Cumhuriyet Tıp Derg 2011; 33: 42-47
Cumhuriyet Med J 2011; 33: 42-47

Original research-Orijinal araştırma

Single center experience related to chronic hepatitis with hepatitis B and D virus infections

Hepatit B virüsü ve hepatit D virüsü ile enfekte kronik hepatit ile ilişkili tek merkez deneyimi

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Abstract

Aim. To present follow-up results of our chronic hepatitis patients infected with HDV treated with subcutaneous interferon (IFN). **Method.** A total of 24 patients, 21 males and 3 females with HBsAg (+), AntiHBc IgM (-), antibody against hepatitis D virus (anti HDV) and/or HDV RNA (+) and with above normal values for serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), who had no contraindications for treatment and had suitable histological activity index (HAI) and fibrosis scores in their liver biopsies were enrolled. Patients treated with three doses of 9-10 MU subcutaneous IFN per week. Serum aminotransferases, HBsAg, antibody against HbsAg (anti HBs), hepatitis B e antigen (HBeAg), antibody against HBeAg (anti HBe), HBV DNA, anti HDV and/or HDV RNA levels were determined before, during and after treatment. **Results.** Nine patients (37.5%) stopped treatment in an early phase. In 3 patients (12.5%), treatment was discontinued due to severe side effects. In the post-treatment period, HBV DNA was negative in all patients. In 4 patients who completed 12-month treatment (33.3%), ALT levels decreased to normal values in the 3rd month and this level was sustained during follow-up of 24 months; in one patient, ALT levels mildly increased in the 6th and 12th months and decrease to normal values were observed in the following visits. **Conclusions.** High dose interferon, a proinflammatory cytokine with antiviral efficacy and biological activity spectrum, seems as an effective agent in treatment of chronic hepatitis D. In addition, use of pegylated IFNs with higher and sustained serum levels may be more promising as compared to classical IFN treatment.

Keywords: Hepatitis delta virus, chronic active hepatitis, interferon alpha, HBsAG, antiHBs

Özet

Amaç. HDV ile enfektia kronik hepatit hastalarımızın cilt altı interferon tedavisi sonrası takip sonuçlarını sunmak. **Yöntem.** Toplam 24 hastanın (21 Erkek, 3 Kadın) HBsAg (+), AntiHBc IgM (-), hepatit D virüsüne karşı antikor (anti HDV) ve/veya HDV RNA (+) ve karaciğer transaminazları normalden üst seviyedeydi. Bu hastaların tedavi için kontraendikasyonları yoktu hastaların uygun histolojik aktivite endeksleri ve karaciğer biyopsilerinde fibrozis skorları kaydedildi. Hastalar haftada 3 doz 9-10 MU cilt altı interferon ile tedavi edildi. Serumaminotransferzları HBsAg, anti HBs, HBeAg, anti HBeAg, HBV DNA, anti HDV ve/veya HDV RNA seviyeleri tedaviden önce tedavi esnasında ve sonrasında belirlendi. **Bulgular.** Dokuz hasta (%37,5) tedaviyi erkan safhada durdurdu. Üç hasta (%12,5) tedavi ciddi yan etkilerden dolayı bırakıldı. Tedavi sonrası dönemde HBV DNA'sı tüm hastalarda negatifdi. Oniki aylık tedaviyi tamamlayan 4 hastada (%33,3) ALT seviyeleri 3. ayda normal değerlere düştü ve 24 aylık takip süresince bu seviyeyi korudu; bir hastadan ALT seviyeleri hafifce arttı 6. ve 12. aylarında hafifce yükseldi sonrası kontrollerinde normal seviyelerine düştüğü görüldü. **Sonuç.** Anti viral etkinliği ve biyolojik aktivite spektrumu olan proinflamatuvar sitokin olan yüksek doz olan interferonun kronik hepaptit D'nin tedavisinde etkin bir ajan olduğu görülmektedir. İlave olarak,

yüksek ve sabit serum seviyelerinde polietilen glikol ile kaplanmış interferonun kullanımının klasik interferon tedavisi ile kıyaslandığında daha ümit vericidir.

