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Comparison of Compliance and Efficacy of Pegylated Interferon α-2a and α-2b in Adults with Chronic Hepatitis C

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This study compares treatment completion rates and outcomes in hepatitis C virus (HCV) patients between those aged <60 and ≥60 years receiving pegylated interferon (PEG-IFN) α-2a or α-2b combined with ribavirin. No significant differences were found in treatment completion rates and virological responses between age-stratified patients or between genotype-stratified patients receiving PEG-IFN α-2a versus PEG-IFN α-2b. Significantly more patients ≥60 years of receiving PEG-IFN α-2b exhibited an early virological response compared to those receiving PEG-IFN α-2a ($P = 0.002$); for patients <60 years of age, treatment outcomes were similar between the 2 groups. More liver fibrosis was observed in patients with HCV of genotype 1 than in those with genotypes 2 or 3. Mean changes in pre- and post-treatment fibrosis variables (bilirubin, platelet count, liver enzymes, FIB-4, and APRI) in HCV genotype 1 patients were greater in those receiving PEG-IFN α-2b than in those receiving PEG-IFN α-2a. Significant differences were not observed between age- and HCV genotype–stratified patients receiving PEG-IFN α-2a and -α-2b, but α-2b appears to have a modest efficacy advantage over α-2b, particularly in male HCV patients ≥60 years of age.

Keywords: hepatitis C virus, pegylated interferon, compliance, efficacy, liver fibrosis, genotype

Introduction

Chronic hepatitis C virus (HCV) infection affects about 3% of the population worldwide and is a major cause of chronic liver disease, leading to cirrhosis in 20% to 30% and hepatocellular carcinoma in 1% to 4% of HCV patients (Lee and others 2014). The highest prevalence of HCV infection is in Southeast Asia and the western Pacific region, and it is endemic in certain Asian countries (Xia and others 1996; Sun and others 1999; Okayama and others 2002; Lee and others 2014). A decrease in the seroprevalence of anti-HCV antibodies is due, in part, to the discontinuation of practices such as treatment by unqualified medical staff in rural and/or impoverished areas, blood transfusions from seropositive donors, and the use of shared needles for medical injections, acupuncture, and tattooing (Sun and others 1999). As a result, chronic hepatitis C in Taiwan is currently found predominantly among older adult patients subjected to those practices. A high prevalence of chronic hepatitis C is found in coastal areas of Yunlin and Chiayi counties in Taiwan. Among the long-lived residents of Yunlin County's coastal area, hepatitis C patients may live to the age of 80. Having a practice and conducting research in this area, it seemed important to determine whether treatment failure occurs more frequently in older patients and whether using a specific pegylated interferon (PEG-IFN) drug might be more effective in these adult populations.

Naturally occurring IFNs are cytokine signaling proteins that mediate communication between cells to trigger immune system activity. Cytokines are produced by cells in response to invasion by viruses, bacteria, parasites, and even tumor cells (Fensterl and Sen, 2009; Hermant and Michiels, 2014). Pharmaceutical forms of IFN therapy are used as

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antiviral agents and work by mimicking proteins used by the body's immune system to increase antiviral defenses, thereby preventing viruses from replicating their RNA and DNA (Fensterl and Sen, 2009). In particular, IFNα is used to treat hepatitis B and hepatitis C infections. Treatment with IFNα is reported to be more effective for certain virus genotypes. For example, about 75% of patients with hepatitis C genotypes 2 and 3 benefit from IFN treatment but those with genotype 1, the most common form in the United States and Europe, may be less responsive (Jamall and others 2008). Long-term IFN therapy is also reported to effectively reduce liver morbidity and mortality in HCV patients (Hallager and others 2017), and differences in pre- and post-treatment fibrosis indicators are anticipated. PEG-IFN is a modified form of IFNα that links polyethylene glycol to the IFN molecule, allowing the drug to stay in the body longer and provide more effective treatment (Foster, 2010). Although PEG-IFN used with the nucleoside analog ribavirin was at one time the treatment of choice for chronic HCV infection (Nyalakonda and Utay, 2015), IFNs have been essentially replaced by second-generation all-oral direct-acting antiviral (DAA) drugs since 2013. DAAs have shown high efficacy and are well tolerated. While these drugs have simpler regimens, shorter treatment duration, and less discontinuation, they also are more expensive (Nyalakonda and Utay, 2015). The exception might be in countries where access to oral antiviral drugs is limited because of financial or administrative issues. In Taiwan, the National Health Insurance has not yet included coverage of costly DAA. However, even in countries with limited access to DAA, PEG-IFN may still be used in combination with ribavirin when drug resistance precludes the use of oral antivirals. Therefore, studies are still needed to understand the use of PEG-IFN in the face of emerging drug-resistance events and in countries not using DAA routinely.

