MAJOR ARTICLE

Efficacy and Safety of Pegylated Interferon Combined with Ribavirin for the Treatment of Older Patients with Chronic Hepatitis C

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Background. The present study evaluated the efficacy and safety of pegylated interferon (PegIFN)/ribavirin treatment in elderly patients with hepatitis C virus (HCV) infection.

Methods. Seventy elderly patients with hepatitis C virus (HCV) infection (group A; age, ⩾65 years) and 140 sex- and HCV genotype–matched controls (group B; age, 50–64 years) were allocated to receive a PegIFN-α-2a/ribavirin standard-of-care regimen.

Results. Group A had a significantly higher rate of treatment discontinuation (21.4% vs 6.4%; $P = .001$) and grade 3 or 4 adverse events (34.3% vs 20%; $P = .002$) than group B. In intention-to-treat analysis, the sustained virologic response (SVR) rate was substantially lower in group A than in group B (67.1% vs 78.6%; $P = .07$). The inferiority of the SVR rate in group A was observed among patients with HCV genotype 1 (HCV-1) (51.9% vs 75.9%; $P = .03$) but not among patients with HCV genotype 2 or 3 (HCV-2/3) (76.7% vs 80.2%; $P = .65$). Among patients in group A who had a rapid virologic response, those infected with HCV-1 and those infected with HCV-2/3 had similar SVR rates (80% and 87.9%, respectively). For patients receiving treatment for >80% of its expected duration, SVR rates were similar between the 2 groups (80.4% vs 82.6%, respectively), regardless of viral genotype.

Conclusions. Older patients with HCV infection, especially those in the subgroup infected with HCV-1, had a greater frequency of adverse events and poorer adherence to the standard-of-care regimen, which may be the major reason for treatment inferiority.

Trial registration. Clinicaltrials.gov identifier NCT00629824.

Hepatitis C virus (HCV) infection affects ~300 million people worldwide [1] and is a major risk factor for the development of serious end-stage liver disease. The prevalence of antibodies to HCV (ie, anti-HCV) among adults was ~4.4% in Taiwan from 1996 to June 2005 [2]. Nevertheless, in several townships in southern Taiwan where HCV is hyperendemic, an anti-HCV prevalence of 15%–60% has been discovered [3, 4]. In addition, in Taiwan, the age when the anti-HCV seroprevalence rate is at its peak (ie, up to 10%–20%) is 60–80 years [2], which is ~30 years older than the age associated with the peak anti-HCV seroprevalence rate in Western countries [5]. Therefore, there is a pressing need for management of chronic HCV infection in this population of older patients, not only in Japan [6], but also in Taiwan.

Interferon (IFN)–based therapy could reduce the risk of cirrhosis and hepatocellular carcinoma (HCC) and improve the survival of patients with chronic hepatitis C (CHC)—in particular, those who achieve a sustained virologic response (SVR) [7, 8]—even if the patients are ⩾60 years of age [9, 10]. However, clinical trials

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generally exclude patients ⩾65 years of age, even though such patients are exactly those who commonly require aggressive treatment, because of the high risk of disease progression [8, 9, 11] and the relatively lower response to antiviral therapy [12–15]. A tendency toward a lower SVR rate was observed among older patients who received combination therapy with conventional interferon (IFN) plus ribavirin in some studies [6, 16, 17] but not in a study by Honda et al [18]. The current standard-of-care regimen for CHC is pegylated interferon (PegIFN) plus ribavirin treatment for 48 weeks' duration, for patients with HCV genotype 1 or 4 (HCV-1/4), and for 24 weeks' duration, for patients with HCV genotype 2 or 3 (HCV-2/3) [19]. Nevertheless, only a few studies with limited case numbers, most of which were retrospective, reported the efficacy and safety of PegIFN/ribavirin in older patients with CHC [11, 20–22]. We conducted a prospective study of the treatment response to and safety profile of the standard-of-care regimen for older patients with CHC (ie, those ⩾65 years of age), compared with sex- and HCV genotype–matched middle-aged patients, to elucidate the management of CHC in older patients.

