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MAJOR ARTICLE

Interferon Treatment Duration in Patients With Chronic Delta Hepatitis and its Effect on the Natural Course of the Disease

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(See the Editorial Commentary by Soriano and Aguilera, on pages 1173–6.)

Background. Interferon is the only treatment option in chronic delta hepatitis (CDH). A CDH database (333 patients, 161 with interferon treatment history) was analyzed for effects of treatment duration on virologic response and clinical outcomes.

Methods. Ninety-nine CDH patients who received at least 6 months of interferon were selected. Maintained virologic response (MVR) was defined as hepatitis D virus RNA negative for 2 years after treatment discontinuation. Cumulative median interferon treatment duration was 24 months (range 6–126 months), with a median of 2 courses (range 1–8). Post-treatment median follow-up was 55 months (24–225 months).

Results. Thirty-five patients achieved MVR. Cumulative probability of MVR increased with treatment duration and reached 50% at 5 years. Patients with MVR were less likely to die from liver disease or develop complications compared to patients without MVR ($P = .032$, $P = .006$, respectively). Cirrhosis at baseline and no response to therapy (odds ratio 16.1 and 5.23, respectively) predicted an adverse endpoint. Hepatitis B surface antigen clearance occurred in 37% of patients with MVR.

Conclusion. Viral response to interferon increases with treatment duration and favorably affects the natural course of disease. Interferon treatment duration has to be individualized with careful post-treatment assessment.

Keywords. Hepatitis B; interferon treatment; hepatocellular carcinoma; liver-related mortality; HBsAg clearance.

Chronic delta hepatitis (CDH) is the most aggressive form of viral hepatitis [1–3]. Interferons continue to be the only treatment option in CDH. Treatment for 1 year with interferons (IFNs) leads to virologic response 6 months post-treatment in roughly 25% to 30% of patients [4–9]. Several pilot studies have suggested that prolonging treatment to 2 years does not add additional benefit [10–13]. Still, there are data to suggest that IFN may need to be given for an extended duration of time [14, 15], along the lines of in vitro studies, which appear to lend support for longer treatment duration [16, 17]. Viral kinetic studies also support the concept that CDH responds slower to interferon compared to hepatitis B or hepatitis C [18].

We explored the effect of treatment duration on maintained virological response, hepatitis B surface antigen (HBsAg) clearance, and clinical outcomes, as well as predictive factors of treatment response in a well-characterized patient cohort.

METHODS

The CDH database of the Department of Gastroenterology of Ankara University Medical School was used. Of 333 patients with CDH, 161 patients with interferon treatment history were identified from 1996 to 2014. CDH patients who had received at least 6 months of conventional or pegylated IFN and at baseline had documented hepatitis D virus (HDV) RNA positivity by qualitative PCR were selected. Patients with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) coinfection were excluded. The remaining 99 patients formed the cohort used in this analysis (Figure 1). IFN treatment was conducted with conventional IFN up to 2002 and with pegylated IFN alpha afterwards. Patients who had received combination treatment with a nucleos(t)ide analog (NA) were included. Patients were seen in the outpatient clinics at 2 to 6 months intervals during treatment and at 3 to 6 months intervals during treatment-free follow-up.

At baseline, the majority (81) of patients had a liver biopsy. Histological assessment at baseline was performed according to Knodell et al [19]. Liver cirrhosis was diagnosed either histologically or clinically. Patients were considered to have cirrhosis when imaging studies were indicative of cirrhosis (nodularity of liver parenchyma or irregularity of the liver surface with splenomegaly) and/or there were esophageal varices on endoscopy.

Patients had received different durations of IFN treatment. Cumulative treatment duration was divided into 6 categories:

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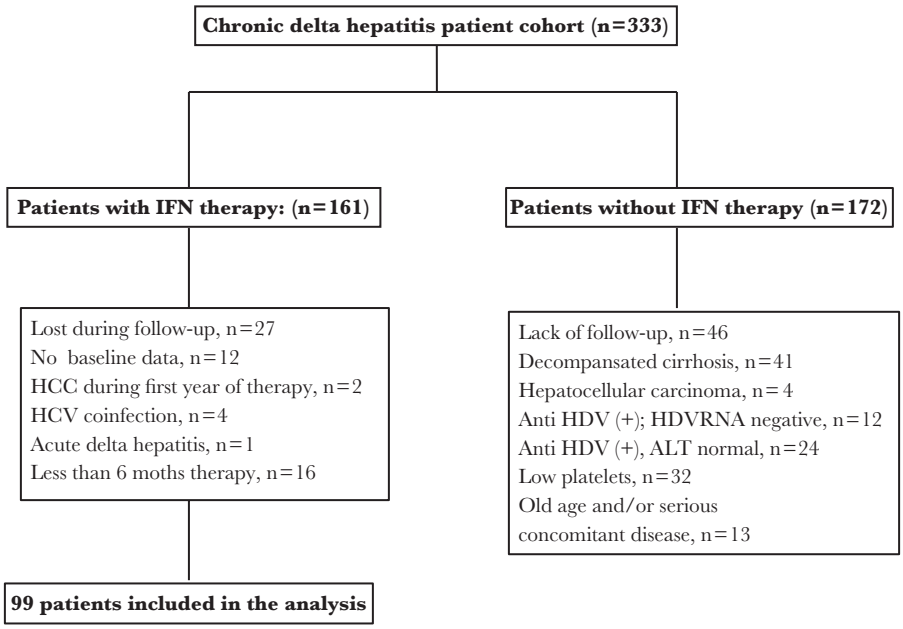


