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Pegylated interferon-based treatment in patients with advanced liver disease due to chronic delta hepatitis

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Background/aims: *The safety and efficacy of interferons in advanced delta hepatitis have not been explored. The aim of this subanalysis of a multicenter clinical trial was to compare the efficacy and safety of 48 weeks of pegylated interferon alpha-2a (180 µg weekly) with or without adefovir (10 mg daily) in patients with chronic delta hepatitis-induced advanced liver disease and in those with non-advanced liver disease.* ***Materials and Methods:*** *Thirty-one patients with advanced and 27 patients with non-advanced liver disease were assessed. Patients were considered to have advanced liver disease when biopsy disclosed a fibrosis score of ≥4 according to Ishak or when imaging studies were indicative of cirrhosis. Virologic response, defined as achievement of undetectable hepatitis D virus RNA, was assessed at the end of treatment and end of 24 weeks of treatment-free follow-up.* ***Results:*** *Patients with advanced disease had lower hepatitis D virus RNA levels and platelet counts (p=0.014 and p=0.0015, respectively). End of treatment and end of follow-up virologic responses in patients with advanced vs. non-advanced liver disease were similar (29% vs. 19% and 32% vs 23%). Proportion of adverse events did not differ between groups except that thrombocytopenia was noted more often in the advanced liver disease group. Further, four cases of clinically important adverse events including two cases of hepatic decompensation and one case of tuberculosis reactivation occurred in the advanced liver disease group.* ***Conclusions:*** *Pegylated interferon is as effective in patients with advanced liver disease due to chronic delta hepatitis as in patients with non-advanced liver disease, but patients should be monitored closely for clinically important side effects.*

Key words: Cirrhosis, hepatitis delta, pegylated interferon, therapy

Kronik delta hepatitine bağlı ileri karaciğer hastalığı olan vakalarda pegile interferon bazlı tedavi

Amaç: *İleri delta hepatitinde interferonların güvenilirlik ve etkinliği araştırılmamıştır. Çok merkezli bir klinik çalışmanın bu alt analizinin amacı, kronik delta hepatitine bağlı ileri karaciğer hastalığı olan ve ileri hastalığı olmayan hasta gruplarını, 48 haftalık interferon alfa-2a (180 µg/hafta) ve/veya adefovir (10 mg/gün) tedavilerinin etkinlik ve güvenilirliği açılarından karşılaştırmaktır.* ***Gereç ve Yöntem:*** *İleri hastalıklı 31 ve ileri hastalığı olmayan 27 hasta değerlendirmeye alındı. Hastalar biyopside fibrosis skoru Ishak'a göre ≥4 ise veya görüntüleme yöntemleri sirozla uyumlu ise ileri karaciğer hastalığı olarak kabul edildi. Hepatit D Virus RNA'sının saptanamaması olarak tanımlanan virolojik yanıt, tedavi sonunda ve 24 haftalık tedavisiz takip sonunda değerlendirildi.* ***Bulgular:*** *İleri hastalığı olan hastaların Hepatit D Virus RNA seviyeleri ve trombosit sayıları daha düşüktü (sırasıyla, p=0.014 and p=0.0015). İleri hastalarla, ileri hastalığı olmayanların tedavi sonu ve takip sonu virolojik yanıt oranları benzerdi (29% vs. 19% and 32% vs 23%). İleri hastalık grubunda daha sık görülen trombositopeni dışında yan etki oranları gruplar arasında farklı değildi. Ancak, ileri karaciğer hastalığı grubunda 4 hastada klinik olarak önemli yan etkiler gelişti, bunlardan 2'sinde hepatik dekompanzasyon ve 1 vakada tüberküloz reaktivasyonu görüldü.* ***Sonuç:*** *Kronik delta hepatitine bağlı ileri karaciğer hastalığında pegile interferon, ileri hastalığı olmayanlardaki kadar etkindir, ancak hastalar klinik olarak önemli yan etkiler açısından yakın takip edilmelidir.*