Two PEG-IFNs are approved and used for treating HCV infection: PEG-IFN α-2a and α-2b. The dosages for these compounds differ, with α-2a given as a fixed once-weekly dose, and α-2b given weekly, sometimes 2 or 3 times a week, depending on patient body weight. PEG-IFN α-2a therapy is associated with higher sustained virological response (SVR) rates (Zhao and others 2010) and greater reductions in neutrophils and platelets (Katano and others 2009), indicating higher efficacy. Ethnic differences may affect the response to PEG-IFN α-2a and α-2b, with α-2b appearing to be more effective in the Chinese population than α-2a (Zhao and others 2008) and equally effective in a Korean population (Jin and others 2013), although evidence is lacking to support such ethnic differences. A recent meta-analysis did not identify specific advantages associated with either IFN therapy on patient-critical outcomes except for an association with higher SVR rates (Hauser and others 2014). Since IFN is associated with side effects, a longer duration of treatment results in greater patient suffering. Consequently, patients require therapeutic drugs that have a short course of treatment (less than 6 months), are well-tolerated, and have a low recurrence rate. In Taiwan, treatment duration is also associated with an insurance coverage issue: patients experiencing rapid virological response (RVR, virus undetectable) can receive treatment covered by health insurance for 6 months, but patients with early virological response (EVR, virus undetectable at 3 months of treatment), but not RVR, must receive treatment for 1 year. Therefore, for most HCV patients in Taiwan, PEG-IFNs remain the first-line treatment for chronic HCV, as the National Health Insurance does not yet cover more expensive DAAs. Evidence is lacking on patient compliance with the use of PEG-IFNs, and the knowledge of patient compliance and outcomes of PEG-IFN treatment is incomplete, especially regarding older versus younger adults. This retrospective, observational cohort study investigates the following questions: (1) which drug achieves successful outcomes with the shortest course or without requiring a second course due to recurrence or treatment failure; (2) do older or younger adult patients have better overall responses in terms of lower treatment dropout rates, higher RVR rates, lower rates of treatment failure (ie, no SVR), and less need for a second course of treatment; (3) among patients with different genotypes, do either of the 2 PEG-IFNs affect completion rates and virological response more effectively, and (4) is there a difference in post-treatment liver fibrosis scores between the 2 drugs? We hypothesize that compliance rates with PEG-IFN treatment may differ between younger and older adults, and rates of RVR and SVR may differ between IFN formulations, different age groups, and different genotypes. The purpose of this study is to compare treatment completion rates and treatment outcomes in patients with chronic HCV infection between those treated with PEG-IFN α-2a and α-2b received in 2 different age groups and with different HCV genotypes and to determine whether treatment with either PEG-IFN affects liver fibrosis scores.

Patients and Methods

Study design

This retrospective, observational cohort study compares treatment completion rates and outcomes (RVR, EVR, SVR), including rates of SVR-24 (aviremia at the 24th week) and late relapse rate (SVR-24 with viremia relapsing) between 2 different pegylated interferons (PFNs), α-2a and α-2b, administered to patients with chronic HCV infection in 2 different age groups (<60 and ≥60 years of age) and with different HCV genotypes. Liver fibrosis scores were also evaluated before and after treatment.

Patients

This study included a total of 627 patients treated for chronic HCV infection between January 2010 and April 2016 at a single hospital in Yunlin County, Taiwan, a coastal area noted for a high prevalence of chronic HCV infection. Inclusion criteria for the study cohort were adult patients aged 20 years old or older diagnosed with chronic HCV infection and treated with injected PFN α-2a or PFN α-2b for at least 6 months. HCV patients younger than age 20, those receiving other forms of treatment, and those with major life-threatening comorbidities such as cancer or chronic renal failure were excluded. Included patients were stratified by age, 1 group <60 years of age ($n = 281$) and 1 group ≥60 years of age ($n = 346$), with 357 males and 270 females. All patients in both groups received PEG-IFN treatment with ribavirin, with 307 receiving PFN-α-2a and 320 receiving PFN-α-2b. Outcomes were also evaluated in patients stratified by HCV genotype: Genotype 1 (Genotype 1, 1a, 1b), Genotype 1 (Genotype 1, 1a, 2b mixed others), Genotype 2 (Genotype 2, 2b), Genotype 3 (Genotype 3),

Genotype 4 (Genotype 4, 4 mixed others), Genotype 6 (Genotype 6), and ''other'' genotypes.

