

virologic rebounds (>1 log increase from nadir by PCR) during ETV therapy were analyzed for ETVr substitutions and decreased susceptibility. In addition, all patients with PCR detectable HBV DNA (limit = 300 copies/mL) at Weeks 48, 96 and 144 or end-of-treatment were sequenced and the phenotypes of any novel emerging substitutions determined. Results: Ninety-one percent (130/143) of HBeAg pos & neg, nucleoside naïve (absence of LVDr substitutions) patients treated with ETV in Yr 3 maintained or achieved PCR undetectability. There were only 3 virologic rebounds in Yr 3. Two of 2 of these rebound patients failed to show evidence of ETVr changes or reduced susceptibility, similar to the 18 virologic rebounds observed during the first 2 years of ETV therapy. The remaining Yr 3 patient did not achieve PCR undetectability on therapy and at Wk 100, received 16 wks of LVD+ETV before switching to 1 mg ETV and subsequently rebounding at Wk 148 with evidence of both LVDr and ETVr substitutions. The pre-existence of these substitutions is under investigation. Ongoing sequencing of available samples from the remaining patients with detectable HBV DNA has not shown any evidence of resistance emergence. In contrast, 41% (28/68) of LVD-refractory ETV-treated patients treated in Yr 3 had undetectable HBV DNA levels. Virologic rebounds were observed in 14 of these 68 patients, with 10 of the 11 rebound patients analyzed having ETVr substitutions. Patients with detectable HBV DNA continue to be analyzed to determine the rate of ETVr emergence in Yr 3. Overall, virologic rebounds due to ETVr were observed in 1%, 9% and 15-19% of LVD refractory patients during Yrs 1, 2 and 3 of ETV therapy, respectively, while 7% of these patients with ETVr changes proceeded to achieve PCR undetectability on continued ETV. Summary: ETV continues to demonstrate a high genetic barrier to resistance amongst nucleoside treatment naïve patients as shown by the Yr 3 results. Among the LVD refractory patients, 41% achieved undetectable HBV DNA levels, while an increasing number of patients experienced virologic rebounds in Yr 3 due to pre-existing or emerging ETVr. The resistance profile over 3 years in nucleoside naïve patients strongly supports the use of ETV as a first line therapy for chronic HBV infection.

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111

A MULTICENTER RANDOMISED STUDY COMPARING THE EFFICACY OF PEGYLATED INTERFERON-ALFA-2A PLUS ADEVOFIR DIPIVOXIL VS. PEGYLATED INTERFERON-ALFA-2A PLUS PLACEBO VS. ADEVOFIR DIPIVOXIL FOR THE TREATMENT OF CHRONIC DELTA HEPATITIS: THE HEP-NET/INTERNATIONAL DELTA HEPATITIS INTERVENTION TRIAL (HID-IT) Cihan Yurdaydin², Heiner Wedemeyer¹, George Dalekos³, Alexander Erhardt⁷, Ya Cakaloglu⁸, Ha Degertekin⁹, Sa. Gurel¹⁰, Stefan Zeuzem⁵, Kalliopi Zachou^{1,3}, Hakan Bozkaya², Hans P. Dienes⁴, Thomas Bock⁶, Michael P. Manns¹, ¹Gastroenterology, Medizinische Hochschule Hannover, Hannover, Germany; ²Ankara University, Ankara, Turkey; ³Larissa University, Larissa, Greece; ⁴University of Cologne, Cologne, Germany; ⁵University of Saarland, Homburg, Germany; ⁶University of Tuebingen, Tuebingen, Germany; ⁷University of Duesseldorf, Duesseldorf, Germany; ⁸Istanbul University, Istanbul, Turkey; ⁹Dicle University School of Medicine, Diyarbakir, Turkey; ¹⁰Uludag University, Bursa, Turkey