Anahtar sözcükler: Hepatit delta virüsü, kronik aktif hepatit, interferon alfa, HBsAg, antiHBs

Geliş tarihi/Received: November 08, 2009; **Kabul tarihi/Accepted:** February 18, 2010

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This study was presented as a poster in 21th National Congress of Gastroenterology in Antalya.

Introduction

Among chronic viral hepatitis cases due to hepatotropic viruses, chronic delta hepatitis is the most rarely seen infection but it has the most severe prognosis due to its consequences. Hepatitis delta virus (HDV) is a defective pathogen and it needs hepatitis B virus (HBV) to induce infection. Among approximately 300 million individuals who are hepatitis B surface antigen (HBsAg) carriers, less than 5% (around 10-15 million individuals) are predicted to be infected with HDV. In 70% of patients with chronic hepatitis D infection, cirrhosis develops. Similarly in our country, delta hepatitis maintains its importance as a critical health issue. HDV may lead to super infection by presenting as a co-infection with HBV or by subsequently superimposing on patients with HBV. While fulminant prognosis is more likely in co-infection, chronicity and cirrhosis is more frequently seen in super infection [1-3].

Treatment of delta hepatitis is problematic and data related to treatment is scarce. Treatment with low dose and/or short term interferon is less successful with transient beneficial effects and relapse is frequently seen [4]. Data on treatment with nucleoside analogues and immune modulators are not sufficient. Experience on combined therapy is also scarce [3, 5]. Still, currently the only agent effective in treatment of chronic hepatitis due to HDV is interferon alpha. Most of the trials are focusing on reducing treatment duration and on importance of dose, dosing frequency and duration of therapy in interferon treatment. High dose and long term treatment protocols may be implemented in order to increase clinical efficacy and to prevent relapses [6].

In this study, we aimed to present findings of follow-up of our chronic hepatitis patients infected with HDV, who were treated with three doses of 9-10 million units (MU) subcutaneous interferon (IFN) per week for a one-year duration.

Material and method

Chronic hepatitis patients followed up and treated for HBV and HDV infections in the Hepatology Department of Turkey High Specialty Education and Research Hospital between 1999-2004 were enrolled in this trial. Files of these patients were evaluated retrospectively. A total of 24 patients, 21 males and 3 females with HBsAg (+), AntiHBc IgM (-), antibody against hepatitis D virus (anti HDV) and/or HDV RNA (+) and with above normal values for serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), who had no contraindications for treatment and had suitable histological activity index (HAI) and fibrosis scores in their liver biopsies were enrolled. In these patients, a treatment with three doses of 9-10 MU subcutaneous IFN treatment per week was initiated. Serum aminotransferases, HBsAg, antibody against HbsAg (anti HBs), hepatitis B e antigen (HBeAg), antibody against HBeAg (anti HBe), HBV DNA, anti HDV and/or HDV RNA levels were determined before, during and after treatment.

Follow-up was maintained after treatment was pursued for 12 months. All examinations were carried in biochemistry, hematology and microbiology laboratories of our hospital. Staging of HAI and fibrosis was performed according to Knodell scoring.

A decrease in serum ALT level to normal was regarded as complete biochemical response; decrease when compared to initial values was accepted as partial response; loss of detectable HDV RNA in serum was regarded as complete virological response and a decrease when compared to basal values were accepted as partial response. HBV DNA was not used as a response to treatment. Complete sustained response was defined as HBsAg seroconversion.

Results

A total of 24 patients, 21 males (87.5%) and 3 females (12.5%) were enrolled. Mean age was 38.5±9.7. In association with transmission of infection, no history of intravenous drug use was present in any of the patients. On the other hand, a history of sexual transmission in 5 patients, surgical transmission in 7 patients, transmission through family in 9 patients and transmission due to other causes were present. Nine patients (37.5%) stopped treatment in an early phase. In 3 patients (12.5%), treatment was discontinued due to severe side effects (leucopenia in one patient, thrombocytopenia in one patient, and depression and severe asthenia in the other patient). Remaining 12 patients (50%), 10 males and 2 females, completed treatment of 12-months.

Initial characteristics of patients who completed 12-month treatment are shown in Table 1; pre-treatment and up to 24 month values of ALT are given in Table 2. Initially, serum HBsAg was positive in all patients while HBV DNA was positive in 3 patients. HBeAg was positive in only one patient and this patient had a negative serum HBV DNA; this condition was sustained during post-treatment period.