METHODS

Study design. This prospective, case-control study was performed at one medical center and one regional core hospital in Taiwan. The study was approved by the ethics committees of the participating hospitals and was performed in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients provided written informed consent before study enrollment. We enrolled 70 consecutively seen patients with CHC who were ⩾65 years of age (group A) and an additional 140 sex- and HCV genotype–matched patients who were 50–64 years of age (group B) and served as a control group. Subjects were treated with PegIFN-α-2a (Pegasys; Roche), 180 μg/week given subcutaneously, plus either (1) oral ribavirin at a dose of 1000–1200 mg/day for 48 weeks, for patients with HCV-1 infection, or (2) oral ribavirin at a dose of 800 mg/day for 24 weeks, for patients with HCV-2/3, with a 24-week follow-up period for both treatment groups. Subjects made biweekly outpatient visits during the first month and then monthly visits during the rest of the treatment period, as well as during the 24-week follow-up. At each visit, subjects underwent a physical examination, and adverse events were recorded. Biochemical and hematologic testing was done using commercial assays. HCV genotypes were determined using the method described by Okamoto et al [23]. The serum HCV RNA levels at baseline, at weeks 4 and 12 of treatment, at the end of treatment, and at 24 weeks after treatment were determined by qualitative polymerase chain reaction (PCR). Serum HCV RNA levels noted at baseline and at week 12 of treatment were measured using the branched DNA assay (Versant HCV RNA 3.0 [Bayer]; quantification limit, 615 IU/mL). In accordance with the scoring system described by Knodell and Scheuer [24], liver histologic findings were graded and staged by a single pathologist, who was blinded as to the treatment received by each patient. Patient education was provided by 3 well-trained, professional study nurses before and throughout the treatment and follow-up periods, to decrease the frequency of adverse events and enhance treatment adherence.

Selection of patients. Eligible subjects were previously untreated Taiwanese patients with CHC (age, 50–80 years) who (1) were seropositive for anti-HCV (as determined by a third-generation enzyme immunoassay; Abbott Laboratories) and for HCV RNA (as determined by a qualitative PCR assay [Cobas Amplicor hepatitis C virus test, version 2.0 {Roche Diagnostics}; detection limit, 50 IU/mL]), or (2) had liver biopsy findings that were consistent with chronic hepatitis during the year before study entry, as well as other eligibility criteria, which included a neutrophil count of >1500 cells/mm^{-3}, a platelet count $>9 \times 10^4$ cells/mm^{-3}, a hemoglobin level >12 g/dL (for men) or >11 g/dL (for women), a serum creatinine level of <1.5 mg/dL, no pregnancy or lactation, and use of a reliable method of contraception.

The following patients were excluded from the study: patients who tested positive for hepatitis B surface antigen; those who had human immunodeficiency virus infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson disease, α_1-antitrypsin deficiency, decompensated cirrhosis, or overt hepatic failure; and those with a current or past history of alcohol abuse (⩾20 g/day), a psychiatric condition, or previous liver transplantation or with evidence of HCC were excluded from the study.

Dose modifications and safety. Adverse events were graded as mild, moderate, severe, or potentially life-threatening. Patients were assessed to determine the incidence of adverse events. For PegIFN and ribavirin, dose modification occurred in accordance with a strategy described elsewhere [25, 26], except that the PegIFN dose was modified by a 45-μg stepwise decrease and the ribavirin dose was modified by a 200-mg stepwise decrease to enhance adherence. Erythropoietin (EPO) administration or blood transfusion during the treatment period was allowed but not encouraged. Treatment discontinuation was defined by PegIFN treatment that was discontinued for >4 weeks. Patients who had received >80% of the expected PegIFN and ribavirin doses and who received treatment for >80% of its expected duration were regarded as achieving 80/80/80 adherence, as mentioned elsewhere [27]. Patients had access to well-trained nursing staff at any time, to ensure drug compliance. Subjects who experienced drug-associated adverse events were treated supportively and referred to specialists such as psychiatrists or ophthalmologists, if needed.

Assessment of efficacy. The primary end point of the present study was to assess SVR, which was defined as an HCV

Table 1. Basic Demographic, Virologic, and Clinical Characteristics and Assigned Doses of Pegylated Interferon (PegIFN) and Ribavirin for the Study Patients

