Meta-Analysis of Factors Associated With Sustained Viral Response in Patients on Hemodialysis Treated With Standard or Pegylated Interferon for Hepatitis C Infection

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Introduction. The efficacy and safety of pegylated and standard interferon (IFN) have been scrutinized in meta-analyses; however, factors associated with hepatitis C viral response in patients on hemodialysis are not well investigated.

Materials and Methods. We evaluated factors that could be associated with sustained virological response (SVR) to pegylated or standard IFN monotherapy in patients on hemodialysis with chronic hepatitis C virus (HCV) infection, by performing a systematic review of the literature with a meta-analysis of clinical trials. We used both Mantel-Haenszel and DerSimonian and Laird random effects models, with heterogeneity and sensitivity analyses.

Results. Twenty-one studies on IFN-α2a or IFN-α2b (491 patients) and 12 on pegylated-IFN-α2a or PEG-IFN-α2b (279 patients) were evaluated. The pooled SVR for standard and pegylated IFN monotherapy in random effects model was 39.1% (95% confidence interval [CI], 32.1 to 46.1) and 39.3% (95% CI, 26.5 to 52.1), respectively. Pooled dropout rates were 22.6% (95% CI, 10.4 to 34.8) and 29.7% (95% CI, 21.7 to 37.7), respectively. Female gender, HCV-RNA copies per milliliter, HCV genotype, alanine transaminase pattern, duration of infection, liver fibrosis stage, and treatment duration were not associated with SVR. Only an age less than 40 years was significantly associated with SVR in both models (odds ratio, 2.17; 95% CI, 1.03 to 4.50).

Conclusions. Additional benefit of monotherapy with pegylated IFN in patients on hemodialysis with HCV infection in terms of viral response and adverse events is still unclear. According the current literature, younger age was the only determinant of SVR.

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INTRODUCTION

Hepatitis C virus (HCV) is a major cause of chronic liver disease and has been compared to a "viral time bomb." The World Health Organization has estimated that already about 180 000 000 people are infected with HCV, 130 000 000 of those being chronic HCV carriers and at a risk of developing liver cirrhosis and cancer. It is also estimated that 3 000 000 to 4 000 000 persons are newly infected each year, and most of them will develop chronic hepatitis.[1] Patients on long-term hemodialysis are the major group at risk of HCV infection. There is a large variety in seroprevalence of HCV in patients on hemodialysis. The reported prevalence of HCV among the hemodialysis population has varied from 1.9% to 84.6% in different countries and even

different regions in one country.[2-12] Nonetheless, in the past decade, seroprevalence of HCV infection in these patients had a globally diminishing trend, reflecting a number of factors; broad use of recombinant erythropoietin and resultant decreased need of transfusion, screening of blood products, quality and quantity improvement of hemodialysis unit staffs, and adherence to universal precautionary measures.[11,13-24]

The natural history of liver disease in patients on hemodialysis is complicated due to comorbidities like cardiovascular diseases. Several studies revealed that clinical course of chronic HCV infection in these patients were generally asymptomatic, and although biochemical dysfunction was often absent in infected patients, an increased rate of mortality from liver disease had been observed in patients on long-term dialysis.[25-30] Nonetheless, in comparison to chronic hepatitis C patients with normal kidney function, chronic hepatitis C among patients on hemodialysis is milder in disease activity, is frequently cleared in asymptomatic patients during a long course, and is less progressive, perhaps because of immunological abnormalities in these patients.[31]

Success of antiviral therapy in end-stage renal disease has been determined by numerous clinical trials, with rates of sustained virological response (SVR) comparable and even higher than those in patients with normal kidney function who were treated with interferon (IFN) alone. However, virological and biochemical relapse after transplantation because of immunosuppressive medicines and chronic allograft nephropathy and rejection caused by IFN has remained the major concern in HCV-positive patients with chronic kidney disease awaiting kidney transplantation, even those with eradicated viral infection. Therefore, pretranspiration treatment and viral eradication has the greatest prognostic value for these patients. At present, pegylated IFN (PEG-IFN) and ribavirin are considered standard treatment in patients with normal kidney function. In patients with end-stage renal disease, ribavirin is not generally prescribed, because it is not filtrated through hemodialysis filters, accumulates in serum, and causes dose-related hemolysis,[32] whereas administration of low-dose ribavirin is currently evolving. There are numerous small studies that have evaluated efficacy of standard IFN and few ones PEG-IFN in patients on hemodialysis, and several meta-analyses of the literature on this issue have been published; however, prognostic factors associated with SVR and advantage of PEG-IFN on standard IFN are not evaluated using meta-analytical procedures, and original studies also have very low statistical power to draw a reliable conclusion. Therefore, in the current analysis, we collected all clinical trials on treatment of HCV infection in patients on hemodialysis and extracted data on reported factors associated with SVR in each one, in order to pool them together to reach to a more robust conclusion.

MATERIALS AND METHODS

Search Strategy and Methods

We made a Medline search through the PubMed, using the terms *peginterferon alfa-2b*, *peginterferon alfa-2a*, *Pegasys*, *Peginteron*, *interferon alfa-2a*, and *interferon alfa-2b* in combination with *renal dialysis*, *chronic kidney failure*, *renal failure*, and *hemodialysis*. Temporal limit was not used. Other databases such as the Scopus, Science Citation Index, and Cochrane Register of Clinical Trials were also searched with relevant terms and without temporal limits. The information in this report is based on peer-reviewed medical articles published from 1995 up to September 2009 in the English language. Bibliographies of the articles retrieved were used to find other references.