Anahtar kelimeler: Siroz, hepatitis delta, pegile interferon, tedavi

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INTRODUCTION

Chronic delta hepatitis (CDH) represents the most severe form of chronic viral hepatitis (1-3). As a sharp paradox to this and in contrast to the progress achieved in chronic hepatitis B (CHB) and CHC treatment, management of CDH has changed little in recent years. The only gain obtained was the use of pegylated interferon alpha (peg-IFNα) for its management, which due to its better pharmacokinetic and pharmacodynamic properties may have been of some additional benefit to patients (4-6). Translation of bench side work to clinical practice has not occurred in CDH, and several attempts to benefit from the progress in CHC or CHB treatment have proved disappointing. In this context, famciclovir, lamivudine, adefovir, and entecavir were without effect in CDH (7-12) or provided no additional benefit when combined with IFNα over IFN monotherapy in the case of ribavirin and lamivudine (6,10,13,14). Peg-IFNα-adefovir combination also had no additional effect over peg-IFNα monotherapy in terms of virologic, biochemical and histologic responses, but appeared to be better compared to monotherapy in decreasing quantitative hepatitis B surface antigen (HBsAg) levels (11).

Interferons (IFNs) have been widely used in CHB and CHC treatment. However, IFNs are contraindicated in patients with decompensated cirrhosis and in general are used with caution in patients with cirrhosis. The main concerns about the use of IFNs relate to fear of significant neutropenia or thrombocytopenia or the fact that the immunomodulatory properties of IFNs, especially in CHB, lead to a flare of disease, which may have devastating consequences in patients with critical liver reserve (15). The general consensus from recent published trials in CHB and CHC, however, is that peg-IFNs are safe in patients with compensated cirrhosis or advanced liver disease (16-18). Although in several previous studies of treatment of CDH with IFNs, an important proportion -up to 65%- of patients have been reported to have cirrhosis (6,19), no study addressed specifically the effect and safety of IFN use in CDH-induced advanced liver disease. This is especially important since IFNs represent the only available treatment option in CDH. Further, CDH may sometimes run a very progressive course with development of cirrhosis within a few years (20). Thus, reason for concern related to IFN use in cirrhosis may be more substantiated in the case of CDH. The current study addresses this issue and compares the efficacy and safety of peg-IFNα 2a-based treatment in CDH-induced advanced liver disease versus in patients with non-advanced disease, through reanalysis of the effective arms of the recently published Hep-Net–International Delta Hepatitis Intervention Trial (HIDIT)-1 Study (11). Further, patients who participated in the study had hepatitis D virus (HDV) genotype I and hepatitis B virus (HBV) genotype D, both of which may be regarded as less favorable viral parameters with regard to treatment response (21,22).

MATERIALS AND METHODS

This study represents a subanalysis of the investigator-initiated multicenter controlled HIDIT trial (Current Controlled Trials number, ISRCTN83587695), the results of which have been reported recently (11). Briefly, patients between 18 and 70 years of age had to have compensated liver disease, had been HBsAg-positive for at least six months and anti-HDV positive for at least three months, and had to be HDV RNA-positive by polymerase chain reaction (PCR) at screening. Exclusion criteria were pregnancy and lactation, complications of liver disease such as decompensation and hepatocellular carcinoma (HCC), and any significant disease that might have interfered with the conduct of the study. Detailed inclusion and exclusion criteria were published in the main manuscript (11). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethics committee of each institution that participated in the study. Informed consent was obtained from all patients prior to study entry. The trial received financial support from F. Hoffmann-La Roche and Gilead Sciences, who approved the study design as proposed by the investigators. The study was conducted at Hannover Medical School in Germany, at centers connected to Hannover Medical School through HepNet in Germany, and at six university hospitals in Turkey and one university hospital in Greece. Patients were recruited between March 2004 and September 2006, and data collection and analysis were completed in March 2010.

