

Standard and pegylated interferon therapy of HDV infection: A systematic review and meta-analysis

Seyed-Moayed Alavian, Seyed Vahid Tabatabaei¹, Bita Behnava, Mario Rizzetto²

Baqiyatallah University of Medical Sciences, Baqiyatallah Research Center for Gastroenterology and Liver Disease, Tehran, Iran, ¹University of Muenster, St.-Marien-Hospital GmbH, Klinik of Gastroenterology, Luenen, Germany, ²Division of Gastroenterology, Molinette, University of Turin, Turin, Italy

Background: Hepatitis D virus (HDV) infection is characterized by rapidly progressive liver disease with adverse prognosis in most patients. Although interferon is the only approved anti-HDV therapy, evidence regarding the efficacy and safety of its various regimens is either old or scattered. **Materials and Methods:** We searched systematically Medline, EMBASE, Scopus, the Cochrane Central Register of Controlled Trials, and ISI. The studies that evaluated treatment of chronic HDV infection with standard or pegylated interferon for at least 48 weeks were identified. Our inclusion criteria were positive anti-HDV antibody for 6 months and positive HDV-PCR at the start of study. We performed a meta-analysis for proportions using the arcsine transformation in random effects model. Sustained virological response (SVR) rate (negative Polymerase chain reaction (PCR) 6 months after cessation of therapy) was the end point of interest. **Results:** Data were abstracted from 14 studies containing 227 chronic HDV-infected patients who received standard or pegylated interferon alpha-2a or -2b. Twenty-one and 30 patients of 71 and 156 who received standard or peginterferon, respectively, beyond 48 weeks achieved SVR. Pooled SVR rates were 29% [95% confidence interval (CI) 19; 41] and 19% (95% CI 10; 29), respectively. The rates of treatment withdrawal were similar. **Conclusion:** Our systematic review indicates that the literature lacks sufficient evidence to establish precise recommendations for treatment of HDV infection. Meta-analysis of these studies shows that standard dose of peginterferon is more effective than high dose of standard interferon as anti-HDV therapy.

Key words: Hepatitis delta virus large antigen, infection, interferons

INTRODUCTION

Hepatitis delta virus (HDV) is a defective single-stranded RNA virus that needs co-infection with hepatitis B virus (HBV) to replicate.^[1,2] The need is limited to the Hepatitis B surface antigen (HBsAg), which is required to encapsidate the HDV genome for viral morphogenesis. The virus was first discovered in Italy in the mid-1970s during a major outbreak of hepatitis D in the Mediterranean basin.^[3]

Although HDV suppresses HBV replication, chronic HDV co-infection significantly enhances the mortality and morbidity from cirrhosis and hepatocellular carcinoma in HBsAg carriers.^[4,5] The prevalence of HDV infection in industrialized countries has declined as a

result of anti-HBV vaccination; however, epidemiologic data show that HDV-related diseases persist in several regions of the world.^[3]

High dose of recombinant standard interferon (IFN) is currently the standard anti-HDV therapy. Although pegylated IFN (peginterferon) has been shown to be significantly superior to standard IFN in the treatment of both chronic hepatitis C and B, its superiority has not been elucidated in the therapy.^[6,7] Randomized controlled studies (RCTs) of HDV disease that have compared peginterferons at any dose with high dose of standard IFN in a head-to-head manner are lacking. Furthermore, although the addition of oral agents to IFN-based therapy might help to reduce intrahepatic HBV cccDNA—a template for HBsAg production—thus diminishing the HBsAg^[8,9] available to HDV to encapsidate and propagate infection, RCTs conducted so far have failed to show that combination therapy with lamivudine, ribavirin, or adefovir improves the efficacy compared with IFN monotherapy.^[10-14] The data regarding combination therapy with other potent anti-viral agents are not available yet.