Methods and outcome measures

All patient data were analyzed retrospectively. The main outcome measures are as follows: treatment completion rate; RVR, defined as an undetectable level of virus 1 month after receiving IFN; EVR, defined as an undetectable level of the virus 3 months after receiving IFN; SVR, defined as aviremia at 6 months of IFN therapy; late relapse, defined as viremia 6 months after completion of IFN treatment; and liver fibrosis. Treatment failure was defined as no SVR. Rates of SVR-24 (aviremia at the 24th week) and late relapse rate (SVR-24 with viremia relapsing) were also evaluated. Liver fibrosis was determined using fibrosis 4 (FIB-4) scores calculated as f [(Age × AST)/(Platelets × sqr (ALT))] (http://gihep.com/calculators/hepatology/fibrosis-4-score) and AST to Platelet Ratio Index (APRI) calculated as [(AST/ULN AST) × 100]/Platelets (109/L) (http://gihep.com/calculators/hepatology/apri).

All outcome variables were measured in the 2 different age groups and between the 2 different PEG-IFN formulations α-2a and α-2b and were also evaluated in gender-stratified and genotype-stratified patient groups by age and treatment.

Treatment of chronic HCV infection

PFN α-2a (Pegasys; Hoffman LaRoche, Clifton, NJ) and PFN α-2b (Pegintron; Merck Sharp & Dohme, Boston, MA) were used to treat chronic HCV in the included patients. Patients were recruited from the practices of 2 different clinicians (Clinician A and Clinician B). At the time of treatment prescription, patients were given information about the 2 drugs, and most patients agreed to the clinicians' recommendation regarding the allocation of treatment. The α-2a regimen was recommended for the majority of patients treated by Clinician A, while α-2b was recommended for the majority of patients treated by Clinician B. PEG-IFN α-2a was administered to patients treated in the outpatient department (not allocated by clinicians) who were treated by Clinician A, while PEG-IFN α-2b was administered to those treated by Clinician B. Dosages varied by IFN formulation and by individual patient but, generally, α-2a was administered as a fixed once-weekly dose, while α-2b was administered weekly according to patient body weight.

Statistical analyses

Continuous variables are presented as medians and interquartile ranges, with the Mann–Whitney U-test used for comparing differences between groups. Categorical variables, including the treatment completion rates, RVR, EVR, and SVR after 6 months, are presented as counts and percentages. Chi-square or Fisher's exact tests were performed to compare variables between the administration of PFN α-2a and PFN α-2b. All statistical analyses were performed using IBM SPSS statistical software version 22 for Windows (IBM Corp., Armonk, New York, NY). A two-tailed $P < 0.05$ was established as statistically significant.

Results

The mean age of the entire patient cohort was 59.2 ± 11 years with 357 males (56.9%) and 270 females (43.1%).

Similar outcomes between patients receiving PEG-IFN α-2a and those receiving PEG-IFN α-2b

After 6 months of treatment, no significant differences were found in the treatment completion rate, RVR, EVR, and SVR between patients receiving PEG-IFN α-2a and those receiving PEG-IFN α-2b (Table 1).

EVR of age-stratified patients differed significantly between those receiving PEG-IFN α-2a and those receivingα-2b

After 6 months of treatment, patients <60 years of age did not differ significantly in treatment completion rate, RVR, EVR, or SVR between those receiving PEG-IFN α-2a and those receiving PEG-IFN α-2b (all $P > 0.05$). Among the patients ≥60 years of age, EVR alone was found to differ significantly between patients receiving PEG-IFN α-2a and those receiving PEG-IFN α-2b ($P = 0.002$); patients

Table 1. Comparison of 6-Month Treatment Outcomes (Treatment Completion Rate, RVR, EVR, SVR) Between Patients Receiving PEG-Interferon α-2a and α-2b

	PEG-interferon α-2a (N = 307)	*PEG-interferon α-2b (N = 320)*	P
Treatment completion rates			
After 24 weeks	130 (52.85%)	128 (50.20%)	0.662
After 25 weeks	0 (0%)	2 (0.78%)	
After 32 weeks	0 (0%)	1 (0.39%)	
After 48 weeks	103 (41.87%)	112 (43.92%)	
RVR (−), EVR (−)	13 (5.28%)	12 (4.71%)	
RVR			
(−)	158 (53.74%)	160 (52.98%)	0.852
(+)	136 (46.26%)	142 (47.02%)	
EVR			
(−)	23 (8.33%)	39 (13.31%)	0.057
(+)	253 (91.67%)	254 (86.69%)	
Relapsed SVR cases 6 months after end of treatment			
(−)	42 (20.39%)	45 (20.36%)	0.995
(+)	164 (79.61%)	176 (79.64%)	

EVR, early virological response; PEG, pegylated; RVR, rapid virological response; SVR, sustained virological response.

receiving PEG-IFN α-2b had a higher percentage of negative results for EVR compared with those receiving PEG-IFN α-2a (18.63% versus 7.14%). However, no other significant differences were found in treatment completion rate, RVR, and SVR between patients in the 2 age groups receiving PEG-IFN α-2a or α-2b for 6 months (all $P > 0.05$) (Table 2).

