

(36% versus 4%; $P=0.001$) were also greater in the patients who relapsed. Normal laboratory indices before termination of treatment reduced the relative risk (RR) of relapse by 3- to 9-fold compared to patients who had not achieved these results (normal AST: RR 0.33, CI 95% 0.13-0.85, $P=0.01$; normal γ -globulin: RR 0.14, CI 95% 0.02-0.96, $P=0.02$; normal IgG: RR 0.11, CI 95% 0.02-0.78, $P=0.005$; normal AST+ γ -globulin+IgG: RR 0.17, CI 95% 0.06-0.56, $P=0.001$). **Conclusions:** Patients with type 1 autoimmune hepatitis who are treated to normal serum AST, γ -globulin and IgG levels have a lower frequency of relapse after corticosteroid withdrawal than patients treated to near-normal levels despite histological remission. The conventional laboratory indices of liver inflammation complement the histological findings in defining the optimal treatment end point, and their normalization should be the goal of therapy prior to drug withdrawal.

Disclosures:

The following people have nothing to disclose: Aldo J. Montano-Loza, Herschel A. Carpenter, Albert J. Czaja

108

MOLECULAR MIMICRY BETWEEN TARGET ANTIGEN OF ANCA AND MICROBIAL PROTEIN FTSZ IN AUTOIMMUNE LIVER DISORDERS Birgit Terjung¹, Jennifer Soehne¹, Howard J. Worman², Tilman Sauerbruch¹, Ulrich Spengler¹; ¹Department of Internal Medicine, University of Bonn, Bonn, Germany; ²Department of Medicine and of Anatomy and Cell Biology, Division of Digestive Diseases, College of Physicians and Surgeons, Columbia University, New York, NY

Background: Recently, we identified tubulin-beta isotype 5 (TBB-5) as target antigen of perinuclear antineutrophil cytoplasmic antibodies (atypical p-ANCA) in autoimmune liver disorders such as primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) (Hepatology 2006;4(Suppl.1):229A). TBB-5 shares high structural homology with the microbial cell division protein FtsZ which is present in almost all bacteria of the intestinal microflora and represents an evolutionary precursor protein of tubulin-beta. Here, we investigated whether atypical p-ANCA also react with FtsZ. **Methods:** Extracts of recombinant FtsZ were resolved by two-dimensional gel electrophoresis and reactive proteins were detected by immunoblotting using atypical p-ANCA positive sera from patients with autoimmune liver disorders ($n=15$). Sera from IL-10 $-/-$ mice ($n=20$), which had been grown either under specific pathogen free conditions (SPF) or in individually-ventilated cages and which developed evidence of an ulcerative colitis-like syndrome, were investigated for reactivity on immunoblots with tubulin extracts from HL-60 cells and recombinant FtsZ. Moreover, the murine sera were tested by immunofluorescence microscopy for the presence of atypical p-ANCA on ethanol-fixed human neutrophils. **Results:** In 85% of the sera from patients with atypical p-ANCA and autoimmune liver disorders, reactive protein spots of approximately 42 kD molecular weight and isoelectric points of 4.8 and 4.9 were detected. MALDI-TOF MS analysis confirmed FtsZ in both reactive spots. Pre-absorbing ANCA-positive sera with recombinant FtsZ abolished the characteristic staining pattern of atypical p-ANCA. Of note, sera from IL-10 $-/-$ mice raised under SPF conditions did not show any atypical p-ANCA staining on neutrophils and no reactivity on immunoblots with tubulin extracts or recombinant FtsZ was found. In contrast, atypical p-ANCA staining as well as reactivity with tubulin extracts and recombinant FtsZ were detected in 80% of the sera from mice whose intestines were colonized by the intestinal microflora in individually ventilated cages. **Conclusions:** Our findings suggest an essential role of the intestinal microflora in the pathogenesis of autoimmune liver disorders: the high structural homology between FtsZ and TBB-5 apparently leads to molecular mimicry between the microbial antigen FtsZ and the TBB-5 autoantigen. Thus, antibodies generated in susceptible individuals exhibit dual reactivity with both FtsZ and TBB-5 and give rise to the characteristic fluorescence pattern of atypical p-ANCA when sera are tested on ethanol-fixed neutrophils by immunofluorescence microscopy.

Disclosures:

The following people have nothing to disclose: Birgit Terjung, Jennifer Soehne, Howard J. Worman, Tilman Sauerbruch, Ulrich Spengler

109

ENTECAVIR MAINTAINED VIROLOGIC SUPPRESSION THROUGH 3 YEARS OF TREATMENT IN ANTIVIRAL-NAIVE HBEAG(+) PATIENTS (ETV 022/901) Ting-Tsung Chang¹, You-Chen Chao², Sabahattin Kaymakoglu³, Hugo Cheinquer⁴, Mario Pessoa⁵, Robert Gish⁶, Fred Poordad⁷, Joanna Yang⁸, Helena Brett-Smith⁷, Robert Hindes⁸; ¹National Cheng Kung University Medical College, Tainan, Taiwan; ²Tri-Service General Hospital, Taipei, Taiwan; ³Department of Gastrohepatology, Istanbul Medical Faculty, Istanbul, Turkey; ⁴Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil; ⁵Instituto De Infectologia Emilio Ribas, Hospital Dia Av. Dr. Arnaldo, Sao Paulo, Brazil; ⁶California Pacific Medical Center, San Francisco, CA; ⁷Department of Hepatology and Liver Transplantation, Cedars-Sinai Medical Center, Los Angeles, CA; ⁸Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT

