ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of Lysosomal Acid Lipase Deficiency for the Gastroenterologist and Hepatologist

Stephen A. Harrison, MD
Chief of Hepatology
Division of Gastroenterology and Hepatology
San Antonio Military Medical Center
Fort Sam Houston, Texas

G&H What is lysosomal acid lipase deficiency, and how prevalent is it in adults and children?

SH Lysosomal acid lipase deficiency is an autosomal recessive lysosomal storage disorder that ultimately results in marked systemic lysosomal accumulation of cholesterol esters and triglycerides. This disease is characterized by multiorgan involvement, which includes the liver, spleen, cardiovascular system, and, to some extent, the gastrointestinal system. According to studies such as one conducted by Bernstein and colleagues, approximately 87% of patients show manifestations in more than 1 organ system, with liver involvement in 86%, cardiovascular involvement in 87%, spleen involvement in 36%, and gastrointestinal involvement (abdominal pain, malabsorption, gastrointestinal bleeding) in 22%.

Lysosomal acid lipase deficiency can be separated into 2 phenotypes. One is Wolman disease, which affects infants and is rapidly fatal; death typically occurs within 12 months. The other phenotypic expression of the disease manifests less quickly and affects both children and young adults. Unfortunately, once symptoms develop, a significant percentage of patients may experience hepatic progression to fibrosis, cirrhosis, or the need for liver transplantation within 3 years of symptom onset.

The median age of the first reported manifestation is 5 years, although the disease has been reported from birth to age 68 years. The majority of patients, approximately 39%, have their first reported manifestation between the ages of 2 and 5 years.

However, it is still not completely known how often the disease occurs. We know that its prevalence varies based upon ethnic background and geographic location. Studies have reported various prevalence estimates, ranging from 1 in 130,000 individuals up to 1 in 300,000 individuals. It appears that the presence of known lysosomal acid lipase mutations predicts a higher incidence than in the general population.

G&H Why is lysosomal acid lipase deficiency important for gastroenterologists and hepatologists to keep in mind when seeing patients?

SH Young adults with the disease typically have elevated liver enzymes, particularly alanine aminotransferase (ALT) and aspartate aminotransferase, and often undergo liver biopsy because an imaging study suggests the presence of fat in the liver. The liver biopsy demonstrates microvesicular steatosis and often fibrosis as well. This can confuse the clinician because nonalcoholic fatty liver disease (NAFLD) can present in much the same way in the same population of patients. Currently, NAFLD is an epidemic in the United States, occurring in approximately 30% to 40% of the adult population. Like lysosomal acid lipase deficiency, NAFLD may be associated with similar elevations in serum aminotransferases and findings suggestive of fatty liver on imaging. Furthermore, some of the other conditions associated with NAFLD are also seen with lysosomal acid lipase deficiency—predominantly, dyslipidemia with an elevated low-density lipoprotein (LDL) cholesterol and a low high-density lipoprotein (HDL) cholesterol. However, in patients with NAFLD, a majority of the hepatic steatosis will be macrovesicular, rather than microvesicular, which is seen more commonly with lysosomal acid lipase deficiency.

In addition, patients with lysosomal acid lipase deficiency can have significant atherosclerotic coronary artery disease, which can also be seen in NAFLD. In fact, the number one killer of a patient with NAFLD is cardiovascular disease, with a recent study by Angulo and colleagues suggesting that cardiovascular disease was the cause of death in 38% of patients with NAFLD.

G&H What is the pathophysiology of lysosomal acid lipase deficiency?

SH Lysosomal acid lipase is an enzyme that processes cholesterol esters and triglycerides within the hepatocytes of individuals. Normally, LDL is taken up via the LDL receptor and transported to the lysosome inside the cell. There, the cholesterol esters are broken down by lysosomal acid lipase into precholesterol and free fatty acids (FFAs), which are released for membrane building, energy storage, and signaling molecules. In lysosomal acid lipase deficiency, when LDL is taken up by the LDL receptor and transported to the lysosome, the lysosome swells and enlarges with excess cholesterol esters and triglycerides. This occurs because lysosomal acid lipase is not abundant enough to break down the cholesterol esters and triglycerides. Thus, free cholesterol and FFAs are not released. In addition, hepatocytes also upregulate the synthesis and packaging of cholesterol, which releases even more cholesterol as a result. Ultimately, the LDL is deposited in hepatocytes, macrophages, and the endothelial wall, which can lead to clinical manifestations of heart and liver disease as well as splenic enlargement and intestinal manifestations.

G&H When should patients be tested for lysosomal acid lipase deficiency?

SH This is a question that we are still trying to answer. One of the ways to approach this issue is to test patients who present with elevated liver enzymes, hepatomegaly and/or splenomegaly, an imaging study suggesting fatty liver, LDL cholesterol greater than 130 mg/dL in children or greater than 160 mg/dL in adults, or HDL cholesterol less than 45 mg/dL in both adults and children. It is not necessary to test all patients who have any of these features, but the more of these features that a patient has, the higher the likelihood of a positive test result. Any suspected patients can be tested with a simple diagnostic enzymatic blood test that can be sent to several laboratories. A test result with undetectable lysosomal acid lipase activity confirms the diagnosis of lysosomal acid lipase deficiency. If, on the other hand, lysosomal acid lipase activity falls within, or above, the reference range, the disease can be ruled out.