EVR differed significantly in male but not female patients ≥60 years of age between those receiving PEG-IFN α-2a and those receiving PEG-IFN α-2b

Among patients aged 60 years and older, the EVR differed significantly between patients receiving PEG-IFN α-2a and those receiving α-2b in males but not in females ($P = 0.02$, 0.049, respectively). No other significant differences were found in treatment completion rate, RVR, and SVR between patients stratified by age and gender receiving either PEG-IFN α-2a or α-2b for 6 months (all $P > 0.05$) (Table 3).

Similar outcomes for patients stratified by genotype between those receiving PEG-IFN α-2a and those receiving PEG-IFN α-2b

Table 4 shows the distribution of the 7 genotypes.

Supplementary Tables show results for completion rates, RVR, EVR, and SVR for patients stratified by genotypes. No significant differences were found in treatment completion rates, RVR, EVR, and SVR of genotype 1 patients between those receiving PEG-IFN α-2a versus α-2b (all $P > 0.05$, Supplementary Table S1). Results were similar for the other genotypes, with no significant differences found in treatment completion rates, RVR, EVR, and SVR between patients receiving PEG-IFN α-2a versus α-2b (all $P > 0.05$) (Supplementary Tables S2–S7).

Greater liver fibrosis observed in patients with HCV genotype 1 than in those with HCV genotypes 2 or 3

Results of liver fibrosis scores before and after treatment in patients with different HCV genotypes are summarized in Table 5. The mean fibrosis 4 scores for genotype 1, genotype 2, and other genotypes were significantly higher after treatment than before treatment in patients receiving PEG-IFN α-2a. The mean APRI index was significantly lower after treatment than before treatment in patients receiving PEG-IFN α-2a and in those with genotype 2. In the group receiving PEG-IFN α-2b, the mean APRI index was significantly lower after treatment than before treatment and in patients with HCV genotype 1, genotype 2, and other genotypes (Table 5).

Differences between treatment groups receiving IFN α-2a and 2b are shown in Supplementary Tables S8–S14.

Table 2. Comparisons of Outcomes (Treatment Completion Rate, RVR, EVR, SVR) Between Age-Stratified Patients Receiving PEG-Interferons α-2a and α-2b

	PEG-interferon α-2a	*PEG-interferon α-2b*	P
Age ≤60 years	$N = 138$	$N = 143$	
Treatment completion rate			
After 24 weeks	71 (62.28%)	67 (57.76%)	0.391
After 25 weeks	0 (0%)	1 (0.86%)	
After 48 weeks	37 (32.46%)	45 (38.79%)	
RVR (−), EVR (−)	6 (5.26%)	3 (2.59%)	
RVR			
(−)	60 (46.15%)	64 (46.38%)	0.971
(+)	70 (53.85%)	74 (53.62%)	
EVR			
(−)	12 (9.84%)	9 (6.82%)	0.383
(+)	110 (90.16%)	123 (93.18%)	
Relapsed SVR cases 6 months after end of treatment			
(−)	16 (17.20%)	15 (14.85%)	0.655
(+)	77 (82.80%)	86 (85.15%)	
Age ≥60 years	$N = 169$	$N = 177$	
Treatment completion rate			
After 24 weeks	59 (44.70%)	61 (43.88%)	0.964
After 25 weeks	0 (0%)	1 (0.72%)	
After 32 weeks	0 (0%)	1 (0.72%)	
After 48 weeks	66 (50.00%)	67 (48.20%)	
RVR (−), EVR (−)	7 (5.30%)	9 (6.47%)	
RVR			
(−)	98 (59.76%)	96 (58.54%)	0.822
(+)	66 (40.24%)	68 (41.46%)	
EVR			
(−)	11 (7.14%)	30 (18.63%)	0.002
(+)	143 (92.86%)	131 (81.37%)	
Relapsed SVR cases 6 months after end of treatment			
(−)	26 (23.01%)	30 (25.00%)	0.722
(+)	87 (76.99%)	90 (75.00%)	

EVR, early virological response; PEG, pegylated; RVR, rapid virological response; SVR, sustained virological response.