Table 1. Basal characteristics of our patients

Patient	Gender	HBeAg	AntiHBe	HBV DNA	Anti HDV	ALT	HAI	Stage
1	Female	-	+	-	+	62	11	0
2	Male	-	+	+	+	82	8	1
3	Male	-	+	-	+	114	6	1
4	Male	-	+	-	+	66	7	0
5	Male	-	+	-	+	184	7	0
6	Female	-	+	+	+	136	14	3
7	Male	-	+	-	+	67	5	0
8	Male	+	-	-	+	74	10	1
9	Male	-	+	-	+	151	15	3
10	Male	-	+	-	+	44	10	0
11	Male	-	+	-	+	187	11	2
12	Male	-	+	+	+	480	13	3

HBeAg:hepatitis B e antigen; anti-HBe: antibody against HBeAg; HBV DNA: hepatitis B virus DNA; Anti-HDV: antibody against hepatitis D virus; ALT: alanine aminotransferase; HAI: histological activity

In the remaining 11 patients, anti HBe was positive. Apart from one patient, transaminase levels were increased in all patients up to 5-times of upper limit of normal values; in one patient, increase was around 12-times of normal.

In the post-treatment period, HBV DNA was negative in all patients. In the patient with initial HBeAg positivity and negative HBV DNA and anti HBeAg values, these levels were sustained after treatment. In one male patient with negative HBeAg and HBV DNA and positive anti HBe (8.3% of treated patients), HBsAg negativity, anti HBs positivity and antiHDV negativity were observed. HAI in this patient was 7 and stage of fibrosis was 0.

Table 2. Pre-treatment and up to 24 months values of alanine aminotransferase (ALT) in our patients

Patient	ALT 0	ALT 3	ALT 6	ALT 12	ALT 18	ALT 24
1	62	31	44	66	35	32
2	82	59	38	38	60	-
3	114	75	102	111	116	154
4	66	21	30	11	17	31
5	184	36	39	30	30	17
6	136	78	111	19	20	24
7	67	37	27	24	20	11
8	74	100	124	76	89	76
9	151	78	124	86	189	142
10	44	60	122	53	48	48
11	187	98	146	51	56	47
12	480	46	64	59	60	70

ALT: alanine aminotransferase

In 4 patients who completed 12-month treatment (33.3%), ALT levels decreased to normal values in the 3rd month and this level was sustained during follow-up of 24 months; in one patient, ALT levels mildly increased in the 6th and 12th months and decrease to normal values were observed in the following visits. In a patient with positive HBV DNA and positive HBe, ALT was within normal values throughout treatment and was increased in the post-treatment phase; in the remaining 6 patients (50%), ALT levels was high at all visits but in 3 of these patients, there was a decrease when compared to basal levels. In conclusion, in 5 patients who completed the 12-month treatment period (41.7%), there was a complete sustained biochemical response; in 3 patients (25%), partial biochemical response was found and in 4 patients (33%), there was no biochemical response.

In one patient who had negative HBV DNA, positive anti HBe, HAI:13 and fibrosis stage:3 and also completed his 12 months of treatment and in another patient who was lost to follow-up with initial positive HBV DNA and anti HBe values, hepatoma developed. Both patients were males.

Discussion

Chronic delta hepatitis is an uncommon form of liver disease which rarely show spontaneous healing. In 70% of these patients, cirrhosis develops and this rate is much higher than in patients with chronic hepatitis B and C [1, 3]. An effective treatment is needed for chronic delta hepatitis, which carries a high risk of liver cirrhosis and hepatoma.IFN treatment, which has antiviral, immunomodulating and antiproliferative effects, decreases serum aminotransferase levels and improves liver histology. Decrease in aminotransferase levels in the course of disease is seen after the first months of treatment. In the present trial, serum transaminase levels were observed to be decreased during 3rd month in all patients. In patients with no biochemical response to treatment, serum aminotransferase levels were seen to be decreased in follow-up visits when compared to initial values. Even though it was declared that serum aminotransferase levels increase after discontinuation of in the responding patients [7], our results indicate that in patients with biochemical response in 3rd month, this response is sustained even at 24 months. In one of our patients, serum aminotransaminase values decreased to normal in the 6th month but increased again after cessation of therapy though the values were lower when compared to initial levels. In one patient, enzyme levels were observed to be high throughout the treatment period but decreased to normal levels after treatment was stopped. Decrease in serum aminotransferases in high dose interferon treatment is more prominent when compared to low doses or placebo [1]. Moreover, in a trial conducted by Rosina et al. [8], decrease in transaminases was observed after a 4-month IFN treatment with 5 million units three times per week while enzyme levels increased again during