Inclusion and Exclusion of Studies

We developed strict inclusion and exclusion criteria before reviewing the studies and extracting the data, in order to ensure maximum possible homogeneity among studies. We included studies that (1) recruited only subjects on hemodialysis or peritoneal dialysis, (2) provided dose and duration of therapy, and (3) reported SVR and defined negative HCV RNA by polymerase chain reaction at least 6 month after the end of treatment.

Our exclusion criteria were as follows: (1) inclusion of patients with organ transplantation or obtaining renal graft before assuring SVR, (2) inclusion of acute HCV-infected patients (3) addition of ribavirin to IFN or PEG-IFN, (4) treatment duration of less than 24 weeks, (5) inclusion of patients not on dialysis, (6) reporting of cases, small case series, and studies on sample sizes less than 9 subjects in the treatment arm, (6) reporting

of viral response rate by methods other than polymerase chain reaction, and (7) reporting of only biochemical response rates.

Data Extraction

A single investigator extracted all relevant data and inserted into an electronic database. These data were reviewed and confirmed twice by the same investigator. When data were unclear or required assumptions, the other author was consulted and achieved consensus before recording an entry in the database. The current report is based on intention-to-treat analysis; thus, only patients who had a negative serum HCV-RNA by polymerase chain reaction methods were considered as having SVR and those who discontinued the treatment or were lost to follow up for any reason, even with end-of-treatment viral response, were regarded as non-SVR. The chance of developing HCV viremia after achieving end of treatment is substantial; therefore, studies that followed up their subjects less than 5 months were excluded. On the other hand, because the risk of relapse after developing negative viremia 6 months after treatment cessation is neglectable, in studies that reported HCV RNA results only beyond 6 months after treatment, we imputed that as SVR. Individual patient data were combined when summary data were not provided. Since the adverse events of IFN therapy in patients on hemodialysis are well discussed in other published meta-analyses, we only indicated treatment withdrawals that have been reported as death or treatment discontinuation caused by adverse events as dropout rate.

Quantitative Data Synthesis

Serum RNA level, liver fibrosis stage, genotype, and alanine transaminase (ALT) pattern are the main factors that affect decision about beginning and duration of a treatment protocol for HCV-infected patients. Sex and age are also factors that have been proposed to influence hepatitis C viral clearance. In the current meta-analysis, we took into account 7 binary covariates to evaluate possible prognostic values of aforementioned factors as well as duration of infection for achieving sustained viral response in patients with ESRD patients. The continuous variables were dichotomized in a way that we could enter the maximum number of studies that reported that variable in continuous or dichotomous form. The dichotomous covariates were as follow: gender (female, male), HCV-RNA (< 400000 copy/mL, ≥ 400000 copy/mL), HCV genotype (genotype 1, nongenotype 1), ALT pattern (normal, abnormal), age (≥ 40 years, < 40 years), duration of infection (> 1 year, ≤ 1 year), and liver fibrosis stage (< 3, ≥ 3; Knodel score). Individual odds ratio (OR) of the attaining SVR and its 95% confidence interval (CI) for dichotomous covariates were extracted from the data provided by each studies and the pooled OR for each covariate was computed by using the random effects model, according to DerSimonian and Laird method. The random effects model provides a more conservative estimate of significance. This model operates under the assumption that included studies are only a random sample of all studies that will be conducted, so that heterogeneity between individual studies will result in a wider CI of the summary estimate. Therefore, using the DerSimonian and Laird random effects model, the reported summary estimate was calculated as an average of the individual study results weighted by the inverse of their variance.[33] The estimate of heterogeneity was taken from the Mantel-Haenszel model; under the null hypothesis of the test of heterogeneity, there is no difference in treatment effect between groups (this follows an x^2 distribution with k-1 degree of freedom, where k is the number of studies contributing to the meta-analysis. Study results were considered heterogeneous if the resultant *P* value was less than .1.[34] The I^2 was also used to provide a measure of the degree of inconsistency in the studies' results. Its quantity describes the percentage of total variation across studies, which is due to heterogeneity rather than chance. The I^2 lies between zero and 100%. A value of zero indicates no observed heterogeneity, and larger values show increasing heterogeneity.[35] Sensitivity analysis, using a random effects model, was also conducted to assess the consistency of final results. Every estimate in figures is given with its 95% CI.