Several studies in the literature have evaluated different doses and treatment duration of anti-HDV therapy with

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Address for correspondence: Prof. Seyed-Moayed Alavian, Baqiyatallah University of Medical Sciences, Baqiyatallah Research Center for Gastroenterology and Liver Disease, Tehran, Iran. E-mail: alavian@thc.ir

Received: 05-04-2012; **Revised:** 29-05-2012; **Accepted:** 21-06-2012

standard or peginterferon; however, they generally lack enough sample power, some are old, and others contain scattered information. In this review, we have summarized and pooled the results of these studies in an effort to reach a reliable estimate of efficacy and safety of both standard and peginterferon in anti-HDV therapy.

MATERIALS AND METHODS

Search methods for identification of studies

An electronic search through Medline, EMBASE, Scopus, the Cochrane Central Register of Controlled Trials, and ISI Web of Knowledge was performed using combination of following terms: "HDV" or "Hepatitis D virus" or "Hepatitis Delta", and "interferon," "interferon alpha-2a," "interferon alpha-2b," "peginterferon," "peginterferon alpha-2a," "peginterferon alpha-2b," and "sustained virological response" or "SVR" to locate articles concerning treatment of HDV infection. The brand names of IFN such as "Pegasys," "Pegintron," "PDferon B," and "Intron A" were also tried, and the references of reviews and interventional trials retrieved were skimmed to locate other relevant studies. Temporal limits were not applied to our search strategy.

Data collection and abstraction

Titles and abstracts of all potentially relevant citations were screened by two authors separately (BB and SVT). Thereafter, the full texts of all selected reports were retrieved and assessed according to the predefined inclusion and exclusion criteria. Data from studies that met the inclusion criteria were extracted by two investigators separately and were rechecked by the third one (SMA). Decision about inclusion or exclusion of studies and predefined assumptions was made and agreed by all authors before running the meta-analysis. Characteristic data of the studies were abstracted using standard questionnaires.

Data synthesis

All analyses were performed in Mix 2.0 professional software for meta-analysis in Excel.^[15] Data of all the included patients were analyzed based on the intention-to-treat principle, irrespective of compliance or follow-up. To manage missing data, we used the worst case scenario analysis; since there was a positive outcome (virological response), all patients with missing data were counted as non-responders. The results are presented as a non-comparative index, the proportion who achieved SVR with 95% confidence interval (CI).

The meta-analysis was performed using the Freeman–Tukey double arcsine transformation in random effects model of DerSimonian and Laird method.^[16] 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 the 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.^[16]

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 a χ^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 0.1.^[17] I² was also used to provide a measure of the degree of inconsistency between the studies' results. Its quantity describes the percentage of total variation across studies, which is due to heterogeneity rather than chance. I² lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.^[18]

Outcome measure

The outcome measure was the SVR, i.e., HDV-RNA remaining undetectable at least 6 months after treatment cessation, regardless of HBsAg or hepatitis B e antigene (HBeAg) loss or seroconversion. The SVR is the most desired treatment outcome of HDV infection and is considered a surrogate marker of liver HDV-Ag loss. Patients who normalize liver enzymes or undergo liver histological improvement but do not have SVR are still at greater significant risk of liver cirrhosis and hepatocellular carcinoma.

To evaluate the safety of anti-HDV therapy, we considered the number of patients who did not complete the treatment for any reasons as an index of safety. To this regard, we considered patients who discontinued treatment due to personal reasons also as treatment failures.

