THE EFFICACY OF THE PEGINTERFERON TREATMENT IN CHRONIC HEPATITIS HDV AND COMPENSATE LIVER CIRRHOSIS

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THE EFFICACY OF THE PEGINTERFERON TREATMENT IN CHRONIC HEPATITIS HDV AND COMPENSATE LIVER CIRRHOSIS (Abstract). **Aim**: to evaluate the efficiency of the treatment with Peginterferon alfa 2a 180 mcg/week, 48 weeks in patients with chronic hepatitis or compensated liver cirrhosis HDV and predictive factors of response to treatment**.** **Material and methods**: prospective study that enrolled 50 patients with chronic hepatitis or compensated cirrhosis HDV between the 1st of January 2011 – 3st of December 2011. The diagnosis of chronic HDV infection was made based on the presence of detectable anti HDV IgG antibodies and HDV-RNA. Patients were evaluated at baseline by CBC, liver function tests, HBV profile, HDV RNA, and by liver biopsy/Fibrotest for evaluating fibrosis and necroinflamatory activity. At 24 weeks CBC (count blood cells), liver function tests, quantitative HBsAg and at 48 and 72 weeks biochemical tests, HDV RNA, HBV DNA, quantitative HBsAg, were performed. Adverse reactions to the treatment were recorded. **Results**: SVR (sustained virologic response) was recorded in 12 patients (24%) and biochemical response in 28 patients (56%). SVR was correlated with low-grade fibrosis, age, the aminotransferase value and the value of HBsAg at the beginning of the treatment. In week 48 HDV RNA was undetectable in 20 patients (40%). The therapy was well tolerated, except two patients for whom the discontinuation of the treatment was decided for severe exacerbation of cytolysis, respectively hepatic decompensation. **Conclusions**: In a representative group of patients, the treatment with Peginterferon once again proves its efficacy in treating chronic HDV. **Keywords**: DELTA HEPATITIS, CIRRHOSIS, PEGINTERFERON TRATMENT.

HDV chronic hepatitis is the most severe of chronic viral hepatitis, representing an important public health problem. The hepatitis delta virus (HDV) is a defective RNA virus that requires the presence of the HBV for replication and transmission. Of the HBsAg carriers, approximately 5% also have the HDV infection, affecting 15 to 20 million people worldwide. The evolution is rapid from chronic hepatitis to liver cirrhosis (1) and hepatocellular carcinoma (2).

HDV infection is difficult to treat;

pegylated interferon seems to be the only efficient molecule naive as well as in pre-treated patients, with a virologic response of ~ 20-47 % (3). HDV activity depends on HBsAg, not on the HBV replication or the HBV DNA level (4). Measurement of HBsAg levels during the treatment may be more useful than HDV RNA negativity in predicting the virologic response. The main concern is the use of interferon is neutropenia, thrombocytopenia, and severe hepatic cytolysis flare that may have dramatic consequences in patients with a deficient hepatic reserve (5). Studies with nucleoside analogues demonstrated that these molecules have no effect on hepatitis delta.

The aim of our study is to evaluate the effectiveness of the treatment with peginterferon α2a 180 mcg/week, 48 weeks in patients with chronic HDV infection in chronic hepatitis or compensated cirrhosis, and the predictive factors of response to treatment. TGP normalization at 48 and 72 weeks, HDV RNA negativity and the decrease of HBsAg levels were followed.

MATERIAL AND METHODS

We performed a prospective study that enrolled patients with chronic hepatitis or compensated cirrhosis VHD, present in the Gastroenterology and Hepatology IC Fundeni Clinic during January 1 2011-31 December 2011. The inclusion criteria were: age over 18 years, HBsAg and anti-HDV antibodies of over 6 months, HDV RNA detectable viremia, hepatic cytolysis with ALT $\geq$ 2xN, and histological evidence of chronic hepatitis or cirrhosis. Exclusion criteria were pregnancy, lactation, other causes of liver damage, hepatocarcinoma or decompensated cirrhosis, thrombocytopenia, neutropenia <1.000/mm^3, Hb <9 g/dl, severe cardiac, lung, neuro-psychiatric co morbidities.

Liver cirrhosis was diagnosed by PBH/FibroMax (F4) or imaging studies: abdominal ultrasound or computer tomography. They were evaluated at baseline with the CBC, liver function tests, profile HBV (HBsAg quantitative HBeAg, HBeAb, AcHBc, DNA-HBV), HDV RNA. At 24 weeks CBC, liver function tests, quantitative HBsAg were performed, and at 48 and 72 weeks CBC, biochemical tests, HDV RNA, HBV DNA, quantitative HBsAg.

