we searched the databases of the 1K Human Genome Project and the NHLBI Exome Sequencing Project to identify nsSNPs in various racial/ethnic populations. Thirteen nsSNPs were identified in Caucasians with allele frequencies from <0.001 to 0.28%, for a surprisingly high combined frequency of 0.73% (1 in 137). Four (combined frequency of 0.44% or 1 in 230) have been reported in HGMD as causing AIP acute attacks. The remaining nine are novel, accounting for a combined frequency of 0.28% (1 in 360). To determine their potential pathogenicity, the novel mutations were analyzed by 18 in silico programs. Of these, three nsSNPs were predicted as deleterious (D65H, I71T, A122P), for a combined allele frequency of 0.15% (1 in 670). Four nsSNPs (V237M, R246C, I54L, S45L) were predicted to be tolerated, benign or likely polymorphisms, while two nsSNPs (R246H and R355Q) had equivocal predictions. All nsSNPs are being expressed in vitro to determine which encode enzymes with markedly reduced HMBS activity. In addition, efforts are directed to identify in the dbGaP database possible disease phenotypes associated with the pathogenic HMBS nsSNPs. Thus, the incidence of the four known and three predicted pathogenic HMBS mutations in Caucasians may be as high as 0.59% (1 in 170). The penetrance of this hepatic porphyria may be unusually low, even if the frequency of pathogenic alleles is 1 in 103. As the prevalence of patients who have had acute attacks is ~ 1 in 20,000 in Sweden to ~1 in 200,000 in Western Europe, our results suggest the importance of modifying genes and environmental triggering factors causing the acute attacks.

Disclosures:

Makiko Yasuda - Patent Held/Filed: Alnylam Pharmaceuticals

Robert J. Desnick - Advisory Committees or Review Panels: Recordati Rare Diseases; Consulting: Alnylam Pharmaceuticals; Grant/Research Support: Alnylam Pharmaceuticals; Patent Held/Filed: Alnylam Pharmaceuticals; Stock Shareholder: Alnylam Pharmaceuticals

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## Lorcaserin Improves the NASH Clinical Score in the Majority of High-Risk Patients: a Retrospective Analysis of Three Phase 3 Studies

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Background: Moderate weight loss has been shown to result in histologic improvement in non-alcoholic steatohepatitis (NASH). Lorcaserin is a selective 5-HT2C agonist approved for chronic weight management. Three large, double-blind, randomized studies (BLOOM: N Engl J Med. 2010;363:245-56; BLOSSOM: J Clin Endocrinol Metab. 2011;96:3067-77; BLOOM-DM: Obesity. 2012;20:1426-36) have demonstrated the effectiveness of lorcaserin in inducing weight loss in patients with a body mass index of 27 to 45. We conducted a retrospective analysis to determine the ability of 52 weeks of lorcaserin 10 mg bid to improve NASH. The NASH clinical score predicts the presence of histologic NASH and was used as an indicator of NASH activity. Methods: Data were pooled from 3 clinical trials of similar design comparing lorcaserin and placebo in overweight or obese patients with or without type 2 diabetes (NCT00603902, NCT00395135, NCT00603291). All patients received diet and exercise counseling. The modified intent-to-treat/last observation carried forward population was analyzed for patients with both baseline and end of treatment NASH clinical score data. Liver parameters (ALT, AST) and weight loss in the MITT/LOCF population were assessed as % change from baseline. The NASH clinical score was analyzed by comparing proportions of patients shifting from high or very high scores at baseline (NASH-pos) to low or intermediate scores (NASH-neg) at week 52. Results: Approximately 7% of control (182/2519) and lorcaserin-treated (190/2702) patients had a high-risk NASH clinical score, and both groups had an AST/ALT ratio of 0.9. Lorcaserin-treated patients showed significant improvements vs placebo in ALT (% change from baseline to week 52, -2.4 vs 3.0), AST (0.1 vs 2.6) as well as significant weight loss (-5.8 vs -2.4), all P<0.001. In an analysis of the time course of treatment effect, significant weight loss with lorcaserin vs placebo was seen as early as week 2, with peak effect at week 36; peak effect of lorcaserin on liver enzyme levels was at week 24. Significantly more patients treated with lorcaserin (120/190, 63.2%) vs placebo (89/182, 48.9%) switched from NASH-pos at baseline to NASH-neg at week 52 (P=0.006). Conclusions: Lorcaserin treatment for 52 weeks was associated with greater improvement in serum LFT parameters than placebo, and improvement in NASH clinical score in the majority of high-risk patients. Lorcaserin may be a treatment option for overweight/obese patients with non-alcoholic fatty liver disease/NASH.

Disclosures:

Wajahat Z. Mehal - Management Position: Gloabl BioReserach Partners

Randi Fain - Employment: Eisai Inc

Alan Glicklich - Employment: Arena Pharmaceuticals; Stock Shareholder: Arena Pharmaceuticals

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## No increased risk of hepatocellular carcinoma in cirrhosis due to Wilson's disease during long term follow up

