Prevalence and Clinical Relevance of Serum Autoantibodies in Patients with Chronic Hepatitis C

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Background: Chronic hepatitis C (CHC) is frequently associated with the presence of serum autoantibodies. The prevalence and clinical relevance of serum autoantibodies in CHC patients and their influence on antiviral treatment have not been well established.

Methods: From February 1999 to July 2004, 460 consecutive adult patients with CHC were studied. Antinuclear antibody (ANA) and smooth muscle antibody (SMA) were determined by indirect immunofluorescence. The presence of these antibodies was related to patient characteristics and to the outcome of 24 weeks of therapy with interferon (IFN) alfa-2b (n = 376) or pegylated-IFN alfa-2b (n = 84) plus ribavirin.

Results: The prevalence of ANA and SMA was 7.4% and 19.3%, respectively. Seropositivity for ANA and/or SMA was associated with old age and high aspartate aminotransferase (AST) levels. The rates of sustained virological response and early withdrawal of therapy were comparable between autoantibody-positive and -negative patients. None of the autoantibody-positive patients experienced a flare-up of transaminase during treatment, or developed severe systemic autoimmune disease.

Conclusion: Serum ANA and/or SMA-positive HCV-infected patients are older, and have higher disease activity and severity than their negative counterparts. However, the presence of ANA or SMA did not influence the response to combination antiviral therapy, which is safe and effective in autoantibody - positive CHC patients.

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Key words: hepatitis C, antinuclear antibody, smooth muscle antibody, sustained virological response, antiviral therapy

Hepatitis C virus (HCV) is a linear, single-stranded RNA virus of the Flaviviridae family which was identified in 1989; its infection causes one of the most common chronic diseases in the world.[1-3] In addition to liver injury, HCV infection has been associated with several immune-mediated phenomena, including autoimmune thyroiditis, Sjogren's syndrome and essential mixed cryoglobulinemia.[4,5] In

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particular, the occurrence of serum non-organ-specific autoantibodies (NOSAs) is common in patients with chronic hepatitis C (CHC).[1,6] Smooth muscle antibody (SMA) and antinuclear antibody (ANA) are frequently detected NOSAs.[7,8] In the general population, the prevalence of NOSAs is higher in anti-HCV-positive subjects than in healthy or disease controls, and is associated with chronic liver disease.[9] Variations in the prevalence of ANA and SMA in Western countries have been reported (from 10-66%).[8-10] In Taiwan, the data reporting the prevalence of serum autoantibodies in CHC are not uniform.[11-13]

Recently, administration of interferon (IFN)-alfa or pegylated-IFN-alfa in combination with ribavirin has proven to be the most promising therapeutic approach for the treatment of CHC.[14-16] To date, more than 300,000 patients with CHC have undergone IFN-based therapies, and 40-60% of them have achieved a sustained virological response (SVR).[14-16] Moreover, available data on the relationship between autoantibody seropositivity and the response to antiviral therapy in CHC patients are limited and controversial.[17-19]

In this study, we aimed to assess the prevalence of serum autoantibodies and to evaluate their clinical relevance in CHC patients, in a large cohort in southern Taiwan. In addition, to investigate the impact of ANA and SMA on the response to combined antiviral therapy (IFN or pegylated IFN plus ribavirin) in CHC patients, we retrospectively analyzed the differences in the SVR in ANA, SMA-positive patients compared with that in ANA, SMA-negative patients.

METHODS

Patients

From February 1999 to July 2004, 460 consecutive adult CHC patients who visited the gastroenterologic clinics of Kaohsiung Chang Gung Memorial Hospital were collected. There were 257 men and 203 women, with a mean age of 50.6 ± 11.2 years. All patients had positive HCV antibody (Ax SYM HCV 3.0, Abbott's Laboratories, Chicago, IL, U.S.A.), detectable HCV RNA (Amplicor™, Roche Diagnostics, Branchburg, NJ, U.S.A.) in the serum, and elevated alanine aminotransferase (ALT) levels. The exclusion criteria included human immunodeficiency virus coinfection, decompensated liver disease, hepatitis other than hepatitis C (hepatitis B, autoimmune hepatitis and alcohol abuse ≥ 20 g daily), and other major contraindications to IFN or ribavirin therapy.

