4±6.2	18.1±6.6	0.7546
Albumin (g/dL)	3.9±0.4	3.7±0.6	0.3361
Total bilirubin (mg/dL)	4.0±7.4	3.6±4.7	0.8243
AST (IU/L)	383.4±424.9	402.0±463.7	0.9123
ALT (IU/L)	563.2±570.4	430.7±495.1	0.4787
γ-glutamyltransferase (IU/L)	146.4±114.1	207.9±158.5	0.2757
Alkaline phosphatase (IU/L)	478.3±255.4	488.8±225.6	0.9020
Prothrombin activity (%)	84.7±19.5	82.2±17.8	0.7100
IgG (mg/dL)	2044.1±574.9	2140.1±762.4	0.7230
ANA positive	9 (100)	40 (90.9)	0.0851
ASMA positive*	6/6 (100)	7/28 (25)	0.0012
HLA-DR4 positive**	8/9 (88.9)	17/29 (58.6)	0.0945
Revised IAIHG score	15.4±2.3	14.7±2.8	0.4436
Definite diagnosis	5 (55.6)	19 (43.2)	0.4968
Severity (%)	1 (11.1)	3 (6.8)	0.6569
Liver histology			
Fibrosis stage F3 or F4	0 (0)	10 (22.7)	0.0779
Acute onset	2 (22.2)	8 (18.2)	0.7777
Concomitant autoimmune disease	0 (0)	9 (20.5)	0.1365
Treatment			
With steroid (predonisolon)	9 (100)	36 (81.8)	0.1651
Initial dose (mg)	39.3±6.1	34.0±10.1	0.1958
Maintainance dose (mg)	3.2±4.0	4.0±3.5	0.6137
Withdrawal	3 (42.9)	6 (20.0)	0.2044
Reduction rate until ALT normalization (mg/week)	1.5±1.2	1.4±1.6	0.8807
Duration to remission (weeks)	3.7±3.5	3.4±3.8	0.8216

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Results are expressed as the mean ± standard deviation or number (%). Statistical differences weres analysed by t-test or χ^2 test. AST – asparate aminotransferase; ALT – alanine aminotransferase; ANA – antinuclear antibody; ASMA – antismooth muscle antibody;

*n=34;
**n=38.

There were no significant differences between the 2 groups with respect to sex, liver function, ANA-positive rate, IgG levels, type of disease presentation, and grade of severity. However, the relapsed group was significantly younger (*P*=0.0028, 50.7 years vs. 63.5 years) and had a significantly higher ASMA-positive rate (P=0.0012, 100% *vs.* 25%) in the 34 patients measured. All 6 of the relapsed patients were positive for ASMA, whereas only 7 of 28 (25%) were positive for ASMA in the non-relapsed group.

Nine patients had a concomitant autoimmune disease: 3 with primary biliary cirrhosis, 2 each with hypothyroidism or rheumatoid arthritis, and 1 each with hyperthyroidism, systemic lupus erythematosus, or systemic sclerosis. The rate of comorbidity with other autoimmune diseases did not differ significantly between the 2 groups.

Fifty-two patients underwent needle biopsy of the liver. There were no patients with advanced fibrosis in the relapsed group. Forty-five patients received prednisolone (PSL)-based treatment, and 8 were treated with ursodeoxycholic acid (UDCA) monotherapy (300–900 mg/day). UDCA monotherapy tended to be applied to elderly patients with low-grade histological and biochemical activity, or patients with comorbidity such as diabetes mellitus and osteoporosis. Relapse was not seen in patients treated with UDCA monotherapy. In the PSL-based treatment group, there was no significant differences between patients with and without relapse with respect to initial dose (39.3 *vs.* 34.0 mg), maintenance dose (3.2 *vs.* 4.0 mg), dose reduction rate (1.5 *vs.* 1.4 mg/week), withdrawal rate (42.9 *vs.* 20.0%), or time to remission (3.7 *vs.* 3.4 weeks).

To investigate the influence of autoantibody titers on relapse, we analyzed the correlation between relapse rate and titer of ASMA and ANA. Relapse rate increased with titer of ASMA, while titer of ANA did not correlate with relapse rate (Figure 1).