Quality Assessment

In the sensitivity analysis, we iterated the analytical procedures as the same time as study numbers, and in each cycle, we removed one study to see if omission of each one would change the direction of the final estimate. Because pooled estimates were in random effects model, sensitivity

analysis was done in random effects model as well. In addition, the data were re-analyzed using the Mantel-Haenszel fixed effects model for comparison with the summary estimates obtained by the DerSimonian and Laird random effects approach. Finally, to ascertain the likelihood of publication bias, the assessment was performed by Begg and Mazumdar as well as Egger test. The publication bias was considered significant if the resultant *P* value was less than .1. The former is a nonparametric Kendal tau correlation test that calculates correlation coefficient of measure of effect size and its standard error in contributing studies. In fact this test evaluates correlation of effect size with study sample size.[36] The latter employs linear regression that predicts the *z* score of effect sizes according to their standard errors in respective studies. In case of nonsignificant publication bias, β is near zero.[37]

RESULTS

Excluded Studies

We identified 76 relevant studies in our literature review. Eight studies were excluded because of their low sample size.[38-45] One study was excluded because it was terminated prematurely due to severe adverse events and treatment protocol modification.[46] Three studies were excluded because they included patients with acute hepatitis C.[47-49] Fourteen studies were excluded because their therapeutic protocols contained ribavirin.[50-63] One study was excluded because it reported only the biochemical response.[64] One study was excluded because it did not state polymerase chain reaction as the method of HCV RNA detection.[65] Six studies were excluded because they included transplant recipient patients or patients had received transplantation in less than 6 months of posttreatment cessation.[66-71] Sixteen patients from 1 study were excluded because they had a previous history of kidney transplantation.[72] Two studies were excluded because their subjects were followed up for 3 months and less.[73,74] Two duplicate publications of the same patients were also excluded.[75,76] Four congress abstracts were also excluded.[77-80] Overall, 35 reports containing 770 patients met the criteria to enter our analysis.[72,81-114]

Studies' Characteristics

Twenty-one studies had evaluated IFN-α2a or IFN-α2b, and 12 had evaluated PEG-IFN-α2a or PEG-IFN-α2b. These reports had been published between 1995 and 2009. Six studies were from Spain, 5 from France, 4 from Turkey, 2 from Brazil and Macedonia, 1 from Greece, Romania, Egypt, Japan, Libya, Malaysia, Taiwan, Hong Kong, and Saudi Arabia. Nineteen studies were single-arm open-label clinical trials, 2 were retrospective evaluation, 8 had a control group of hemodialysis patients who received either no treatment or different doses or treatment duration from those in the study group. Two studies were controlled randomized trials. In the study by Liu and colleagues,[92] randomization was applied using computer-generated random numbers. Because the control group was receiving IFN-α2a (study group received PEG-IFN-α2a), the blindness was not possible. In the study by Fernandez and coworkers,[86] the control group received albumin placebo; however, it was unknown whether the study was double-blinded or only the participants did not know their therapeutic regimen. Fernandez and coworkers did not describe the randomization process either. Table 1 outlines the characteristics of the studies included in the meta-analysis.

Patients' Characteristics

A total of 770 patients met our inclusion criteria; 491 (63.7%) received IFN-α2a or IFN-α2b and 279 (36.2%) received PEG-IFN-α2a or PEG-IFN-α2b. The mean ages of the patients ranged between 31 and 56 years old. The mean durations of hemodialysis ranged between 2 and 11 years. The mean ALT levels were between 42 U/mL and 80 U/mL. The proportion of genotype 1 infected subjects and male gender from study sample sizes ranged 56% to 100% and 44% to 78%, respectively. Overall, 266 of 770 patients (44.5%) attained SVR and 174 of 770 (22.7%) discontinued the treatment because of adverse events. Table 2 lists the characteristics of the patients included in our meta-analysis.

Efficacy of Interferon-α2a and Interferon-α2b

Table 3 presents SVR and dropout rates in each study. Twenty-six studies containing 491 patients evaluated IFN-α2a or IFN-α2b. Eleven studies treated patients 251 patients for a period of 48 weeks and 12 studies treated 150 patients for 24 weeks. Treatment according to the genotypes was considered in 82 patients of 4 studies. In 1 study,