In the HIDIT Study, patients had been randomized to receive peg-IFNα 2a, 180 μg, qw + placebo (n=29), peg-IFNα 2a + adefovir dipivoxil (AD), 10 mg, qd (n=32), or AD alone (n=30) for 48 weeks. Patients were followed for an additional 26 weeks after treatment discontinuation. As AD was without effect, in the current study, only the 61 pati-

ents who were randomized for a peg-IFNα 2a-based regimen were considered for analysis. Since peg-IFN + placebo and peg-IFN + AD had been found to be equally effective in the main study, patients who received peg-IFN with or without AD were not separately assessed in the current analysis (Figure 1).

The decision of advanced liver disease was based on both liver histology and imaging studies. Patients were considered to have advanced liver disease when their baseline biopsy disclosed a fibrosis score of ≥4 according to Ishak et al. (23) or when imaging studies such as ultrasound and/or abdominal tomography were indicative of cirrhosis irrespective of the liver histology fibrosis score. Findings indicative of cirrhosis on imaging studies were nodularity or irregularity of the liver surface and coarse, nodular appearance of liver parenchyma.

Patients were seen monthly for the first three months and then every six weeks until the end of treatment. During 26 weeks of treatment-free follow-up, patients were seen at post-treatment weeks 4, 12 and 24. At every visit, patients received a complete physical examination and safety assessment, and blood was taken for biochemistry and virology. Hepatitis flares were defined as a three-fold increase in serum alanine (ALT) or aspartate (AST) aminotransferase compared to baseline according to Flink et al. (24). Assessments were made at week 48 (end of treatment) and at week 72 (end of treatment-free follow-up). The primary outcome measures were HDV RNA negativity and ALT normalization at week 72.

HDV genotype was assessed at baseline by sequencing analysis of the hepatitis delta antigen (25). Patients with sufficient HBV viremia were genotyped for hepatitis B using the Innolipa assay (Innogenetics, Gent, Belgium). HDV RNA was measured as previously reported (25,26). The lower limit of detection of HDV RNA was 120 copies ml^{-1}. HBV DNA was measured with Cobas TaqMan HBV test (Roche Molecular Systems, Inc, USA) using the high pure system viral nucleic acid kit for manual specimen preparation and the Cobas Taqman 48 analyzer for automated amplification and detection. The results are expressed in International units ml^{-1} (IU ml^{-1}). HBsAg was quantified by Architect HBsAg assay (Abbott Diagnostics, Germany) according to the manufacturer's instructions. This is a chemiluminescent microparticle immunoassay with sensitivity ≤0.05 IU ml^{-1}.

Histology was assessed by two blinded assessors in patients with paired pre- and post-treatment biopsies. Fibrosis was assessed according to the Ishak fibrosis score (23). A change in fibrosis was defined as a change in the fibrosis score by 1 or more, and a change in necroinflammation was defined as a change in the necroinflammatory score by 2 or more.

Statistical assessment of treatment outcome was performed by intent-to-treat (ITT) analysis on all subjects receiving at least one dose of the study medication in the main study. Patients with missing values were considered as non-responders. In the current subanalysis, baseline assessment was performed in all subjects randomized to a peg-IFN-based regimen who could be classified as having advanced liver disease or non-advanced liver disease (n=58). Treatment outcomes were assessed in those subjects who had received at least one dose of study medication (n=57). All data are presented as mean or median values as specified. Comparisons were made using unpaired and paired Student's t test or Mann-Whitney U test and Wilcoxon signed rank test, where appropriate, for continuous variables and with the Fisher's exact test for categorical variables, with p values <0.05 considered significant.

RESULTS

Patient Characteristics

Of the 61 patients who had been randomized to receive a peg-IFNα-based treatment in the HIDIT Study, 31 patients were considered to have advanced liver disease and 27 patients to have mild or moderate liver disease. Three patients in whom liver biopsy was not available and imaging studies did not suggest cirrhosis were not included in this analysis. One patient in the non-advanced disease group withdrew consent after randomization but before receiving any treatment drug, and this patient was not included in the treatment analysis (Figure 1). The decision of advanced liver disease was based on liver histology in 23 patients (10 of them had Ishak fibrosis scores of 5 or 6) and on an imaging study indicative of cirrhosis in 8 patients. Decision of non-advanced liver disease was based on liver biopsy in all of the 27 patients. The HDV genotype was 1 and hepatitis B genotype was D, in those patients for whom such analysis was possible, as pointed out earlier (24). Patient characteristics are summarized in Table 1. Patients with advanced disease had lower platelet counts and the-