treatment with 3 million units three times per week. In terms of distribution of delta hepatitis and expression of disease, presence of HBsAg is more important than HBV replication. In all patients with delta hepatitis, HbsAg is positive in serum but in most of these patients, active HBV replication indicators like HBeAg and HBV-DNA are usually negative [5, 9]. Similarly in our patients, HBeAg was positive in only one patient and negative in the remaining patients. HBV-DNA was negative in this HBeAg(+) patient. Rarely, post-treatment levels of HBeAg, HBV-DNA, anti HDV IgM and HDV-RNA are determined as negative. Loss of HDV-RNA from serum is not an indicator of sustained response and in most patients whose HDV-RNA values returned to negative, relapse is observed. Farci et al. [1] treated patients with high dose interferon (9 MU/3 times per week) for 48 weeks and observed complete virological response in most patients; besides, relapse was seen frequently. On the other hand, complete sustained response is seen in patients with HBsAg seroconversion, though it's not readily achievable [5]. This indicates a complete response to treatment and no risk of relapse. We determined this in one of our cases. In a 20 year-old male patient with HBV-DNA (-), anti HBeAg (+), HAI: 7 and a fibrosis stage of 0, we observed HBsAg and anti HDV negativity after treatment. Control HBV-DNA was also negative in this patient. Since HDV may suppress HBV replication during the course of infection, this condition was not associated with loss of HBsAg and HBV-DNA. Furthermore, anti HBs positivity developed in this patient. Lau et al. [10] observed HBsAg seroconversion in 4 of 6 patients who were treated with high dose IFN treatment. Battegay et al. [11] also observed this seroconversion in three of 17 patients with HDV who were treated with 5 million units/day. Seroconversion was not seen in low dose interferon treatments [4]. Data indicate that HBsAg seroconversion is rather seen in patients treated with high dose interferon. This suggests that use of pegylated IFNs with higher and sustained serum levels is more appropriate. This is supported by the fact that following development of pegylated IFNs, better results are reported both in naive patients and in patients who did not respond to standard IFN treatment [12, 13]. In Turkey, Ormeci et al. [7] observed HBsAg seroconversion in two of 12 patients in their trial with pegylated IFN.

In which patients, loss of HBsAg and sustained response is observed? "Early treatment, histological status of liver, factors related to host and factors associated with HDV and HBV" may be the answers to this question. Further trials are needed to confirm these statements. Besides, it will be possible to make more accurate decisions if late responders are determined based on HDV RNA [14].We did not perform post-treatment control liver biopsies. The reasoning for this approach was that in previous trials, it was shown that decrease or normalization in liver enzymes leads to decrease or loss of HDV-RNA levels in most cases and may impose positive effects on liver histology. Besides, HDV antigen may not be detectable in liver tissue while HDV RNA is still detectable in plasma [3, 7, 15]. We believe that it's not cost-effective since it does not impose an additional benefit.Treatment of chronic delta hepatitis is one of the most complicated issues in hepatology and more effective agents are needed in treatment of chronic HDV. For this purpose other antiviral agents (like corticosteroids, adenine arabinosid, azathioprine, levamisol, ribavarin, lamivudine, famciclovir) were used but results were not successful [14, 5]. Currently, in chronic HDV infection, both in naive patients and in patients not responsive to conventional IFN treatment, first treatment option and the single most effective agent is pegylated IFN [14].

In conclusion, high dose interferon, a proinflammatory cytokine with antiviral efficacy and biological activity spectrum, seems as an effective agent in treatment of chronic hepatitis D. In addition, use of pegylated IFNs with higher and sustained serum levels may be more promising as compared to classical IFN treatment.

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