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Alcoholism and Susceptibility to Alcoholic Liver Disease

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To the Editor: We have read with great interest the study by Gleeson *et al.* (1), and we would like to congratulate the authors as it represents the most comprehensive approach so far to the relationship between polymorphisms of inflammatory-related genes and the genetic susceptibility to alcoholic liver disease (ALD). Among other findings, the authors have replicated an association shown earlier between the −592C>A polymorphism of the interleukin-10 gene and the presence of ALD.

With regard to this, we would like to comment on the fact that we have recently published a meta-analysis on this topic (2) that did not confirm this relationship. A further meta-analysis with the inclusion of the data from Gleeson *et al.* (1) does not show any significant association either, with an odds ratio of 1.19 (confidence interval: 0.83, 1.69) for the association of the AA genotype with the presence of ALD. Nonetheless, the number of studies available for inclusion is small, and several factors may explain the conflicting results found. First, we have to consider the potential presence of true genetic heterogeneity across different populations: the two studies with positive findings included patients from the United Kingdom or Ireland (1,3), whereas the studies with negative results were performed in Spain, Portugal, and France (2,4–6). Second, we would like to highlight the fact that we found an association of the aforementioned polymorphism with alcohol use disorders (2), defined as alcohol abuse or dependence in our sample, suggesting a potential role of alcoholism itself as a confounding factor for the relationship of this genetic variant with ALD.

Therefore, although the well-designed study from Gleeson *et al.* (1) has taken into account several confounding factors, an uneven distribution of patients with alcohol use disorders between cases and controls could help explain the discrepant results obtained across studies. In line with this, it is usually recommended that Hardy–Weinberg equilibrium should be tested in healthy controls but not in any group of patients, as the presence of any disease or condition (such as being a heavy drinker) may be associated *per se* with a specific genotype.

The study of the genetic susceptibility to ALD is hampered by specific methodological challenges that are difficult to overcome. The consideration of all the factors potentially involved as well as the systematic integration of previous data may help us solve the puzzle.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Older Age *Per Se* Has Negative Effect On Hepatitis C Patients Treated With Peginterferon and Ribavirin

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To the Editor: Previous large randomized multicenter trials of therapy with peginterferon and ribavirin showed that age was associated with a poorer response to treatment for hepatitis C–infected patients (1). However, only limited reports addressed the feasibility of such a combination therapy in older adults. A representative single-center retrospective study conducted in Italy concluded that the effect of treatment is decreased for patients aged more than 40 years infected with genotype-1 or -4, but patients aged more than 65 years had a similar rate of response to those aged 40–64 years (2). On the other hand, for patients infected with genotype-2 or -3, no association was found between age and sustained response (2,3).

Table 1. Baseline patient characteristics and drug exposure of 182 patients with chronic hepatitis C according to age group

Characteristics	Age (years)			*P* value
	<50	50–59	≥60	
	n=73	*n*=51	*n*=58	
Age, years	39.0±8.3	54.3±2.6	66.2±3.9	
Female sex	21 (28.8%)	16 (31.4%)	25 (43.1%)	0.203
Body weight, kg	70.7±13.6	66.5±12.1	62.6±9.9	0.001
ALT≥3 times ULN	40 (54.8%)	28 (54.9%)	39 (67.2%)	0.285
Creatinine clearance, ml/min[a]	89.5±19.9	81.9±16.0	71.3±13.3	<0.001
Platelets >150×10^9/l	49 (67.1%)	28 (54.9%)	23 (39.7%)	0.007
METAVIR fibrosis stage				<0.001
F1–2	35 (47.9%)	20 (39.2%)	12 (20.7%)	
F3	24 (32.9%)	13 (25.5%)	12 (20.7%)	
F4	14 (19.2%)	18 (35.3%)	34 (58.6%)	
Genotype 1/genotype 2	45/28	26/25	28/30	0.264
Baseline HVL (>800,000 IU/ml)	27 (37.0%)	17 (33.3%)	15 (25.9%)	0.396
Concomitant hypertension	7 (9.6%)	16 (31.4%)	25 (43.1%)	<0.001
Concomitant diabetes mellitus	8 (11.0%)	14 (27.5%)	16 (27.6%)	0.026
Discontinuation	4 (5.5%)	7 (13.7%)	4 (6.9%)	0.234
Mean ribavirin dose, mg/kg/day	14.7±2.9	14.0±3.5	12.9±3.8	0.016
80/80/80 adherence[b]	58 (82.9%)	37 (72.5%)	31 (57.4%)	0.007