Table 3. Comparison of Outcomes (Treatment Completion Rate, RVR, EVR, SVR) Between Age- and Gender-Stratified Patients Receiving PEG-Interferons α-2a versus α-2b

	PEG-interferon α-2a	*PEG-interferon α-2b*	P
Males ≤60 years	*N* = 84	*N* = 104	
Treatment completion rate			
After 24 weeks	47 (68.12%)	53 (61.63%)	0.324
After 25 weeks	0 (0%)	1 (1.16%)	
After 48 weeks	18 (26.09%)	30 (34.88%)	
RVR (–), EVR (–)	4 (5.80%)	2 (2.33%)	
RVR			
(–)	34 (43.59%)	45 (44.55%)	0.897
(+)	44 (56.41%)	56 (55.44%)	
EVR			
(–)	8 (10.67%)	4 (4.21%)	0.103
(+)	67 (89.33%)	91 (95.79%)	
Relapsed SVR cases 6 months after end of treatment			
(–)	10 (17.85%)	10 (13.51%)	0.497
(+)	47 (82.14%)	64 (86.48%)	
Females ≤60 years	*N* = 94	*N* = 83	
Treatment completion rates			
After 24 weeks	24 (53.33%)	14 (46.67%)	0.838
After 48 weeks	19 (42.22%)	15 (50.00%)	
RVR (–), EVR (–)	2 (4.44%)	1 (3.33%)	
RVR			
(–)	26 (50.00%)	19 (51.35%)	0.900
(+)	26 (50.00%)	18 (48.65%)	
EVR			
(–)	4 (8.51%)	5 (13.51%)	0.462
(+)	43 (91.49%)	32 (86.49%)	
Relapsed SVR cases 6 months after end of treatment			
(–)	6 (16.22%)	5 (18.52%)	0.809
(+)	31 (83.78%)	22 (81.48%)	
Males ≥60 years	*N* = 75	*N* = 94	
Treatment completion rates			
After 24 weeks	34 (54.84%)	27 (37.50%)	0.120
After 48 weeks	24 (38.71%)	40 (55.56%)	
RVR (–), EVR (–)	4 (6.45%)	5 (6.94%)	
RVR			
(–)	37 (51.39%)	56 (63.64%)	0.118
(+)	35 (48.61%)	32 (36.36%)	
EVR			
(–)	4 (5.97%)	16 (18.82%)	0.020
(+)	63 (94.02%)	69 (81.18%)	
Relapsed SVR cases 6 months after end of treatment			
(–)	5 (9.80%)	13 (21.67%)	0.091
(+)	46 (90.20%)	47 (78.33%)	
Females ≥60 years	*N* = 94	*N* = 83	
Treatment completion rate			
After 24 weeks	25 (35.71%)	34 (50.75%)	0.079
After 25 weeks	0 (0%)	1 (1.49%)	
After 32 weeks	0 (0%)	1 (1.49%)	
After 48 weeks	42 (60.00%)	27 (40.30%)	
RVR (–), EVR (–)	3 (4.29%)	4 (5.97%)	
RVR			
(–)	61 (66.30%)	40 (52.63%)	0.072
(+)	31 (33.70%)	36 (47.37%)	
EVR			
(–)	7 (8.05%)	14 (18.42%)	0.049
(+)	80 (91.95%)	62 (81.58%)	
Relapsed SVR cases 6 months after treatment			
(–)	21 (33.87%)	17 (28.33%)	0.509
(+)	41 (66.13%)	43 (71.67%)	

EVR, early virological response; PEG, pegylated; RVR, rapid virological response; SVR, sustained virological response.

Table 4. Distribution of Hepatitis C Virus Genotypes

	PEG-interferon α-2a	*PEG-interferon α-2b*	P
Genotype 1 (genotype 1, 1a, 1b)	149 (51.2%)	151 (51.54%)	0.648
Genotype 1 (genotype 1, 1a, 2b mixed others)	8 (2.75%)	4 (1.37%)	
Genotype 2 (genotype 2, 2b)	77 (26.46%)	78 (26.62%)	
Genotype 3 (genotype 3)	2 (0.69%)	3 (1.02%)	
Genotype 4 (genotype 4, 4 mixed others)	0 (0%)	3 (1.02%)	
Genotype 6 (genotype 6)	5 (1.72%)	6 (2.05%)	
Other genotypes	50 (17.18%)	48 (16.38%)	

HCV genotype 1. Eight patients in this group received PEG-IFN α-2a, and 4 received PEG-IFN α-2b. No significant differences were found in changes from pre- to post-treatment in all liver fibrosis variables between patients receiving the 2 PEG-IFNs, α-2a, and IFN α-2b (all $P > 0.05$) (Supplementary Table S9).

HCV genotype 2. In this group, 77 patients received PEG-IFN α-2a, and 79 patients received PEG-IFN α-2b. The median pretreatment total bilirubin was significantly higher in patients receiving PEG-IFN α-2b than in those receiving PEG-IFN α-2a (1.1 versus 0.9; $P = 0.005$). The median post-treatment platelet count was significantly higher in patients receiving PEG-IFN α-2b than in those receiving PEG-IFN α-2a (149 versus 122; $P = 0.033$). The median post-treatment FIB-4 score and APRI index were significantly higher in patients receiving PEG-IFN α-2a than in those receiving PEG-IFN α-2b (FIB-4 score: 2.95 versus 2.28, $P = 0.018$; APRI index: 0.79 versus 0.54, $P = 0.018$). Median changes in total bilirubin and FIB-4 scores between pre- and post-treatment were significantly higher in patients receiving PEG-IFN α-2a compared with those receiving IFN α-2b (changes in total bilirubin: 0 versus –0.1, $P = 0.011$; changes in FIB-4 scores: 0.63 versus 0.07, $P = 0.011$) (Supplementary Table S10).