Eligibility criteria

Randomized and non-randomized controlled clinical trials and cohort studies were considered. Patients who had both HBsAg and HDV-RNA in serum were included if they had received at least 48 weeks of peginterferon alpha-2a, -2b or other recombinant IFN-alpha with various dose schedules. The diagnosis of chronic HDV infection required the presence of antibody to HDV (anti-HDV) for at least 6 months prior to the study and HDV-RNA detectable in serum (qualitative or quantitative methods) at the start of therapy. Only the studies which reported HDV-RNA status with a sensitive enough polymerase chain reaction

(PCR) method at least 6 months after cessation of therapy were considered. The studies with previous antiviral therapy older than 6 months, study dose modification, administration of growth factors, and seropositivity for HCV and HIV without immunodeficiency syndrome were allowed. Patients were not considered if: (1) they had history of decompensated liver disease including ascites, bleeding esophageal varices, hepatic encephalopathy, bilirubin level >4 mg/dl, serum albumin level <3 g/dl, prothrombin time >4 seconds longer than the control, platelet count <50,000–100,000/mm³, a leukocyte count <3000/mm³, granulocyte count <1500/mm³; (2) they had significant co-morbidities such as autoimmune diseases, hemoglobinopathies, chronic kidney disease (serum creatinine level >1.7 mg/dl), immune-deficient status due to AIDS or immunosuppressant medications; (3) they had received oral anti-nucleoside analogs such as adefovir, lamivudine, or ribavirin; or (4) they had positive liver biopsy staining for HDV-Ag but negative for serum HDV-RNA.

RESULTS

Results of the search

We found 45 reports of anti-HDV therapy. Thirty-one studies were excluded for the following reasons: administration of human lymphoblastoid IFN,^[19,20] no-report of HDV-RNA status, at least 24 weeks after completion of treatment,^[21-27] combination therapy with ribavirin,^[14] short duration of treatment,^[28-32] combination therapy with lamivudine,^[11,23,33] case report or letter,^[34-39] retrospective design,^[21,40] and duplicate publication of the same patients' data^[41-45] [Figure 1].

Included studies

Fourteen relevant studies containing 474 patients that met our inclusion criteria were identified.^[10,12,13,28,29,46-56] Table 1 summarizes the study characteristics. The publication years of the studies ranged from 1991 to 2011. Five studies were single-treatment arm prospective studies, one trial was non-randomized controlled study, and 10 studies

