

ANNALS OF HEPATOLOGY

Volume **4**

Number **1**




January-March **2005**

Artículo:




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Original Article

Combination of Peginterferon α -2b (12 kDa) and Lamivudine in difficult-to-treat chronic hepatitis B- an Indian experience

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Abstract

Introduction: Treatment strategies for chronic hepatitis B (CHB) using either interferon or Lamivudine can achieve sustained response in 30-40 % in HBeAg positive CHB. Retreatment of treatment failure in CHB and treatment of HBeAg negative patients pose major therapeutic challenge. Because of success story of Peginterferon in hepatitis C and some preliminary data in CHB, we undertook this open-labeled prospective study to study the response of Peginterferon α -2b (PegIFN) and Lamivudine combination in patients of CHB. **Materials and methods:** Following 4 groups of patients of CHB with persistently elevated transaminases were treated with Lamivudine 100 mg PO daily and PegIFN 1.5 μ g/kg SC once a week- 1) HBeAg negative treatment naïve patients- for 12 months 2) HBeAg negative patients who were nonresponsive to at least two treatment regimens- for 12 months, 3) HBeAg positive treatment naïve patients- for 6 months 4) HBeAg positive patients who were treatment failure at least with two regimens- for 6 months. Patients were tested for LFT, HBeAg, antiHBe, quantitative HBVDNA (only in HBeAg negative CHB) and liver biopsy when possible at inclusion. During treatment period, LFT was tested at monthly interval and HBeAg, antiHBe and HBVDNA (in HBeAg negative CHB) at 3 monthly intervals. End of treatment response (EOR) was assessed at end of treatment period and sustained response (SR) at 6 months post treatment. Treatment response was defined in HBeAg positive patients with normalization of enzymes and disappearances of HBeAg & in antiHBe positive patients with normalization of enzymes and loss of detectable HBVDNA. **Results:** Total 25 patients with CHB were in-

cluded in this study with mean age of 37.9 ± 4.6 years (range 20-56) and male: female= 11.5:1. 1) In HBeAg negative treatment naïve patients, 4/6 patients achieved EOR (66.6%), whereas in 3/6 patients (50%) had SR. 2) In HBeAg negative treatment failure group, 4/5 patients had EOR (80%) and 3/5 patients achieved SR (60%), of which 1 patient lost HBsAg. 3) In HBeAg positive treatment naïve patients, 4/5 patients achieved EOR (80%) and 3/5 patients obtained SR (60%). One patient in this group lost HBsAg. 4) In HBeAg positive treatment failure group, 5/9 patients achieved EOR (55.5%), whereas 3/9 patients (33.3%) obtained SR. **Conclusion:** Overall, in difficult-to-treat patients (considering groups 1, 2 & 4- total 20 patients) with combination of PegIFN and Lamivudine, EOR was seen in 13 patients (65%), SR was obtained in 9 patients (45%) and loss of HBsAg was seen in 1 patient (5%).

Key words: HBeAg positive hepatitis B infection, HBeAg negative hepatitis B infection, pegylated interferon, combination therapy, treatment failure group.

Introduction

Chronic hepatitis B (CHB) can manifest from asymptomatic infection to cirrhosis and HCC. Almost 15-40% of patients among 350 million patients with CHB worldwide will develop serious sequelae in lifetime.^{1,2} Treatment strategies using either interferon or Lamivudine can achieve sustained response in 30-40%. Retreatment of treatment failure in CHB and treatment of naïve HBeAg negative patients pose major therapeutic challenge. Because of success story of Peginterferon in hepatitis C and some preliminary data in CHB,³ we undertook this single-center open-labeled prospective study to study the response of Peginterferon α -2b (PegIFN) and Lamivudine combination in patients of CHB.

Materials and Methods:

During the study period from January 2001 to October 2003, patients with diagnosis of CHB (HBsAg positive > 6 months with persistent/intermittent elevation of ALT or

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Manuscript received 29 August 2004
and accepted 5 February 2005.

AST over the last 6 months) were included in the study. At baseline, all the patients underwent detailed history taking, clinical examination, review of previous treatment and previous serial investigations, liver function tests (LFT), ultrasonography of abdomen, viral markers like HBeAg, antiHBe, IgM antiHBc, antiHCV, antiHDV and HIV, HBVDNA by b-DNA technique (Versant HBV DNA 1.0 assay, Bayer Corp, NY) with Dynamic range of quantification: 700000-5000000000 genomes equivalents/mL and liver histology whenever permissible.