Hepatitis delta virus (HDV) infection affects 10-15 million individuals world-wide and frequently causes severe liver disease with limited treatment options available. The efficacy of pegylated-interferon alfa-2a and/or adefovir dipivoxil in delta hepatitis is unknown. Trial Design: 90 patients (42 in Germany, 39 in Turkey and 9 in Greece) with chronic HDV infection and compensated liver disease were randomized to receive either 180µg PEG-IFNa-2a qw plus 10mg adefovir dipivoxil qd (group A, n=31), 180µg PEG-IFNa-2a qw plus placebo (group B, n=29) or 10mg adefovir dipivoxil qd alone (group C, n=30) for 48 weeks. HBV-

DNA and HDV-RNA were investigated by real-time PCR. Results: Ten patients did not complete 48 weeks of therapy because of disease progression (n=6) or interferon-associated side-effects (n=4). By week 48, seven patients in each PEG-IFN group (23% and 24%, ITT) and none of the patients in group C had normalized ALT levels (p=0.004). Mean ALT levels (IU/ml) dropped significantly in group A (p=0.009) and B (p=0.05) but not in group C (p=0.24). Median baseline HDV-RNA viremia was 6.3, 5.9 and 5.7 log₁₀-copies/ml in groups A, B and C, respectively. Both PEG-IFN groups showed a significantly higher reduction in mean HDV-RNA levels than the adefovir monotherapy group by week 48 (2.54±2.4, 2.46±2.1 and 0.79±1.5 log₁₀-copies/ml for groups A, B and C, respectively; group A vs. C p=0.008 and group B vs. C p=0.006). An at least 2xlog₁₀-decline of HDV-RNA was observed in 39% of patients treated with PEG-IFNa-2a plus adefovir, 44% of patients treated with PEG-IFNa-2a and placebo and 8% of patients receiving adefovir alone (Group A and B vs. group C p=0.002). HDV-RNA became negative in 21%, 30% and 8% of patients, respectively (PEG-IFN vs. Adefovir p=0.06). The median HBV-viral load was 2.1 log₁₀-IU/ml at baseline, 48% of patients had HBV-DNA levels below 100 IU/ml. HBV-DNA levels significantly declined in all treatment groups by week 48 (group A p=0.002, group B p<0.001, group C p=0.002) not showing any differences in strength or frequency of HBV-DNA suppression. Conclusion: This so-far largest randomized treatment trial for delta hepatitis showed that (i) PEG-IFNa-2a displays a significant antiviral efficacy against HDV in more than 40% of patients with 25% becoming HDV-RNA negative after 48 weeks; (ii) adefovir dipivoxil has little efficacy in terms of HDV-RNA reduction but may be considered for patients with significant HBV-replication; (iii) combination therapy of PEG-IFNa-2a plus adefovir has no advantages for HBV-DNA or HDV-RNA reduction. 24 week follow-up data will be presented at the meeting. C. Yurdaydin and H. Wedemeyer contributed equally.

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112

TELBIVUDINE GLOBE TRIAL: MAXIMAL EARLY HBV SUPPRESSION IS PREDICTIVE OF OPTIMAL TWO-YEAR EFFICACY IN NUCLEOSIDE-TREATED HEPATITIS B PATIENTS Adrian DiBisceglie¹, Ching-Lung Lai², Edward Gane³, Yi-Cheng Chen⁴, Satawat Thongsawat⁵, Yumin Wang⁶, Yagang Chen⁷, Elizabeth J. Heathcote⁸, Stefan Zeuzem⁹, Jens Rasenack¹⁰, Natalie Bzowej¹¹, Steven-Huy Han¹², Nikolai Naoumov¹³, Seong Gyu Hwang¹⁵, Seng-Gee Lim¹⁴, George C. Chao¹⁶, Barbara A. Fielman¹⁶, Nathaniel A. Brown¹⁶, Study Group The GLOBE¹⁶, ¹St. Louis University, St. Louis, MO; ²University of , Hong Kong, Hong Kong; ³Middlemore Hospital, Auckland, New Zealand; ⁴Chang Gung Memorial Hospital, Taipei, Taiwan; ⁵Chiang Mai University, Chiang Mai, Thailand; ⁶Military Medical University, Chongqing, China; ⁷Zhejiang University College of Medicine, Hangzhou, China; ⁸Toronto Western Hospital, Toronto, ON, Canada; ⁹Saarland University Hospital, Homburg, Saar, Germany; ¹⁰Albert Ludwigs University, Freiburg, Germany; ¹¹Sutter Health, San Francisco, CA; ¹²UCLA School of Medicine, Los Angeles, CA; ¹³Institute of Hepatology, University College, London, United Kingdom; ¹⁴National University Hospital, Singapore, Singapore; ¹⁵Bundang CHA Hospital, Gyeonggi-Do, South Korea; ¹⁶Idenix Pharmaceuticals, Cambridge, MA