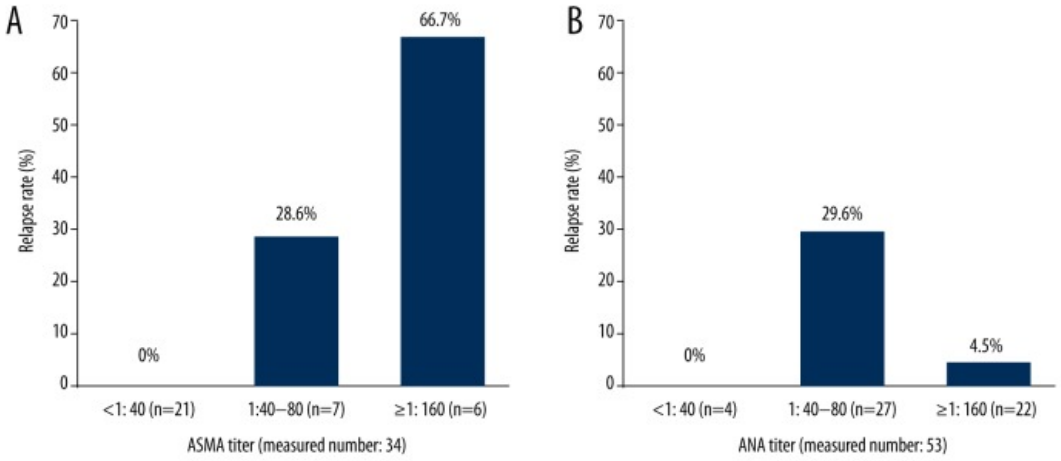

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Figure 1

Relapse rates according to titers of ASMA and ANA. Bar graph (**A**) shows 34 patients who had ASMA checked and (**B**) shows 53 patients who had ANA checked. (**A**) Cases with an ASMA titer of 1: 160 or higher had significantly higher relapse rates than those with a titer of <1: 80 or negative (*P*=0.0005). (**B**) There was no association between relapse rates and ANA titers. ASMA – anti-smooth muscle antibody; ANA – antinuclear antibody.

To clarify the usefulness of ASMA measurement, the positive predictive value (PV+) and the negative predictive value (PV−) for relapse were analyzed. When the cut-off value of ASMA titer was set at 1: 40, PV+ and PV− were 0.46 and 1.0, respectively, and if set at 1: 160, PV+ and PV− were 0.67 and 0.93, respectively.

We also investigated the characteristic differences between patients with and without ASMA. There were no significant intergroup differences with respect to age, sex, liver function, ANA positive rate, IgG levels, type of disease presentation, or grade of severity, except HLA-DR4 (Table 2).

Table 2

Comparison of patients characteristics between with and without ASMA.

Characteristic	ASMA +ve (n=13)	ASMA −ve (n=21)	P
Age (years)	55.5±8.7	60.6±9.9	0.1360
Female	13 (100)	17 (81.0)	0.0939
Body mass index (kg/m^2)	23.8±4.0	22.0±3.9	0.2329
Platelet (×10^4/mm^3)	20.2±4.4	19.1±7.5	0.6318
Albumin (g/dL)	3.9±0.4	3.7±0.6	0.2059
Total bilirubin (mg/dL)	3.6±6.3	4.0±4.6	0.8605
AST (IU/L)	415.8±361.8	447.0±505.3	0.8480
ALT (IU/L)	620.6±524.1	458.0±558.3	0.4049
γ-glutamyltransferase (IU/L)	221.9±134.8	241.1±187.5	0.7503
Alkaline phosphatase (IU/L)	555.0±292.0	491.4±198.4	0.4544
Prothrombin activity (%)	91.5±18.9	81.8±16.4	0.1298
IgG (mg/dL)	1989.5±508.0	2072.5±637.4	0.6941
ANA positive	10 (76.9)	20 (95.2)	0.1072
HLA-DR4 positive*	10/10 (100)	7/17 (41.2)	0.0022
Revised IAIHG score	16.2±2.6	14.2±2.7	0.0474
Definite diagnosis	9 (69.2)	8 (38.1)	0.0776
Severity (%)	1 (7.7)	1 (4.8)	0.7242
Liver histology			
Fibrosis stage F3 or F4	0 (0)	5 (23.8)	0.0568
Acute onset	4 (30.8)	3 (14.3)	0.1276
Concomitant autoimmune disease	0 (0)	5 (23.8)	0.0568
Treatment			
With steroid (predonisolon)	10 (76.9)	17 (81.0)	0.7777
Initial dose (mg)	26.9±18.0	30.0±17.4	0.6313
Maintainance dose (mg)	4.7±8.3	2.8±3.4	0.3656
Withdrawal	3 (30.0)	5 (29.4)	0.9742
Reduction rate until ALT normalization (mg/week)	1.7±1.6	1.6±1.5	0.8639
Duration to remission (weeks)	4.6±3.1	6.4±6.1	0.4193