On the basis of these investigations, they were divided into 4 groups: a) HBeAg negative treatment naïve group: included patients with HBeAg negative, antiHBe positive, HBVDNA positive, elevated ALT and necroinflammatory score > 4. b) HBeAg negative treatment failure group: included patients with HBeAg negative, antiHBe positive, HBVDNA positive, elevated ALT, necroinflammatory score > 4 and lack of response to at least 2 adequate regimens (either Interferon- α 5 MIU SC daily for 12 months or Lamivudine 100 mg PO daily for 24 months or combination of Interferon and Lamivudine for at least 12 months or combination of Interferon and Thymosin- α 1.6 mg SC twice weekly for at least 12 months). c) HBeAg positive treatment naïve patients: included patients with HBeAg positive, antiHBe negative, elevated ALT and necroinflammatory score > 4. d) HBeAg positive treatment failure group: included patients with HBeAg positive, antiHBe negative, elevated ALT, necroinflammatory score > 4 and lack of response to at least 2 adequate regimens (either Interferon- α 5 MIU SC daily for 6 months or Lamivudine 100 mg PO daily for 24 months or combination of Interferon and Lamivudine for at least 12 months or combination of Interferon and Thymosin- α 1.6 mg SC twice weekly for at least 12 months).

Exclusion criteria were: 1. any disease with life expectancy < 1 year, 2. associated HCV/HDV infection or any other coexistent chronic or acute liver disease other than CHB, 3. major depressive or psychiatric illness, 4. immunosuppressive therapy or associated HIV infection or patients with solid-organ transplantation, 5. use of hepatotoxic drugs, herbal medications or steroids in the last 6 months, 6. interferon therapy in the last 6 months or Thymosin therapy in the last 12 months, 7. cytopenias (hemoglobin < 9 gm%, TLC < 3000 cells/cmm and platelet < 90000 cells/cmm), 8. patients with multiple transfusions or IV drug abuse, 9. patients with thyroid disease or alcoholism and 10. previous or present history of decompensated liver disease.

All the 4 groups were treated with Lamivudine 100 mg PO daily and PegIFN 1.5 μ g/kg SC once a week- 1) HBeAg negative treatment naïve group- for 12 months 2) HBeAg negative treatment failure group- for 12 months, 3) HBeAg positive treatment naïve group- for 6 months 4) HBeAg positive treatment failure group- for 6 months.

During treatment period, LFT was tested at monthly interval and HBeAg, antiHBe and HBVDNA (in HBeAg

negative CHB) at 3 monthly intervals. End of treatment response (EOR) was assessed at end of treatment period and sustained response (SR) at 6 months post treatment. Treatment response was defined in HBeAg positive patients with normalization of enzymes and disappearances of HBeAg & in HBeAg negative patients with normalization of enzymes and loss of detectable HBVDNA. At end of the treatment period, all the patients were evaluated for end-of-treatment response and sustained response.

Results

Total 25 patients with CHB were included in this study with mean age of 37.9 ± 4.6 years (range 20-56) and male: female= 11.5:1.

- 1) In HBeAg negative treatment naïve group, out of 6 patients (mean age 41.6 ± 4.4 years, M:F=5:1), at baseline, mean ALT levels were 183.3 ± 50.3 u/L with 2 patients having ALT elevation < 2 x ULN and 2 patients showed evidence of cirrhosis on histology. EOR was seen in 4 patients (66.6%), whereas in 3 patients SR was seen (50%).
- 2) In HBeAg negative treatment failure group, out of 5 patients (mean age 36.4 ± 5.2 years, M:F=5:0), at baseline, mean ALT levels were 274.6 ± 98.2 u/L and none had cirrhosis on the histology. Prior treatment regimens given to the patients were as follows: Interferon monotherapy in 2 patients (40%), Lamivudine monotherapy in 4 patients (80%), combination of Interferon and Lamivudine in 3 patients (60%) and combination of Interferon and Thymosin- α in 2 patients (40%). Sequence and results of previous therapies were as follows: patient 1: Interferon monotherapy (no EOR or SR) followed by Interferon-Thymosin- α combination (no EOR or SR) followed by Lamivudine monotherapy (EOR but no SR); patient 2: Interferon monotherapy (EOR but no SR) followed by Lamivudine monotherapy (EOR but no SR); patient 3: Interferon-Thymosin- α combination (EOR but no SR) followed by Interferon-Lamivudine combination (EOR but no SR) followed by Lamivudine monotherapy (EOR but no SR); patient 4: Interferon-Lamivudine combination (EOR but no SR) followed by Lamivudine monotherapy (EOR but no SR); and patient 5: Interferon-Lamivudine combination (EOR but no SR). Of these 5 patients with PegIFN-Lamivudine combination, EOR was seen in 4 (80%) patients (patient numbers: 2, 3, 4 and 5) and in 3 patients (60%), SR was obtained (patient numbers: 2, 4 and 5). Of which, 1 patient lost HBsAg (patient number: 4).
- 3) In HBeAg positive treatment naïve group, out of 5 patients (mean age 40.6 ± 4.2 years, M:F=4:1), at baseline, mean ALT levels were 170.6 ± 48.6 u/L and none of the patients had cirrhosis on the histology. EOR was

seen in 4 (80%) and SR obtained in 3 patients (60%). One patient in this group lost HBsAg.