The patients underwent liver biopsies within three months before the start of therapy. The histological grading and staging of chronic liver diseases were based on a modified Knodell histology index, reflecting the degree of hepatic inflammation and fibrosis, respectively.[20] Before treatment, informed consent was obtained from each patient and the study was carried out in accordance with the provisions of the Declaration of Helsinki.

The patients received a 24-week course of IFN alfa-2b (Intron A, Schering-Plough Corporation, New Jersey, U.S.A.) 3 or 5 million units subcutaneously thrice weekly (n = 376) or pegylated-IFN alfa-2b 1-1.5 micrograms/ kg subcutaneously once weekly (n = 84) plus oral ribavirin (Rebetal, Schering-Plough). The choice and dosage of IFN was not randomized and was given by the clinical doctor. Ribavirin was initially given at a total daily dose of 1000 mg for patients who weighed 75 kgs or less and 1200 mg for patients who weighed more than 75 kgs.

NOSA detection and virological assays

ANA and SMA were investigated by indirect immunofluorescence on cryostat sections of rat liver, kidney, and stomach specimens. Positive reactions were titered by double dilution to the end point. ANA ≥ 1:40 and SMA ≥ 1:20 were considered positive results. Qualitative detection of HCV RNA was performed by a standardized qualitative reverse transcription-polymerase chain reaction assay (Amplicor™, Roche Diagnostics) using biotinylated primers for the 5' noncoding region. The lowest detection limit of this assay was 100 copies/ml. Serum HCV RNA levels were determined by a branched-DNA (b-DNA) signal amplification assay (VERSANT HCV RNA 3.0. Assay, Bayer Diagnostics, Emeryville, CA, U.S.A.). Genotyping of HCV was done by reverse hybridization assay (Inno-LiPA™ HCV II; Innogenetics N.V., Gent, Belgium) using the HCV-Amplicor products. An SVR was defined as undetectable HCV RNA at the end of 24 weeks of follow-up with combined antiviral therapy.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation. Comparisons of differences in categorical data between groups were performed using chi square analysis. Distributions of continuous variables were analyzed by the t-test or Mann-Whitney U test for the two groups where appropriate. Stepwise logistic regression analysis was used to identify the independent variables associated with serum autoantibodies. All analyses were carried out using SPSS software version 11.0 (SPSS Inc., Chicago, IL, U.S.A.). All tests were 2-tailed, and a *p-value* of less than 0.05 was considered statistically significant.

RESULTS

Prevalence of ANA and SMA in CHC patients

Fig. 1 shows the prevalence of ANA and SMA in the 460 adult CHC patients on entry. Thirty-four (7.4%) had an ANA titer ≧ 1:40 and were positive for ANA. The titers ranged from 1:40 (14 cases) to 1:1280 (1 case). Eighty-nine (19.3%) had an SMA titer ≧ 1:20 and were positive for SMA, ranging from 1:20 (40 cases) to 1:1280 (1 case).

Clinical correlation of ANA and SMA in CHC patients

Table 1 lists the patient characteristics and the clinical and biochemical features of the serum ANA and/or SMA-positive and -negative patients at baseline. The mean age of the serum autoantibody-positive patients was significantly higher than that of their negative counterparts (52.6 ± 9.8 vs. 49.9 ±

Table 1. Comparison of Baseline Characteristics between Patients with and without Anti-nuclear Antibody and Smooth Muscle Antibody