Figure 1. Flow diagram displaying selection of patients for the current study from the chronic delta hepatitis patient cohort. Abbreviations: ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; IFN, interferon.

6–12, 13–24, 25–36, 37–48, 49–60 months, and more than 60 months of treatment. Patients received longer duration of treatment as multiple courses of IFN treatment. Up to 8 courses of IFN treatment have been recorded. Treatment duration of one course was between 6 and 48 months.

Viral response was assessed by maintained virologic response (MVR), defined as being HDV RNA negative for 2 years or more after stopping treatment because we recently reported that post-treatment week 24 virologic response was not a reliable marker of sustained virologic response [20]. Characteristics of patients with MVR were compared to patients without a MVR. Several clinical endpoints were investigated. Effect of treatment response on liver-related mortality, liver transplantation, hepatocellular carcinoma development, hepatic decompensation, and HBsAg clearance was assessed. The study was approved by the Ankara University Ethics Committee and informed consent was obtained from patients, or in case of death from their relatives.

Laboratory Analyses

Hematological and biochemical tests were performed in the central laboratories of Ankara University Medical School using routine automated techniques. Qualitative hepatitis serologies, including HBsAg, hepatitis B surface antibody (HBsAb), hepatitis E antigen and antibody (HBeAg and HBeAb), were determined by a microparticle enzyme immunoassay method (Abbott Laboratories, IL) and antihepatitis D virus (anti-HDV) was determined by an enzyme immunoassay (Abbott Laboratories, IL). Serum hepatitis B virus DNA (HBV DNA) was measured with an in-house PCR assay with a detection limit of 100 copies/mL until December 2009 (as described previously [21]) and with the Cobas TaqMan HBV test (Roche Molecular Systems, Inc., USA) thereafter, with a detection limit of 20 IU/mL. Serum HDV RNA had been measured by an in-house qualitative PCR with a detection limit of 1000 copies/mL until 2012 [12]. Serum quantitative HBsAg and serum quantitative HDV RNA were determined at the time of treatment initiation in stored sera when available. HBsAg was quantified by the Architect HBsAg assay (Abbot Diagnostics, Germany), according to the manufacturer's instructions. Quantitative HDV RNA measurements were performed as described previously [22]. This assay has a limit of quantification of 1000 IU/mL and limit of detection of 100 IU/mL, and has been standardized against the WHO HDV RNA standard.

Statistics

Data were analyzed using the SPSS software version 21 (SPSS, Inc., Chicago, IL). Continuous variables are presented as mean values ± standard deviation (SD) or as median values and interquartile range (IQR). Categorical variables were summarized as number of cases. Continuous variables were compared using Student's *t* test or Mann-Whitney U test. For categoric variables, the chi square/Fischer's exact tests were used. Univariate and multivariate logistic regression models with backward Wald deletion were used to estimate the effect of various variables on clinical outcome measures. Odds ratios (OR) and their 95% confidence intervals (CI), along with corresponding *P* values, are presented. Variables found to be at the significance level of 0.1 in the univariate analysis were used in the multivariate analysis. Cumulative rates of maintained virologic response were

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calculated using the formula $P = 1-(1-n1/N1\ (1-n2/N2....(1-nx/Nx)$ where P is the cumulative probability that the event will occur, nx is the number of cases at year x and Nx is the number of patients still followed up at year x [23]. The cumulative probabilities of hepatocellular carcinoma (HCC), decompensation, mortality/liver transplantation, or any event occurrence were estimated by the Kaplan-Meier method and compared with the log-rank test. A P value of $< .05$ was considered to be statistically significant.