Table 1. Summary of Literature Data: Characteristics of Studies*

Authors	Sample Size	Country of Participants' Origin	Study Design	Publication Year	Treatment Duration, w	Type of IFN-α	IFN-α Dosage
Casanovas et al[72]	29	Spain	CT	2001	48	IFN-α	3 mU × 24 w TW + 1.5 mU × 24 w TW
Ozdemir et al[81]	20	Turkey	CCT	2004	24 (n = 10) 48 (n = 10)	IFN-α2b	6 mU (n = 10) 3 mU (n = 10)
Rocha et al[82]	46	Brazil	Retrospective	2006	48	IFN-α	3
Rocha et al[83]	23	Brazil	CCT	2007	48 (n = 16) 24 (n = 7)	IFN-α	3 mU (n = 16) 3 mU × 2 w TW + 5 mU × 22 w (n = 7)
Raptopoulou et al[84]	19	Greece	CT	1995	24	IFN-α	3 mU
Chan et al[85]	11	Hong Kong	CT	1997	24	IFN-α2b	3 mU
Fernandez et al[86]	14	Argentina	T	1997	24	IFN-α2b	1.5 to 3 mU
Izopet et al[87]	23	France	CCT	1997	24 (n = 12) 48 (n = 11)	IFN-α2b	3 mU
Campistol et al[88]	19	Spain	CT	1999	24	IFN-α2b	3 mU
Degos et al[89]	37	France	CT	2001	48	IFN-α2b	3 mU
Hanrotel et al[90]	12	France	CT	2001	48	IFN-α2b	3 mU
Mahmoud et al[91]	18	Egypt	CT	2005	24	IFN-α2b	3 mU
Liu et al[92]	25	Taiwan	RCT	2008	24	IFN-α2b	3 mU
Liu et al[92]	25	Taiwan	RCT	2008	48	PEG-IFN-α2a	135 μg
Huraib et al[93]	17	Saudi Arabia	CT	1999	48	IFN-α2b	3 mU
Rostaing et al[94]	11	France	CT	1997	24	IFN-α2b	3 mU
Pol et al[95]	19	France	CT	1996	24	IFN-α2b	3 mU
Buargub et al[96]	35	Libya	CT	2006	48	IFN-α	3 mU
Espinosa et al[97]	13	Spain	CT	2001	48	IFN-α	3 mU
Huang et al[98]	10	Taiwan	CCT	1996	24	IFN-α	3 mU
Zoppoli et al[99]	10	Italy	CT	2008	24 to 48	PEG-IFN-α2a	135 μg
Akhan et al[100]	12	Turkey	CCT	2008	48	PEG-IFN-α2a	135 μg
Ayaz et al[101]	22	Turkey	CCT	2008	48	PEG-IFN-α2a	135 μg
Sikole et al[102]	14	Macedonia	CT	2007	48	PEG-IFN-α2a	135 μg
Casanovas et al[103]	12	Spain	CT	2007	48	PEG-IFN-α2a	135 μg
Espinosa et al[104]	16	Spain	CCT	2007	48	PEG-IFN-α2a PEG- IFN-α2b	135 μg 1 to 1.5 μg/kg/w
Kokoglu et al[105]	12	Turkey	CCT	2006	48	PEG-IFN-α2a	135
Covic et al[106]	78	Romania	Retrospective	2006	48	PEG-IFN-α2a	135
Dzekova et al[107]	14	Macedonia.	CT	2009	48	PEG-IFN-α2a	135
Tan et al[108]	34	Malaysia	CT	2009	24 to 48	PEG-IFN-α2b	1 μg/kg/w
Okuda et al[109]	15	Japan	CT	1995	24	IFN-α2a	6 × 2 w daily + 5.5 × 22 w TW
Sporea et al[110]	18	Spain	CT	2001	24 to 48	IFN-α2b	3 × 2 w daily + 3 × 24 or 48 w
Sauk et al[111]	13	USA	CCT	2006	24 to 48	PEG-IFN-α2a PEG-IFN-α2b	135 1 μg/kg
Sporea et al[112]	10	Romania	CT	2006	48	PEG-IFN-α2a	180
Koeing et al[113]	37	Austria	CT	1994	20	IFN-α	5
Rivera et al[114]	27	Spain	CCT	2005	24 to 48	IFN-α2b (n=20) PEG-IFN-α2a (n=7)	3 135

*IFN-α indicates interferon-α; CT, clinical trial; CCT, controlled clinical trial; RCT, randomized controlled trial; mU, million units; and TW, 3 times per week.

Table 2. Summary of Literature Data: Characteristics of Patients*

Authors	Age, y	Dialysis Duration	Duration of HCV infection, y	Liver Histology (Knodel)	ALT	Male, %	Genotype 1, %
Casanovas et al[72]	44.7 ± 10.9	5.82 ± 5.12 y	...	≥ 2, 10.3%	...	62	82.8
Ozdemir et al[81]	44.9 ± 9.8	114.9 ± 28.6 mo	...	...	...	55	73
Rocha et al[82]	46 ± 11	5 y	6	Cirrhosis, 7 %	56 U/mL	61	86
Rocha et al[83]	42 ± 12	12 mo	...	...	Elevated, 74%	47.8	59
Raptopoulou et al[84]	...	...	...	...	...	...	...
Chan et al[85]	41.6 ± 7.7	122.0 ± 47.7 mo	...	4.3 to 4.5	...	73	91
Fernandez et al[86]	44.5	...	19.6	...	106 U/mL	55	43
Izopet et al[87]	47 ± 11	99 ± 57 mo	7.4 ± 5.3	5.3 ± 2.8	78 U/mL	74	56
Campistol et al[88]	42 ± 12	6.4 ± 4.0 y	...	...	42 U/mL	90	89
Degos et al[89]	45 ± 12	...	7.8 ± 6.8	1.1 ± 0.8	Elevated, 30%	68	78
Hanrotel et al[90]	38 ± 10	88 ± 69 mo	...	...	45 ± 38 U/mL	67	67
Mahmoud et al[91]	31.9 ± 6.5	39 ± 25 mo	...	1.4 ± 0.9	71 ± 11 U/mL	83	...
Liu et al[92]	49.4	...	...	≥ 3, 48%	60 U/mL	56	76
Liu et al[92]	48.2	...	...	≥ 3, 60%	56 U/mL	64	80
Huraib et al[93]	38.6 ± 11.1	3.0 ± 1.1 y	...	3.40 ± 1.12	80 ± 30.8 U/mL	53	36
Rostaing et al[94]†	...	...	...	...	...	...	...
Pol et al[95]†	...	...	...	...	Elevated, 68%	74	60
Buargub et al[96]†	41	2 y	...	...	37 U/mL	57	30
Espinosa et al[97]†	...	...	...	...	...	...	...
Huang et al[98]†	...	...	...	...	...	...	...
Zoppoli et al[99]	62	...	...	...	33 U/mL	50	60
Akhan et al[100]	39.4 ± 6.4	...	...	...	52.2 U/mL	75	100
Ayaz et al[101]	35.2 ± 12.1	52.4 ± 24.7 mo	...	...	59.2 ± 22.4 U/mL	54	86
Sikole et al[102]	43.3 ± 9.7	8.5 y	4.3	...	...	78	93
Casanovas et al[103]	50 ± 8	...	...	...	...	83	60
Espinosa et al[104]	56	11 y	...	...	...	62	...
Kokoglu et al[105]	37.3 ± 11.1	66.5 ± 32.5 mo	...	...	56.8 ± 32.1 U/mL	92	100
Covic et al[106]	47.0 ± 8.8	8.1 ± 5.6 y	41.8 ± 8.3	...	...	54	...
Dzekova et al[107]	43.3 ± 9.7	...	...	...	...	78.5	92.8
Tan et al[108]	41.4 ± 11.9	5.8 y	...	≥ 2, 26.5%	≤ 50 U/mL, 55.9%	44	70.6
Okuda et al[109]	50	...	...	≥ 2, 100% Scheuer's scheme	40.5 ± 27.2 U/mL	67	...
Sporea et al[110]†	...	...	...	...	...	...	...
Sauk et al[111]	54 ± 11	2.5 y	...	≥ 3, 30%	29 U/mL	54	85
Sporea et al[112]	40.2	...	...	...	...	40	...
Koeing et al[113]	52.7	...	...	...	...	59.4	...
Rivera et al[114]	43.7 ± 9.3	161 ± 93 mo	...	1.2	...	55.5	...