G&H Is a liver biopsy required when diagnosing or evaluating these patients?

SH A liver biopsy is not required for diagnosis, although it can be helpful for staging and monitoring disease progression once lysosomal acid lipase deficiency is confirmed. However, it is important to remember that many of the features observed on liver biopsy are not unique to lysosomal acid lipase deficiency. Patients with confirmed disease should be followed for disease severity because the majority will have fibrosis at the time of diagnosis. In the future, hopefully there will be noninvasive means of following these patients, such as noninvasive imaging with FibroScan (Echosens) or magnetic resonance elastography.

G&H What are the current treatment options for these patients?

SH Historically, treatment has been symptomatic. Clinicians have tended to treat high cholesterol with statins and placed patients on dietary restrictions. Hematopoietic stem cell transplants have also been tried. However, none of these therapies address the underlying pathology of the disease, and there have been no well-controlled studies showing that supportive therapy is safe or effective in lysosomal acid lipase deficiency.

Recently, the US Food and Drug Administration approved the use of sebelipase alfa (Kanuma, Alexion), a hydrolytic lysosomal cholesterol ester and triacylglycerol-specific enzyme indicated for the treatment of lysosomal acid lipase deficiency. For children 6 months and younger, it can be administered intravenously at doses of 1 mg/kg once weekly as an initial dose and then escalated to 3 mg/kg once weekly in patients who do not achieve an optimal clinical response. In pediatric and adult patients, the dose is 1 mg/kg via intravenous infusion every other week.

G&H What research has been conducted on this drug?

SH The phase 3, multicenter, randomized, placebo-controlled, double-blind ARISE (Acid Lipase Replacement Investigating Safety and Efficacy) study was conducted in children and adults with lysosomal acid lipase deficiency. Study participants were randomized to 1 mg/kg every other week (n=36) or placebo (n=30) for 20 weeks and then entered an open-label extension (still ongoing) in which all participants received the drug at 1 mg/kg every other week. The patients who received the drug had greater reductions in ALT from baseline (the primary endpoint) than patients who received placebo. The mean change was approximately 50 U/L and was seen as early as 4 weeks into the study period. When the placebo group switched over to the open-label group after 20 weeks, their enzyme levels had not dropped; however, by 8 weeks of therapy, the patients' enzymes had almost

reached the levels of the group that had received treatment from the start of the study.

In addition, there was an approximately 28% decrease in LDL cholesterol at week 20 compared with a 6% decrease in the placebo group ($P<.001$) as well as improvements in HDL cholesterol in the treatment group. Magnetic resonance imaging found that patients treated with the drug had greater reductions from baseline in liver fat content than those treated with placebo (also significant at week 20).

However, we do not know the long-term outcomes of patients treated with this therapy, which is why these patients are still being followed in the open-label extension.

G&H What adverse events and contraindications are associated with this treatment?

SH Sebelipase alfa is a recombinant human lysosomal acid lipase. It should be avoided in patients who are hypersensitive to egg or egg products because it is produced in egg whites of genetically engineered hens. Additionally, in clinical trials, approximately 3% of patients experienced some evidence of anaphylaxis, chest discomfort, conjunctival injection, dyspepsia, dysemia, and rash. These adverse events occurred as early as the sixth infusion and as late as 1 year after treatment initiation. In addition, approximately 20% of patients experienced signs or symptoms thought to be related to a hypersensitivity reaction. Most occurred within 4 hours of infusion.

Other adverse events associated with the drug include diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis, and urticaria, which occurred in at least 30% of patients with rapidly progressive disease within the first 6 months of life (Wolman disease); in addition, headache, fever, oropharyngeal pain, nasopharyngitis, asthenia, constipation, and nausea occurred in over 8% of pediatric and adult patients.

G&H Are there any special considerations that should be kept in mind when managing patients with lysosomal acid lipase deficiency?

SH The biggest issue is to be cognizant of the organs and organ systems that can be involved with the disease (the liver, heart, spleen, and gastrointestinal tract). Clinicians should have a discussion with their patients about complications that could arise in those organ systems as a result of the accumulation of cholesterol esters. For instance, adult patients should be asked if they are having any gastrointestinal symptoms or cardiovascular complaints, such as shortness of breath or chest pain, and should undergo a thorough physical examination in which the clinician looks for evidence of end-stage liver disease, hepatomegaly, splenomegaly, or jaundice.

G&H What unmet needs remain in this area?

SH The most significant unmet need is disease state awareness. It is important to find and identify these patients because the sooner that this can be done, the better off they will be as far as starting treatment and managing any complications that they may have related to the underlying disease. Many physicians are not familiar with lysosomal acid lipase deficiency and do not consider it when working up a patient with fatty liver, elevated LDL cholesterol, or elevated liver enzymes.

G&H What are the next steps in research?

SH The next steps are to hone in on the true incidence and prevalence of the disease and to determine how the natural history of the disease is altered with the utilization of enzyme replacement therapy.

Dr Harrison is a member of the speakers bureau and is a paid consultant for Alexion.

Suggested Reading

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