RESULTS

Patient Characteristics

All patients were treatment naive at onset of this study. Cumulative treatment duration of conventional versus pegylated IFN was similar (110 vs 104 treatment years, respectively). Selection of patients for interferon treatment was based on the discretion of the treating physician. It is assumed that all patients with no contraindication to IFN were offered this treatment. Characteristics of patients at initiation of a first interferon regimen are shown in Table 1. In brief, the mean age of patients was 40 years, and 70 were male. Hepatitis B serology revealed HBeAg negativity in 81 and HBeAg positivity in 19 patients.

Cumulative median treatment duration with an IFN regimen was 24 months (range 6–126 months). Patients received a median of 2 courses (range 1–8) of IFN treatment. Treatment duration of one course was between 6 and 48 months. Post-treatment median follow-up duration was 55 months (24–225 months). Interferons were in general well tolerated. However, 14 patients, who were not included in this analysis due to short interferon treatment duration, had discontinued early because of side effects. Another patient, who discontinued at treatment month 6 due to side effects, is included in the analysis. Finally, 1 patient discontinued interferon at month 8 due to active tuberculosis infection. Interestingly, this patient was among those who responded to treatment.

We identified 41 relapses after the end of treatment viral response; 15 (37%) occurred after post-treatment month 6 and were late relapsers (Supplementary Figure 1) [20]. There was 1 patient, classified as having MVR, who relapsed later than 36 months after viral response.

Viral Response to Interferon Treatment

Thirty-five patients achieved MVR. Patients receiving conventional versus pegylated IFN and IFN monotherapy versus combination with NAs had similar rates of MVR (data not shown). Of 99 patients in the database, 16 (16%) had MVR after 6–12 months of treatment; 16 patients without MVR did not receive further treatment with interferon; 67, 41, 30, and 15 patients received up to 2, 3, 4, and 5 years of treatment and 8 patients had more than 5 years of IFN treatment (Supplementary Figure 2). There were a total of 13 patients whose initial treatment course was more than 12 months (18 months in 5, 24 months in 7, and 48 months in 1 patient). All 13 patients who received IFN treatment for more than 12 months were HDV RNA positive by qualitative PCR at month 12 of treatment and are reported here as nonresponsive to 1 year of treatment. Of these 13 patients, 3 of 7 patients receiving 24 months and the 1 patient with 48 months of treatment had a MVR. We excluded 2 patients who developed HCC during the first year of therapy.

Table 1. Baseline Characteristics of Patients With and Without Virologic Response to Interferon Treatment

	Overall (n = 99)	IFN responders (n = 35)	IFN nonresponders (n = 64)	*P* value
Age	40.0 ± 10.6	41.6 ± 9.4	39.2 ± 11.2	.28
Gender	70 M/29 F	24 M/11 F	46 M/18 F	.81
HDV RNA[a] (log_{10} IU/mL) (n = 59)	5.98 ± 1.4	6.1 ± 1.6	5.9 ± 1.3	.6
HBV DNA[a] (log_{10} IU/mL, median (range)(n = 63)	1.70 (1.0–7.62)	1.67 (1.0–4.90)	1.70 (1.0–7.62)	.34
HBeAg status	81 (–) / 15 (+)	29 (–) /4 (+)	52 (–) /11 (+)	.56
ALT (U/L)[b]	107 ± 108	97 ± 86	112 ± 119	.53
AST (U/L)[b]	76 ± 73	76 ± 76	77 ± 71	.9
ALP (U/L)[b]	115 ± 52	102 ± 52	123 ± 51	.07
GGT (U/L)[b]	83 ± 78	55 ± 53	100 ± 86	.007
PT (seconds)	13.3 ± 1.4	13.2 ± 1.4	13.3 ± 1.4	.6
Total bilirubin (mg/dL)	1.01 ± 0.5	0.89 ± 0.5	1.08 ± 0.6	.12
Platelet ($\times 10^9$/L)	161 ± 52	181 ± 54	150 ± 48	.004
HAI (n = 78)	10.9 ± 3.9	10.5 ± 4.7	11 ± 3.5	.56
Cirrhosis present	19/99 (19%)	5/35 (14%)	14/64 (22%)	.26
Fibrosis score (n = 78)	2.15 ± 1.4	1.97 ± 1.4	2.26 ± 1.3	.36
HBsAg (log_{10} IU/mL) (n = 49)	3.70 ± 0.66	3.40 ± 0.79	3.96 ± 0.35	.004

All values are mean ± SD unless otherwise indicated.

Abbreviations: IFN, interferon; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltranspeptidase; ALP, alkaline phosphatase; HAI, histologic activity index; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; F, female; M, male; HBV, hepatitis B virus; HDV, hepatitis D virus; PT, prothrombin time.