ALT, alanine aminotransferase; HVL, high viral load; ULN, upper limit of normal.
Mean±s.d. or *n* (%).
[a]Creatinine clearance: estimated by the Cockcroft–Gault equation.
[b]80/80/80 adherence: patients who had received 80% or more of expected peginterferon and ribavirin dose and completed at least 80% of expected duration (*n*=175).

The Bureau of National Health Insurance in Taiwan enforced the hepatitis C trial treatment program and reimbursed for a standard 24-week combination therapy of peginterferon and ribavirin regardless of genotype. Between December 2003 and November 2008, we treated 182 consecutive patients with hepatitis C infection who had completed 24 weeks of follow-up after the end of treatment, including 99 genotype-1- and 83 genotype-2-infected patients. Eligible subjects in our daily practice were patients with detectable hepatitis C virus RNA in serum and aged more than 18 years old. The starting dose of peginterferon α-2b was 1.5 mcg/kg per week and fixed 180 mcg per week for peginterferon α-2a. The dose of rivabirin was adjusted by body weight and computed as follows: <75 kg, 1,000 mg/day; and 75 kg or more, 1,200 mg/day, irrespective of genotype. All patients received a standard 24-week treatment course, and liver biopsy was performed before treatment. Patients were excluded if they had decompensated cirrhosis, abnormal serum creatinine (2 mg/dl or higher), or coexistent hepatitis B virus infection. The concept of on-treatment virological monitoring was not regularly integrated into the management of standard therapy.

Baseline characteristics and drug exposure according to age group are summarized in **Table 1**. Older age groups had unfavorable treatment-related variables, including lower creatinine clearance, lower platelet count, more advanced fibrosis stage, concomitant chronic disease (hypertension, diabetes mellitus), less mean ribavirin dose exposure during treatment, and inadequate 80/80/80 adherence ($P<0.05$). But older patients in this study had leaner body weight and tended to have more genotype-2 infection.

One hundred and twenty-nine (70.9%) patients achieved a sustained virological response (SVR), including 56 (56.6%) patients with genotype-1 infection and 73 (88.0%) patients with genotype-2 infection. Among the entire cohort, those younger than 50 years had no dissimilar SVR rate (68.5%) compared with patients 50–59 years (76.5%) and those 60 years or more (69.0%) for the crude parameters ($P=0.584$). We then adjusted for baseline differences (body weight, creatinine clearance, platelet count, fibrosis, concomitant chronic disease), genotype (genotype 1 vs. 2), and drug exposure (mean ribavirin dose during treatment, 80/80/80 adherence) using logistic regressions. First, we found that those aged 50–59 years did not have dissimilar odds of SVR compared with patients <50 years (adjusted odds ratio 0.416; 95% confidence interval, 0.105–1.655; $P=0.213$). However, as shown in **Table 2**, the age group <50 years had a higher odds of achieving an SVR compared with patients 60 years or more ($P=0.041$), but not for ages in the 50- to 59-year group ($P=0.768$).