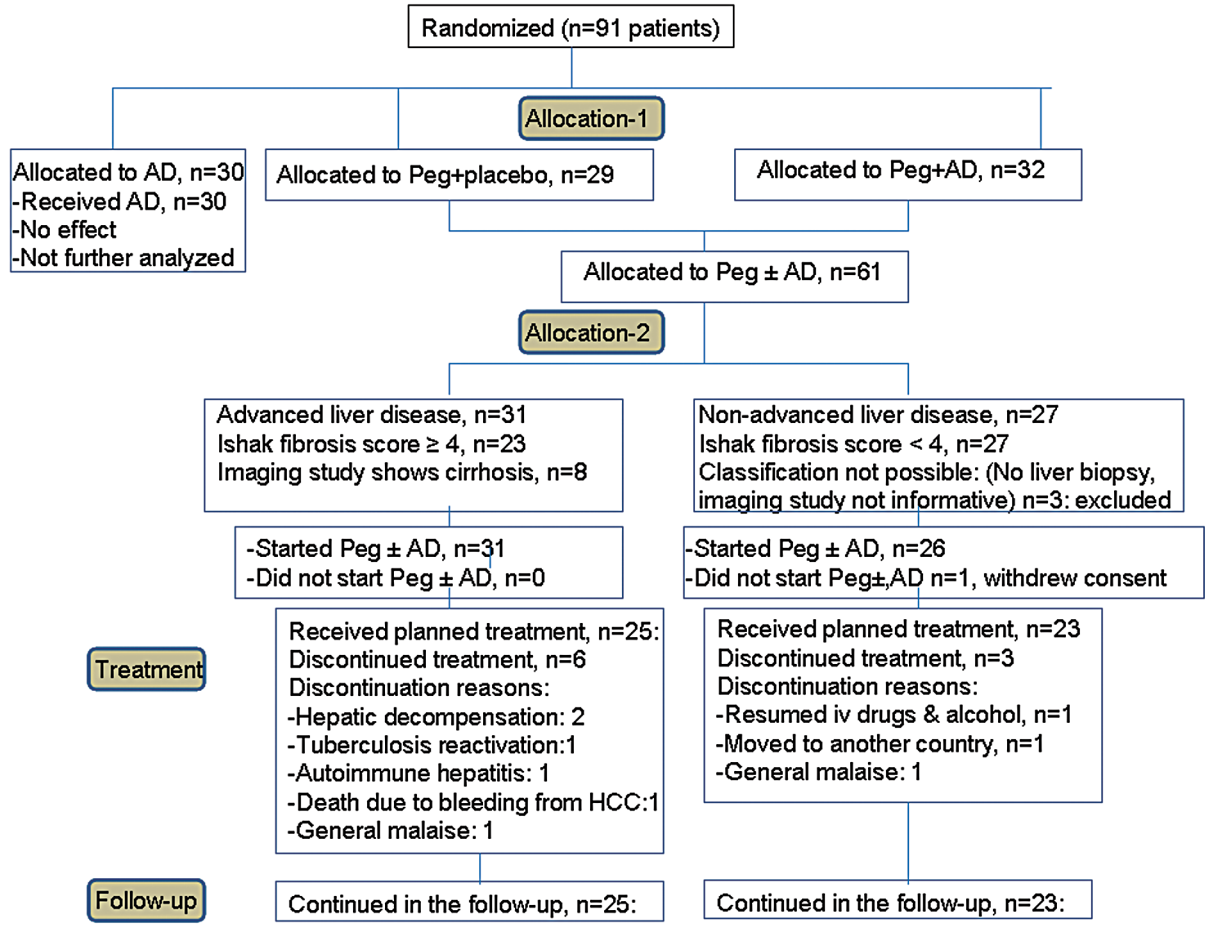

Figure 1. Flow diagram of the patients' allocation to treatment arms.

ir serum HDV RNA levels were lower than in patients with non-advanced liver disease (p=0.0015 and p=0.014, respectively). Patients with non-advanced liver disease had HBeAg-positive and anti HBe-negative hepatitis B serology more often (p=0.023). Further, serum gamma-glutamyltransferase (GGT) levels were higher and serum albumin levels were lower in patients with advanced liver disease when compared to those with less advanced liver disease (p=0.027 and p=0.048, respectively, Table 1).