Quantitative HBV DNA was detected by using the Real Time PCR (detection limit of 5 IU/ml), anti-HDV antibodies through the method ETI-AB-DELTA-2 (Diasorin), HDV RNA by Real Time- PCR (limit of detection 500 IU/ml). The flare was defined as an increase of aminotransferase levels of 3 times in comparison with the value from the onset of treatment (6).

Sustained virological response (SVR) was defined as undetectable HDV RNA at 48 and 72 weeks. The biochemical response is represented by the normalization ALT at the end of treatment. Non-responders were defined as still having detectable HDV-RNA viral load at the end of treatment.

The fibrosis and necro-inflammatory activity were evaluated by liver biopsy (METAVIR score) or Fibrotest, performed at baseline and at the end of the treatment. An improved histological aspect was considered to be the regression by at least 1 point in the fibrosis score and 2 points in the necro-inflammatory activity for the two determinations. The adverse reactions to treatment were also recorded.

Statistical analysis: the continuous variables such as age, the aminotransferasis, the viremia, platelet counts were expressed as mean value +/- SD (standard deviation).

Categorical variables such as gender, environment, response to treatment, stage of fibrosis were expressed as a percentage (and no. of Patients). Comparisons were made using Fisher's exact t-test, the Pearson correlation coefficient and Anova method (unidirectional analysis of variant), through which the predictive response factors were calculated. Differences were considered statistically significant at a p value <0.05. All data were processed using *SPSS 13.0* statistical analysis program.

RESULTS

50 patients were included in the study, 39 (78%) patients with chronic hepatitis and 11(22%) patients with liver cirrhosis (tab. I).

TABLE I

Baseline characteristics of patients

Characteristics	Chronic hepatitis (39p)	Cirrhosis (11p)	p
Age at onset (years)	41.72+/-12.61	49.36+/-10.03	0.0710
Sex	20F/19M	3F/8M	0.1430
Environment	6R/33U	0R/11U	0.2050
AST at onset (UI/l)	77.44+/-29.45	99.45+/-35.78	0.0420
ALT at onset (UI/l)	97.23+/-47.43	126.55+/-37.07	0.0650
Bil T at onset (mg/dl)	0.77+/-0.22	0.97+/-0.19	0.0110
Albumin (mg/dl)	4.52+/-0.45	3.79+/-0.68	0.0000
INR	0.98+/-0.167(1-1)	1.1+/-0.21 (1-2)	0.0600
Leukocytes (/mm3)	6471.03+/-1735.4	4940+/-2116.7	0.0170
Hb (g/dl)	13.82+/-1.35	13.33+/-1.21	0.2790
Platelets ($X10^{3/mm3}$)	192.667+/-52.226	103.091+/-13.397	0.0000
HBsAg	3598.87+/-2661.25	5227.27+/-2446.26	0.0750
HBsAg ($X10^{6}$)	2.41+/-14.75	0.021+/-0.067	0.5960
HDV RNA ($X10^{6}$)	12.66+/-34.083	8.19+/-9.92	0.6710
HBeAg (+) / HBeAg (-)	2p/37p	0p/11p	0.6050
HBeAb (+) / HBeAb (-)	34p/5p	10p/1p	0.6040
AcHBc (+) / AcHBc (-)	38p/1p	11p/0p	0.7800

SVR was recorded in 12 patients (24%), 11 patients with chronic hepatitis and 1 patient with liver cirrhosis, and biochemical response in 28 patients (56%): 25 patients with chronic hepatitis and 3 patients with liver cirrhosis. Among patients with SVR, 3 were pretreated with standard IFN, the remaining 9 patients were naive.

Alanine amino transferase (ALT) was normal in 28 patients at week 48, and in 29 patients at week 72 (fig.1).

At end of treatment (EOT) 20 patients had undetectable HDV RNA viremia. Only 12 of them maintain the same status of HDV RNA. For 8 EOT patients the viremia becomes detectable at 72 weeks. 30 patients (60%) were considered non-responders, 23 with chronic hepatitis and 7 patients with liver cirrhosis (fig.2).