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Results are expressed as the mean ± standard deviation or number (%). Statistical differences weres analysed by t-test or χ^2 test. AST – asparate aminotransferase; ALT – alanine aminotransferase; ANA – antinuclear antibody; ASMA – antismooth muscle antibody;

*n=27.

Discussion

This is the first study to show that seropositivity and titer of ASMA were associated with relapse after treatment withdrawal or during maintenance therapy in type 1 AIH patients who reached remission once after medication. There were no similar results for ANA. Although ANA and ASMA are the most common markers for type 1 AIH, the etiological role of these autoantibodies has still not been elucidated. Some studies have shown the relationship between seropositivity of autoantibodies and biochemical activity of AIH. In a longitudinal study on childhood AIH, Gregorio et al. reported that ASMA and anti-LKM1 titers were associated with biochemical disease activity [15]. Moreover, a recent, larger cohort study reported that ASMA titers during treatment were significantly associated with histological and biochemical activity of AIH, but ANA titers were not [16]. Considering these results from previous studies and our present study, ASMA might be an important marker for disease activity associated with relapse of type 1 AIH.

Several studies demonstrated that relapse occurred in 25–30% of Japanese AIH patients on tapered schedules or after drug withdrawal [6,7,17]. Although suppression of relapse is important to improve prognosis of AIH, risk factors for relapse before initiation of treatment are not fully understood. Other than ASMA, only onset age differed significantly between relapsed and non-relapsed patients in our study. It was also reported that patients aged <45 years had an increased risk of relapse compared with elderly patients [18]. Al-Chalabi et al. indicated that there were no significant differences between patients presenting at age >60 years and <60 years with respect to mode of onset, other clinical signs at presentation, biochemical parameters, types or titers of autoantibodies, incidence of histological cirrhosis, response to therapy, and prognosis. They speculated that disease severity or activity of AIH might be related to immunological factors more than age *per se* [19]. In terms of treatment method, there were no differences between relapsed and non-relapsed patients in terms of initial dose, maintenance dose, and reduction rate of PSL in our study. The rate of PSL withdrawal and the time to remission in the relapsed group were also comparable to those in the non-relapsed group. Our results strongly suggest that ASMA could be an independent predictor for relapse during treatment or after withdrawal, because ASMA seropositivity and its titers had no association with factors such as age or corticosteroid treatment procedure (Table 2). In the present study, HLA-DR4 frequency was significantly higher in patients with ASMA. In terms of HLA phenotype, HLA-DR3 was reported to be associated with vigorous immune response [20]. On the other hand, HLA-DR4 was considered to have nothing to do with prognosis in a Japanese study [14]. We could not determine why the HLA-DR4-positive rate was higher in patients with ASMA in this study.

One major limitation was that our study was carried out in a small number of patients, and the data on ASMA, HLA, and histological findings were not available for all patients because it was a retrospective study. To confirm our results, prospective studies in a larger cohort are needed.

Conclusions

Our study suggests that ASMA positivity and its titer might have some association with refractory AIH pathogenesis, although its accuracy is not sufficient because of small its small sample size and retrospective nature.

Footnotes

Source of support: Departmental sources

Conflicts of interest

None.

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