New medication shows promise as lipid-lowering therapy for rare cholesterol disorder

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An international effort led by researchers at the Perelman School of Medicine at the University of Pennsylvania has resulted in positive phase 3 clinical trial results for a new medicine to treat patients suffering from a rare and deadly cholesterol disorder.

Penn researchers report in *The Lancet* that lomitapide, a first-in-class microsomal triglyceride transfer protein (MTP) inhibitor, substantially and stably reduced LDL cholesterol (the "bad" cholesterol) in patients with the orphan disease homozygous familial hypercholesterolemia (HoFH). Lomitapide works by inhibiting MTP, which is required for the production of VLDL—the precursor to LDL.

HoFH patients have markedly elevated blood levels of cholesterol—generally greater than 500 mg/dL—due to genetic mutations in the LDL receptor gene that result in impaired ability of the liver to remove LDL from the blood. Heart and vascular disease often develop in childhood, and the average age of death even with current therapies is about 30 years. HoFH patients do not respond well to the usual treatments for elevated cholesterol, such as statins. The only effective therapy for these patients is apheresis, an invasive and time-consuming procedure that involves physically removing excess LDL from the bloodstream and must be repeated every one to two weeks.

The current study was an open-label trial that comprised a six-month phase designed to assess the efficacy of lomitapide when added to standard of care and an additional year-long phase to assess safety and

tolerability. Twenty-nine adult HoFH patients from across the world were enrolled, with 23 patients completing both the efficacy and the safety phases. All of the patients received lomitapide along with conventional lipid-lowering therapies including statins and, in some cases, apheresis. The lomitapide dose was gradually increased from five mg to a maximum tolerated dose of up to 60 mg per day. Median dose was 40 mg per day. At the end of the efficacy phase, LDL-C levels were reduced by an average of 50 percent from baseline. Approximately one-third of the patients experienced levels of LDL-C that were less than 100 mg/dl—close to the recommended therapeutic goals— at some point during the study, and concomitant lipid-lowering therapy was modified in a subset of these patients during the safety phase. Despite these changes in treatment, patients' mean LDL-C levels were still reduced by 38 percent at the end of the study.

"The magnitude of this reduction in LDL-C and the fact that some patients reached or approached the LDL-C therapeutic goals is truly remarkable for this high risk population that historically doesn't respond to lipid-lowering drugs," said the study's lead author, Marina Cuchel, MD, PhD, research assistant professor of Medicine at Penn. "A reduction in LDL-C of this magnitude is certainly expected to favorably alter the clinical course of this devastating disease."

Senior study author Daniel J. Rader, MD, chief, Division of Translational Medicine and Human Genetics at Penn, has treated HoFH patients for more than two decades. In the early 1990s, Rader worked with colleagues to determine that mutations in MTP were the cause of a rare condition characterized by absent LDL in the blood, establishing MTP as a therapeutic target to reduce LDL. His colleagues then went on to discover the MTP inhibitor lomitapide at Bristol-Myers Squibb (BMS). Rader led a study at Penn in the late 1990s showing that lomitapide substantially reduced LDL in patients with moderately elevated LDL. However, because the agent caused some gastrointestinal

side effects and increased liver fat, BMS decided to abandon further development of lomitapide for a much larger population of patients with elevated levels of cholesterol. Rader convinced BMS to donate the drug to Penn so that he could continue to develop it in patients with HoFH. Based on its mechanism and on a study in a rabbit model of the disease, Rader felt it would be effective against HoFH.

A proof of principle study conducted by Drs. Cuchel and Rader at Penn in six HoFH patients confirmed that lomitapide was highly effective in reducing LDL and provided the basis for the international phase 3 study, which was funded in part by the Office of Orphan Product Development at the Food and Drug Administration (FDA). Aegerion Pharmaceuticals in-licensed lomitapide from Penn in 2006, helping fund the completion of the study and the additional work required to submit a new drug application to the FDA.

On October 17, 2012, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended by a vote of 13 to 2 the approval of lomitapide to reduce LDL in patients with HoFH. The FDA is scheduled to make a final decision on approval of the medication by the end of year.

"The more than 15-year story of this therapy is the result of an enormous collaboration between academia, foundation, pharmaceutical and biotech industries, and the government," said Rader. "If lomitapide is approved and is made available to patients with this fatal disease, it will serve as a model for how different sectors can work together to bring new medicines to patients with large unmet medical need."

Provided by University of Pennsylvania School of Medicine