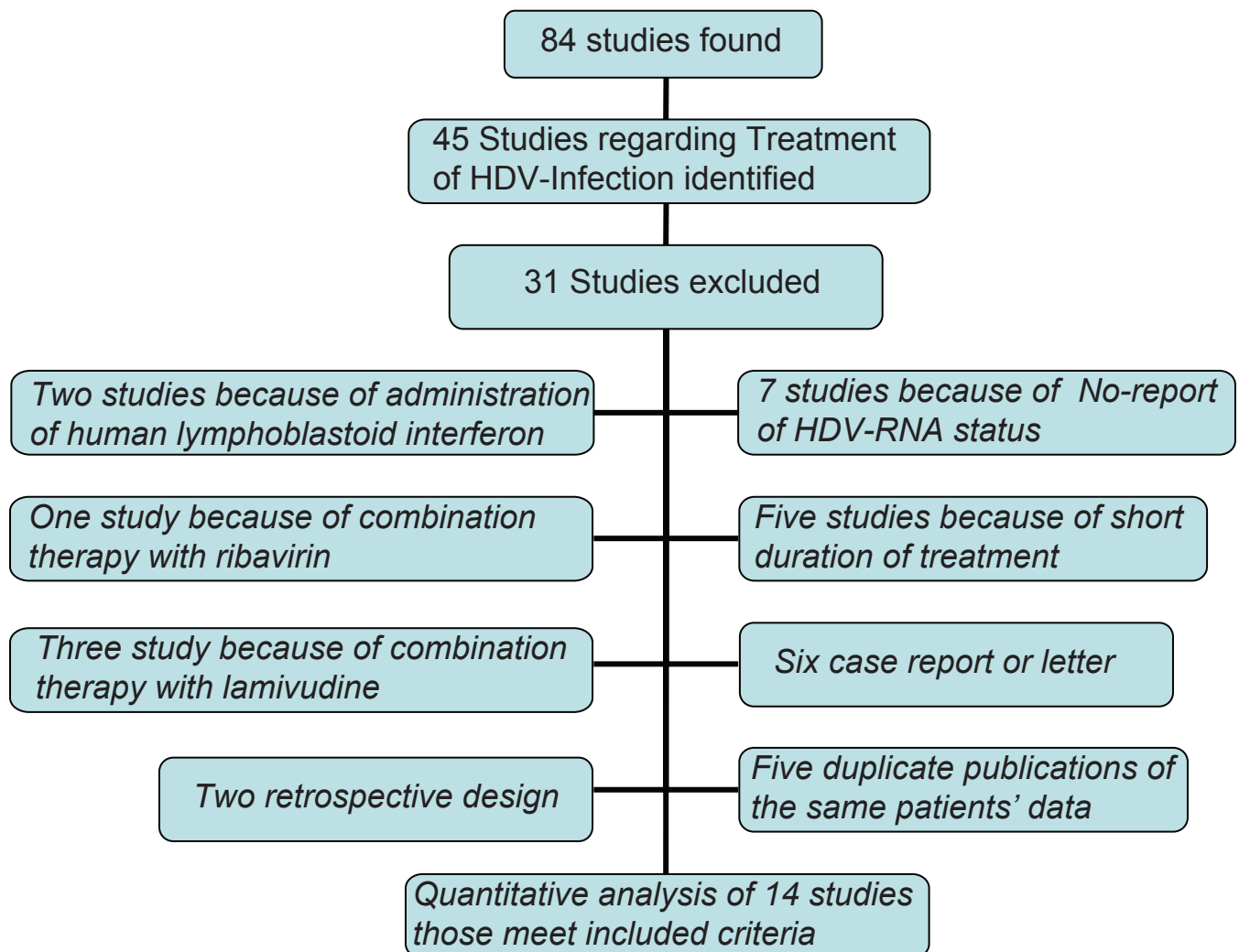


Figure 1: Process of study identification

Table 1: Design of the studies considered

Author	Publication year	Country of samples' origin	Design	Type of interferon	Regimen	Follow-up
Castelnau <i>et al.</i> ^[46]	2006	US	Prospective	PEG-2 beta	1.5 µg/kg QW×1 year	6–42 months; median 16 months
Erhardt <i>et al.</i> ^[47]	2006	Germany	Prospective	PEG-2 beta	1.5 µg/kg QW×48 weeks	6 months
Niro <i>et al.</i> ^[48]	2006	US	RCT	PEG-2 beta	1.5 µg/kg QW×72 weeks	6 months
Wedmeyer <i>et al.</i> ^[10]	2011	Germany	RCT	PEG-2 alpha	180 µg QW×48 weeks	6 months
Canbakan <i>et al.</i> ^[49]	2006	Turkey	RCT	2 beta	10 MU t.i.w.×48 weeks	96 weeks; mean 3.1 years
Craxi <i>et al.</i> ^[50]	1991	Italy	Prospective	2 beta	5 MU/m ² t.i.w. 3 months+3 MU/m ² t.i.w. 9 months	6 months
Di Marco <i>et al.</i> ^[51]	1996	Italy	CCT	2 beta	5 MU/m ² t.i.w. 3 months+3 MU/m ² t.i.w. 9 months	12 months
Farci <i>et al.</i> ^[52]	1994	Italy	RCT	2 alpha	9 or 3 MU t.i.w.×48 weeks	6–48 months
Gaudin <i>et al.</i> ^[53]	1995	France	RCT	2 beta	5 MU/m ² for 4 months+3 MU/m ² for 8 months	6 months
Gunsar <i>et al.</i> ^[13]	2005	Turkey	RCT	2 alpha	9 MU t.i.w.×2 years	6 months
Madejon <i>et al.</i> ^[54]	1994	Spain	RCT	2 alpha	3 MU QD 3 months+1.5 MU QD 9 months or decreasing dose of 18 MU t.i.w. 6 months	18 months
Rosina <i>et al.</i> ^[55]	1991	Italy	RCT	2 beta	5 MU/m ² t.i.w. 4 months and then 3 MU/m ² t.i.w. for 8 months	12 months
Yurdaydin <i>et al.</i> ^[12]	2008	Turkey	RCT	2 alpha	9 MU t.i.w.×1 year	6 months
Yurdaydin <i>et al.</i> ^[56]	2007	Turkey	Prospective	2 alpha	10 MU t.i.w.×2 years	6 months