[a] HBV DNA detection limit: 20 IU/mL; HDV RNA detection limit: 100 IU/mL.

[b] Upper limits of normal for both female and male: ALT, 49 U/L; AST, 49 U/L; ALP, 129 U/L; GGT, 38 U/L).

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Of these 2 patients, 1 developed a MVR. If we had included these 2 patients in the analysis, the overall results would not have changed.

Treatment-free interval after the first course of treatment was a median 15 months. Patients with an MVR had a shorter mean treatment interruption period than patients who did not have a MVR (15.0 ± 14.8 months [mean ± SD; n = 19] vs 30.3 ± 32.6 [n = 45]; $P < .05$). Patients with MVR had more often treatment interruption period of 30 months or less than those without MVR (17/19 vs 27/45, $P = .022$).

The cumulative probability of obtaining MVR increased with treatment duration and reached 27% at 3 years, 50% at 5 years, and 75% at more than 5 years of total treatment duration (Figure 2). Of the 8 patients whose total treatment duration exceeded 5 years, 5 received 6.5 to 8 years, and 2 received a total duration of 9 to 10.5 years of treatment.

Comparison of Treatment Responders to Nonresponders

Treatment responder patients had lower gamma-glutamyl-transpeptidase (GGT) and HBsAg levels and higher platelet counts compared to treatment nonresponder patients (Table 1, $P = .007$, 0.004, and 0.004, respectively). In the treatment responder group, only 28% of patients had platelet counts below 150 × 10^9/L, whereas this was 59% in treatment nonresponders. After multivariate logistic regression analysis, baseline platelet count and quantitative HBsAg levels remained as independent predictors of treatment response (Supplementary Table 1A). A 50 × 10^9/L increase in baseline platelets was associated with an OR of 1.95 (95% CI, 1.05–3.6) and a 0.5 log IU/mL decrease in baseline HBsAg was associated with an OR of 2.38 (95% CI, 1.26–4.40) of developing a MVR. However, HBsAg levels were available in only half of the patients.

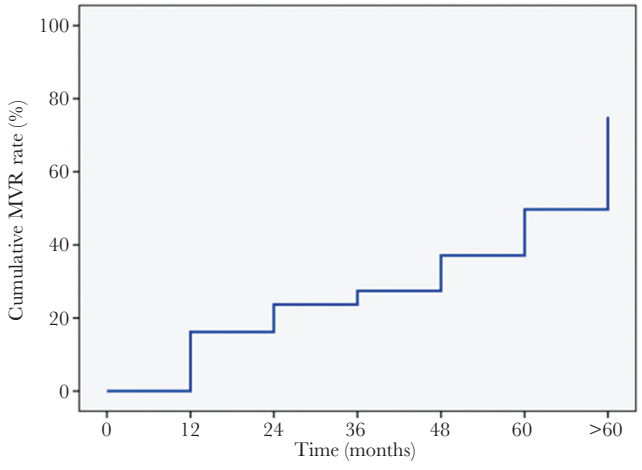


Figure 2. Probability of developing maintained virologic response (MVR) in relation to cumulative interferon/pegylated interferon treatment duration.

Effect of Maintained Virologic Response on Development of a Clinical Event

Patients with MVR had a tendency not to develop HCC ($P = .052$; Figure 3A). These patients were less likely to develop hepatic decompensation ($P = .013$; Figure 3B) or to die from a liver disease-related cause than patients without MVR ($P = .032$; Figure 3C). Similarly, liver transplantation was performed more in patients without MVR than patients with MVR ($P = .012$; Figure 3D). Liver transplantation and mortality combined was observed much less in patients having MVR, compared to those without ($P = .004$; Figure 3E). Any adverse clinical event, defined as occurrence of hepatic decompensation, HCC, mortality, or liver transplantation, developed much less in patients with MVR compared to those without MVR ($P = .006$, Figure 3F).

Patients who developed a clinical event were older ($P = .02$), had lower platelet count ($P < .001$), and higher GGT levels ($P = .03$). They were less likely to have had MVR ($P = .006$) compared to patients who did not develop a clinical event (Table 2). Furthermore, the former group had more frequent cirrhosis at baseline ($P < .001$), and had higher histologic activity index (HAI; $P = .02$) and fibrosis grade ($P = .04$) on liver biopsy. By multivariate analysis, cirrhosis at baseline (OR, 16.1; 95% CI, 4.34–62.5; $P = .002$) and no response to therapy (OR, 5.23; 95% CI, 1.4–18.8; $P = .013$) were independent factors for development of a clinical endpoint (Supplementary Table 1B). In Supplementary Figure 3A the effect of cirrhosis versus chronic hepatitis at treatment initiation on clinical event development is provided. A similar comparison is provided on the effect of platelet count at treatment initiation on development of a clinical event in Supplementary Figure 3B. In noncirrhotic patients at baseline, MVR to IFN treatment decreased clinical events compared to patients without MVR ($P = .026$) whereas this was not evident in patients with cirrhosis ($P = .055$) (Supplementary Figures 4A and 4B). MVR was effective in decreasing clinical events in patients with high platelets ($P = .044$) but not in patients with low platelets at baseline ($P = .29$) (Supplementary Figure 5A, B). Both in the cirrhotic and in the low platelet count, the number of patients responding to treatment was very low, which needs to be considered.