	SMA and/or ANA (+) (n = 112)	SMA and ANA (-) (n = 348)	*p*-value
Age (yrs)	52.6 ± 9.8	49.9 ± 11.5	0.031
Sex (M/F)	59/53	198/150	0.250
Body weight (kgs)	64.6 ± 10.4	64.5 ± 10.4	0.934
Genotype (1/non-1)	44/43	146/152	0.445
Log HCV-RNA (copies/ml)	5.9 ± 0.9	5.8 ± 1.1	0.317
HAI inflammation score	6.9 ± 2.5	6.4 ± 2.6	0.143
HAI fibrosis score	2.0 ± 1.7	1.6 ± 1.6	0.046
Fibrosis score 3,4/0-2	49/53	120/207	0.027
WBC (10^3/mm^3)	5.8 ± 1.8	6.0 ± 1.7	0.377
Hemoglobin (g/dL)	13.8 ± 1.5	14.1 ± 1.5	0.124
Platelets (10^4/mm^3)	15.9 ± 5.6	17.7 ± 6.5	0.009
Platelets < 15/ ≥ 15 (10^4/mm^3)	50/59	123/217	0.046
AST (U/L)	120 ± 90	95 ± 71	0.004
ALT (U/L)	185 ± 159	164 ± 146	0.138
AFP (ng/ml)	18.8 ± 30.3	13.2 ± 24.6	0.195

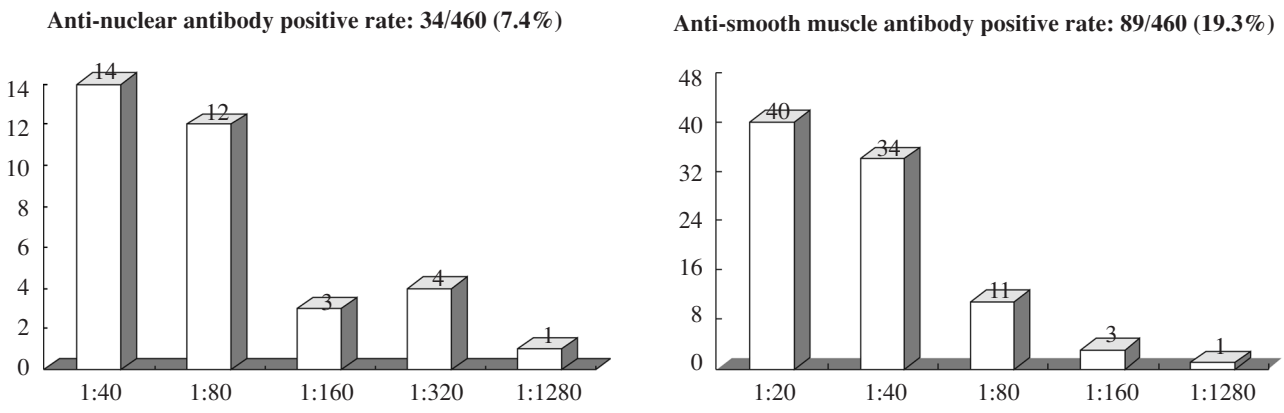

Fig. 1 Prevalence of antinuclear antibody (ANA) and smooth muscle antibody (SMA) in CHC patients.

11.5, *p-value* = 0.031). At baseline, the serum autoantibody-positive patients had higher serum levels of aspartate aminotransferase (AST) and alfa-fetoprotein (AFP) than the autoantibody-negative patients, but there were no differences in virological features (genotype and log HCV-RNA) between these two groups. The serum autoantibody-positive patients had also higher fibrosis scores and lower platelet counts than autoantibody-negative patients.

Table 2 presents the results of stepwise logistic regression analysis correlating the positive serum autoantibodies (either positive vs. both negative). Age and the aspartate aminotransferase (AST) level were the independent variables associated with the presence of serum autoantibodies. When comparing the SMA-positive patients with SMA negative patients, the independent variables were age and advanced fibrosis (scores of 3 and 4).

Response to combined antiviral therapy for different autoantibody statuses

Fig. 2 shows the association of serum autoantibodies with the SVR and withdrawal rate. The SVR rates were comparable between ANA (+) *vs*. ANA (-), SMA (+) *vs*. SMA (-), or Any (+) *vs*. both (-). There were also no significant differences in withdrawal rates between these groups. Notably, none of our patients with positive serum autoantibodies experienced a flare-up of ALT levels up to 5 times the upper limit of normal during treatment, or developed systemic autoimmune disease that required withdrawal of combination therapy, including the 5 patients with high ANA titers (≥ 1:320) and the 4 patients with high SMA titers (≥ 1:160).