Efficacy

Treatment with a peg-IFN-based regimen led to a significant reduction in HDV RNA at the end of treatment compared to baseline both in patients with advanced as well as non-advanced liver disease (5.26±1.20 [x±SD] $\log_{10}$ copies ml^{-1} vs. 2.50±2.00, n=21, p<0.0001 and 6.32±0.93 vs. 3.67±2.80, n=17, p=0.0011, respectively, Table 2). The proportion of patients who at end of treatment had a virologic or biochemical response was similar (29 vs. 19% and 19 vs. 29%, respectively). After 24 weeks of treatment-free follow-up, the proportions of patients with a virologic response, with a biochemical response and with combined virologic and biochemical response did not differ between patients with advanced vs. non-advanced liver disease (32 vs. 23%, 32 vs. 42% and 16 vs. 19%, respectively). Likewise, the end of treatment vs. baseline delta differences in HDV RNA and HBV DNA levels were similar. The proportions of patients who had at least 1 $\log_{10}$ decline in HBsAg levels and histologic response were also similar in the two groups (Table 2).

Safety

The most frequently encountered adverse events were, among others, fatigue, muscle pain, headache, and arthralgia, and are listed in Table 3. Adverse events were generally seen with similar frequency in patients with advanced vs. non-advanced liver disease. However, more patients with advanced liver disease developed thrombocytopenia

Table 1. Patient characteristics

	Patients with advanced liver disease n=31	Patients with mild-moderate liver disease n=27	P value
Age	42.1±10.5 (n:31)	39.2±12.2 (n:27)	0.31
Sex	16M/15F	20M/7F	0.11
ALT	79 (35-660) (n:31)	94 (23-360) (n:27)	0.76
Platelets	142±42.2 (n:30)	182±47.0 (n:27)	0.0015
HBeAg(+) HBeAb(-)	1/29	7/27	0.023
HBV DNA (log10 IU mL-1)	1.77±1.94 (n:30)	2.58±2.13 (n:25)	0.15
HDV RNA (log10 copies mL-1)	5.36±1.23 (n:23)	6.24±0.93 (n:19)	0.014
HBsAg (log10 IU mL-1)	4.14 (1.83-4.63) (n:29)	3.96 (2.26-4.90) (n:26)	0.69
γ-GGT	66.5 (16-401) (n:28)	36 (14-288) (n:27)	0.003
Albumin	3.92±0.48 (n:26)	4.18±0.36 (n:24)	0.048
Histology: Necroinflammation	7.77±2.07 (n:26)	6.44±2.10 (n:27)	0.025

HBsAg, ALT and γ-GGT given in median and range, others except sex and serology given in mean and SD.

Table 2. Treatment response to peg-IFN-based treatment at end of treatment -if not otherwise indicated- of patients with advanced vs. non-advanced liver disease

	Patients with advanced liver disease n=31	Patients with mild-moderate liver disease n=26	P value
HDV RNA decline by >2 log	13/31 (41.9%)	8/26 (30.8%)	0.42
HDV RNA (-) at week 48	9/31 (29.0%)	5/26 (19.2%)	0.54
HDV RNA (-) at week 72	10/31 (32.3%)	6/26 (23.1%)	0.56
Delta decline in HDV RNA	2.76±172 log10	2.65±2.76 log10	0.88
Delta decline in HBV DNA	0.77±1.26 log10	1.21±1.26 log10	0.25
ALT normal at week 48	6/31 (19.4%)	8/26 (29.6%)	0.37
ALT normal at week 72	10/31 (32.3%)	11/26 (42.3%)	0.58
ALT normal and HDV RNA negative at week 72	5/31 (16.1%)	5/26 (19.2%)	1.0
≥1 log decline in HBsAg levels	4/31 (12.9%)	8/26 (29.6%)	0.12
Improvement in inflammation	4/14 (28.6%)	8/21 (38.1%)	0.72
Improvement in fibrosis	7/15 (46.6%)	5/21 (23.8%)	0.18

NS: Not significant. Improvement in inflammation and fibrosis: decrease in necroinflammatory and fibrosis score by ≥2 and ≥1, respectively.

