ORIGINAL ARTICLE

# TREATMENT OUTCOME IN PATIENTS OF HEPATITIS B WITH HEPATITIS D: EXPERIENCE OF 4 YEARS AT A TERTIARY CARE CENTRE IN PAKISTAN

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## ABSTRACT

**Objective:** To determine HBV suppression in patients with dual HBV and HDV infection after 48 weeks with 10.0 MIU of interferon-a 2b.

**Design:** Quasi experimental study.

**Place and Duration of Study:** Civil Hospital, Karachi and Lyari General Hospital, Karachi, from July 2003 to June 2005.

**Patients and Methods:** All HBsAg positive patients were screened for anti-HDV, all positives were included. Baseline investigations, liver chemistries and HBsAg; HBeAg; anti-HBcore IgM; HBV DNA quantitative PCR were done. Patients with hepatocellular carcinoma and decompensated cirrhosis were excluded. Patients were treated with Interferon-a 10.0 MIU sc t.i.w. for 48 weeks. HBeAg and quantitative HBV DNA was done at week 0, 24 and 48 while CBC and SGPT were done monthly. HBV suppression was defined as levels <400 copies/ml.

**Results:** Fifty-two patients were selected for intervention, including 34 males and 18 females. At the end of therapy after 48 weeks, HBV DNA suppression was achieved in 51.9% and HBeAg became undetectable in 53.8% of patients. Twenty -one patients with HBV suppression still had raised SGPT.

**Conclusion:** HDV should be screened in all patients eligible for HBV treatment.

**KEY WORDS:** *HDV. HBV. Chronic hepatitis. Interferon. Hepatitis B. Hepatitis delta. Hepatitis D.*

## INTRODUCTION

Hepatitis B (HBV) is one of the most common infections worldwide with the prevalence of about 2 billion.[1] Cirrhosis and liver failure of hepatocellular carcinoma (HCC) develop in 15-40% patients of HBV.[2] Over a million die annually due to HBV related complications.[3, 4] Hepatitis D (HDV) is an incomplete virus, which requires HBV for its assembly and transmission.[5] It was first described in Italy in 1977 and is a small 1.7 Kb RNA virus.[6] It employs a unique self-cleaving catalytic RNA motif, the HDV ribozyme, during double-rolling circle replication that is peculiar to it.[7] Infection with HDV causes most severe type of chronic hepatitis with high and rapid rate of progression to cirrhosis.[8] Neither lamivudine nor ribavirin, acyclovir, or famciclovir are effective at controlling HDV replication.[9-11] The only approved drug interferon-a in higher doses has also shown limited response.[12]

Reports of HDV prevalence varies from 6.1% to 28.0% from different parts of the world.[13-16] The reported prevalence is 26.8% in patients of HBV at our centre.[17] There is no report of treatment outcome of HBV with HDV from Pakistan. An earlier report of HBV treatment from Pakistan did not screen patients for HDV.[18] The aim of this study was to determine the effect of screening and treatment of HBV with HDV.

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## PATIENTS AND METHODS

All HBsAg positive patients presenting at Civil Hospital and Lyari General Hospital, Karachi, during the period from July 2003 to June 2005 were screened for anti-HDV. Informed consent was taken from all patients. Patients with hepatocellular carcinoma (HCC), having decompensated cirrhosis or having hypersensitivity to the drugs used were excluded. All selected patients were subjected to Complete Blood Counts (CBC); HBsAg; HBeAg; anti-HBcore IgM; HBV DNA PCR; anti-HDV; anti-HCV; serum albumin; SGPT; serum bilirubin and ultrasound abdomen. At the time of conduction of this study, facility of HDV RNA PCR was not available in Pakistan.

Only patients who tested positive to anti-HDV were selected. Patients were labeled as decompensated if they had any one of the following: ascities, hepatic encephalopathy or variceal bleed. HBV DNA suppression was defined as viral load of < 400 copies/ml.

Patients who were anit-HBcore IgM negative were started with Inj. Interferon -a 2b 10.0 MIU sc thrice weekly (t.i.w.) for 48 weeks immediately while those who were positive to anti-HBcore IgM were started with same treatment after an observation period of 24 weeks and re-determination of HBeAg and HBV DNA. HBeAg and quantitative HBV DNA was done at week 0, 24 and 48. CBC and SGPT were done monthly. Frequencies of those patients who achieved HBV DNA suppression were calculated. Means of SGPT were compared statistically by Student's 't' test between those who had HBV DNA suppression and those who didn't. Statistical analysis was done by software STATA version 9.2.

# RESULTS

Two hundred and forty-six (246) HBsAg positive patients presenting at our center during the study period were screened for anti-HDV. Sixty-six (66) patients who tested positive to anti-HDV were selected for further workup. Out of these 66 patients, decompensation was present in 14 patients and were excluded. Thus, the results are reported on the remaining 52 patients. These included 34 (65.4%) males (mean age 23.2 ±8.5 years) and 18 (34.6%) females (mean age 24.0 ±10.1 years). Nine (17.3%) patients tested positive to anti-HBcore IgM showing co-infection of HDV with acute HBV (SGPT 1600.0 ±433.0 IU/l) the rest 43 (82.7%) were having HDV super-infection (SGPT 170.4 ±79.9 IU/l).