Background: In hepatitis B patients (pts) receiving antiviral therapy, previous reports have linked the degree of early HBV suppression with subsequent virologic and clinical efficacy. Here we report an analysis of efficacy outcomes at 2 years in relation to viral load at 24 weeks of treatment, using data from a large Phase III trial. Methods: The GLOBE trial enrolled 1,367 hepatitis B pts from 20 countries with pretreatment HBV DNA >6 log₁₀ copies/mL, ALT 1.3-10 xULN, and compensated liver disease randomized

to receive telbivudine or lamivudine for 2 years. For the present analysis, efficacy outcomes at 2 years were assessed in relation to 4 categories of HBV DNA level at Week 24 (W24): PCR-negative (<300 copies/mL by COBAS™ Amplificor); PCR-detectable but <3 log; 3-4 log; and >4 log₁₀ copies/mL, combining responses in both treatment arms. Results: Two-year data were available for 1346/1367 pts at abstract deadline. For all clinical and virologic efficacy parameters, efficacy at 2 years was incrementally proportional to HBV DNA level at W24 (Table). More telbivudine recipients were PCR negative at W24 (57%), vs lamivudine (45%), and fewer telbivudine pts had residual viral load >4 logs at W24 (17% and 27% respectively). Pts with PCR non-detectable HBV DNA at W24 showed high positive predictive values for achieving all efficacy endpoints at Year 2. In contrast, negative predictive values for 2-yr efficacy outcomes were high for pts with HBV DNA >4 logs at Week 24. Similar relationships were seen for telbivudine and lamivudine, although 2-year rates of efficacy responses overall were proportionally higher with telbivudine. Resistance analyses are underway. Conclusions: The magnitude of early viral suppression with antiviral nucleosides influences subsequent efficacy outcomes for at least 2 years. Two-year efficacy responses are high when HBV DNA is maximally suppressed at W24, consistent with the greater antiviral effects seen with telbivudine. The reduced efficacy seen in pts with HBV DNA >4 log at W24 suggests consideration of intensified treatment. These relationships may be useful for optimizing patient management.

Serum HBV DNA at Week 24 (copies/mL)		Response at Year 2			
		PCR -ve	<3 log	3-4 log	>4 log
HBeAg + Pts	Number of pts	349	120	162	272
	HBeAg seroconversion (%)	45	38	19	6
	ALT normalization (%)	79	76	63	43
	PCR-negative (%)	77	58	32	12
HBeAg - Pts	n	335	38	40	30
	ALT normalization (%)	77	74	58	21
	PCR-negative (%)	74	66	40	10

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113

THERAPY WITH ADEFOVIR ALONE OR COMBINED WITH LAMIVUDINE IN PATIENTS WITH LAMIVUDINE-RESISTANT CHRONIC HEPATITIS B: CLINICAL AND VIROLOGICAL ASPECTS Alfredo Marzano, Silvia Gaia, Valeria Barbon, Silvia Carezzi, Antonina Smedile, Antonella Olivero, Marco Lagget, Carlo Alessandria, Mario Rizzetto; Gastroenterology, Molinette Hospital, Turin, Italy