Characteristic or dose	Group A[a] (n = 70)	Group B[b] (n = 140)	P
Sex			1
Male	36 (51.4)	72 (51.4)	
Female	34 (48.6)	68 (48.6)	
Genotype			1
1	27 (38.6)	54 (38.6)	
2 or 3	43 (61.4)	86 (61.4)	
Age, mean ± SD, years	68.3 ± 3.6	55.6 ± 4.1	<.001
Body weight, mean ± SD, kg	65.1 ± 10.1	63.2 ± 10.1	.19
BMI, mean ± SD, kg/m^2	25.0 ± 2.9	25.3 ± 3.2	.52
Diabetes mellitus	14 (20.0)	26 (18.6)	.88
Fasting glucose level, mean ± SD, mg/dL	111 ± 42	108 ± 35	.61
HCV RNA level at baseline, mean ± SD, log IU/mL	5.25 ± 1.21	5.28 ± 1.22	.85
Fibrosis score of 3–4	23 (32.9)	38 (27.1)	.39
AST level, mean ± SD, IU/L	118 ± 62	112 ± 72	.55
ALT level, mean ± SD, IU/L	158 ± 95	161 ± 109	.85
Ccr, mean ± SD, mL/min	70 ± 20	93 ± 24	<.001
WBC count, mean ± SD, $\times 10^3$ cells/L	5.3 ± 1.7	5.4 ± 1.6	.84
Hemoglobin level, mean ± SD, g/dL	13.8 ± 1.6	14.1 ± 1.5	.30
Platelet count, mean ± SD, $\times 10^3$ cells/mm^3	147 ± 51	156 ± 54	.22
PegIFN dose, mean ± SD, μg/week	2.86 ± 0.48	2.77 ± 0.41	.25
Ribavirin dose, mean ± SD, mg/kg/day	17.9 ± 3.1	17.4 ± 3.4	.32

NOTE. Data are the no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Ccr, creatinine clearance rate; HCV, hepatitis C virus; SD, standard deviation; WBC, white blood cell.

[a] Patients ⩾65 years of age.

[b] Patients 50–64 years of age.

RNA PCR-seronegative status by the end of treatment and throughout follow-up. A rapid virologic response (RVR) was defined as a serum HCV RNA PCR-negative status at week 4 of therapy. Early virologic response (EVR) was defined as a PCR-negative status or a ⩾2-$\log_{10}$ decrease in the serum HCV RNA level from baseline, as noted at week 12 of treatment. The end-of-treatment virologic response (ETR) was defined as a serum HCV RNA PCR-negative status at the end of treatment.

Statistical analyses. Evaluation of the efficacy of antiviral treatment was based on an intention-to-treat analysis and a per-protocol analysis. The intent-to-treat population was defined as all enrolled patients who had received ⩾1 dose of treatment medication. The per-protocol population consisted of patients in the intent-to-treat population who received treatment for ⩾80% of its expected duration and completed 24 weeks of follow-up. Frequency was compared between groups by use of the χ^2 test, with Yates correction, or Fisher's exact test. Group means, presented as mean values ± standard deviations, were compared using analysis of variance and Student's t test. Serum HCV RNA levels were expressed after logarithmic transformation of original values. Creatinine clearance was estimated using the Cockcroft-Gault equation, which includes sex, age, body weight, and serum creatinine level in the calculation. Stepwise logistical regression was used to analyze which variables had a better predictive value for SVR. Procedures were performed using the SPSS 12.0 statistical package (SPSS). All statistical analyses were based on 2-sided hypothesis tests with a significance level of $P < .05$.

RESULTS

Patient characteristics. The basic demographic, virologic, and clinical characteristics and baseline doses of PegIFN and ribavirin were similar in the patients in groups A and B (Table 1), except that patients in group B were significantly younger than those in group A (mean ± SD, 55.6 ± 4.1 vs 68.3 ± 3.6 years, respectively; $P < .001$) and that patients in group A had a significantly lower creatinine clearance rate than did those in group B (mean ± SD, 70 ± 20 vs 93 ± 24 mL/min; $P <$ .001). Eighty-one (38.6%) of the 210 patients were infected with HCV genotype 1 (HCV-1).

Safety. The rate of achievement of 80/80/80 adherence; the incidence of drug modification, including dose reduction and dose discontinuation; and adverse events associated with treat-

ment are presented in Table 2. Group A had significantly higher rates of dose modification (66% vs 51%, respectively; $P = .039$) and drug discontinuation (21% vs 6%, respectively; $P = .001$) than did group B. Group A had significantly lower exposure doses of ribavirin by body weight than did group B (mean ± SD, 11.4 ± 5.4 mg/kg/day vs 13.8 ± 4.3 mg/kg/day; $P = .001$). Group B had a significantly higher rate of achieving 80/80/80 adherence than did group A (77% vs 58%; $P = .002$). Grade 3 or 4 adverse events were more frequent in group A than in group B (34% vs 20%; $P = .024$). Group B had a significantly higher rate of skin rash than did group A (44% vs 26%; $P = .01$). Group A tended to have a higher rate of anemia than did group B (71% vs 59%; $P = .09$). In group A, 6 patients terminated treatment early because of an abnormal laboratory finding, whereas 9 patients did so because of adverse events. In group B, 7 patients terminated treatment early because of adverse events, and 2 patients were lost to follow-up (because of business abroad and an unknown reason, respectively). The abnormal laboratory findings that led to treatment termination in group A included neutropenia ($n = 1$), anemia ($n = 2$), thrombocytopenia ($n = 2$), and an elevated creatinine level ($n = 1$). The adverse events leading to treatment termination included fatigue (2 patients in group A and 1 patient in group B), acute gastroenteritis (1 patient in group A), oral ulcer (1 patient in group A), gum bleeding (1 patient in group A), dyspnea (1 patient in group A), myalgia (1 patient in group A), suicide ideation (1 patient in group A), and cellulitis (1 patient in group B). Five serious adverse events that led to treatment termination were recorded, including 1 biliary tract infection in group A and 1 case each of tongue cancer, acute cholecystitis, urosepsis, and acute myocardial infarction with death in group B.

