Updates on new therapies in development for rare liver diseases

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Promising results for three drugs for the treatment of three rare liver diseases were presented today at The International Liver Congress 2018 in Paris, France. Sebelipase alfa, approved for treatment of lysosomal acid lipase (LAL) deficiency in 2015, showed sustained improvements and long-term tolerability in a diverse patient population. Preliminary findings with two investigational RNA interference (RNAi) therapeutics were also positive; givosiran substantially reduced the annualized attack rate in patients with acute intermittent porphyria (AIP), and ARO-AAT demonstrated positive preclinical safety and efficacy in alpha-1 antitrypsin (AAT) deficiency—pointing to the developing potential of this new therapeutic strategy in patients with few treatment options. LAL deficiency, an underappreciated cause of cirrhosis and severe dyslipidaemia, is a rare autosomal recessive disorder characterized by accumulation of cholesteryl esters and triglycerides in the liver.25 The age at onset and rate of progression vary greatly.25 Sebelipase alfa is a recombinant human LAL enzyme indicated for the treatment of LAL deficiency which was approved in 2015 following successful Phase 2/3 trials.

"It is exciting to see clinical benefits and good tolerability confirmed in this long-term follow-up across a diverse population of adult and paediatric patients with LAL deficiency," said Dr. Florian Abel from Alexion Pharmaceuticals, Inc., New Haven, CT, USA. "This population included patients who would have been ineligible to participate in previous clinical studies because of their age or prior transplant status."

Data were presented today for 31 patients who were enrolled in a multicentre, open-label study of sebelipase alfa 1 mg/kg by intravenous (IV) infusion every other week for up to 96 weeks. Permitted dose escalation/reduction was from a maximum of 3 mg/kg weekly to a minimum of 0.35 mg/kg every other week.

There were marked reductions from baseline in alanine aminotransferase (ALT; -44.4%) and aspartate aminotransferase (AST; -38.4%). There were also reductions from baseline in liver volume (-17.6%), liver fat content (-14.9%), and spleen volume (-16.5%). In the 7/13 patients with data available, liver fibrosis improved or did not progress. Most adverse events were mild to moderate in severity, three patients experienced infusion-associated reactions. Two patients were positive for anti-drug antibodies, on one occasion each, but neither developed neutralizing antibodies.

"We were pleased to see that long-term treatment with sebelipase alfa was well tolerated and that improvements in markers of liver injury were sustained," said Dr. Abel.

AIP is the most common form of acute hepatic porphyrias (AHPs), a family of rare, inherited metabolic diseases resulting in deficiencies in the liver enzymes responsible for haem biosynthesis.28 Central to the pathophysiology of all AHPs is the induction of aminolevulinic acid synthase 1 (ALAS1), which can lead to accumulation of the neurotoxic haem intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), which are causal for potentially life-threatening disease manifestations.29 RNAi is a naturally occurring cellular mechanism mediated by small interfering RNA (siRNA) that allows for the inhibition of protein synthesis through the cleavage and degradation of a specific mRNA.30 Givosiran is an investigational, subcutaneously administered RNAi therapeutic targeting liver ALAS1 to reduce ALA and PBG accumulation in patients with AHPs.

A Phase 1, multinational, randomized, placebo-controlled study of givosiran has been conducted in three parts; Part A: single ascending dose, Part B: multiple ascending dose and Part C: multiple dose (four cohorts of four to five patients each), to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of givosiran in patients with AIP (ClinicalTrials.gov Identifier: NCT02452372). The study has now been completed and givosiran was generally well tolerated, with no serious adverse events or clinically significant laboratory abnormalities related to the study drug.

Monthly dosing of givosiran led to rapid, dose-dependent, and durable silencing of induced ALAS1 mRNA of approximately 60%, with concomitant lowering of ALA and PBG by >80% in patients with recurrent attacks. Patients treated with a monthly dose of 2.5 mg/kg of givosiran had an 83% mean decrease in the annualized attack rate (requiring hospitalization, urgent care, or haemin) compared with placebo, and an 88% decrease in the number of haemin doses. Patients completing the Phase 1 study were eligible to enrol in an open-label extension study (NCT02949830). As of February 2018, the safety profile in patients in the open-label extension (n=16) was consistent with that observed in Part C. Patients that had received givosiran in Part C (n=12) had further reductions in annualized attack rate of 93%, relative to the 3-month run-in period.

"Givosiran has the potential to significantly lower liver ALAS1 levels in a sustained manner and to thereby decrease the accumulation of neurotoxic intermediates that potentially lead to severe or life-threatening neurovisceral attacks. We're very encouraged by our results, as treatment was associated with marked reductions in both annualized attack rate and haemin use," said Dr. Eliane Sardh from the Karolinska University Hospital, Stockholm, Sweden. "These results suggest that givosiran, which is currently being studied in a Phase 3 trial, has the potential to become a transformative treatment option for patients with

hepatic porphyrias, a debilitating and potentially life-threatening disease." (NCT03338816).

AAT deficiency is an autosomal, co-dominant genetic disorder in which the PiZ mutation results in the misfolded protein (Z-AAT) that accumulates in hepatocytes and can lead to fibrosis, cirrhosis and hepatocellular carcinoma.31 The only current treatment option for AAT deficiency-related liver disease is liver transplant.31 ARO-AAT is a second-generation, subcutaneously adminstered RNAi therapeutic that replaces ARC-AAT, a first-generation intravenously administered RNAi therapeutic that previously demonstrated proof of concept in the PiZ mouse model expressing human Z-AAT, and achieved deep knockdown in healthy volunteers and patients.32,33

"ARO-AAT is a liver-targeted RNAi therapeutic that durably reduced Z-AAT liver mRNA and serum protein in PiZ mice. The degree of mRNA reduction correlated with the amount of siRNA in the liver," said Dr. Christine Wooddell of Arrowhead Pharmaceuticals, Madison, WI, USA. "We have also assessed the pharmacokinetics and biodistribution of ARO-AAT in rats, efficacy in PiZ mice, and pharmacological activity in non-human primates."

In the studies presented today, ARO-AAT in rats demonstrated high tissue distribution, with the highest exposure in the liver through Day 16, peaking at 4 hours. Repeat dosing (4 mg/kg once every 2 weeks, four times) of young PiZ mice reduced Z-AAT liver mRNA by 95%, plasma Z-AAT by 96%, monomeric liver Z-AAT by 98%, and polymeric Z-AAT by 41%. ARO-AAT prevented increases of Z-AAT polymer globules that were observed in untreated controls of the same age, with a 2.6-fold increase in number, an 8-fold increase in affected liver area, and a 3.3-fold increase in globule size. Non-human primates had a mean reduction of serum AAT of 89-91% that was sustained for more than 7 weeks after the second dose received, following administration of two

doses of 3 mg/kg, 4 weeks apart. These results are supportive of monthly or less frequent dosing for ARO-AAT.

"We believe that the results from these studies strongly support advancement of ARO-AAT into the clinic," said Dr. Wooddell. "A Phase 1 single- and multiple-ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and effect of ARO-AAT on serum alpha-1 antitrypsin levels in healthy adult volunteers started administering doses to subjects on 12 March 2018."

"Rare diseases are a greater challenge than you might expect, as apart from the difficulties in reaching a full diagnosis, there are often no effective treatments available," said Prof. Marco Marzioni from the University Hospital of Ancona, Italy, and EASL Governing Board Member. "For instance, the study investigating a treatment for LAL deficiency is important, as this is a disease that we only recently learned to identify."

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