Effect of Maintained Virologic Response on HBsAg Clearance

HBsAg clearance developed in 14 (14%) of 99 patients and in 13 (37%) of 35 patients with a MVR. Median time for HBsAg clearance after treatment discontinuation was 46.5 months (IQR, 27.4–63.1). In 8 out of 13 patients anti-HBs became positive within 0 to 42 months. All patients maintained their HBsAg-negative status (follow-up 15–96 months). The cumulative probability of HBsAg clearance from the time of first treatment initiation was 0% at 1 year, and 2.9%, 9.2%, 22.4%, and 33% at 3, 5, 7, and 10 years, respectively (Figure 4). Corresponding cumulative probability figures after treatment discontinuation in patients with MVR were 8.6%, 14.5%,

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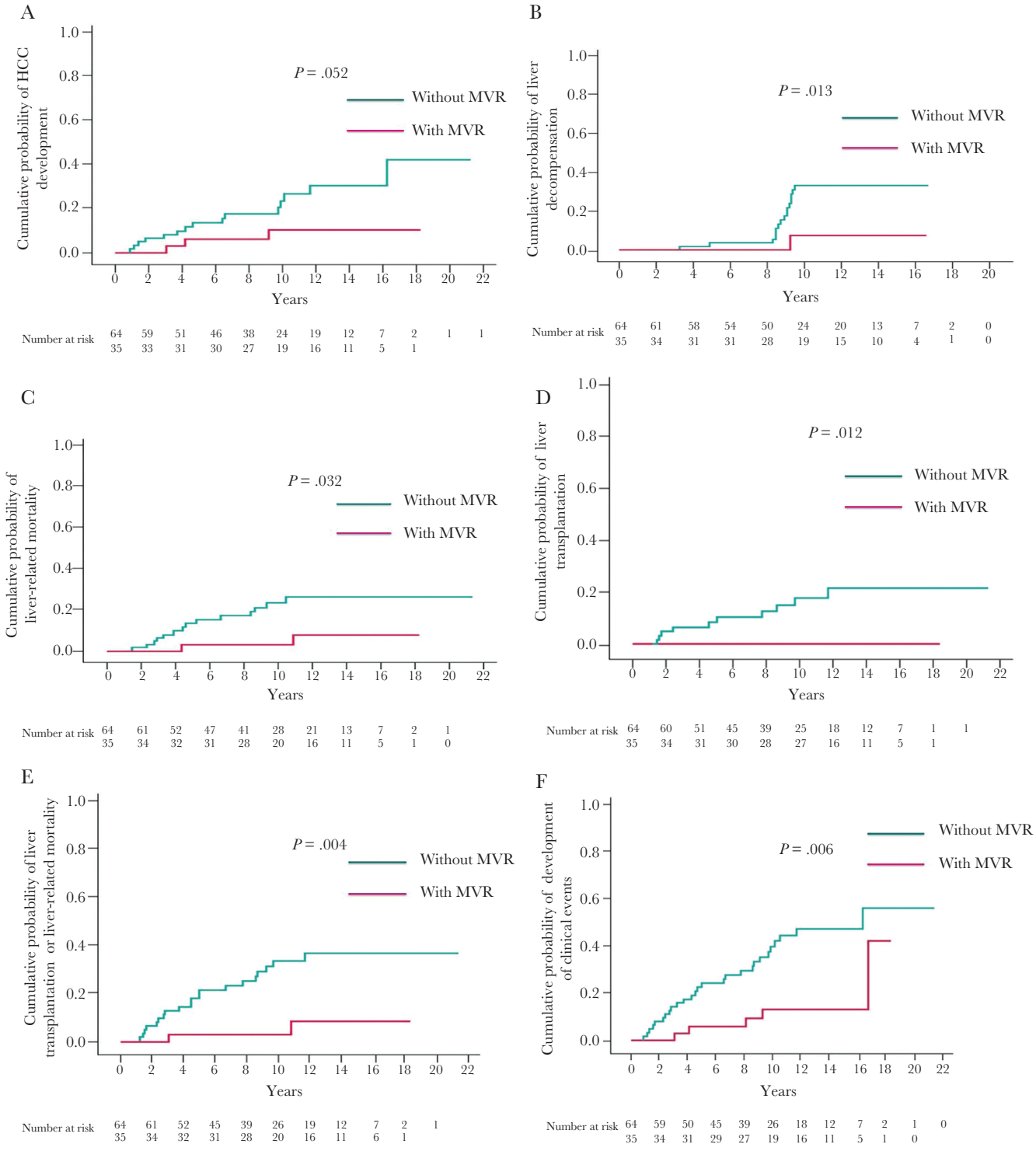