Predictors of SVR to combined antiviral therapies

To understand the factors correlated with combined antiviral therapies, we compared patients with and without a SVR (Table 3). Serum autoantibodies were not associated with the SVR to combined antiviral therapy. In contrast, the predictors of a SVR were young age ($p = 0.010$), higher ribavirin dosage ($p < 0.001$), non-genotype 1 ($p < 0.001$), low viral

Table 2. Stepwise Multiple Logistic Regression Analysis of Factors Associated with Serum Autoantibodies

	Comparison	Odds ratio	95% CI	*p*-value
ANA and/or SMA(+) vs. both(-)				
Age (yrs)	per 1 increase	1.024	1.002~1.046	0.036
AST (U/L)	per 1 increase	1.003	1.000~1.006	0.044
SMA(+) vs. SMA(-)				
Age (yrs)	per 1 increase	1.029	1.003~1.056	0.030
Fibrosis	F3,4 vs. F0-2	1.840	1.087~3.113	0.023

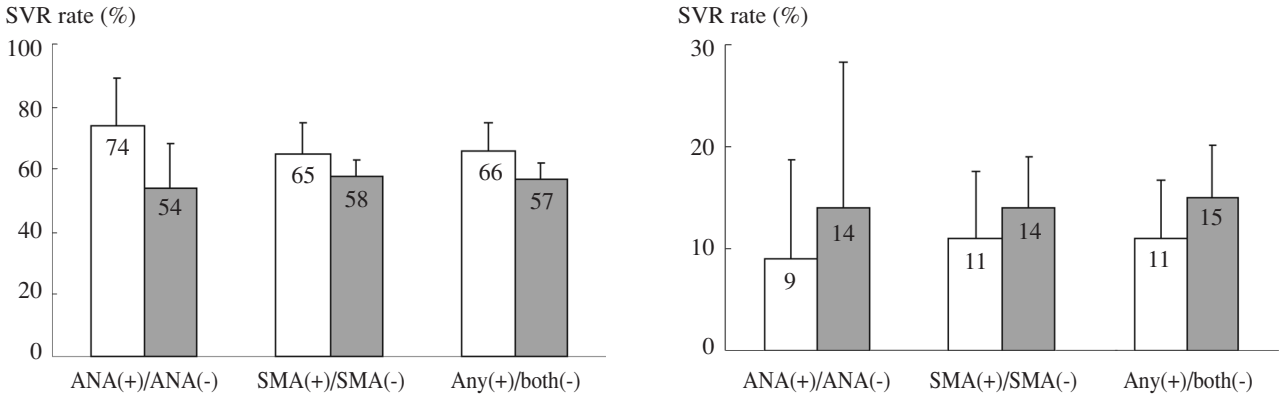

Fig. 2 Association of serum autoantibodies with the SVR and withdrawal rate.

Table 3. Comparisons between Patients With SVR and Non-SVR

	SVR (n = 274)	Non-SVR (n = 186)	*p*-value
Age (yrs)	49.5 ± 11.1	52.2 ± 11.1	0.010
Sex (M/F)	221/168	93/90	0.105
Body weight (kgs)	63.9 ± 10.4	65.6 ± 10.2	0.081
ANA (+/-)	25/249	9/177	0.059
SMA (+/-)	58/216	31/155	0.140
ANA and/or SMA+/both-	74/200	38/148	0.066
IFN (conventional/ pegylated)	220/54	156/30	0.198
Ribavirin (per kg, per day)	14.9 ± 3.2	13.6 ± 3.5	< 0.001
Genotype (1/non-1)	88/161	102/34	< 0.001
Log HCV-RNA (copies/ml)	5.6 ± 1.1	6.1 ± 0.9	< 0.001
HAI inflammation score	6.7 ± 2.6	6.2 ± 2.6	0.061
HAI fibrosis score	1.5 ± 1.6	2.0 ± 1.7	0.004
Platelet (10^4/mm^3)	18.2 ± 6.0	15.9 ± 6.5	< 0.001
AST (U/L)	106 ± 77	95 ± 76	0.174
ALT (U/L)	189 ± 159	141 ± 131	0.001

load ($p < 0.001$), low fibrosis score ($p = 0.004$), high platelet count ($p < 0.001$) and high ALT level ($p = 0.001$).