*HCV indicates hepatitis C virus and ALT, alanine trasaminase. Ellipses indicate that data were not available.
†These studies were retrieved in the abstract format.

37 patients were under treatment for 5 months. The pooled SVR was 39.1% (95% CI, 32.1 to 46.1; $P < .001$; $I^2 = 64.7\%$). In the subgroups of patients who received treatment for 24 weeks and 48 weeks, the pooled SVR was 38.6% (95% CI, 29.9 to 47.3; $P = .10$; $I^2 = 31.2\%$) and 40.8% (95% CI, 28.1 to 53.5, $P < .001$; $I^2 = 80.2\%$), respectively. Three studies compared 24 weeks and 48 weeks of treatment with IFN aplha-2b. The OR of SVR in 48 weeks versus 24 weeks was 2.3 (95% CI, 0.8 to 6.5; $x^2[2] = 0.1$; $I^2 = 0\%$; $P = .90$) in both Mantel-Haenszel and DerSimonian and Laird models. The pooled dropout rate for 24 weeks and 48 weeks of treatment was 21.0% (95% CI, 9.6 to 32.4; Q[7] = 22.6; $P = .002$; $I^2 = 69\%$) and 22.6% (95% CI, 10.4 to 34.8; Q[6] = 30.9; $P < .001$; $I^2 = 80.5\%$).

Table 3. Summary of Literature Data: Response and Dropout Rates*

Authors	Sustained Virological Response, %	Dropout, %
Casanovas et al[72]	69	0
Ozdemir et al[81]	30	0
Ozdemir et al[81]	66.6	0
Rocha et al[82]	22	24
Rocha et al[82]	38	6.2
Rocha et al[83]	57	28.5
Raptopoulou et al[84]	63	31
Chan et al[85]	27	0
Fernandez et al[86]	14	21
Izopet et al[87]†	42	0
Izopet et al[87]	64	0
Campistol et al[88]	36	52
Degos et al[89]	19	51
Hanrotel et al[90]	33	0
Mahmoud et al[91]	44	11
Liu et al[92]‡	48	0
Liu et al[92]§	20	20
Huraib et al[93]	71	5
Rostaing et al[94]	45	0
Pol et al[95]	36	5
Buargub et al[96]	26	34
Espinosa et al[97]	38	23
Huang et al[98]	30	40
Zoppoli et al[99]	20	50
Akhan et al[100]	50	0
Ayaz et al[101]	65	23
Sikole et al[102]	36	36
Casanovas et al[103]	16	50
Espinosa et al[104]	37	37
Kokoglu et al[105]	75	0
Covic et al[106]	14	32
Dzekova et al[107]	35.7	21.4
Tan et al[108]	50	32.3
Okuda et al[109]	53	6
Sporea et al[110]	28	28
Sauk et al[111]	0	7.6
Sporea et al[112]	30	40
Koeing et al[113]	32.4	37.8
Rivera et al[114]§	40	11.1

*For maintaining homogeneity, groups of patients with similar therapeutic protocols in each study pooled together
†First line for Izopet and colleagues' study is for the 24-week treatment and the second, for the 48-week treatment.
‡Results are related to the pegylated interferon group.
§Results are related to the standard interferon group.

Efficacy of Pegylated Interferon-α2a and Interferon-α2b

Table 3 presents SVR and dropout rates in each study. A total of 279 patients in 14 studies received PEG-IFN-α2a or PEG-IFN-α2b. Twenty-five patients in 1 study received 24 weeks of treatment and 64 in 4 studies were treated according to their genotype infection. In 9 studies, there were 190 patients with 48-week treatment. The pooled SVR was 39.3% (95% CI, 26.5 to 52.1; Q[11] = 55; $P < .001$, $I^2 = 80\%$). The pooled dropout rate was 29.7% (95% CI, 21.7 to 37.7; Q[9] = 15; $P = .09$; $I^2 = 40\%$).