Drug compliance profiles (rates of 80/80/80 adherence and drug discontinuation) in the 2 groups were further stratified by HCV genotype. Among patients with HCV-1 infection, those in group A had a significantly lower rate of 80/80/80 adherence (8 [29.6%] of 27 patients vs 38 [70.4%] of 54 patients; $P < .001$) and a significantly higher rate of treatment discontinuation (9 [33.3%] of 27 patients vs 4 [7.4%] of 54 patients; $P = .008$) than did those in group B. Of 13 patients with HCV-1 infection who experienced drug discontinuation, 4 (44%) of the 9 patients in group A discontinued therapy after week 24 of treatment, which was comparable to 2 (50%) of the 4 patients in group B. Among patients with HCV-2/3 infection, rates of 80/80/80 adherence and treatment discontinuation did not differ between the 2 groups (31 [72.1%] of 43 patients vs 70 [81.4%] of 86 patients [$P = .23$] and 6 [14.0%] of 43 patients vs 5 [5.8%] of 86 patients [$P = .18$], respectively). Overall, 44 patients (21%) received ⩾1 dose of EPO, and only 1 patient received blood transfusion during the antiviral treatment period. The frequency of EPO use in the older patient group and the younger patient group did not differ (18.6% vs 22.1%; $P = .55$).

Table 2. Rates of 80% Adherence, Grade 3 or 4 Adverse Events, Dose Modification, and Adverse Events

Variable	Group A[a] ($n = 70$)	Group B[b] ($n = 140$)	P
80/80/80 adherence[c]	39 (56)	108 (77)	.002
Grade 3 or 4 adverse event	24 (34)	28 (20)	.024
Dose modification, type and result	46 (66)	71 (51)	.039
Dose reduction	31 (44)	62 (44)	1
Adverse event	8 (11)	11 (8)	
Abnormal laboratory finding	23 (33)	51 (36)	
Discontinuation	15 (21)	9 (6)	.001
Adverse event	9 (13)	7 (5)	
Abnormal laboratory finding	6 (9)	0 (0)	
Influenza-like symptom			
Fever	4 (6)	16 (11)	.17
Chills	6 (9)	11 (8)	.88
Headache	19 (27)	40 (29)	.80
Myalgia	35 (50)	63 (45)	.55
Gastrointestinal symptom			
Anorexia	38 (54)	60 (43)	.14
Nausea	8 (11)	16 (11)	.97
Diarrhea	10 (14)	16 (11)	.58
Psychiatric symptom			
Anxiety	15 (21)	32 (23)	.77
Depression	13 (19)	33 (24)	.35
Insomnia	40 (57)	86 (61)	.47
Dermatologic symptom			
Hair loss	25 (36)	57 (41)	.44
Skin rash	18 (26)	61 (44)	.01
Injection-site reaction	2 (3)	10 (7)	.35
Hematologic abnormality			
Leukopenia[d]	6 (9)	11 (8)	.86
Anemia[e]	50 (71)	83 (59)	.09
Thrombocytopenia[f]	12 (17)	18 (13)	.40

NOTE. Data are the no. (%) of patients, unless otherwise indicated.

[a] Patients ⩾65 years of age.

[b] Patients 50–64 years of age.

[c] Patients who received >80% of expected pegylated interferon and ribavirin doses and completed at least 80% of its expected duration.

[d] White blood cell count <1500 cells/mm^3.

[e] Hemoglobin level <10 g/dL.

[f] Platelet count <50,000 cells/mm^3.