Fig. 3 shows the association of serum autoantibodies with the SVR in different HCV genotypes. Among the genotype-1 patients, there was no significance in the SVR rate between ANA (+) *vs*. ANA (-), SMA (+) *vs*. SMA (-), and any (+) *vs*. both (-). In the genotype non-1 patients, the SVR rate was also comparable between these groups.

DISCUSSION

Previous studies have shown that serum autoantibodies are commonly found in CHC patients.[1,6] HCV infection plays an important role in the pathogenesis of the immunologic derangement, but the mechanism remains unclear.[21] A frequently offered explanation is that the release of intracellular antigens at the time of hepatocellular injury triggers immune responses in the form of autoantibody production.[22] In our cohort, we observed a prevalence of 7.4% for ANA and 19.3% for SMA in CHC patients. This prevalence is slightly lower than the high prevalence of ANA and SMA in CHC patients shown in previous studies.[9,23] The difference in autoantibody prevalence between the various studies may derive from technical factors or differences in the populations investigated. Recently, much research has described an age-dependent increased production of autoantibodies.[24,25] In our study, we confirmed that those patients with CHC who were

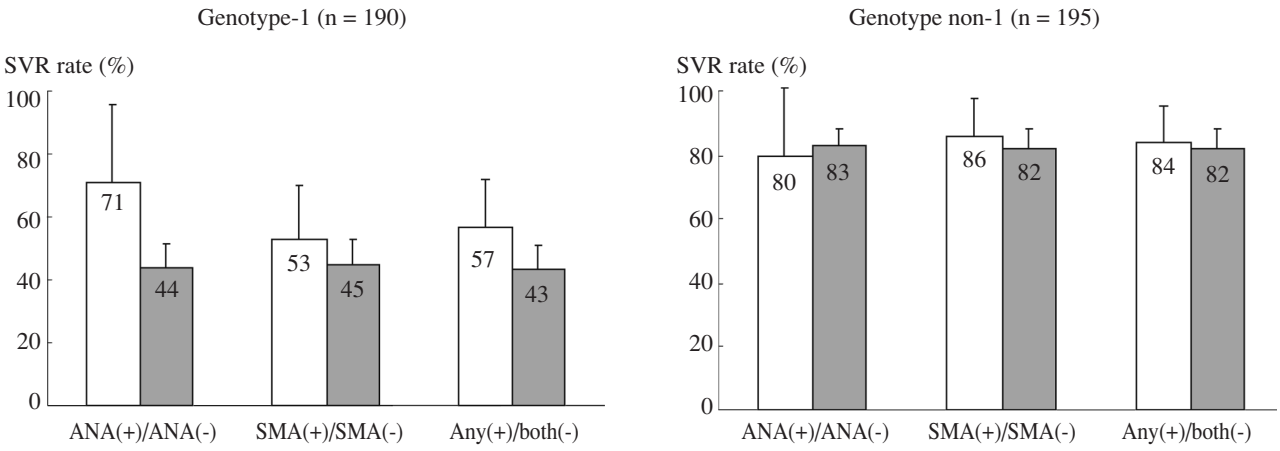

Fig. 3 Association of serum autoantibodies with the SVR in different genotypes.

autoantibody-positive were older than those who were autoantibody-negative. This phenomenon might result from functional defects in suppressor T cells in older patients.[25,26] Although some reports observed that women were more likely than men to develop ANA,[8,27] gender was not a significant factor associated with the presence of autoantibodies in our series. In addition, autoantibody-positive CHC patients had higher serum AST levels and more severe fibrosis scores than their seronegative counterparts. These results are in accordance with most published data, suggesting that HCV-infected autoantibody-positive patients have higher disease activity and severity than those who are autoantibody-negative.[8,28]

At present, IFN-alfa is the most effective treatment for CHC patients; however, a potentially severe side effect is the induction of autoimmunity.[29] It is important to understand the factors predictive of these unfavorable conditions to prevent them or minimize adverse effects. In our cohort, the withdrawal rates during therapy with IFN or pegylated IFN plus ribavirin were not significantly different in the groups. It is worth noting that none of the autoantibody -positive patients experienced a flare-up of ALT levels during treatment, or developed severe systemic autoimmune disease that required withdrawal of combination therapy. Our data was in accordance with previous reports suggesting that chronic hepatitis C patients with autoantibodies showed a favorable response to IFN,[19,30] but not to prednisone. The latter regimen can exacerbate liver necrosis in these subjects.[19,30] This finding implies that the presence of these autoantibodies in CHC patients is more closely associated with clinical or biochemical factors such as old age or higher AST levels, and is not associated with combination with autoimmune hepatitis or any other systemic autoimmune disease.

