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COMBINATION OF PEGYLATED INTERFERON AND LAMIVUDINE IS SUPERIOR TO LAMIVUDINE MONOTHERAPY IN THE TREATMENT OF CHRONIC HEPATITIS B - A RANDOMIZED TRIAL

J.J.Y. Sung*, H.L.Y. Chan, A.Y. Hui, F.K.L. Chan, A.M.L. Chim, M.L. Wong, N.W.Y. Leung, *Presenting Author
Department Of Medicine & Therapeutics, Chinese University Of Hong Kong, Hong Kong

Background: Previous studies combining interferon with lamivudine failed to prove additional benefit in clearance of HBV infection. We aimed to study the anti-viral effects of pegylated interferon (Peg-IFN) and lamivudine combination. Patients and Methods: Treatment-naïve chronic hepatitis B patients who had positive HBeAg, HBV DNA >1, 000, 000 copies/ml and ALT 1.3-5X upper limit of normal were recruited into an open-labeled, randomized study.

Patients received either combination treatment (Combo group) with Peg-IFN 1.5 mcg/kg for 8 weeks, then Peg-IFN plus lamivudine 100mg daily for 24 weeks followed by lamivudine alone for 28 weeks, or lamivudine monotherapy 100mg daily for 52 weeks (Lam group). End-of-treatment and sustained (24-week post-treatment) virological response (VR, defined as HBeAg seroconversion and undetectable HBV DNA) and biochemical response (BR, defined as normalization of ALT) were analyzed.

Results: The interim results of first 40 patients who finished treatment and follow-up were analyzed. There was no difference in the gender, age and ALT levels between the two groups. The proportion of patients achieving end-of-treatment and sustained VR in Combo group was significantly higher than that of Lam group (75% vs 25%, $p=0.0005$ and 50% vs 10%, $p=0.02$ respectively). There was no significant difference in the end-of-treatment and sustained BR between the Combo and Lam groups (95% vs 70%, $p=0.1$ and 50% vs 30%, $p=0.3$ respectively). Four patients receiving Peg-IFN had premature termination of treatment due to serious adverse events.

Conclusion: Combination of Peg-IFN and lamivudine has superior anti-viral effect to lamivudine monotherapy in the treatment of chronic hepatitis B infection.

CURRENT THERAPEUTIC APPROACHES IN CHILDHOOD CHRONIC HEPATITIS B INFECTION

B. Dikici, ¹F. Ozgenc*, ²A. Kalayci, ³S. Targan, ⁴T. Ozkan, ⁵A. Selimoglu, ⁶T. Doganci, ⁷A. Kansu, ⁸S. Tosun, ⁹N. Arslan, ¹⁰E. Kasirga, ²M. Bosnak, ¹A. Ece, ¹B. Buyukgebiz, ¹⁰S. Aydogdu, ²N. Girgin, ⁸R.V. Yagci, ²*Presenting Author

¹*Pediatrics, Dicle Univ. Medical Faculty, Diyarbakir* ²*Pediatric Gastroenterology, Ege Univ. Medical Faculty, Izmir*, ³*Pediatric Gastroenterology, 19 Mayıs Univ. Medical Faculty, Samsun*, ⁴*Pediatrics, Behcet Uz Hospital, Izmir*, ⁵*Pediatric Gastroenterology,*

Background/aims: To compare efficacy of three different therapy regimens in childhood chronic hepatitis B (CHB) infection. Methods: Children with CHB infection (n: 182) were prospectively evaluated in three random groups. First group (n: 62) of patients received high dose interferon alpha2b (10 MU/ m², 3/week) alone for six months. In the second (n: 60) and third groups (n: 60) INF alpha2b was used for six months (5 MU/m², thrice/weekly) in combination with LAM (4 mg/kg, max 100 mg/d) for 12 months. LAM was started simultaneously with INF in the second while it was started two months prior to INF injections for third group.