Virologic responses and factors associated with an SVR. The rates of RVR, EVR, and ETR were 61.4%, 91.4%, and 84.3%, respectively, in group A; these rates were comparable to those of 63.6%, 94.3%, and 88.6%, respectively, in group B (Table 3). After stratification by HCV genotype, virologic responses during treatment remained similar between the 2 groups, with regard to HCV genotype. In intention-to-treat analysis, the SVR rate tended to be lower in group A than in group B (67.1% vs 78.6%; $P = .07$). The relapse rate was higher

Table 3. Rates of Virologic Responses in 2 Age Groups

Response, HCV genotype	Group A[a]		Group B[b]		P
	n/N[c]	% (95% CI)	n/N[c]	% (95% CI)	
RVR					
All	43/70	61.4 (0.50–0.73)	89/140	63.6 (0.56–0.72)	.76
1	8/27	29.6 (0.12–0.47)	21/54	38.9 (0.26–0.52)	.41
2/3[d]	35/43	81.4 (0.70–0.93)	68/86	79.1 (0.71–0.88)	.76
EVR					
All	64/70	91.4 (0.85–0.98)	132/140	94.3 (0.90–0.98)	.56
1	23/27	85.2 (0.72–0.99)	49/54	90.7 (0.83–0.98)	.47
2/3	41/43	95.3 (0.89–1.02)	83/86	96.5 (0.93–1.00)	1
ETR					
All	59/70	84.3 (0.76–0.93)	124/140	88.6 (0.83–0.94)	.38
1	20/27	74.1 (0.58–0.91)	45/54	83.3 (0.73–0.93)	.32
2/3	39/43	90.7 (0.82–0.99)	79/86	91.9 (0.86–0.98)	1
Relapse					
All	12/59	20.3 (0.10–0.31)	14/124	11.3 (0.06–0.17)	.10
1	6/20	30.0 (0.10–0.50)	4/45	8.9 (0.01–0.17)	.06
2/3	6/39	15.4 (0.04–0.27)	10/79	12.7 (0.05–0.20)	.68
SVR (ITT)					
All	47/70	67.1 (0.56–0.78)	110/140	78.6 (0.72–0.85)	.07
1	14/27	51.9 (0.33–0.71)	41/54	75.9 (0.64–0.87)	.03[e]
2/3	33/43	76.7 (0.64–0.89)	69/86	80.2 (0.72–0.89)	.65
SVR (PP)					
All	45/56	80.4 (0.70–0.91)	109/132	82.6 (0.76–0.89)	.72
1	12/18	66.7 (0.45–0.88)	41/51	80.4 (0.70–0.91)	.33
2/3	33/38	86.8 (0.76–0.98)	68/81	84.0 (0.76–0.92)	.68

NOTE. CI, confidence interval; ETR, end of treatment response; EVR, early virologic response; ITT, intention-to-treat analysis; PP, per-protocol analysis; RVR, rapid virologic response; SVR, sustained virologic response.

[a] Patients ⩾65 years of age.
[b] Patients 50–64 years of age.
[c] No. of patients with the response indicated/total no. of patients in group assessed.
[d] Genotype 2 or 3.
[e] Statistically significant.

in group A than in group B (20.3% vs 11.3%; $P = .1$). When HCV genotype was taken into consideration, the significantly lower SVR rate in group A than in group B was observed only among patients infected with HCV-1 (51.9% vs 75.9%, respectively; $P = .03$), but not among patients infected with HCV-2/3 (76.7% vs 80.2%, respectively; $P = .65$). Similar results were also observed for relapse rate, as stratified by genotype (Table 3). In per-protocol analysis, SVR rates were similar between groups A and B in all populations (80.4% vs 82.6%, respectively; $P = .72$) and in patients infected with HCV-2/3 (86.8 % vs 84.0%, respectively; $P = .68$). The difference in the SVR rate in patients infected with HCV-1 became not significant between groups A and B (66.7% vs. 80.4%, respectively; $P = .33$).

In univariate analysis, factors associated with the SVR included male sex, higher pretreatment aspartate aminotransferase levels, higher white blood cell count and platelet count at baseline, higher hemoglobin level at baseline, lower fibrosis score, lower pretreatment HCV RNA level, better adherence to therapy, less drug discontinuation and modification, higher dose of weight-based ribavirin exposure, and achievement of RVR (Table 4). By use of multivariate analysis, the independent predictive value of age, sex, histopathologic findings of fibrosis of the liver, HCV RNA levels, HCV genotype, mean doses of ribavirin by body weight, serum alanine aminotransferase concentrations before treatment, diabetes, and discontinuation of therapy for the achievement of SVR was determined using stepwise logistic regression analysis. The factor most strongly predictive of SVR was achievement of an RVR, followed by early termination of treatment and the exposure dose of ribavirin by body weight (Table 5). Age group was not an independent factor for SVR, after adjustment for predictive factors.