In this study, we found that the presence of serum autoantibodies in CHC patients did not influence the response to combined antiviral therapy, which was similar in both serum autoantibody-positive and -negative patients (SVR rate about 70%). In contrast, the predictors of a SVR were young age, higher ribavirin dosage, non-genotype 1, low viral load, low fibrosis score, high platelet count and high ALT level. Of these variables, HCV genotype may be the most important prognostic factor associated with a SVR. We therefore analyzed the differences in the SVR in autoantibody-positive patients compared with autoantibody-negative patients by dividing into two groups (genotype-1 and genotype non-1). However, the SVR rates were also comparable between ANA (+) *vs*. ANA (-), SMA (+) *vs*. SMA (-), or any (+) *vs*. both (-) for different genotypes.

Some major limitations should be considered when interpreting our findings. First, this retrospective observational study was based on our hospital medical records, so it would be difficult to validate whether some information is lacking. For example, there was no complete record of the ANA distribution type in ANA-positive patients in our series. Whether the distribution type has clinical relevance is worthy of future study. Second, because two pathologists checked most of the liver histology specimens in our hospital, we could not avoid the possibility of inter-observer variation. However, this bias might be smaller in our large cohort. Third, the external validity of this study is questionable, since only our hospital patients were included in the data analysis; therefore, it is possible that our findings can not be extrapolated to all CHC patients in Taiwan.

In conclusion, serum ANA and/or SMA-positive HCV-infected patients were older, and higher AST levels and fibrosis scores than their negative counterparts. The presence of ANA or SMA did not influence the response to combination antiviral therapy. Combined antiviral treatment is safe and effective in ANA or SMA-positive patients with CHC.

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慢性 C 型肝炎病人血清自體抗體之盛行率與臨床之相關性

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背 景： 慢性 C 型肝炎病人血清經常出現自體抗體，其臨床意義與對 C 型肝炎抗病毒治療之影響仍尚未確立，本文探討慢性 C 型肝炎病人血清自體抗體之盛行率、臨床特徵及是否影響抗病毒治療之療效。

方 法： 回溯分析本院 460 名慢性 C 型肝炎病人 (含 257 位男性及 203 位女性，平均年齡 50.6 ± 11.2 歲) 其臨床資料、抗核抗體 (ANA) 及抗平滑肌抗體 (SMA) 陽性率、血液及生化檢驗、C 型肝炎病毒及病理特徵。病人接受傳統干擾素 α-2b 一週三次 (376 人) 或長效干擾素-α-2b 一週一次 (84 人)，合併每天口服 ribavirin 1000-1200 毫克治療 24 週。

結 果： ANA 及 SMA 之陽性率分別爲 7.4% 及 19.3%。比較陽性 ANA 或 SMA 病人與 ANA、SMA 皆陰性之患者發現前者的年齡較高、有較高 AST 值。比較陽性 ANA 或 SMA 病人與皆陰性之患者其治療中斷率並無差別，且無人因 ALT 值疾速上升而中斷治療。

結 論： 本研究顯示慢性 C 型肝炎病人合併血清 ANA 或 SMA 陽性者相較於兩抗體皆陰性之患者，其年齡較大且疾病嚴重度較高。然而陽性 ANA 或 SMA 並不會影響抗病毒治療的成效，所以 C 型肝炎合併自體免疫抗體陽性之病患，接受抗病毒治療仍是有效且安全的。

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關鍵詞： C 型肝炎，抗核抗體，抗平滑肌抗體，持續性病毒反應，抗病毒治療

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