HCV genotype 3. In 2 patients receiving PEG-IFN α-2a and 3 patients receiving PEG-IFN α-2b (with no data for cholesterol, triglyceride [TG], or glucose), no significant differences were found in any of the liver fibrosis variables or changes between pre- and post-treatment in the 2 groups (all $P > 0.05$) (Supplementary Table S11).

HCV genotype 4. In this group, 3 patients received IFN α-2b, and no patients received IFN α-2a. Only patients receiving PEG-IFN α-2b had liver fibrosis data (Supplementary Table S12).

HCV genotype 6. Five patients received PEG-IFN α-2a, and 6 patients received α-2b (with no data on cholesterol, TG, or glucose). No significant differences were found in liver fibrosis variables and changes from pre- to post-treatment scores between patients receiving the 2 PEG-IFNs (all $P > 0.05$) (Supplementary Table S13).

"Other" genotypes. In this group, 46 patients received IFN α-2a, and 54 patients received IFN α-2b. No significant differences were found in pretreatment liver fibrosis variables between patients receiving PEG-IFN α-2a and α-2b

Table 5. Summary of Changes in Liver Fibrosis Scores

	PEG-interferon α-2a			*PEG-interferon α-2b*		
	Pretreatment	*Post-treatment*	P	*Pretreatment*	*Post-treatment*	P
Fibrosis 4 score (total)	2.29 (1.48–3.70)	2.97 (2.00–5.14)	<0.001	2.35 (1.55–3.76)	2.28 (1.58–3.67)	0.922
Genotype 1 (genotype 1, 1a, 1b)	2.49 (1.64–3.70)	3.22 (2.00–5.64)	<0.001	2.20 (1.54–3.34)	2.12 (1.56–3.54)	0.808
Genotype 1 (genotype 1, 1a, 2b mixed others)	1.89 (1.15–3.14)	2.76 (1.12–7.17)	0.263	3.51 (1.41–7.14)	4.19 (1.81–5.87)	1.000
Genotype 2 (genotype 2, 2b)	2.33 (1.5–4.41)	2.95 (2.19–4.69)	<0.001	2.37 (1.46–3.79)	2.28 (1.55–3.85)	0.476
Genotype 3 (genotype 3)	1.39 (1.06–1.73)	1.57 (0.78–2.36)	0.655	2.66 (1.67–2.82)	5.33 (1.93–9.19)	0.109
Genotype 4 (genotype 4, 4 mixed others)				4.04 (2.50–4.75)	3.38 (2.54–5.44)	1.000
Genotype 6 (genotype 6)	1.73 (0.85–1.92)	1.61 (1.17–1.69)	0.686	1.07 (0.84–3.01)	1.51 (1.08–5.47)	0.345
Other genotypes	2.08 (1.25–3.52)	2.71 (1.66–4.15)	0.002	2.49 (1.77–3.95)	2.36 (1.79–3.65)	0.219
APRI Index (total)	0.84 (0.51–1.57)	0.72 (0.42–1.3)	0.002	0.85 (0.54–1.55)	0.50 (0.34–0.87)	<0.001
Genotype 1 (genotype 1, 1a, 1b)	0.86 (0.54–1.45)	0.71 (0.42–1.32)	0.062	0.75 (0.51–1.45)	0.44 (0.33–0.78)	<0.001
Genotype 1 (genotype 1, 1a, 2b mixed others)	0.62 (0.46–1.46)	0.61 (0.22–3.14)	0.263	1.45 (0.36–3.31)	0.73 (0.3–1.22)	0.068
Genotype 2 (genotype 2, 2b)	0.95 (0.50–2.20)	0.79 (0.48–1.37)	0.025	0.98 (0.61–1.92)	0.54 (0.36–0.87)	<0.001
Genotype 3 (genotype 3)	1.25 (0.47–2.03)	0.71 (0.35–1.06)	0.655	0.94 (0.78–1.43)	0.92 (0.55–3.67)	0.593
Genotype 4 (genotype 4, 4 mixed others)				1.06 (0.7–4.96)	0.93 (0.44–1.66)	0.285
Genotype 6 (genotype 6)	0.71 (0.56–1.37)	0.33 (0.29–0.52)	0.080	0.48 (0.38–1.69)	0.58 (0.41–1.32)	0.753
Other genotypes	0.78 (0.41–1.47)	0.71 (0.4–1.25)	0.176	1.00 (0.67–1.52)	0.62 (0.35–0.94)	<0.001

APRI, AST to Platelet Ratio Index.