We further explored the influence of virologic responses during treatment and treatment efficacy between the 2 groups, on the basis of findings for the per-protocol population (Table 6). Patients in group A with an RVR tended to have higher rates

Table 4. Risk Factors Associated with a Sustained Virologic Response (SVR)

Risk factor	With an SVR (n = 157)	Without an SVR (n = 53)	P
Male sex	88 (56.1)	20 (37.7)	.02
Age ⩾65 years	47 (29.9)	23 (43.4)	.07
HCV genotype 1	55 (35.0)	26 (49.1)	.07
Body weight, mean ± SD, kg	65.0 ± 9.8	63.2 ± 11.0	.28
AST level, mean ± SD, IU/L	113 ± 73	117 ± 57	.73
ALT level, mean ± SD, IU/L	168 ± 112	135 ± 71	.02
WBC count, mean ± SD, $\times 10^3$ cells/L	5.5 ± 1.7	4.9 ± 1.5	.03
Hemoglobin level, mean ± SD, g/dL	14.2 ± 1.4	13.4 ± 1.6	.001
Platelet count, mean ± SD, $\times 10^3$ cells/mm^3	159 ± 53	136 ± 50	.01
Fibrosis score F3–4, no. (%)	39 (24.8)	22 (41.5)	.02
HCV RNA level at baseline, mean ± SD, log IU/mL	5.19 ± 1.32	5.50 ± 0.80	.04
80/80/80 adherence[a]	123 (78.3)	24 (45.3)	<.001
Drug discontinuation	6 (3.8)	18 (34)	<.001
Drug dose modification	80 (51.0)	37 (69.8)	.02
Ribavirin dose, mean ± SD, mg/kg/day	13.8 ± 3.9	10.0 ± 6.0	<.001
RVR	118 (75.2)	14 (26.4)	<.001

NOTE. Data are the no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; RVR: rapid virologic response; SD, standard deviation; SVR, sustained virologic response; WBC, white blood cell.

[a] Patients who received >80% of expected doses of pegylated interferon and ribavirin and received treatment for ⩾80% of its expected duration.

of relapse than did those in group B who had an RVR, for both the HCV-1 subgroup (14.1% vs. 0%, respectively) and the HCV-2/3 subgroup (14.7% vs. 4.6%, respectively), and they also tended to have lower rates of an SVR (80.0% vs. 100%, respectively, for patients with HCV-1 infection; 87.9% vs. 95.3%, respectively, for patients with HCV-2/3 infection).

Table 7, which appears only in the electronic version of the *Journal*, presents information from 4 studies of PegIFN-based therapy in older patients.

DISCUSSION

To our knowledge, the current study is the first prospective study of—and has the largest sample size of any study of—the efficacy and safety of the current standard-of-care regimen for the treatment of older patients with CHC [19]. We controlled the most important prognostic factor at baseline—viral genotype [13–15]–to straightforwardly elucidate the effect of age on PegIFN/ribavirin therapy. We demonstrated that approximately two-thirds of Taiwanese patients with CHC who were ⩾65 years of age could achieve an SVR with the use of standard-of-care regimens. The treatment response was substantial lower in patients ⩾65 years of age than in patients 50–64 years of age. Nevertheless, the inferiority of treatment efficacy in older patients was observed only in those infected with HCV-1 (51.9% vs 75.9%) and not in those infected with HCV-2/3 (76.7% vs 80.2%). Caution should be exercised when treating

Table 5. Multivariate Logistic Regression Analysis of the Factors Associated with a Sustained Virologic Response (SVR)

Variable	OR (95% CI)	P
RVR at week 4		
No	1	
Yes	12.264 (4.822–31.189)	<.001
Early termination of treatment		
No	1	
Yes	0.152 (0.034–0.676)	.013
Ribavirin by body weight, per 1-mg/kg/day increase	1.128 (1.008–1.263)	.036

NOTE. CI, confidence interval; OR, odds ratio; RVR, rapid virologic response. The independent predictive variables included age, sex, histopathologic findings of liver fibrosis, hepatitis C virus (HCV) RNA levels, HCV genotype, mean doses of ribavirin by body weight, serum concentrations of alanine aminotransferase before treatment, diabetes, and discontinuation of therapy.