Figure 3. Comparison of the cumulative probability of development of a clinical outcome in patients with or without maintanied virologic response (MVR) to interferon treatment: (*A*) cumulative incidence of hepatocellular carcinoma (HCC); (*B*) hepatic decompensation; (*C*) liver-related mortality; (*D*) liver transplantation; (*E*) liver-related mortality and liver transplantation combined; (*F*) and any clinical outcome.

22.8%, 42.1%, and 49.4%. The association of several patient characteristics with HBsAg clearance are presented in Table 3. Patients with HBsAg clearance on long-term follow-up had lower baseline quantitative HBsAg and GGT levels ($P = 0.005$ and $P = 0.03$, respectively) and were more likely to have MVR ($P < .001$) compared to those who did not have HBsAg clearance. Only 1 patient without MVR cleared HBsAg and this occurred after hepatic decompensation. After multivariate

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Table 2. Comparison of Baseline Characteristics of Patients who Developed a Clinical Event During Long-Term Follow-Up With Those Who Did not Develop a Clinical Event

	Clinical event (+)	Clinical event (–)	*P* value
Age	43.5 ± 10.1	38.3 ± 10.5	.02
Gender	22 M/10 F	48 M/19 F	.81
HBeAg status	28 (–)/4 (+)	53 (–)/11 (+)	.67
ALT (U/L)	99.6 ± 69.5	111.1 ± 124	.56
AST (U/L)	78.5 ± 47.0	75.9 ± 83	.84
GGT (U/L)	107.7 ± 68.8	71.9 ± 81	.03
ALP (U/L)	119.0 ± 43.7	114.0 ± 56.2	.65
PT (seconds)	13.6 ± 1.5	13.1 ± 1.3	.19
Bilirubin (mg/dL)	1.11 ± 0.63	0.96 ± 0.53	.23
Platelet count ($\times 10^9$/L)	134 ± 41	174 ± 52	<.001
HAI (n = 78)	12.5 ± 3.3	10.2 ± 4.0	0.02
Fibrosis score (n = 78)	2.68 ± 1.35	1.95 ± 1.3	.04
HDV RNA ($\log_{10}$ IU/mL) (n = 59)	6.26 ± 1.4 (n = 18)	5.85 ± 1.4 (n = 41)	.31
HBV DNA ($\log_{10}$ IU/mL) (n = 63)	2.57 ± 1.5	2.0 ± 1.3	.2
Cirrhosis present	15/32	4 / 67	<.001
IFN response present	5/32	30/67	.006
HBsAg ($\log_{10}$ IU/mL) (n = 49)	9239 ± 6757	9252 ± 7965	.9

All values are mean ± SD unless otherwise indicated.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltranspeptidase; ALP, alkaline phosphatase; HAI, histologic activity index; HBsAg: hepatitis B surface antigen; HBeAg, hepatitis B e antigen; IFN, interferon; F, female; M, male; HBV, hepatitis B virus; HDV, hepatitis D virus; PT, prothrombin time.

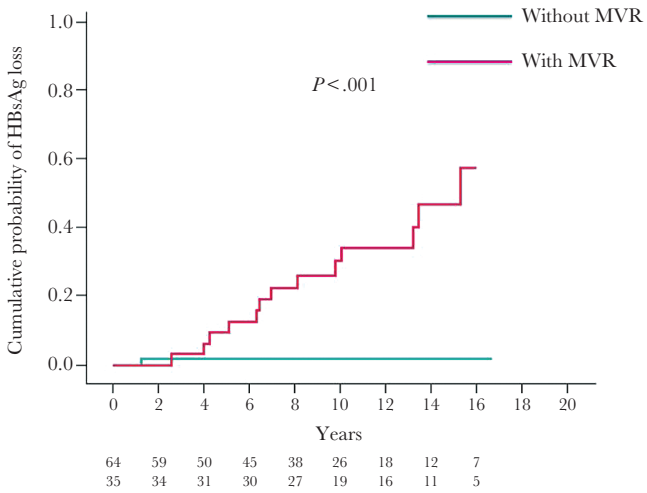


Figure 4. Cumulative probability of hepatitis B surface antigen (HBsAg) clearance in patients with and without maintained virologic response (MVR).