Results of therapy with Adefovir (ADV) alone (Group 1) or combined with ongoing Lamivudine (LAM) (Group 2) in 52 LAM-resistant patients with chronic hepatitis B are reported. Twenty-nine patients were randomly assigned to Group 1 and 23 to Group 2 and treated for a median time of 18 months (range 12-30). Overall biochemical response was achieved in 85% (80% in group 1 and 91%, in group 2, NS) and complete virological response (cVR: HBV DNA negative by amplified assay, PCR) in 67% patients, (55% in Group 1 and 83% in Group 2, p NS). The basal HBV DNA load influenced timing and the rate of virological response. A cVR was obtained in 100% of patients with HBV DNA <5 Log at baseline with both strategies, while in 60% of subjects with a basal viral load 5 Log (p<0.0001); in particular in 38% of patients in Group 1 and 81% in Group 2 (p<0.05). Seventeen patients (33%) did not achieve a cVR during therapy with ADV alone (13 pa-

tients) or in combination (4 patients). Three of them (treated with ADV alone), experienced a virological and biochemical rebound (HBV DNA rebound greater than 1 Log copies/ml compared with on treatment nadir). ADV mutants evaluation showed that i) basal mutation at locus rt181 was already present in 24% (4/17) of patients without a cVR and in none with a cVR, ii) after over 12 months of therapy, mutations at rt181 and rt236 were respectively present in 29% and 18% of the 17 patients without a cVR. Conclusions: in lamivudine-resistant patients with low HBV DNA (genotypic resistance) at baseline the addition to ongoing LAM or the shift to ADV were similar in obtaining complete viral response. By contrast, in subjects with a high viral load (HBVDNA >5Log copies/ml), combined therapy was far more effective than shifting to ADV. In these patients, a high basal viral load, the presence of the rt181 mutation, the presence of HBeAg positive and ADV monotherapy were associated with the risk of incomplete response and/or virological rebound.

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114

SUSTAINED BIOCHEMICAL AND VIROLOGICAL REMISSION AFTER DISCONTINUATION OF 4 TO 5 YEARS OF ADEFOVIR DIPIVOXIL (ADV) TREATMENT IN HBEAG-NEGATIVE CHRONIC HEPATITIS B Stephanos J.

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Background; ADV treatment of HBeAg (-) pts with chronic hepatitis B (CHB) has been found to be effective (serum HBV DNA undetectable by sensitive PCR assays) and ALT getting normalized in 70% of them. These benefits are lost when treatment of 1-2 year duration is discontinued. Aim: To investigate if the benefits of effective of ADV treatment in HBeAg (-) CHB continued for 4 or 5 yrs without development of resistance can be sustained after its discontinuation and for how long. Patients and methods: Thirty three HBeAg (-) pts with compensated CHB, all with precore HBV mutant genotype D infection and HBV DNA persistently undetectable by Cobas TaqMan PCR assay, all in biochemical remission maintained for 4 or 5 yrs under ADV therapy were included. Noone had developed genotypic HBV resistance to ADV. They represented 80% of the total population of pts from the same center who were treated with ADV for 4 or 5 yrs. They underwent a needle biopsy of the liver and then discontinued ADV therapy. Histological improvement in terms of liver necroinflammation and fibrosis had been achieved in 80% and 70% of them respectively. Frozen liver specimens from most of them were stored at -80 °C for immunohistochemical studies and for cccDNA, RNA transcripts and total HBV DNA assays. After stop of therapy all pts were followed-up at monthly intervals for the first six months and every 3 months thereafter. All serum samples were tested biochemically and HBV DNA was measured by R-T PCR. Several host and viral variables, including HBV expression and replicative activity in the liver at stop of therapy, were evaluated as possible determinants of sustained response or relapse. Results: Median duration of follow-up is 18 months (range 15-20). Three months after discontinuation of ADV treatment 22/33 pts (67%) have entered in sustained biochemical remission keeping for a median period of 17 months. Serum HBV DNA levels became again detectable by PCR in all pts but at relatively low levels similar to those in the inactive HBsAg carrier state (from hardly detectable to 50,000 cps /ml). HBV DNA values have been further decreased over time of follow-up. Biochemical relapses without evidence of spontaneous remission during a 3 month period of observation have occurred in 1/3 of the pts and have been managed successfully in all instances with reinstitution of ADV. Conclusions: 1) The goal of sustained biochemical and virologic response is achievable in HBeAg (-) CHB after discontinuation of 4 or 5 yrs of effective ADV treatment 2) Three months after stopping ADV