CCT=controlled clinical trial; RCT=randomized clinical trial; t.i.w.=Thrice weekly HDV and HB viral load, copy/ml

had a randomized design. Four studies had evaluated pegylated IFN (one peginterferon alpha-2a) and 12 trials had different regimens of standard recombinant IFN alpha (five alpha-2b). The follow-up ranged from 24 weeks to 48 months. Craxi *et al.* had included pediatric patients also.

Exclusion criteria were similar across studies and were as follows: white cell count less than 3000/mm³, absolute neutrophil count less than 1500/mm³, a platelet count under 50,000–100,000/mm³, presence of decompensated liver disease or a history of ascites, variceal hemorrhage or hepatic encephalopathy or hepatocellular carcinoma, pregnancy or lactation, a course of antiviral or immunosuppressive therapy within 6 months to 1 year before consideration for enrollment, evidence of autoimmune hepatitis or metabolic liver disease, serious psychiatric disorders or severe systemic illness, hemoglobin less than 12–10 g/dl, serum creatinine level greater than 1.7 mg/dl.

Two hundred and forty-seven subjects were excluded from the analysis: 55 were untreated controls,^[52,53,55] 13 with undetermined virological response, 3 subjects for unknown HDV-RNA status at the start of therapy,^[51] 19 for negative HDV-RNA prior to therapy,^[53,55] 28 for combination therapy with lamivudine,^[12,49] 43 for combination therapy with ribavirin^[13,48] 17 for monotherapy with lamivudine,^[12] 31

for combination therapy with adefovir and 30 for adefovir monotherapy,^[10] 8 patients for therapy with beta IFN.^[53] Ultimately, a total of 227 patients were included in the analyses.

Included patients

Table 2 shows the demographic, clinical, and virological features of the patients included. Their mean age ranged from 11 to 46 years. The proportion of males varied from 50 to 100%. Except for few patients in Rosina *et al.*'s study and one patient in Erhardt *et al.*'s study, all the patients had liver histology compatible with chronic active hepatitis. Seventy-three subjects were reported to have cirrhosis. Fifty-three patients were not screened for antibody against HCV (anti-HCV). Twenty patients had anti-HCV. Ten were negative by PCR for HCV-RNA (studies of Castelnau *et al.* and Erhardt *et al.*). The serostatus of HCV-RNA was unknown in the other 10 patients in the studies of Madejon *et al.* and Gaudin *et al.* One hundred four patients were negative by PCR for HBV-DNA and 155 had anti-HBe. Two patients in Madejon *et al.*'s study were positive for anti-HIV, but had not a clinical immunodeficiency syndrome.

Efficacy and safety of standard and pegylated IFN for treatment of HDV infection

One hundred and fifty-six patients received recombinant standard IFN alpha for 48–96 weeks.^[1] Twenty-one patients