(all $P > 0.05$). However, median post-treatment glucose levels were significantly higher in patients receiving PEG-IFN α-2a compared with those receiving α-2b (101 versus 91; $P = 0.029$). Median changes from pre- to post-treatment in total bilirubin, FIB-4 scores, and APRI index were significantly higher in patients receiving IFN α-2a than in those receiving α-2b (changes in total bilirubin: 0 versus −0.2, $P = 0.03$; changes in FIB-4 scores: 0.68 versus −0.07, $P = 0.001$; changes in APRI index: −0.11 versus −0.42, $P = 0.026$); the median change in platelet count was significantly higher in patients receiving PEG-IFN α-2b than in those receiving PEG-IFN α-2a (−15.5 versus −45; $P = 0.002$) (Supplementary Table S14).

Changes in fibrosis variables in patients carrying HCV of genotype 1 were greater in those receiving PEG-IFN α-2b than in those receiving PEG-IFN α-2a

The median total bilirubin and FIB-4 scores were significantly higher in patients with erythropoietin (EPO) use compared to those without in the PEG-IFN α-2a group (total bilirubin: 1.15 versus 0.9, $P = 0.018$; FIB-4 score: 3.32 versus 2.12, $P = 0.018$). No significant differences were found in the PEG-IFN α-2b group ($P > 0.05$) (Supplementary Table S15).

For post-treatment liver fibrosis factors, the median cholesterol, FIB-4 score, and APRI index were significantly higher in patients with EPO use than in those without in the PEG-IFN α-2a group (cholesterol: 207 versus 171, $P = 0.028$; FIB-4 score: 4.44 versus 2.51, $P = 0.002$; APRI index: 0.89 versus 0.65, $P = 0.033$). The median glucose level and platelet counts were significantly lower in patients with EPO use compared to those without (glucose: 97.5 versus 117, $P = 0.016$; platelet count: 99.5 versus 145.5, $P = 0.021$). No significant differences were found between patients with and without EPO use in the PEG-IFN α-2b group ($P > 0.05$) (Supplementary Table S15).

Mean changes in FIB-4 score were significantly higher in patients with EPO use than in those without (0.97 versus 0.64; $P = 0.018$) in patients receiving PEG-IFN α-2a. No significant differences were found between patients with and without EPO use in the PEG-IFN α-2b group ($P > 0.05$) (Supplementary Table S15).

No significant differences were found between patients with and without EPO use in treatment completion rates, RVR, EVR, or SVR, regardless of PEG-IFN treatment group (Supplementary Table S15).

Discussion

The present study reveals no significant difference in the treatment completion rate, RVR, EVR, or SVR between patients <60 and ≥60 years of age between the 2 PEG-IFN groups after 6 months of treatment. Only the EVR differed significantly between patients aged 60 or older receiving PEG-IFN α-2a and those receiving α-2b ($P = 0.002$). No significant differences were found in treatment completion rates or virological response between genotype-stratified patients receiving PEG-IFN α-2a and α-2b. However, significantly more patients ≥60 years of age receiving PEG-IFN α-2b exhibited EVR compared to those receiving α-2a, while in patients <60 years of age, the treatment outcomes were similar between the 2 IFN groups. Changes in liver fibrosis parameters before and after treatment were greater in HCV patients with hepatitis genotype 1 than in those with genotypes 2 and 3 and were greater in those receiving PEG-IFN α-2b than in those receiving α-2a.

Although no differences were found between younger and older adults in their responses to the 2 PEG-IFNs or outcomes, a stronger EVR was observed in adults over age 60 after treatment with PEG-IFN α-2b than treatment with PEG-IFN α-2a. This result suggests a slight advantage of α-2b over α-2a treatment in older adults. However, later in the course of treatment (24th week), no differences were found in the SVR or rate of SVR-24 showing aviremia between these patients.

This difference might be explained by the ability of the physician to adjust the dosage during the therapy with PEG-IFN α-2b but not PEG-IFN α-2a. This factor may affect compliance, as severe side effects, which are greater in older patients, may be managed by dosage adjustments (Papić and others 2018). If patients receiving PEG-IFN α-2b are more likely to complete the entire drug regimen, they are likely to have a stronger EVR than those treated with PEG-IFN α-2a. Since chronic HCV infection is most prevalent in the older generation in Taiwan, these results are quite instructive and encouraging for this population, showing a comparatively equal response to the 2 PEG-IFNs by older and younger adults, with no outstanding differences in adverse events between ages or PEG-IFN formulations.