(platelets <50 x 10^9 L^{-1}) compared to patients with non-advanced liver disease (p=0.047). Bleeding tendency became clinically evident in 5 cases in the form of gingival, menstrual and rectal bleeding. Four of them occurred in patients with advanced liver disease. Reported serious adverse events suggested to be drug-related occurred more often in patients with advanced liver disease. Only one drug-related serious adverse event was reported from patients with non-advanced liver disease, and this case had been hospitalized because of fever, which subsequently resolved. Overall, however, there were 4 clinically important adverse events considered to be peg-IFN-related, all of which occurred in the advanced liver disease group: these were 2 cases of hepatic decompensation, of which only 1 had been reported as a serious adverse event, 1 case of tuberculosis reactivation, and 1 case of exacerbation of liver disease due to autoimmune hepatitis. Tuberculosis reactivation occurred in a patient of Syrian descent at week 24 of treatment. Treatment was discontinued, and the patient was put on triple anti-tuberculosis treatment. There were 2 cases of hepatic decompensation: serum bilirubin rose and serum albumin dropped at week 8 to 8.4 mg dl^{-1} (143.6 µmol L^{-1}) and 2.2 g dl^{-1}, respectively, in the first case, and in the other case, the corresponding values were 3.8 mg dl^{-1} (65 µmol L^{-1}) and 2.5 g dl^{-1} at week 24 . One death occurred as a result of intraperitoneal bleeding from HCC. This patient was in the cirrhotic group as well. Another patient was listed for liver transplantation because of a solid mass suggesting HCC in imaging studies. Subsequent successful liver transplantation in this patient did not reveal HCC, however, but a macroregenerative nodule.

Table 3. Frequently observed adverse events in patients with advanced vs. non-advanced liver disease at baseline

	Patients with advanced fibrosis n=31	Patients with mild-moderate fibrosis n=26	P value
Fever	16.1%	11.1%	1.0
Fatigue	29%	25.9%	0.19
Headache	22.6%	29.6%	0.59
Arthralgia	22.6%	11.1%	0.22
Hair loss	12.9%	14.8%	1.0
Abdominal pain	19.4%	25.9%	0.77
Muscle pain	25.8%	22.2%	0.22
Sleep disorder	6.5%	14.8%	0.24
Depression	3.2%	7.4%	0.34
Bleeding	12.9%	3.7%	0.11
Thrombocytopenia (<50 x 10^9)	32.3%	7.7%	0.047
Neutropenia (<1000)	45.2%	34.6%	0.30
SAE related to Peg-IFN	12.9%	3.8%	0.36
Hepatic decompensation	6.5%	0%	0.49
Withdrawal due to AE	12.9%	3.6%	0.36

SAE: Serious adverse event.

Nine patients did not complete the 48-week treatment period. The reason for withdrawal was the patient's own decision in 1 patient and unrelated to the study medications. One patient resumed heavy alcohol drinking and intravenous drug use and was non-compliant. Another patient died of bleeding from HCC. In the other 6 patients, withdrawals were related to adverse events linked to peg-IFN in 5 patients in the advanced liver disease arm (2 cases of hepatic decompensation, 1 case each of tuberculosis reactivation, hepatitic exacerbation due to autoimmune hepatitis and general malaise/arthralgia) and in 1 patient in the non-advanced liver disease arm who discontinued treatment because of general malaise. The 7 patients who did not finish the study because of disease-related or peg-IFN-related factors had lower platelet counts and higher GGT levels at baseline compared to the rest of the patients ($116x10^9$ L^{-1}±$32x10^9$ [x±SD] vs. $167x10^9$±$47x10^9$; p=0.0084 and 160 IU mL^{-1} [median, range 23-401] vs. 46.5 [14-497]; p=0.0086, respectively).