The clearance of HBsAg at 48 weeks of treatment was observed in 1 patient. At 72 weeks from the start of treatment the HBsAg was negative in 12 patients (tab. II). Patients who presented the negativation of the HBsAg were compared with those who did not show the negativation, and it

was found that HBsAg negativation is not correlated with young age 44.42+/-13.44 (p=0.749), sex (F/M 7p/5p) (p=0.257), progressive form of liver disease – chronic hepatitis/cirrhosis (11 p/1p) (p=0.184). HBsAg clearance was associated with decreased ALT 30.05+/-7.052 (p=0.002) and low-grade fibrosis (p=0.048).

HBs seroconversion, with the appearance of anti HBs antibodies was recorded in 5 patients at 48 weeks of treatment and in 17 patients at week 72.

The reduction of the HBsAg level may be a prognostic factor of response to treatment, because HDV requires the presence of HBsAg as an envelope (7).

At baseline the HBV DNA viral load was undetectable in 20 patients, knowing that HBV replication is inhibited by the presence of HDV virus that is dominant. Reactivation of HBV under treatment was recorded in 2 patients from those with SVR.

A liver biopsy was performed for 32 patients, and 18 were evaluated by Fibrotest. The same evaluation by liver biopsy or Fibrotest was performed at the end of treatment. Histological improvement was recorded in 26 patients (52%). No patient recorded a deterioration of the histological aspect.

Predictors for the onset of the response (tab. III): the degree of fibrosis (the lower the degree of fibrosis, the higher is the probability of response) p=001, age of patients at the beginning of the treatment p=0.007, ALT and AST at the onset of treatment p=0.017 vs p=0.030, total bilirubin p=0.005, albumin p=0.000, INR p=0.031, HBsAg at start p=0.000.