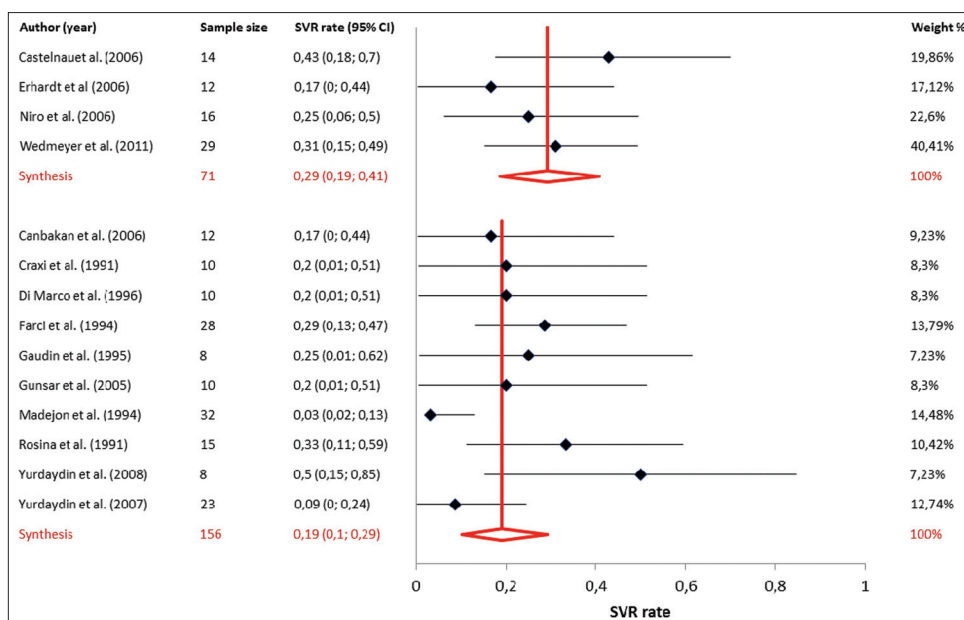


Figure 2: Individual and pooled estimates of SVR rates after at least 48 weeks of pegylated (the first) and standard interferon (the second)

Table 2: Demographic, clinical, and virological features of the patients

Author	Mean age	Male (%)	HB viral load	ALT	Fibrosis	Cirrhosis (%)	HBeAg (%)	Anti-HCV	HDV-RNA level	IV drug (%)	Previous treatment (%)
Castelnaeu <i>et al.</i> ^[46]	42 (28-52)	86	<50 (<50-1.9×10 ⁶)	1.95 (1.3-7.5) ULN	3 (1-4) M	29	0	57%	9×10 ⁵ (4.8×10 ⁴ -1.1×10 ⁷)	50	86
Erhardt <i>et al.</i> ^[47]	34±15	75	NR	72±36	3.7±1.3 I	27	0	17%	NR	17	25
Niro <i>et al.</i> ^[48]	45.4±8.8	50	18%>10 ³	147±110	4.7 (2-6) I	75	NR	0	NR	NR	63
Wedmeyer <i>et al.</i> ^[10]	38 (17-62)	59	8×10 ⁵	73	4 I	20	17	0	398	NR	52
Canbakan <i>et al.</i> ^[49]	43.83±8.57	67	NR	139.83±80.14	2.25±1.54 K	33	17	0	NR	NR	NR
Craxi <i>et al.</i> ^[50]	11 (8-14) mean	50	NR	2 ULNxc	NR	40	60	NT	NR	0	NR
Di Marco <i>et al.</i> ^[51]	11.3 (8-16) mean	-	NR	6.3 (3-19) ULN	-	-	-	0	NR	0	NR
Farci <i>et al.</i> ^[52]	35±9	79	0	201±125	NR	64	0	0	NR	7	NR
Gaudin <i>et al.</i> ^[53]	29.6 *(22-5)	100	NR	147±100	NR	73	27	36	NR	NR	NR
Gunsar <i>et al.</i> ^[13]	39±9	70	0	74 (52-126)	13±5 K	30	0	0	NR	NR	0
Madejon <i>et al.</i> ^[54]	27±8	81	NR	187±101	NR	13	44	19	NR	53	NR
Rosina <i>et al.</i> ^[55]	-	-	-	-	-	-	-	-	-	-	-
Yurdaydin <i>et al.</i> ^[12]	46 (38-67)	100	200	106±66	3 K	NR	0	0	1.6×10 ⁶	NR	0
Yurdaydin <i>et al.</i> ^[56]	40.6±10.0	74	25,000 (120-7.2×10 ⁷)	120±109	3 K	35	4	0	104 (103-107)	NR	NR