Dose reduction or interruption of peg-IFN was deemed necessary by the investigator in 12 patients in the advanced liver disease group and in 4 patients in the non-advanced liver disease group (p=0.076). These dose reductions or interruptions occurred only once (2 patients) or twice (2 patients) in the non-advanced liver disease group, whereas this was required on 2-8 visits in the advanced liver disease group (1.5±0.58 vs. 5.91±2.47, p=0.0042).

Side effects occurred at any time, although thrombocytopenia and leukopenia were first noted within the first 24 weeks of treatment in 75% and 82% of patients (p=0.039 and p=0.009, respectively). Neutropenia was detected within the first 12 weeks of treatment in 80% of patients (p<0.0001).

On-treatment flare occurred in 8 patients, without clinical consequences in 7 patients and with hepatic decompensation in 1 patient. Flares occurred at weeks 12, 18 and 24 in 4, 2 and 2 patients, respectively. None of the patients with such on-treatment flares had a virologic response at the end of treatment. An increase in ALT more than twice the baseline value occurred in 14 patients (24.6%). In 11 of them, this ALT increase first occurred within the first 12 weeks. There was no link between the increase in ALT to end of treatment or end of follow-up virologic responses (data not shown). The course of ALT during treatment is shown in figures 2A and 2B.

DISCUSSION

The main finding of the study is that patients with advanced liver disease due to CDH responded to peg-IFN-based treatment at a similar level as patients with non-advanced liver disease. This is in variance with studies performed in CHC (27-29). In contrast, studies in CHB have reported both favorable (16) and unfavorable results (30). Similar

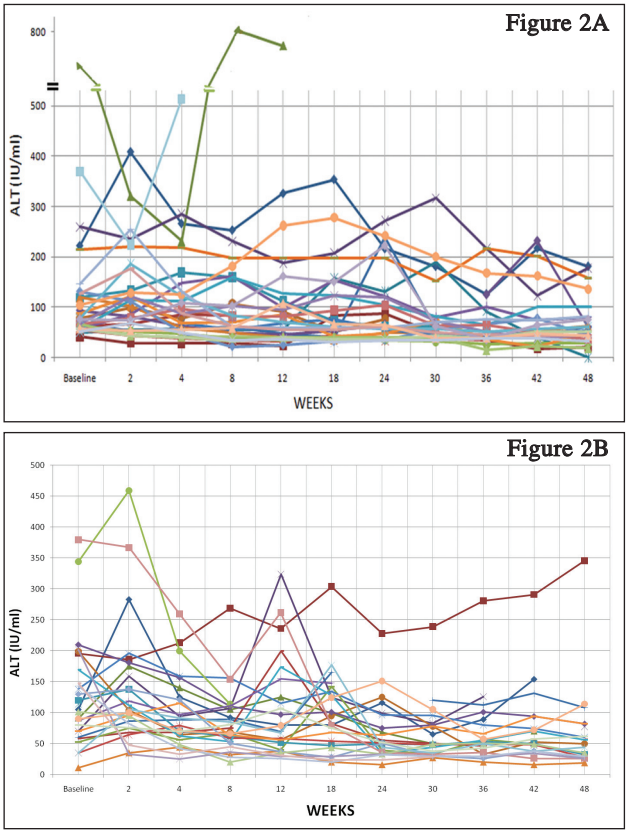

Figure 2. Flow chart of ALT levels during treatment in patients with advanced (Figure 2A) and non-advanced liver disease (Figure 2B).

efficacy of peg-IFN treatment in patients with advanced and non-advanced liver disease in CDH is important, as many patients with CDH seek treatment when the disease is in an advanced stage.