analysis, having a MVR to IFN treatment was the only independent predictor of HBsAg clearance with a OR of 14.3 (95% CI, 1.72–142, *P* 0.014; Supplementary Table 1C). There was no difference in baseline variables among patients with MVR who cleared HBsAg versus patients who did not clear HBsAg (Supplementary Table 2). Patients with HBsAg clearance tended not to develop a clinical event compared to patients without HBsAg clearance, although this did not reach statistical significance (*P* = 0.08; Supplementary Figure 6). However, a type 2 statistical error due to low number of patients with HBsAg clearance is likely (N = 14).

DISCUSSION

This study is important in several aspects: (1) it is one of very few studies exploring optimal IFN treatment duration in a relatively large group of CDH patients; (2) it shows that response to IFN treatment favorably affects the natural course of CDH; (3) it reports on baseline factors associated with treatment response; (4) it reports on factors affecting development of a clinical event; (5) it reports on the effect of viral response to the most robust surrogate efficacy parameter, HBsAg clearance; and finally (6) it explores variables associated with HBsAg clearance.

The optimal treatment duration of conventional or pegylated IFN has not been defined. In several studies, 2 years of treatment appeared similar to 1 year of treatment [11–13, 24]. However, a head to head comparison could be made in only one of these studies, and this included only 18 patients [24]. On the other hand, 2 studies suggested prolonged interferon treatment is necessary for higher viral response rates [18, 25], along the line of the current study. Cumulative probability of MVR reached 50% after 5 years of IFN treatment. These data need careful interpretation. One drawback of assessing cumulative probability of treatment response is that it contains a certain bias effect, as patients who have some response to an interferon treatment course would be more willing to go through a new course of INF treatment. As such, the cumulative probability of treatment response in CDH, presented here, is more likely an overestimation. How long to treat a CDH patient with pegylated IFN has to be decided on an individual basis, with careful on-treatment and post-treatment assessment. The issue is further enforced by our demonstration of the favorable effect of MVR on the natural history of the disease.

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Table 3. Comparison of Patients Who Cleared HBsAg With Those Who Did not Clear HBsAg

	HBsAg clearance	No HBsAg clearance	*P* value
Treatment duration (months)	29.4 ± 21.2	31.8 ± 24.4	.70
Gender	11 M/3 F	59 M/26 F	.75
HBsAg (log_{10} IU/mL) (n = 49)	3.22 ± 0.88	3.84 ± 0.52	.005
HBeAg status	11 (–)/2(+)	70 (–)/13(+)	.90
HBV DNA (log_{10} IU/mL) (n = 63)	2.47 ± 1.8	2.4 ± 1.5	.90
HDV RNA (IU/mL) (n = 59)	6.15 ± 1.5	5.95 ± 1.4	.70
Age	39.6 ± 6.8	40.1 ± 11.1	.87
ALT (U/L)	102 ± 54	108 ± 115	.86
AST (U/L)	86 ± 86	75 ± 71	.58
GGT (U/L)	42 ± 26	91 ± 82	.03
ALP (U/L)	115 ± 54	115 ± 52	.98
PT (seconds)	13.8 ± 2.2	13.2 ± 1.2	.38
Total bilirubin (mg/dL)	1.06 ± 0.8	1.01 ± 0.5	.75
Platelet count ($\times 10^9$/L)	176 ± 62	158 ± 50	.32
Fibrosis score, (n = 78)	2.18 ± 1.1	2.14 ± 1.4	.92
HAI (n = 78)	11.0 ± 5.0	10.8 ± 3.8	.85
Response to IFN present	13 /14	22/85	<.001

All values are mean ± SD unless otherwise indicated.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltranspeptidase; ALP, alkaline phosphatase; HAI, histologic activity index; HBsAg: hepatitis B surface antigen; HBeAg, hepatitis B e antigen; IFN, interferon; PT, prothrombin time; F, female; M, male; HBV, hepatitis B virus; HDV, hepatitis D virus.