At the initiation of therapy on week 0, HBV DNA was > 400 copies/ml in 37 (71.2%) and HBeAg was detectable in 26 (50.0%) of patients. Results after 24 weeks of therapy showed suppression of HBV DNA in 20 (38.5%) and clearance of HBeAg in 18 (34.6%) of patients. Four patients were lost to follow-up at this stage. See Table I for details. At the end of therapy after 48 weeks, the total clearance of HBV DNA increased to 27 (51.9%) and that of HBeAg to 28 (53.8%). Four more patients were lost to follow-up during this period raising the total follow-up loss to 8 (15.4%, Table I). Nine patients presented with acute HBV infection as documented by presence of anti-HBcore IgM while 43 patients were having chronic HBV infection.

Treatment of acute HBV+HDV was started after observing them for 6 months but none of them became HBV negative. Among the patients who were having anti-HBcore IgM positive, the HBV DNA became undetectable in 5 (55.6%) and it became undetectable in 22 (51.2%) patients who were negative for anti-HBcore IgM. There was no statistically significant difference in the clearance of HBV DNA by anti-HBcore IgM (p= 0.9). The means of SGPT values at the end of therapy (week 48) were compared statistically by Student's 't' test according to the HBV DNA status and no significant difference was detected. Mean SGPT at week 48 in HBV DNA +ve patients was 57.6 IU/l and those in which it was cleared was 83.3 IU/l (P = 0.2; 95% CI = - 65.8 to 14.4). By recording the values of SGPT at week 48 of more than 40 IU/l into a different variable it was found out 21 (40.4%) patients who cleared the HBV DNA were still having raised SGPT levels.

# DISCUSSION

Hepatitis B is conventionally more commonly treated with oral nucleosides/nucleotides as compared to interferon mostly due to patients and doctors preferences to the oral drugs. In many instances, the HDV status was not being determined due to presumed low prevalence of HDV in our area.[18] There was a previous report documented the frequency of HDV at 26% in patients reporting for treatment at our centre.[17]

Oral nucleosides/nucleotides have failed to show any beneficial effect on HDV so they are not recommended for treating HDV.[19] Long-term studies have confirmed the better responses with high dose of interferon in treating HDV.[20] The patients who have normalization of SGPT levels at the end of therapy and continue to have sustained normal levels thereafter have shown progressive decrease in anti-HDV IgM titers with its ultimate loss and could be used as indicator of clearance of HDV in the absence of availability of HDV RNA PCR.[21] This study had limitation due to non-availability of PCR for HDV RNA during the study period and till the submission of this manuscript to JCPSP, so we were unable to document the HDV RNA clearance. In this study, at the end of 48 weeks of therapy, HBV PCR was undetected in 51.9% of patients and HBeAg became undetected in 53.8%. It was of concern that 40.4% of patients who had undetected HBV DNA at 48 weeks were still having raised SGPT levels. This showed that biochemical response was not achieved in these patients, probably the HDV activity persisted in these patients. This also highlights the importance of availability of HBV RNA PCR testing and limitation. We suspect presence of continued HDV activity in these patients and need HDV RNA PCR for confirmation. With reports that this facility will soon be available in Pakistan, we have continued therapy of these patients beyond 48 weeks and will report on these later as there are reports of resolution of HDV even after 12 years of therapy.[22]

Interferon has been used in different doses and duration with varying results. Rosina et al. reported clearance of HDV RNA in 4/12 (33%) with 5 MIU t.i.w. for 3 months.[23] Farci et al. reported 10/14 (71%) HDV RNA clearance by using 9 MIU t.i.w. for 12 months.[24] Another trial used decreasing dosage schedule by starting with 18 MIU t.i.w. for 6 months followed by 9 MIU for 1 month, 6 MIU for 1 month and finally 3 MIU for 4 months. The results was successful clearance of HDV in 6/12 (50%) patients.[25] Studies with 10 MIU daily and then decreasing the dose to 10 MIU t.i.w. have also been undertaken with variable results.[12]

Recent reports are favoring use of pegylated interferon in HDV with better results[16]. In two recent studies, in using peginterferon 2a and 2b, a virological response of 19% and 17% was achieved after 48 weeks of therapy.[26] Recent discovery of immunogenic epitopes, especially cytotoxic-T-lymphocyte ligands, associated with chronic HDV infection, may be crucial for further development of novel treatments or designs in vaccine for HDV superinfection.[27]

**Table I**: Details of treatment outcome.

| | HBeAg week 0 | | HBV DNA week 0 | | HBeAg week 24 | | HBV DNA week 24 | | HBeAg week 48 | | HBV DNA week 48 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Count | % | Count | % | Count | % | Count | % | Count | % | Count | % |
| Lost to follow-up | - | - | - | - | 4 | 7.7% | 4 | 7.7% | 8 | 15.4% | 8 | 15.4% |
| Positive* | 23 | 44.2% | 37 | 71.2% | 30 | 57.7% | 28 | 53.8% | 16 | 30.8% | 17 | 32.7% |
| Negative † | 29 | 55.8% | 15 | 28.8% | 18 | 34.6% | 20 | 38.5% | 28 | 53.8% | 27 | 51.9% |

* For HBV DNA read > 400 copies/ml; † For HBV DNA read <400 copies/ml.

## CONCLUSION

HDV screening by anti-HDV should be done in all patients of HBV before starting therapy. Till PCR is commercially available, SGPT could be used as a marker of HDV activity in such patients. Compared to chronic hepatitis B or C, HDV treatment requires a higher dosage and a longer duration of treatment, and posttreatment relapses are common. In order to prevent the progression of HDV and its related morbidity and mortality, more effective treatments are the need of time.

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