Background: Entecavir (ETV) demonstrated superior virologic suppression compared to lamivudine (LVD) after 96 weeks in antiviral-naïve HBeAg(+) chronic hepatitis B (CHB) patients (study ETV-022). Patients achieving a Virologic Response (VR) defined as HBV DNA < 0.7 MEq/mL and HBeAg(+) during the 2nd year of therapy could roll-over to study ETV-901, where they received open-label ETV 1 mg QD. Preliminary efficacy results of ETV after 3 years of treatment in patients with a VR are presented here. **Methods:** 198 of 243 patients who entered the 2nd year of therapy in ETV-022 achieved a VR through Week 96. 151 patients then entered study ETV-901, and 122 received open-label entecavir for at least 1 additional year. The proportions of patients with HBV DNA < 300 copies/mL by PCR assay, HBeAg loss or seroconversion, and ALT normalization were evaluated. **Results:** Efficacy parameters through 3 years of ETV therapy are presented in the table below. **Conclusions:** HBeAg(+) CHB patients who achieved VR after 2 years of entecavir therapy in ETV-022 maintained virologic suppression and ALT normalization during the third year of therapy in ETV-901, with continued HBeAg loss and seroconversion.

	Wk 144(%) N=122*
HBV DNA <300 copies/mL	87%
ALT <1xULN	83%
HBeAg loss during 3rd year of treatment†	31%
HBeAg seroconversion during 3rd year of treatment†	16%

Disclosures:

Ting-Tsung Chang - Investigator: BMS
 You-Chen Chao - Investigator: BMS
 Sabahattin Kaymakoglu - Investigator: BMS
 Hugo Cheinquer - Investigator: BMS, GSK, Novartis, Roche; Consultant: BMS, Roche
 Mario Pessoa - Investigator: BMS, Roche; Consultant: BMS, Roche, GSK
 Robert Gish - Consultant and Speakers Bureau: Bayer, BMS, Eximius F.Hoffmann-La Roche, Gilead; Consultant and Speakers Bureau: GSK, InterMune, Orthobiotech, Schering-Plough; Consultant and Speakers Bureau: Valeant; Consultant: Amgen, Anadys, Chiron, Corixa; Consultant: Human Genome Sciences, Metabasis Therapeutics; Consultant: SciClone, United Therapeutics, Pharmasset, Idenix; Consultant: Hepa-hope, Nucleonics, Imogenetics, XTL; Consultant: Zymogenics
 Fred Poordad - Investigator: BMS; Speakers Bureau: BMS
 Joanna Yang - Employee: BMS
 Helena Brett-Smith - Employee: BMS
 Robert Hindes - Employee: BMS

110

ASSESSMENT AT THREE YEARS SHOWS HIGH BARRIER TO RESISTANCE IS MAINTAINED IN ENTECAVIR-TREATED NUCLEOSIDE NAIVE PATIENTS WHILE RESISTANCE EMERGENCE INCREASES OVER TIME IN LAMIVUDINE REFRACTORY PATIENTS Richard J. Colomno, Ronald E. Rose, Kevin Pokornowski, Carl J. Baldick, Kenneth Kleszczewski, Daniel Tenney; Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT

Background: Entecavir (ETV) is a potent inhibitor of hepatitis B virus (HBV) with proven clinical efficacy. ETV resistance (ETVr) requires pre-existing lamivudine resistance (LVDr) substitutions and an additional change at RT residues T184, S202 or M250. ETVr substitutions are observed following LVD therapy, but only in the presence of LVDr substitutions. **Methods:** Patients exhibiting vi-

rologic 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.

Disclosures:

Richard J. Colonna - Employee: Bristol-Myers Squibb Co.
 Ronald E. Rose - Employee: Bristol-Myers Squibb Co.
 Kevin Pokornowski - Employee: Bristol-Myers Squibb Co.
 Carl J. Baldick - Employee: Bristol-Myers Squibb Co.
 Kenneth Kleszczewski - Employee: Bristol-Myers Squibb Co.
 Daniel Tenney - Employee: Bristol-Myers Squibb Co.

111

A MULTICENTER RANDOMISED STUDY COMPARING THE EFFICACY OF PEGYLATED INTERFERON-ALFA-2A PLUS ADEFOVIR DIPVOXIL VS. PEGYLATED INTERFERON-ALFA-2A PLUS PLACEBO VS. ADEFOVIR DIPVOXIL FOR THE TREATMENT OF CHRONIC DELTA HEPATITIS: THE HEP-NET/INTERNATIONAL DELTA HEPATITIS INTERVENTION TRIAL (HID-IT) Cihan Yurdaydin², Heiner Wedemeyer¹, George Dalekos³, Alexander Erhardt², Ya Cakaloglu⁸, Ha Degertekin⁹, Sa. Gurel¹⁰, Stefan Zeuzem³, Kalliopi Zachou^{4,5}, Hakan Bozkaya², Hans P. Dienes⁴, Thomas Bock⁶, Michael P. Manns⁷, 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-IFNα-2a qw plus 10mg adefovir dipivoxil qd (group A, n=31), 180µg PEG-IFNα-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-IFNα-2a plus adefovir, 44% of patients treated with PEG-IFNα-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-IFNα-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-IFNα-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.

Disclosures:

Cihan Yurdaydin - Research Grant: Roche; Research Grant: Gilead
 Heiner Wedemeyer - Research grant, lecturer fees: Roche; Research grant, lecturer fees: Gilead Sciences
 Stefan Zeuzem - Research Grant, Boards: Gilead; Research Grant, Boards: Roche
 Thomas Bock - Research Grant: Gilead
 Michael P. Manns - Research Grant, lecturer fee, advisory board: Roche; Research Grant, lecturer fee, advisory board: Gilead
 The following people have nothing to disclose: George Dalekos, Alexander Erhardt, Ya Cakaloglu, Ha Degertekin, Sa. Gurel, Kalliopi Zachou, Hakan Bozkaya, Hans P. Dienes

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, Sawat 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