- 4) In HBeAg positive treatment failure group, out of 9 patients (mean age 33 ± 4.6 years, M:F=9:0), at baseline, mean ALT levels were $251.6 \pm 1.3.2$ u/L and 4 patients had cirrhosis on the histology. Prior treatment regimens given to the patients were as follows: Interferon monotherapy in 4 patients (44%), Lamivudine monotherapy in 9 patients (100%), combination of Interferon and Lamivudine in 4 patients (44%) and combination of Interferon and Thymosin- α in 3 patients (33%). Sequence and results of previous therapies were as follows: patients 1 and 4: Interferon monotherapy (no EOR or SR) followed by Lamivudine monotherapy (no EOR or SR); patients 2, 5 and 6: Interferon-Lamivudine combination (EOR but no SR) followed by Lamivudine monotherapy (EOR but no SR); patients 7 and 8: Interferon-Thymosin- α combination (EOR but no SR) followed by Lamivudine monotherapy (EOR but no SR); patient 3: Interferon monotherapy (no EOR or SR) followed by Interferon-Lamivudine monotherapy (EOR but no SR) followed by Lamivudine monotherapy (EOR but no SR); and patient 9: Interferon monotherapy (no EOR or SR) followed by Interferon-Thymosin- α combination (EOR but no SR) followed by Lamivudine monotherapy (EOR but no SR). With PegIFN-Lamivudine combination, EOR was achieved in 5 (55.5%) patients (patient numbers: 1, 5, 6, 7 and 9). In 3 patients (33.3%), SR was obtained (patient numbers: 1, 6 and 7).

In all the groups, adverse events reported were fever in 17 (68%), myalgia in 15 (60%), headache in 12 (48%), insomnia in 10 (40%), alopecia in 5 (20%) and depression in 2 (8%) patients. All these adverse events were controlled by simple measures like analgesic-antipyretics and antidepressant drugs. None of the patients had life-threatening major cytopenia or infections. None of the side-effects required discontinuation of the therapy.

Overall, in difficult-to-treat patients (considering groups 1, 2 & 4- total 20 patients) with combination of PegIFN and Lamivudine, EOR was seen in 13 patients (65%), SR was obtained in 9 patients (45%) and loss of HBsAg was seen in 1 patient (5%). Considering all the groups of CHB, EOR was obtained in 17 patients (68%) and SR was obtained in 14 patients (56%).

Discussion

This study on efficacy of PegIFN is the first report from India on the use of a Pegylated interferon in the treatment of CHB. In comparison to conventional interferon, the addition of polyethylene glycol molecule to interferon significantly increases half-life of the molecule and yields more sustained interferon activity, and thus allows more convenient once-a-week admin-

istration schedule. In the recently published study by Cooksley et al, in HBeAg positive treatment naïve patients with therapy of Pegylated interferon α -2a (40 kDa) for 6 months combined sustained response was seen in 24% patients compared to 12% with conventional interferon.³ Treatment with Pegylated interferon achieved higher i.e. 33.3% sustained combined response (vs 25% with interferon) in genotype B and 21.3% combined response (vs 6.3% with interferon) in difficult-to-treat genotype C.³ Sequential therapy with Pegylated interferon and Lamivudine in HBeAg positive chronic hepatitis B achieved 50% sustained virological response as compared to 10% with Lamivudine monotherapy, but had similar biological responses (50% vs 30% respectively).⁴ From India, ours is the first study carried out for role of combination of Pegylated interferon and Lamivudine in treatment failure groups whether HBeAg positive or negative and HBeAg negative CHB patients.

Theoretically rationale of combination therapy is based on following facts: Interferon has mild-to-moderate virus-suppressive activity, but can induce good host immune response; in contrast Lamivudine has excellent virus-suppressive activity, but has no immunomodulatory action. So, it is logical to explore possibility of combination therapy to increase virus-suppression, increase host immune response and decrease emergence of Lamivudine-resistant mutants.⁵

In HBeAg positive treatment naïve patients with raised ALT, response rates with conventional interferon for 4-6 months and Lamivudine for 12 months are 25-40% and 16-18% respectively.^{6,7} In HBeAg negative treatment naïve patients with elevated ALT, EOR response rates with interferon for 12 months and Lamivudine for 12 months are 38-90% and 60-70% respectively which is sustained in 10-47% patients treated with interferon and in less than 10% patients treated with lamivudine.⁸ In treatment failure CHB patients with raised ALT, response rates with repeat prolonged course of interferon or Lamivudine for 12 months or combination therapy with Lamivudine for 2 months followed by interferon for 4 months vary from 12-18%.^{9,10} In our study in these different groups of CHB patients response rates of combination therapy with PegIFN and Lamivudine vary from 55.5-80% (EOR) and 33.3-60% (SR at 6-months). Two patients (8%) lost HBsAg during their follow up period of 6 months in our study. In our study, combination therapy was well tolerated and none of the patients required treatment discontinuation. In previous study by Zonneveld et al, Pegylated interferon had similar safety profile as conventional interferon.¹¹

Despite small study population, our study has obtained encouraging results and a new hope for the difficult-to-treat CHB patients. Further multi-centric randomized controlled studies are required to reproduce the same results.

Acknowledgement:

We thank all the trial participants for their consent and participation in the study. We thank the authorities of the hospital for their kind permission to conduct the study and publish the results. We also thank staff of the Gastroenterology department and laboratory of the hospital.

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