Results: Mean initial ALT values of first, second and third groups were 109±93 IU/L, 101±64 and 92±42 IU/L respectively (p>0.05). At the 12th month, ALT values of groups decreased to 55±42 IU/L, 38±41 IU/L and 29±16 IU/L, respectively. Mean ALT value of the first group was significantly different from the second and third groups (p=0.046 and p=0.002, respectively) and was sustained at 18th month. However, these results in second and third groups were similar (p>0.05). DNA clearance was significantly higher in LAM combined groups compared to INF alone (p<0.05) Complete response (normalization of ALT, clearance of DNA, seroconversion of anti-Hbe) was achieved in 33%, 49% 34% of first, second and third group at 18th month, respectively (p>0.05).

Conclusions: Although, ALT normalization and DNA clearance of combination therapies were found better than high dose interferon alone, no significant difference was found in the complete response rates of all three groups.

TREATMENT OF HBEAG-NEGATIVE CHRONIC HEPATITIS B (CHBE-) WITH SEQUENTIAL LAMIVUDINE (LAM) AND INTERFERON-ALFA (IFN) COURSES OF 12-MONTH DURATION AND A 6-MONTH OVERLAP

E.K. Manesis*, G.V. Papatheodoridis, A. Alexopoulou, *Presenting Author
2nd Academic Dept. Of Medicine, Hippokration Hospital, Athens, Greece

Treatment of CHBe- with IFN or LAM monotherapy has been generally inefficient. In this pilot trial, we evaluated the efficacy of a 12-month LAM course, overlapped with a 6-month phase difference, by a 12-month IFNa course in 33 patients with CHBe-. All patients had ALT>1.5xULN, HBV viremia and histological evidence of chronic hepatitis (grade 7.6±2.4, stage 3.4±1.4, 27% compensated cirrhosis). LAM 150mg/daily was given for 12-months and IFN-2b 3MU tiw also for 12-months starting at 6-months of LAM therapy. Patients were followed-up clinically and biochemically every month, while serum HBV-DNA levels were evaluated every 6-months (PCR Monitor, Roche). Todate, 5 (16%) patients have discontinued IFN due to side effects after a median of 3.6 (1.8-7.5) months (4/5 in both biochemical and virological remission), 16 (49%) patients have completed the entire 18-month LAM+IFN course (end-of-therapy, EOT) and 7 of them the 6-month follow-up observation period (end-of-follow-up, EFU). At EOT, biochemical response (ALT<ULN) was observed in 9/16 (69%) and virological response (HBV-DNA<105cp/mL) in 12/16 (75%) patients. At EFU, sustained biochemical remission was observed in 4/7 (57%) and sustained virological remission in 2/7 (29%) patients.

Conclusions: These preliminary results suggest that a 18-month course of sequential LAM and IFN therapy with a 6-month overlap phase may achieve sustained biochemical response in the majority and sustained virological response in approximately 1/3 of patients with CHBe-. Such an efficacy is not attainable by either LAM or IFN monotherapy and, if confirmed by this or subsequent studies, this combination might be an important therapeutic option for HBeAg–negative chronic HBV liver disease.

LONG-TERM EFFECTS OF INTERFERON ALPHA THERAPY IN CHILDREN WITH CHRONIC B HEPATITIS IN OWN OBSERVATIONS

A. Szaflarska-Szczepanik*, A. Chrobot,

*Presenting Author

Clinic Of Pediatrics, Allergology And Gastroenterology, Medical University, Bydgoszcz, Poland

Aim: The study was to estimate the results of interferon alpha treatment (IFN- α) in children with chronic B hepatitis in own long-term observations. Retrospective study included 140 children (99 M, 41 F) aged from 2 to 16 years (mean age 6.62 years) with chronic B hepatitis, who were treated with recombinant interferon alpha in 1994-2000. A course of IFN- α (Intron-A[®] Schering-Plough, Roferon-A[®] F.Hoffmann-La Roche Ltd) was injected as 3 million U or 5 million U subcutaneously, thrice a week for 20 weeks (1.6-6.0 million U/m², mean doses 3.77 million U/m²). Laboratory investigation, including ALT activity and serological HBV markers were measured during the treatment and every 6 months after its completion.