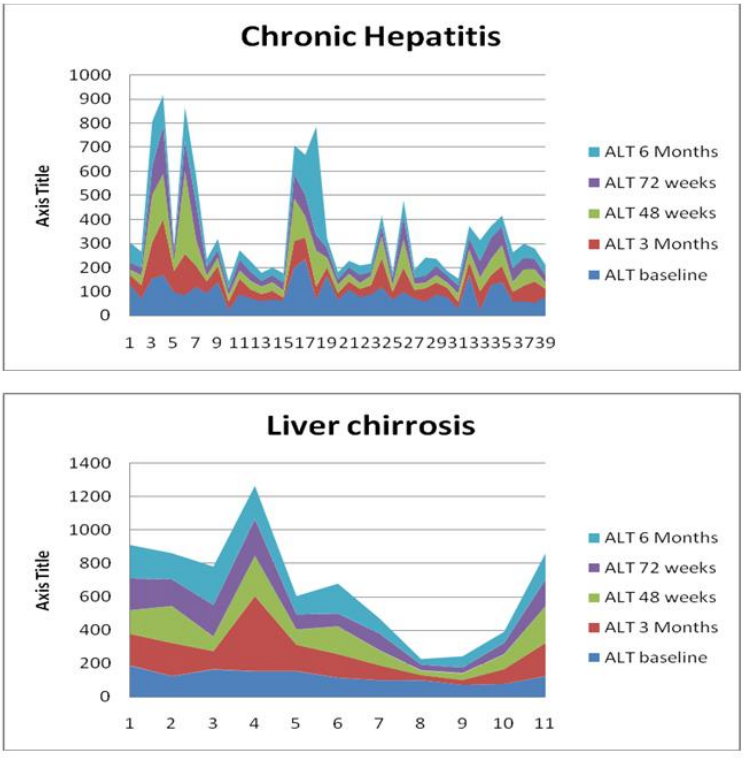

Fig. 1. Evolution of ALT in patients with chronic hepatitis and cirrhosis

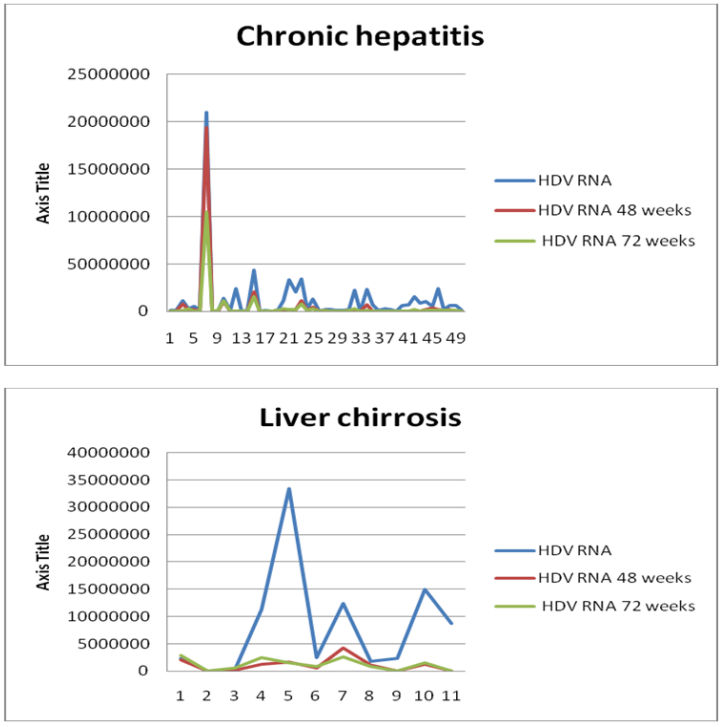

Fig. 2. Evolution of HDV RNA in chronic hepatitis and cirrhosis

TABLE II

Evolution of Ag HBs

	HBsAg at start	**HBsAg at 3 months**	**HBsAg 48 weeks**	**HBsAg 72 weeks**
Mean	3957.12	2251.28	1724.82	1573.16
Std.Deviation	2679.171	2357.786	2072.711	2068.699
Minimum	100	50	0	0
Maximum	9000	8000	7006	7006

The treatment response does not correlate with: sex (p=0.800), HBeAg (p=0.442), baseline viraemia: HBV DNA (p=0.270), HDV RNA (p=0.227).

Although patients with liver cirrhosis were included, tolerability was good (tab. IV).

Thrombocytopenia was more common in patients with cirrhosis: 10% versus 2% in chronic hepatitis (p=0.001); it was not symptomatic and no hemorrhaging manifestations or bleeding was recorded.

Hepatic decompensation occurred in 1 patient (2%): jaundice syndrome (bil T = 3 mg/dl) in week 40 when the treatment was discontinued.

In one of the non-responders, a severe hepatic cytolysis flare was recorded AT x 5 N (2%), the deterioration of the general status caused the discontinuation of treatment at week 26. The only cirrhotic patient who recorded SVR, presented elevated aminotransferases over the entire course of the treatment, but remained asymptomatic.

TABLE III

Evolution of treatment response

Results	Chronic hepatitis	Liver cirrhosis	p
HDV RNA negative at 48 weeks	18p/39p(46.15%)	2p/11p(18.18%)	0.090
HDV RNA negative at 72 weeks	12p/39p(30.8%)	1p/11p(9.1%)	0.144
Normal ALT at 48 weeks	24p/39p(61.5%)	2p/11p(18.18%)	0.013
Normal ALT at 72 weeks	24p/39p(61.5%)	2p/11p(18.18%)	0.013
Normal ALT and HDV RNA negative at 72 weeks	11p/24p(45.8%)	0p/2p(0%)	0.323
HBsAg at 3 months	1954.21+/-2295.19	3304.55+/-2378.49	0.094
AST at 3 months	60.21+/-32.418	119.73+/-101.17	0.002
ALT at 3 months	64.49+/-43.82	153.27+/-115.75	0.000
HBV DNA 48 weeks	$0.032*10^6$+/-$0.200*10^6$	31.36+/-74.36	0.600
HDV RNA 48 weeks ($X10^6$)	6.75+/-30.94	1.11+/-1.25	0.551
HBsAg 48 weeks	1227.82+/-1522.72	3486.91+/-2803.79	0.001
AST 48 weeks	55.23+/-45.49	103.82+/-60.81	0.006
ALT 48 weeks	65.82+/-66.47	127.82+/-74.35	0.011
HBV DNA 72 weeks ($X10^6$)	0.018+/-0.075	0.012+/-0.040	0.806
HDV RNA 72 weeks ($X10^6$)	3.938+/-16.916	1.175+/-1.079	0.593
HBsAg 72 weeks	931.51+/-1440.43	3848.09+/-2405.56	0.000
AST 72 weeks	46.46+/-26.73	90.45+/-46.56	0.000
ALT 72 weeks	56.1+/-39.94	120.09+/-66.09	0.000
AST 6 months	58.67+/-43.965	99.27+/-41.988	0.009
ALT 6 months	69.87+/-74.46	135+/-65.2	0.012