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Background and aims: Although liver cirrhosis is a frequent complication in Wilson's disease (WD), data on risk of hepatocellular carcinoma (HCC) in these patients are scarce. We here report HCC risk in a well-defined cohort with unequivocally proven WD with long-term follow-up (FU) and correlate HCC risk to efficacy of decoppering treatment and severity of liver disease. Methods: All patients with a confirmed diagnosis of WD (Leipzig score ≥ 4) in three Dutch university referral hospitals were included in this retrospective cohort study. End of FU was defined as date of diagnosis of HCC, liver transplantation, death or last available hospital visit. Results: In total, 130 patients with WD were followed during a median FU of 15 years (range 0.1-51.2). Total years of FU was 2336. Median age at diagnosis was 16 years (range 0-43). Presentation was asymptomatic, exclusively hepatic, neurologic, combined and unknown in 4%, 55%, 9%, 30% and 2% of cases, respectively. Median Leipzig score was 8 points (range 4-13). At baseline, cirrhosis was present in 74 patients (57% of total: 64%

compensated and 36% decompensated). At end of FU, liver disease severity was improved, stable or deteriorated in 20%, 46% and 24% of all cases, respectively. Twenty-eight patients received a liver transplant. Five patients died due to complications of their liver disease and two deaths were related to liver transplantation. In patients who were treated for at least one year (n=111), zinc, penicillamine or trientine (alone, sequentially or combined) were prescribed in 92%, 69% and 14% of patients, respectively. At the end of FU, efficacy of decoppering, based on values of serum non-ceruloplasmin-bound copper concentration (aim: <10 μg/dL) and 24-hour-urinary copper excretion (aim: <100 μg/24 hours), was excellent in 34% of patients, moderate in 42%, poor in 13% and unknown in 11%. Two patients developed HCC. The first patient was a 39-year-old male and presented with decompensated cirrhosis in combination with HCC. The second patient was a 63-year-old female with unequivocal WD diagnosed 50 years earlier. Despite excellent decoppering at the end of FU, she progressed to decompensated cirrhosis in which an HCC developed. No additional risk factors for liver disease were present in both patients. Estimated annual HCC risk for all patients was 0.09% (95% confidence interval: 0.01-0.28). Subgroup analysis in cirrhotic patients revealed an annual HCC risk of 0.14% (95% confidence interval: 0.02-0.45). Conclusion: Even in case of cirrhosis, HCC risk is low in Wilson's disease and appears not related to efficiency of decoppering. Our data do not support regular HCC surveillance in WD.

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Karel J. van Erpecum - Advisory Committees or Review Panels: Bristol Meyers Squibb, Abbvie

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## 464
## Patients with Wilson disease without detectable ATP7B mutations

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Background/aim: Wilson disease (WD) is an inherited autosomal-recessive disorder of hepatic copper excretion resulting in copper accumulation in the liver. The responsible gene mutation is located within the ATP7B gene encoding for a P-type copper transporting ATPase. More than 500 mutations in the ATP7B gene have been described so far. Nevertheless, in up to seven percent of patients with WD, no mutation can be found. Aim of our study was to identify diagnostic characteristics of patients with WD without detectable mutations in ATP7B. Methods: Clinical data and DNA for genetic analysis were obtained from WD patients as part of an international cooperation project. The diagnosis of WD was established if the WD diagnostic score recommended by the EASL Clinical Practice Guidelines on WD was ≥ 4. Mutation analysis was carried out by direct sequencing on an ABI Prism 310 Genetic Analyzer (Perkin Elmer, Norwalk, USA). Next-generation sequencing is ongoing and was performed in ten patients so far. Results: Out of 1294 WD patients collected since 1985 in 65 (5.0%) patients no mutation in the ATP7B gene could be detected. Thirty-nine (60.0%) of them were male. Thirty-one patients (47.7%) presented with neurologic symptoms and 29 (44.6%) with hepatic symptoms (of whom one had fulminant hepatic failure). Five (7.7%) patients were asymptomatic siblings of patients with WD. Mean age at onset of WD was 19.5±10.9 years and 21.4±10.5 years at diagnosis. Kayser-Fleischer corneal rings were present in 38 (58.5%) patients. Hepatic copper content was available in 33 patients (784±586 μg/g dry weight; SD) and coeruloplasmin was decreased in 50 (76.9%) patients (mean: 8.9±7.6 mg/dL). Conclusions: Our data suggest that yet unidentified mutations of genes other than ATP7B might lead to a disease identical to WD. Further research is needed to get more insights into the causes of copper overload in patients without mutations in ATP7B.

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Harald Hofer - Speaking and Teaching: Janssen, Roche, MSD, Gilead, Abbvie

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## Sex differences in liver SAM:SAH ratios and gene transcript levels after pre-and post-natal choline supplementation and copper chelation treatment in an animal model of Wilson disease

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Background. Methionine metabolism, central to DNA methylation reactions, may provide epigenetic regulation of genes involved in liver damage in Wilson disease (WD). We hypothesized that peri-natal maternal treatment with choline could modify the sex specific response to penicillamine in offspring in the tx-j model of WD. Methods. Control (choline 8 mmol/Kg) or choline supplemented (36 mmol/Kg) diets were fed to wildtype and tx-j female mice starting at 2 weeks before mating and continuing in offspring up to 24 weeks of age. A subgroup of tx-j of both sexes received oral penicillamine with or without choline supplemented diet from 12 to 24 weeks of age. Results. Decreased S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) ratio, an index of DNA methylation capacity, was decreased in each sex of offspring tx-j mice, compatible with the known down-regulation of SAH hydrolase levels in this mouse model of WD (Table 1). The SAM:SAH ratio was higher in untreated female versus male tx-j mice ($p<0.05$). Separate choline or penicillamine treatments were associated with similar increases of SAM:SAH ratio in male tx-j vs wildtype levels. Whereas the ratio was increased by each separate treatment in tx-j males, it was reduced by each separate treatment in tx-j females, but was unchanged in either sex by the combination of choline and penicillamine. Transcript levels of Dnmt3b, a regulator of DNA methylation in tx-j mice, were increased in untreated tx-j of either sex, and were down-regulated by separate or combined penicillamine and choline treatment in male tx-j, but were unchanged by any treatment in female tx-j mice. Grp78 transcript levels were increased in tx-j mice of