In this brief report, we defined elderly patients with chronic hepatitis C as a difficult group to treat. Patient age was associated with higher rates of impaired renal function, advanced fibrosis, and hypertension or diabetes as comorbid conditions. In addition, more elderly patients needed dose modification during treatment; therefore, the proportion of patients who had 80/80/80 adherence and the mean ribavirin dose were lower in the elder group. However, after adjusting for all

Table 2. Comparisons of efficacy response in HCV patients with various age groups

Age group	Adjusted OR (95% CI)[a]	*P* value
≥60 years	1	
50–59 years	1.194 (0.368–3.876)	0.768
<50 years	3.970 (1.061–14.856)	0.041

OR, odds ratio; CI, confidence interval.
[a]Adjusted for body weight, creatinine clearance, platelet count, fibrosis, concomitant chronic disease (hypertension and diabetes mellitus), genotype (genotype 1 vs. 2), mean ribavirin dose during treatment, and 80/80/80 adherence.

of the above treatment-related confounders and for genotype, we found that older age *per se* (specific for age ≥60 years vs. age <50 years) had an unfavorable outcome pertaining to peginterferon and ribavirin combination treatment for hepatitis C patients. Age-specific differences in the immune response and therefore in the interactions between virus and host immune defense may explain different rates of response to treatment in different age groups (4).

In conclusion, older hepatitis C patients not only represented a difficult-to-treat population, age in itself might participate in the determination of therapeutic outcome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Severe Intestinal Bleeding in a Patient With Wegener's Granulomatosis

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To the Editor: Wegener's granulomatosis (WG) is a systemic vasculitis of unknown etiology characterized mainly by inflammation of the small arteries and veins (1). The involvement of the upper airways, lungs, and kidneys is common (2). WG may rarely involve the gastrointestinal tract. Only a few cases of severe gastrointestinal bleeding because of ulcers associated with WG have been reported (3,4,5).

A 40-year-old man was admitted to our hospital with complaints of dyspnea, hemoptysis, and leg edema for the preceding 4 months. He had been hospitalized in a chest disease clinic 2 months previous and diagnosed with WG (he had had sinusitis, granulomatous inflammation at bronchoscopy, and circulating anti-neutrophil cytoplasmic antibody (c-ANCA) positivity). He had been given pulse steroid treatment thrice during hospitalization. He was referred to our hospital because of deteriorating renal function. His general health status was moderate at the time of admission. Physical examination revealed a decreased breath sound at the base of the left lung and bilateral pretibial edema. Laboratory findings showed metabolic acidosis, microscopic hematuria, hypoalbuminemia (2.5 g/dl), blood urea nitrogen (213 mg/dl), creatinin (7.8 mg/dl), erythrocyte sedimentation rate (80 mm/h), hemoglobin (7.7 g/dl), white blood cell count (15.300/mm^3), and platelets (556.000/mm^3). Owing to impaired renal functions, a jugular catheter was inserted for hemodialysis. He was administered intravenous pulse steroids (1,000 mg/day) and cyclophosphamide (750 mg/day) for 3 days and continued on oral steroid treatment (60 mg/day). A proton pump inhibitor (omeprazole) was initiated on the first day of hospitalization. He had melena on the seventeenth day of hospitalization. Upper gastrointestinal endoscopy revealed normal esophagus, stomach, and first part of the duodenum; however, there was a visible vessel in the center of an ulcer at the top of the second part of the duodenum (**Figure 1**). Sclerotherapy was performed because of potential rebleeding. Supportive management with erythrocyte transfusion (4 units of erythrocyte suspension), hydration, and intravenous proton pump inhibitor was performed. Although the patient's gastrointestinal bleeding did not recur, he had sepsis and his general status became worse, and he died 3 days later.

WG is an inflammatory disorder of unknown etiology characterized by necrotizing vasculitis affecting the small and medium-sized arterial, venous, and capillary vessels (1). WG mainly affects the upper airways, lungs, and kidneys (85% of cases) (2). It predominantly affects patients over the age of 40 years and has a male-to-female ratio of 2:1. Although it is a multisystemic disease, gastrointestinal involvement is uncommon; in particular, large-volume gastrointestinal bleeding is a very rare manifestation (6). WG may affect any area of the gastrointestinal tract, from