TABLE IV

Treatment side effects

Side effects	Total value	Chronic Hepatitis	Liver cirrhosis	p
Physical asthenia	46% (23/50)	36%(18/50)	10%(5/50)	0.62
Arthralgia	12% (6/50)	10%(5/50)	2%(1/50)	0.604
Weight loss	30% (15/50)	20%(10/50)	10%(5/50)	0.184
Myalgia	16% (8/50)	14%(7/50)	2%(1/50)	0.43
Nervousness	6% (3/50)	4%(2/50)	2%(1/50)	0.534
Thrombocytopenia	12% (6/50)	2%(1/50)	10%(5/50)	0.001
Anemia	2%(1/50)	2%(1/50)	0	0.78
Leukopenia	6%(3/50)	4%(2/50)	2%(1/50)	0.534
Jaundice	2%(1/50)	0	2%(1/50)	0.22
Insomnia	6%(3/50)	6%(3/50)	0	0.466
Depression	8%(4/50)	8%(4/50)	0	0.357
Alopecia	2%(1/50)	2%(1/50)	0	0.78
Loss of appetite	12%(6/50)	8%(4/50)	4%(2/50)	0.396
Fever	12%(6/50)	12%(6/50)	0	0.205
Cytolysis	20%(10/50)	8%(4/50)	12%(6/50)	0.004
Nausea	6%(3/50)	2%(1/50)	4%(2/50)	0.118
No adverse effects	24%(12/50)	20%(10/50)	4%(2/50)	0.472

Peg IFN dose reductions due to leukopenia was necessary in 3 patients.

Under treatment HBsAg, HDV RNA and HBV DNA have the same trend (fig. 3).

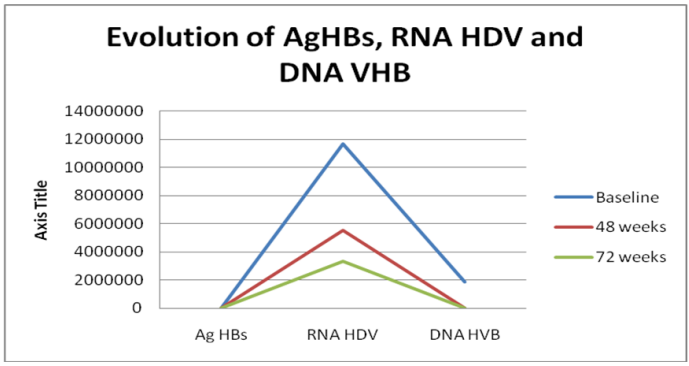

Fig. 3. Evolution of AgHBs, HDV RNA and HBV DNA

DISCUSSION

The Peginterferon treatment resulted in a important reduction of the HDV-RNA at the end of the 48 weeks of treatment, both in patients with hepatitis and with liver cirrhosis, but without statistical significance.

Similar studies have reported values of SVR in chronic HDV infection between 17 and 43%. Niro (37%) (8), Wedemeyer (28%) (9). Erhardt reports a biochemical response in 3 patients (25%) and SVR in 2 patients (17%) (10). Castelnau, in his study conducted on 12 patients, obtains a biochemical response in 8 patients (57%), EOT in 8 patients (57%) and SVR in 6 patients (43%) (11). These results with such different values are probably due to the fact that the studies were conducted on small groups of patients. However, all of them prove the superiority of the Peginterferon treatment versus the standard IFN.

During treatment, ALT levels remain high in many of the patients, especially those with SVR, but there are patients with normal ALT that have not managed to turn their HDV RNA negative. No evidence of a parallel decrease of aminotransferases and HDV RNA was emphasized, so their determination is not of accuracy in the monitoring of the treatment effectiveness.

Although there are studies that show that in the HDV infection as well, HBsAg levels correlate with HDV viremia and can be used as a surrogate marker in monitoring the treatment with PegIFN, in our study we found only the same trend of evolution (12).

In patients with a slow response, which significantly reduce their viremia, but without managing to turn it negative, we wonder if they would benefit from increasing the treatment period beyond 48 weeks. However, there were authors that showed that a 2-year period, is not superior to a 1 year one (13).

As in other studies, the response to treatment was correlated with patient age, low grade fibrosis, the HBsAg and aminotransferases values at the onset of treatment (14, 15). No apparent correlation between the treatment response and HDV viremia was observed, as in other studies (16, 17).

CONCLUSIONS

The treatment with Peg IFNα 2 for a period of 48 weeks is effective. Results, although encouraging, are not maintained over time, at 72 weeks many patients relapse (18).

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