Factors Associated With Sustained Viral Response

Table 4 summarizes all detailed meta-analytical procedures carried out in this report. As it is shown in this table, ORs of SVR for female gender (Figure 1), HCV-RNA < 400000 copy/mL, HCV genotype 1 (Figure 2), normal ALT-pattern, duration of infection ≤ 1 year, and liver fibrosis stage < 3 did not attained statistical significance; however, the odds of SVR for an age < 40 years were significantly higher than those for an age ≥ 40 years old (Figure 3). Publication bias assessment according to Begg and Egger's statistical methods showed that all pooled ORs for the abovementioned factors were not influenced by missing of literature studies. Heterogeneity was not statistically significant for all covariates, which means results of the studies were homogenous and consistent with each other. When I^2 is near zero (no heterogeneity at all) both Mantel-Haenszel and DerSimonian and Laird models are almost the same, whereas greater I^2 values mean more departure of results of these models. Therefore, the pooled ORs were recalculated for gender, genotype, and HCV infection duration using Mantel-Haenszel model to see the differences of results in two different meta-analytical models as a part of sensitivity analysis.

Table 4. Rates of Sustained Virological Response in Subgroups of Patients Stratified According to Predictors

Subgroup	Number of Patients	Effect Size (95% Confidence Interval)	Publication Bias Assessment†		Sensitivity Analysis†	Heterogeneity Assessment			
			Begg	Egger		x^2/Q (df)	τ^2	I^2, %	*P*
Pegylated and standard IFN									
ALT (abnormal vs normal)	117	1.04 (1.00 to 1.01)				1.6 (3)	0	0	.60
Females vs males	212	1.93 (0.88 to 4.24)	0.7	0.6	R	13.6 (9)	0.5	33.8	.10
Age (< 40 y vs ≥ 40 y)	167	2.17 (1.03 to 4.50)	0.8	0.7	R	6 (7)	0	0	.50
HCV-RNA (≥ 400000/mL vs < 400000/mL)	89	0.45 (0.16 to 1.28)	…	…	…	2.8 (3)	0	0	.40
Genotype (1 vs others)	205	0.83 (0.37 to 1.83)	0.17	0.2	R	13.9 (11)	0.45	20	.20
HCV infection duration (≤ 1 y vs > 1 y)	45	0.45 (0.04 to 4.50)	…	…	…	1.8 (1)	1.3	44.4	.10
Knodel Score (≥ 2 vs < 2)	139	0.7 (0.3 to 1.3)	…	…	…	2.5 (3)	0	0	.40
Overall SVR	770	39.2% (33.0 to 45.4)	0.08	0.001	R	129 (37)	0.02	71	< .001
Overall dropout	770	25.6% (19.2 to 31.9)	0.005	0.002	R	84 (27)	0.01	67.8	< .001
Males	121	37.4% (24.4 to 50.4)	0.03	0.006	R	20.8 (8)	0.02	61.5	.009
Females	91	56.9% (47.0 to 66.8)	0.6	0.8	R	7.7 (8)	0	0	.40
Genotype 1	127	42.4% (34.0 to 50.7)	0.8	0.6	R	7 (11)	0	0	.70
Non-genotype 1	77	46.7% (30.3 to 63.1)	0.07	0.17	R	10.6 (6)	0.02	43.3	.10
Age ≥ 40	107	34.7% (25.9 to 43.5)	1	0.6	R	4.3 (7)	0	0	.70
Age < 40	60	52.6% (36.5 to 68.7)	0.1	0.3	R	10 (6)	0.01	40	.10
Abnormal ALT	39	51.1% (35.7 to 66.5)	…	…	…	1.5 (2)	0	0	.40
Normal ALT	41	43.9% (28.7 to 59.0)	…	…	…	0.1(2)	0	0	.90
HCV-RNA ≥ 400000/mL	47	36.3% (22.1 to 50.5)	…	…	…	1 (2)	0	0	.50
HCV-RNA < 400000/mL	42	49.3% (28.1 to 70.6)	0.17	0.13	R	6.2 (3)	0.02	51.6	.09
HCV infection duration > 1 y	30	53.0% (34.3 to 71.7)	…	…	…	1.1 (1)	0.002	9	.20
Pegylated IFN									
SVR	272	39.3% (26.5 to 52.1)	0.8	0.02	R	55 (11)	0.03	80	< .001
Dropout	272	29.7% (21.7 to 37.7)	0.08	0.2	R	15 (9)	0.006	40	.09
Genotype 1 infected patients	50	35.8% (22.5 to 49.0)	0.17	0.2	R	0.2 (3)	0	0	.90
Non-genotype 1 infected patients	58	41.3% (27.0 to 55.6)	…	…	…	2.3 (4)	0	0	.60
Genotype (1 vs others)	48	1.04 (0.16 to 6.72)	…	…	…	5.8 (3)	1.7	48	.10
Females vs males	58	0.93 (0.10 to 5.10)	…	…	…	3 (2)	0.8	33.3	.20
Age ≥ 40 y	39	35.7% (20.7 to 50.7)	…	…	…	0.2 (2)	0	0	.80
Age < 40 y	19	55.4% (30.5 to 80.3)	…	…	…	2.4 (2)	0.01	16.6	.20
Age (< 40 y vs ≥ 40 y)	116	2.3 (0.7 to 7.5)	…	…	…	1.4 (2)	0	0	.50
Standard IFN									
SVR	491	39.1% (32.1 to 46.1)	0.08	0.01	R	71 (25)	0.02	64.7	< .001
Dropout	491	22.6% (15.5 to 29.8)	0.009	0.005	R	61 (17)	0.01	72.1	< .001
Genotype 1 infected patients	78	46.7% (36.0 to 57.5)	0.4	0.3	R	5.2 (7)	0	0	.60
Genotype 1 vs other genotypes	135	0.85 (0.34 to 2.09)	0.4	0.3	R	8.1 (7)	0.2	13.5	.30
Males	91	37.3% (18.9 to 55.7)	0.05	0.02	R	16.4 (6)	0.02	63.4	.01
Female	63	59.9% (47.8 to 72.1)	0.8	0.5	R	6.6 (6)	0.003	9	.30
Females vs males	154	2.5 (1.05 to 5.96)	0.8	0.6	R	8.4 (6)	0.3	28.5	.20
Age ≥ 40 y	68	34.2% (23.0 to 45.5)	…	…	…	4.1 (4)	0.001	2.4	.30
Age < 40 y	41	52% (28.9 to 75.0)	…	…	…	7.5 (3)	0.03	60	.05
Age (< 40 y vs ≥ 40 y)	109	2.2 (0.7 to 6.7)	…	…	…	5 (4)	0.3	20	.20