Values=mean±SD = median, median (range) ULN=Upper limit of normal; NR=Not reported; K=Knodell score; I=Ishak score; M=Metavir; ALT= Alanine Aminotransferase *Mean In the studies of Di Marco *et al.* and Rosina *et al.*, since some studied patients were ineligible for inclusion, some baseline data provided by authors were not valid anymore to be presented in this table

discontinued treatment (no data in the studies of Gaudin *et al.* and Rosina *et al.*). Based on normal approximation method, 16% (95% CI 10%; 23%) of patients were withdrawn from treatment mainly due to safety reasons. Thirty of the 156 patients cleared HDV-RNA during treatment course and remained HDV-RNA negative at

the end of therapy. By the intention-to-treat analysis, the pooled rate of SVR was 19% (95% CI 10%; 29%) [Figure 2]; however, there was a significant heterogeneity between the results of the various studies [Q (9) = 16.8, P = 0.05, I² = 47%].

Seventy-one patients underwent therapy with peginterferon

alpha for 48-72 weeks. Eight patients [11% (95% CI 5%; 20%)] did not complete the treatment protocol. Twenty-one patients achieved an SVR. Based on the intention-to-treat analysis, the pooled rate of SVR was 29% (95% CI 19%; 41%) [Figure 1]. There was consistency among the study results [$Q(3) = 2, P = 0.5, I^2 = 0\%$].

DISCUSSION

The sum of clinical data indicates that HDV co-infection increases the morbidity and mortality of liver disease significantly in HBsAg carriers, compared with HBV infection alone; unfortunately, however, therapy against the HDV remains a critical and unmet need.

The potent nucleic analogs currently used for the treatment of HBV—adefovir, entecavir, telbivudine, and tenofovir—were not efficacious against HDV; this virus lacks any replicative function of its own that could be targeted by these drugs which selectively block the reverse transcription of the HBV. Early studies have shown that the less potent HBV agents, lamivudine and famcyclovir, as well as ribavirin, a drug active against RNA viruses (such as the HDV), were also of no therapeutic use.

IFN, first used empirically in the 1980 on the wake of its partial efficacy in HBV disease, remains the only approved therapy for hepatitis B. However, the use of IFN is still based on accepted common practice rather than on precise guidelines based on RCTs. We therefore performed this study to evaluate the true therapeutic potential of IFN in chronic hepatitis D. Our meta-analysis suggests that approximately one-fifth and one-third of those who receive standard and peginterferon have a chance of sustained HDV eradication. Furthermore, a sub-analysis did not indicate that extending the duration of peginterferon therapy for 2 years was more effective than the standard 48-week therapy. The major limitations to this meta-analysis are the variability of the design of the studies that made use of standard IFN and the clinical heterogeneity across treatment regimens; we could not identify even two such studies which adopted similar therapy regimens. Given this problem and in view of the few number of patients treated in each study, no definite conclusion on the superiority of peginterferon over standard IFN for anti-HDV therapy could be reached. However, because of the similar safety index between standard and peginterferon and the slightly higher rate of SVR with peginterferon, considering also its weekly administration and the better compliance of the patient, peginterferon alpha-2a or -2b for 48 weeks appears to be a preferable option for anti-HDV therapy.

CONCLUSION

This systematic review indicates that the literature lacks sufficient evidence to make precise recommendations for treatment of HDV infections. The meta-analysis of these

studies shows that standard dose of peginterferon might be more effective than high dose of standard interferon.

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How to cite this article: Alavian SM, Tabatabaei SV, Behnava B, Rizzetto M. Standard and pegylated interferon therapy of HDV infection: A systematic review and meta- analysis. *J Res Med Sci* 2012;17:967-974.

Source of Support: Nil, **Conflict of Interest:** None declared.