However, clinically important adverse events occurred in patients with advanced liver disease, which included two cases of hepatic decompensation and one case of tuberculosis reactivation. The latter may need particular attention for patients from areas where both CDH and tuberculosis may be endemic, such as Turkey, Eastern Europe and the Middle East (10,31). It may be important to note that in the three patients in whom decompensation or tuberculosis reactivation occurred, baseline platelets counts were 74, 122 and $105x10^9$ L^{-1}, respectively. Although not analyzed in detail in this study, patients with platelet counts of $125x10^9$ L^{-1} or less were reported to be associated more frequently with splenomegaly and esophageal varices in the HALT-C cohort of CHC patients (27), emphasizing that patients with advanced liver disease should be considered to represent a heterogeneous clinical spectrum.

Eight patients (13.3%) had a hepatitic flare, of whom one developed hepatic decompensation. None of the patients with a hepatitic flare had a virologic response at the end of treatment, which suggests that ALT elevation in CDH does not herald treatment response. These data are in variance to the situation in CHB, where on-treatment hepatitis flares occur in around one- third of patients during IFN treatment and may herald treatment response, especially in HBeAg-positive CHB (24,32), but perhaps also in patients with HBeAg-negative CHB (33). On-treatment ALT flares are infrequently encountered in CHC patients (34). Overall, the data indicate that besides the usual concern of hematological side effects, a close on-treatment clinical assessment is needed in CDH patients with advanced liver disease and especially with signs of portal hypertension at baseline, where patient complaints should be seriously approached and biochemical parameters such as serum albumin, bilirubin and prothrombin time followed closely.

HBeAg-positive, anti-HBe-negative serology was observed more often in the non-advanced liver disease group. The importance or meaning of HBeAg-positive CDH is not well studied. Most CDH cases occur as a result of superinfection with HDV of an HBsAg carrier, and since most of the latter are expected to possess HBeAg-negative, anti-HBe-positive serology, most CDH cases also have this latter serological pattern. Theoretically, coinfection could be the reason for the high proportion of HBeAg-positive cases in the non-advanced liver disease group. However, chronicity development is rare after coinfection (3), and mathematical reasoning would point against such a possibility. The more likely explanation is that superinfection may have occurred rather early in life when patients were still HBeAg-positive. A cohort study delineating that HBeAg (+) CDH patients are younger than HBeAg-negative CDH patients supports this view (35). HDV RNA levels were lower in the advanced liver disease group, as is generally expected in patients with advanced chronic viral hepatitis and has also been shown for CDH (36).

A limitation of this study is that it represents a subanalysis, and patients with advanced disease were not stratified according to portal pressure. With this reservation in mind, it can be concluded that in CDH, patients with advanced liver disease can respond to peg-IFN as well as those patients with less advanced disease. The importance of this fin-

ding is obvious in a condition where treatment with IFNs continues to be the only management option. However, such patients, especially when associated with baseline portal hypertension, should be monitored closely for clinically important side effects and necessary action taken without delay.

Potential competing interests: *Dr. Cihan Yurdaydin has been on the Advisory Boards of Roche Pharma, Merck Pharma and Gilead Pharma and on the Speakers Bureau of Roche Pharma and Gilead Pharma. George Dalekos is on the Speakers Bureau of Gilead. Stefan Zeuzem is on the Advisory Board of Gilead and Roche and on the Speakers Bureau of Gilead and Roche. Michael Manns has been on the Advisory Boards of Schering Plough, Roche, BMS, Gilead, Valeant, Boehringer Ingelheim, Novartis, Idenix, Tibotec, Vertex, and GlaxoSmith Kline and on the Speakers Bureau of Roche, BMS, GlaxoSmithKline, and Gilead. Heiner Wedemeyer has been on the Advisory Boards of Roche and Gilead and on the Speakers Bureau of Roche and Gilead. Gökhan Kabaçam, Yılmaz Çakaloğlu, Kalliopi Zachou, Thomas Bock, Andreas Erhardt, Fehmi Tabak, Kendal Yalçın, Ulus S. Akarca, Ramazan Idilman, A. Mithat Bozdayı, Hans P. Dienes, and Hakan Bozkaya have nothing to declare.*

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