*IFN indicates interferon; ALT, alanine transaminase; R, robust; HCV, hepatitis C virus; and SVR, sustained virological response.
†Publication assessment and sensitivity analysis were conducted for meta-analytic procedures including more than 5 studies. Ellipses indicate not performed.

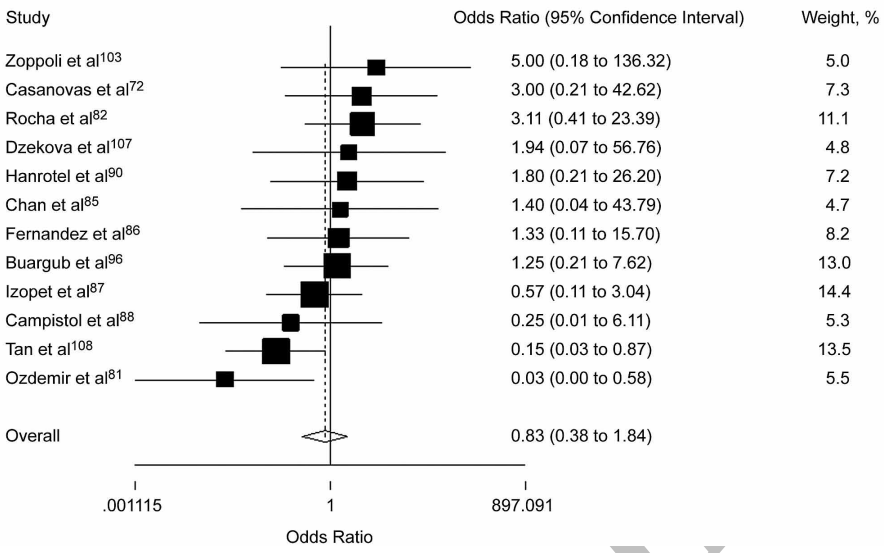

Figure 1. Pooled odds ratio estimates and their 95% confidence intervals for the outcome of sustained virological response in patients with genotype 1 compared with non-genotypes 1. Studies are identified by the first author. Size of squares is proportional to weighted odds ratio.

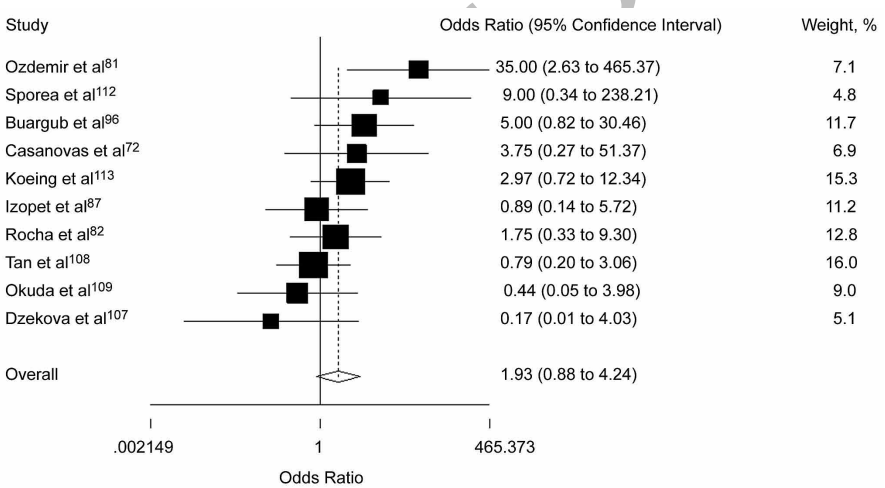

Figure 2. Pooled odds ratio estimates and their 95% confidence intervals for the outcome of sustained virological response in women versus men. Studies are identified by the first author. Size of squares is proportional to weighted odds ratio.