Table 6. Influence of Virologic Responses during Treatment on Rates of End-of-Treatment Virologic Response (ETR), Relapse, and Sustained Virologic Response (SVR) in the 2 Age Groups, Based on a Per-Protocol (PP) Population

HCV genotype, response	ETR				Relapse				SVR (PP)			
	Group A[a]		Group B[b]		Group A[a]		Group B[b]		Group A[a]		Group B[b]	
	n/N	% (95% CI)	*n/N*	% (95% CI)	*n/N*	% (95% CI)	*n/N*	% (95% CI)	*n/N*	% (95% CI)	*n/N*	% (95% CI)
1												
RVR positive	7/7	100	21/21	100	1/7	14.3 (−0.12–0.40)	0/21	0	4/5	80.0 (0.45–1.15)	21/21	100
RVR negative	13/14	92.9 (0.79–1.06)	24/30	80.0 (0.66–0.94)	5/13	38.5 (0.12–0.65)	4/24	16.7 (0.02–0.32)	8/13	61.5 (0.35–0.88)	20/30	66.7 (0.50–0.84)
EVR negative	…	…	2/4	50.0 (0.01–0.99)	…	…	2/2	100	…	…	0/4	0
2 or 3												
RVR positive	34/34	100	65/65	100	5/34	14.7 (0.03–0.27)	3/65	4.6 (0–0.10)	29/33	87.9 (0.77–0.99)	61/64	95.3 (0.90–1.00)
RVR negative	5/6	83.3 (0.53–1.13)	14/17	82.4 (0.64–1.01)	1/5	20.0 (−0.15–0.55)	7/14	50.0 (0.24–0.76)	4/5	80.0 (0.45–1.15)	7/17	41.2 (0.18–0.65)
EVR negative	…	…	0/2	0	…	…	…	…	…	…	0/2	0

NOTE. CI, confidence interval; EVR, >2-$\log_{10}$ decrease in the hepatitis C virus (HCV) RNA level from baseline or the HCV RNA–seronegative status at week 12 of treatment; RVR, HCV RNA seronegative at week 4 of treatment.

[a] Patients ⩾65 years of age.

[b] Patients 50–64 years of age.

older patients, because of significantly higher associated rates of grade 3 or 4 adverse events, dose modification, and discontinuation of treatment in the population. In particular, up to one-third of older patients infected with HCV-1 experienced treatment discontinuation. Relatively poor adherence might be the major reason for treatment inferiority in older patients infected with HCV-1. The SVR rate could reach 67% in older patients infected with HCV-1, if their treatment could last for ⩾80% of its expected duration. Furthermore, even in the group ⩾65 years of age, both HCV-1–infected patients and HCV-2/3–infected patients who had an RVR had high SVR rates of ⩾80%. RVR, treatment adherence, and weight-based ribavirin exposure, but not age group, were independent factors associated with treatment efficacy. The data encourage antiviral treatment with a standard-of-care regimen in older patients, with careful monitoring.

PegIFN/ribavirin has adverse event profiles and drug modification rates similar to those of conventional IFN/ribavirin in patients with CHC who are <65 years of age, except that a lower frequency of flulike symptoms and depression but more potent bone marrow suppression have been noted in the patients receiving PegIFN [13, 14]. We observed that the incidences of adverse events and abnormal laboratory findings associated with PegIFN/ribavirin treatment were similar in the older and middle-aged patients, except that older patients had a numerically higher rate of anemia and a significantly lower rate of skin rash. However, it is noteworthy that older patients had significantly higher rates of profound adverse events and treatment discontinuation, a finding consistent with previous studies of conventional IFN-based therapy [16–18]. It would be helpful to preselect patients ⩾65 years of age who did not have prominent underlying diseases and manage the side effects more aggressively during therapy. In the present study, treatment inferiority in elderly patients was observed only among patients infected with HCV-1 and not among patients infected with HCV-2/3; this finding was similar to that noted in a previous retrospective study of older patients [20]. Nevertheless, the treatment inferiority in elderly patients infected with HCV-1 became nonsignificant if ⩾80% of the expected treatment duration could be achieved. The results suggested that minimizing adverse events and maintaining the prescribed course of treatment are key to successful treating older patients. By doing so, these patients might no longer be regarded as a population that is difficult to treat.

By clearing HCV and stopping the progression of liver fibrosis, IFN-based therapy could reduce the risk of cirrhosis and HCC and improve the survival of patients with CHC who have an SVR. However, age remains an independent factor associated with the development of cirrhosis and HCC [28, 29]. Two retrospective cohort studies demonstrated that conventional IFN monotherapy was beneficial for older patients with CHC in terms of reducing the incidences of HCC and liver-related death through achievement of an SVR [9, 10]. Nevertheless, the benefits of PegIFN/ribavirin combination therapy in improving the long-term outcome for older patients with CHC remain to be studied.