According to the epidemiological analysis a duration of HBV infection ranged from 1 year to 13 years (mean 2.97 year). The route of HBV transmission were nosocomial (62.9%), horizontal (15%) and perinatal (5.7%). Pretreatment serum ALT activity ranged from 15 to 810 U/l (mean activity 122.36 U/l). The most children in the histopathological picture of the liver had mild (48.6%) or moderate inflammation activity (47.9%) without fibrosis (30%) or with trace of fibrosis (53.6%).

The loss of HBeAg and HBsAg was achieved in 6 patients (4.3%). The loss of HBeAg without loss of HBsAg was observed in 81 children (57.9%), mostly during the first year after completion of the IFN- α treatment (71.6%). The biochemical response (ALT normalisation without loss of HBeAg) was achieved in 10 patients (7.1%). There was no response to the IFN- α therapy in 49 patients (35%). The response rate marked by the loss of HBeAg with or without the loss of HBsAg was more often in children with higher (>100 U/l) pretreatment ALT activity ($p < 0.001$). The progression of histopathological changes on liver biopsy was not correlated with the response rate to the IFN- α therapy.

The positive response to IFN- α treatment in children with chronic B hepatitis marked by the loss of HBeAg occurred mostly during the first year after completion of antiviral therapy. In the following years the loss of HBeAg occurred at the rate similar to spontaneous seroconversion. The predictive factor for likelihood of the positive IFN- α response in children with chronic B hepatitis is high pretreatment ALT activity. The progression of histopathological changes of the liver seems to not have a predictive value to positive IFN- α response.

CHRONIC HBV TREATMENT WITH ONE YEAR OF PEGYLATED-INTERFERON ALPHA-2B (PEG-IFN) HAS A COMPARABLE SAFETY PROFILE TO SHORT TERM CONVENTIONAL INTERFERON ALPHA-2B

M. van Zonneveld*, A.B. van Nunen, R.A. de Man, S.W. Schalm, H.L.A. Janssen,

*Presenting Author

Hepatogastroenterology, Erasmus Mc, Rotterdam, Netherlands

Interferon-alpha (IFN) treatment in chronic hepatitis B is associated with clinically relevant adverse effects.

Aim In an international multicenter randomized controlled trial we studied the safety of PEG-IFN in combination with lamivudine. Three-hundred HBeAg-positive patients (ALT > 2xULN) with compensated liver disease were treated with PEG-IFN for 52 weeks, combined with either lamivudine 100mg/day or placebo. The dose of PEG-IFN was 100 μ g once a week and halved after 32 weeks.

Results As yet all patients have been treated for at least 32 weeks and 221 patients have finished treatment. The most frequently encountered side-effects were flu-like symptoms (67%), headache (36%), myalgia (29%), fatigue (26%) and anorexia (25%). No deaths occurred during treatment or follow-up. A total of 24 (8%) serious adverse events were reported, of which 11 were regarded to be probably related to PEG-IFN (psychiatric n=5; neutropenia n=3; hepatitis flare n=2; seizures n=1). In 55 (18%) patients the dose of PEG-IFN was reduced prematurely, in 39 (13%) because of a granulocytopenia. Therapy was discontinued early in 24 (8%) patients. The most frequent reasons for early discontinuation were psychiatric side-effects (depression, psychosis) and flu-like symptoms. The number of side effects and the proportion of patients requiring dose reduction or interruption were similar to 162 historical controls treated with 10 MU t.i.w. of conventional IFN 10MU tiw for 16-32 weeks IFN reduction 14% and IFN interruption 9% (Hepatology 1999;30 238-43).

Conclusion We conclude that in compensated CHB patients prolonged PEG-IFN therapy has a comparable safety profile to short courses of conventional IFN therapy.

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