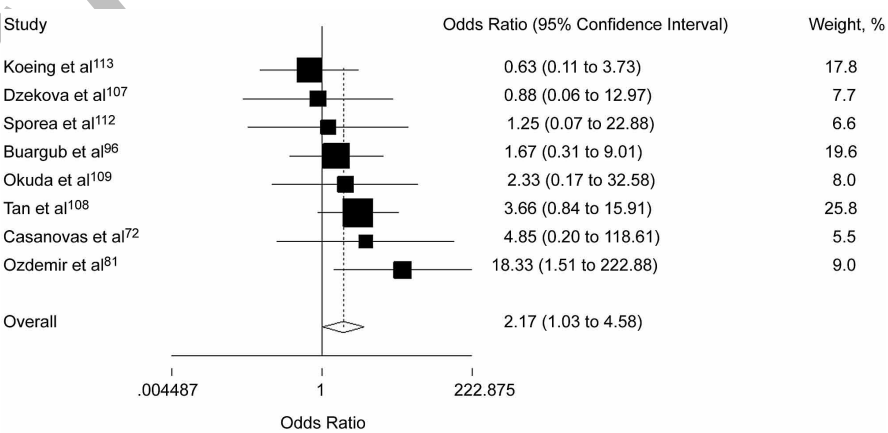

Figure 3. Pooled odds ratio estimates and their 95% confidence intervals for the outcome of sustained virological response in patients younger than 40 years old compared older patients. Studies are identified by the first author. Size of squares is proportional to weighted odds ratio.

These ORs were 1.9 (95% CI, 0.8 to 4.2), 0.7 (95% CI, 0.3 to 1.2) and 0.5 (95% CI, 0.1 to 1.9) for the abovementioned factors, respectively. In comparison with their values in Table 4, the direction of ORs remained constant and only slightly different. At the bottom of Table 4, factors that mentioned above are separately reported in studies that used PEG-IFN and conventional IFN. The small number of patients and studies in each group made any comparison unreliable.

DISCUSSION

Several important points can be identified from our search results and analysis. Most studies of patients on hemodialysis with HCV infection are small non-randomized prospective studies. Efficacy and safety of PEG-IFN with 6-month therapy duration have not been investigated yet. In comparison with the standard IFN, fewer studies investigated PEG-IFN in end-stage renal disease, and the literature still lacks studies of PEG-IFN-α2a or PEG-IFN-α2b in dialysis patients. There was only 1 study by Liu and colleagues that compared PEG-IFN-α2a and standard IFN-α2a.[92] The authors concluded that PEG-IFN-α2a is more effective and safer. Four studies assessed 2 phases of therapy, including induction and maintenance phases; however, none of them were randomized and none reported any promising results.[72,83,110] It is noteworthy that in 5 patients who received IFN-α2a or IFN-α2b monotherapy, SVR was not durable as anticipated and developed HCV viremia even though they were negative based on polymerase chain reaction assay 6 months after completion of therapy. However, viral relapse after achieving SVR was not reported in patients who received PEG-IFN-α2a or PEG-IFN-α2b.[84,87,88] Studies that investigated PEG-IFN-α2a or PEG-IFN-α2b are more recent than those investigated standard IFN, and a higher sensitivity of polymerase chain reaction test in these trials can somehow justify this issue. On the other hand, one study on the treatment of patients with PEG-IFN was terminated prematurely because of severe adverse events (this study was excluded from analysis), and another similar study reported an SVR rate of zero. Our pooled estimates for SVR and dropout rates were completely compatible with other meta-analyses published in the literature.[115-117] In our meta-analysis of factors that might be associated with sustained viral response, we found that similar to a meta-analysis with limited number of patients and studies conducted before,[115] the SVR was lower with genotype 1, abnormal ALT level, higher serum HCV RNA level, duration of infection more than 1 year, and 24 weeks of treatment; however, these findings did not reach statistical significance. In our meta-analysis, the only factor that was significantly associated with SVR was an age of less than 40 years old. As it is shown in Table 4, heterogeneity and publication bias was nonsignificant for all of the above factors; therefore, we could conclude that the evidence is sound and consistent upon significant association of the age less than 40 years old and nonsignificant association of other factors with outcome of IFN therapy in hemodialysis patients. Recently, Gordon and coworkers in an individual patient data meta-analysis explained that women had a significantly higher SVR than men (OR, 2.1; 95% CI, 1.3 to 3.5), and a lower baseline HCV RNA was associated with a higher likelihood of SVR (OR, 11.1; 95% CI, 1.4 to 100; for HCV RNA ≤ 400,000 IU/mL). Age was also a nonsignificant factor (OR, 1.1; 95% CI, 0.9 to 1.3; for age [per additional 10 years]). Data for gender, HCV RNA level, and age were available for 275, 112, and 271 patients in Gordon and colleagues' meta-analysis, respectively.[118] Our findings on gender, HCV RNA, and age was based on smaller number of patients (Table 4). Furthermore, they did not include 2 studies published in 2009 that we used to conduct meta-analysis procedures[107,108]; therefore, there could be 3 reasons to describe differences between our and Gordon and colleagues' results: (1) lower statistical power of our meta-analysis, (2) differences in statistical methodology (Gordon and colleagues obtained their results using logistic regression model), and (3) discrepancy between patients included in analysis.

CONCLUSIONS

Additional benefit of monotherapy with PEG-IFN on the viral response and adverse events in hemodialysis patients is still unclear. An age less than 40 years old, based on our findings, is the determinant of viral response in hemodialysis patients.

CONFLICT OF INTEREST

None declared.

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