A similar lack of significant differences was found in a fairly recent meta-analysis (Zhao and others 2010) and a multicenter comparison (Jin and others 2013) of the 2 PEG-IFNs. These studies considered differences between the 2 PEG-IFNs and between different age groups, although study groups were not stratified precisely the same as our age groups. Zhao and others (2010) found that PEG-IFN α-2a treatment of chronic HCV infection was associated with higher SVR rates than PEG-IFN α-2b treatment in 7 randomized controlled trials that compared responses to the 2 PEG-IFNs combined with ribavirin. Although adverse events were not reported due to lack of data, the discontinuation rates were generally low across all trials. Jin and others (2013) conducted a multicenter study in patients with different HCV genotypes 1 and 2/3 and found no significant differences in EVR and SVR rates between the 2 PEG-IFN groups by genotype or by age (<50 years, >50 years). Adverse events were also similar between groups. All patients were of Asian ethnic heritage as in the present study, and those authors concluded that, unlike Western data showing differences in safety and efficacy between PEG-IFN α-2a and α-2b (Backus and others 2007; Witthoeft and others 2008; Ascione and others 2010; Rumi and others 2010; Hauser and others 2014), no differences were found in chronically infected Korean HCV patients regardless of age, viral load, or genotype. Since ethnic differences have been suggested (Zhao and others 2008), it is interesting that Asian populations known to have a higher prevalence of chronic HCV infection have not shown differences in compliance and responses to IFN administration (Zhao and others 2010; Jin and others 2013).

Studies in Western countries, where PEG-IFNs are used routinely with ribavirin, show different virological responses. Two Italian studies showed that PEG-IFN α-2a had higher rates of SVR than α-2b (Ascione and others 2010; Rumi and others 2010). Two large retrospective

studies conducted in the United States and Germany (Backus and others 2007; Witthoeft and others 2008) also found that PEG-IFN α-2a had higher SVR rates than did α-2b in routine HCV treatment. A systematic review of randomized clinical trials (Awad and others 2010) also suggested that the SVR rate of PEG-IFN α-2a was superior to that of α-2b. The above studies all combined IFN treatment with ribavirin, which may account, in part, for these differences. However, a Korean study (Jin and others 2013) compared PEG-IFN treatment with ribavirin to IFN treatment only and found no significant differences in completion rates or virological response, as found in the present study. We might add that, in Taiwan, where nucleoside analogs such as ribavirin are not yet covered by insurance and are not a routine part of treatment, achieving successful treatment with PEG-IFNs alone becomes especially important. However, the meta-analysis by Hauser and others (2014) found that patients receiving PEG-IFN+ribavirin who developed anemia and required reduction of the ribavirin dose actually achieved higher SVR rates than patients who did not require ribavirin dose reduction. This observation seems to suggest that the effects of different PEG-IFN formulations may not be influenced by variations in ribavirin dosage associated with adverse effects. In fact, those authors suggest instead that the high risk of bias in studies included in the meta-analysis may be more apt to influence the apparent superiority of PEG-IFN α-2a effects than ribavirin dosage. It is important to note that, in the present study, patients were allocated randomly between 2 clinicians, with odd-numbered patients treated by Clinician A and even-numbered patients treated by Clinician B, assuring that the 2 groups had similar numbers of patients and less bias.

Since HCV infection is a major cause of liver-related morbidity, liver function in HCV is of particular interest. Reductions in liver morbidity have been reported in those receiving long-term treatment with PEG-IFN α-2a and α-2b, especially if SVR is achieved (Awad and others 2010; Hallager and others 2017). However, the results of the present study did not show major differences in fibrosis scores for patients in the 2 treatment groups, although changes in liver fibrosis parameters between pre- and post-treatment were greater in HCV patients with HCV genotype 1 than in those with genotypes 2 and 3 and were greater in those receiving PEG-IFN α-2b than in those receiving α-2a. Nevertheless, a review of 72 trials by Brok and others (2010) found that PEG-IFN+ribavirin therapy had a significant effect on the histological response, reduced the risk of anemia and other adverse events, and related morbidity and mortality.

The present study has certain limitations. Interpretation of the study results is limited by the retrospective design, since it precludes consideration of causality. The study was also conducted in a single institution in an area of Taiwan noted for chronic HCV infection; therefore, the results may not be generalizable to other populations, even in other locations within Taiwan. However, for the same reasons, this area was considered ideal for exploring patient compliance and treatment outcomes for the 2 PEG-IFN formulations to help understand the comparative value of these treatment options. An additional prospective study at multiple institutions and geographic sites is needed to confirm the results of the present study.

Conclusion

Adverse events and discontinuation of IFN treatment do not differ significantly between younger and older adults, and neither PEG-IFN formulation appears to be associated with significantly greater improvement or more adverse events. More of the older adults had EVR, suggesting a slight advantage to treating older adults with PEG-IFN α-2b. Additional studies are needed to further explore the differences between PEG-IFN treatment and effects associated with HCV genotypes and the development of liver fibrosis.

Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

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Supplementary Table S2
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