Along with completing treatment for the recommended duration, attainment of an RVR is the most powerful predictor of SVR, followed by treatment adherence and the exposure dose of ribavirin, irrespective of age group and viral genotype. Our study demonstrated that patients—even older patients ⩾65 years of age—with an RVR could achieve high rates of SVR. Several studies have observed that an abbreviated duration of PegIFN treatment with a weight-based dose of ribavirin (16

Table 7. Studies of Pegylated Interferon–Based Therapy for Older Patients

The table is available in its entirety in the online version of the *Journal of Infectious Diseases*

weeks for patients infected with HCV-2/3 and 24 weeks for those infected with HCV-1 who had lower viral loads at baseline) could reduce the incidence of adverse events without compromising treatment efficacy for patients with a RVR, compared with corresponding standard regimens [25, 30]. Although outcomes of a tailored treatment duration might be translated to all age groups and, in particular, to the Asian population [3], the application of HCV-personalized medicine to older patients requires further study. A recent large-scale study demonstrated that not only the SVR rate but, also, the safety profile did not differ when standard-dose (1.5 μg/kg/week) and low-dose (1.0 μg/kg/week) PegIFN-α-2b therapy was administered [31]. Ferenci et al [32] also observed that, with PegIFN-α-2a given for 24 weeks, ribavirin doses of 400 mg/day and 800 mg/day could produce equivalent outcomes in patients infected with HCV-3, but not in those infected with HCV-2. Therefore, whether a reduced dose of PegIFN or ribavirin could maintain treatment efficacy concomitant with a reduction in the incidence of adverse events in older patients remains unclear. On the other hand, the exposure dose of ribavirin by body weight has been one of the most important factors that is predictive of RVR [33] and SVR [25, 30], not only in younger patients but also in older patients. A higher exposure dose of ribavirin has improved treatment efficacy, especially among difficult-to-treat patients infected with HCV-1 [34, 35]. Therefore, reducing the ribavirin dose for patients $\geqslant$65 years of age is not supported by current evidence. However, higher rates of ribavirin-associated adverse events resulting from poorer renal function and underlying comorbidity in older patients might compromise treatment adherence and efficacy. Recently, EPO therapy has been shown to improve quality-of-life and fatigue scores, reduce the risk and magnitude of anemia, and provide space for a higher ribavirin dose [36], although whether this intervention improves treatment efficacy has not been well established [34, 37]. Careful ribavirin titration, in addition to the use of EPO to maintain higher weight-based exposure doses of ribavirin, might be particularly beneficial in this special population.

The SVR rate noted for Asian patients in the current study was higher than that noted in studies from Western countries (~45%) [11, 21, 22], but it was comparable to the 70% rate in the study by Antonucci et al [20]. A similar observation has been noted among patients 18–65 years of age. Increasing evidence has demonstrated that Asians have a higher likelihood of achieving an SVR than do their white counterparts, when they are treated with the corresponding regimen [3, 38]. The rates of treatment discontinuation and RVR associated with PegIFN/ribavirin therapy were 16.7%–24.2% and 54.5%, respectively, among elderly patients in Western countries [11, 20–22]; these rates were comparable to the rates of 21.4% and 61.4%, respectively, noted in the current Asian study. Host and viral genetic variations may be involved in the clinical issues [3].

Age, particularly age >50 years, is considered to be an independent risk factor for progression of fibrosis and development of cirrhosis in patients with CHC [39]. It has been suggested that patients infected with HCV should be identified and treated before they reach 50 years of age [40]. We therefore included middle-aged patients (those 50–64 years of age) instead of younger patients (those <50 years of age) as controls, to clearly elucidate the issues of safety and efficacy associated with the use of standard-of-care regimens in older patients. Four previous studies of the use of PegIFN/ribavirin therapy in elderly patients were small-scale studies including 6–33 patients [11, 20–22]; most of these studies were retrospective [11, 20, 21], and 2 of the 4 studies enrolled both treatment-naive and treatment-resistant patients [11, 20]. Although the current prospective trial had the largest sample size of treatment-naive older patients with CHC, the numbers of cases in the elderly group, especially the subgroups of HCV-1–infected patients and patients with an RVR, remained too small for a conclusive recommendation to be made. Additional larger series of prospective studies are needed to validate our observations. Nevertheless, the strength of our findings will be enough to persuade some clinicians to offer antiviral therapy to older patients with CHC, albeit with close monitoring.

In conclusion, PegIFN/ribavirin therapy is effective in treating older patients infected with HCV. However, older patients experienced adverse events more frequently and had poorer treatment adherence, leading to inferior treatment efficacy, in particular among patients infected with HCV-1. Nevertheless, standard treatment regimens could achieve high SVR rates (>80%) in patients $\geqslant$65 years of age who had an RVR. Other treatment modalities to enhance compliance and reduce side effects should be considered in older patients infected with HCV-1.

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