From multivariate analysis, high platelet count and low HBsAg levels were significant predictors of treatment response. As low platelet count is, in general, associated with advanced liver disease; this suggests that patients with mild disease were more likely to have a MVR. These data are at variance with subanalyses of the HIDIT-1 study [26, 27] and the recently presented results of the HIDIT-2 study [13]. In both HIDIT studies the patient cohorts comprised treatment-naive as well as treatment-experienced patients. In the current study, all patients in the database were treatment naive when they started interferon therapy, which is a strength of the study. Although both HIDIT studies were randomized controlled trials, which should have prevented selection bias, treatment-experienced patients may have been more likely partial responders or relapsers to previous treatment regimens, as patients who display no biochemical or virologic response will be less motivated to receive another treatment course with side effects. In our study, patients with less-advanced disease may have tolerated treatment better and therefore received longer treatment, enabling them to have a MVR. On the other hand, in a study from Italy, low HBsAg levels at baseline were associated with treatment response [28] in line with the results of the current study.

A MVR was associated with favorable effect on the natural course of the disease. Patients with MVR were less likely to die from liver disease compared to those without a MVR. Hepatic decompensation also occurred less in patients with a MVR. Our data thus supports 2 recent observational studies [29, 30]. However, in these 2 latter studies IFN treatment overall resulted in decreasing the occurrence of a clinical event, whereas in the current study we have shown that patients with viral response do better than those without. These results are in line with natural history studies in HDV and HIV-HDV cohorts, where patients with persistent HDV replication were more likely to develop cirrhosis, hepatocellular carcinoma, and death [31, 32]. By multivariate analysis, having cirrhosis at baseline and not developing MVR were independent predictors of the development of a clinical event. Similarly, in the Spanish HIV coinfection cohort study, baseline liver stiffness was an independent predictor of liver decompensation and death [33]. Patients with MVR continued to favorably effect the natural course of the disease in chronic hepatitis patients whereas in patients with cirrhosis or low platelet count MVR did not appear to decrease the development of a clinical event. Taken together, this suggests that CDH patients may better be considered for treatment early in the course of the disease rather than later.

The most robust surrogate marker of treatment efficacy, HBsAg clearance, was achieved in 14 of the 99 patients who received variable durations of treatment with IFNs. More importantly, it developed in 37% of patients with MVR. These data indicate that HBsAg clearance can be achieved in a sizeable proportion of patients with MVR on long-term follow-up and are similar to data on IFN treatment of patients with HBeAg-negative CHB [34, 35]. Patients who cleared HBsAg had lower GGT and quantitative HBsAg levels at baseline compared to patients who did not clear HBsAg. The data on HBsAg levels, with reservations already mentioned, suggest that baseline HBsAg may be used for predicting HBsAg clearance in CDH, an issue which has been reported recently [28] and which needs further exploration.

One caveat of this study is that it is retrospective and has some of the pitfalls of a retrospective study, that is baseline

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quantitative HDV RNA and HBsAg levels could not be measured in all patients. On the other hand, we did not attempt to compare patients receiving interferon versus those who did not. In the vast majority of the latter cases, patients did not receive interferon because it was not indicated due too far-advanced liver disease, which already would have made such a comparison attempt biased and futile. Furthermore, such studies have been reported [29, 30]. We also did not assess efficacy of NAs in this study. Although NAs were found ineffective in several studies [14], long-term use of tenofovir appear efficacious in HIV-HDV coinfection [36–38] and this strategy needs assessment in CDH without HIV. HIV-HDV coinfection was an exclusion criteria in the current study. However, HIV infection incidence has increased in Turkey in the last 15 years at an exponential rate (Turkish Ministry of Health registry) [39] and HIV-HDV infection needs special attention because HDV is independently associated with death in HIV-coinfected patients [32, 33].

Taken together, the results of this retrospective cohort study indicate that MVR to IFN treatment may favorably affect the natural course of disease and that patients with MVR have a reasonable chance of clearing HBsAg on long-term follow-up. The data further suggest that patients need to be closely assessed and followed after a course of interferon treatment and treatment may need to be continued or reinstituted depending on response to treatment. Thus interferon treatment duration has to be individualized. Contraindications to treatment and tolerability also have to be considered, and actual treatment success with IFNs is much lower than reported here and elsewhere. New treatment options are urgently needed in CDH [40–42]. They are currently being tested in phase 2 clinical trials and are targeted to interfere with various steps of the HDV life cycle, such as HDV virion entry into hepatocytes, HDV virion assembly, and extrusion of HDV from hepatocytes [43].

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Previous presentation. Part of this study was presented as a poster at the AASLD Meeting in 2015 (Keskin O, et al. Hepatology 2015; 62:p1000A).

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Potential conflicts of interest. C. Y. has been in the advisory boards of Merck Pharma, Janssen Pharma, AbbVie Pharma, and Gilead Pharma and in the Speakers bureau of Roche Pharma, AbbVie Pharma, Eiger Biopharma, and Gilead Pharma. He has received research grants from Roche and BMS Pharma and Eiger Biopharma. All other authors have nothing to disclose. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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