

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Current and Emerging Treatments for Alpha-1 Antitrypsin Deficiency



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### **G&H** What is alpha-1 antitrypsin deficiency?

**DP** Alpha-1 antitrypsin deficiency, which was first described 53 years ago, is an autosomal codominant disorder resulting from defective biogenesis of the serum protein alpha-1 antitrypsin by the liver. Essentially, the protein is misfolded, causing it to accumulate in liver cells, and this accumulation produces proteotoxic effects in the liver. The reduction of functional alpha-1 antitrypsin levels in the circulating blood and body fluids is particularly problematic for the lungs because uninhibited proteolytic enzymes can destroy the connective tissue matrix of the lungs in a way that predisposes these individuals to the destructive process of chronic obstructive pulmonary disease.

### **G&H** What are the liver-related consequences of alpha-1 antitrypsin deficiency?

**DP** Alpha-1 antitrypsin deficiency can produce hepatic fibrosis, cirrhosis, and carcinoma, although there is a large variation in the incidence and severity of liver disease in these patients. Although the exact incidence of liver cancer in patients with this deficiency is still unclear, in my experience hepatocellular carcinoma and cholangiocarcinoma are more common among adult patients with this diagnosis than previously recognized.

### **G&H** Does alpha-1 antitrypsin deficiency directly cause liver disease?

**DP** Absolutely. We know this from the severe liver disease that affects some infants, older children, and adolescents

with the deficiency. We are also now beginning to better appreciate that liver disease can first arise in adults with the deficiency, and this is probably more common than the infantile/childhood/adolescent presentations. In some cases, alpha-1 antitrypsin deficiency is the only cause of cirrhosis and/or hepatocellular carcinoma, but in other cases there are additional factors that contribute to hepatic disease, including alcohol abuse, obesity, and chronic viral infection. It is still not proven but it is likely that heterozygotes for the deficiency have a higher incidence of liver disease than the general population, especially if the affected individuals have other liver comorbidities. When my colleagues and I conducted a review of the United Network for Organ Sharing database, we noticed that many patients who undergo liver transplantation with a diagnosis of alpha-1 antitrypsin deficiency are actually heterozygotes for the deficiency who also have other conditions that predispose them to liver disease, such as hepatic steatosis and excessive alcohol intake.

### **G&H** How effective is liver transplantation for this deficiency, and are any other treatments currently available?

**DP** Liver transplantation for alpha-1 antitrypsin deficiency is associated with 5-year survival rates of more than 90% for children and more than 80% for adults. Interestingly, although it is generally thought that liver transplantation for severe liver disease due to alpha-1 antitrypsin deficiency is mostly performed in children, data from the United Network of Organ Sharing and other liver transplant registries show that more than 85% of all

liver transplants performed in the United States for this indication are for adults, with peak ages of 50 to 65 years.

There are currently no other established therapies to treat liver disease in patients with alpha-1 antitrypsin deficiency.

### **G&H** What treatments are currently being investigated for patients with alpha-1 antitrypsin deficiency?

**DP** There are a number of therapeutic ideas currently in various stages of evolution. Alternative therapies to liver transplantation could offer the possibility of treating liver disease before it progresses to the point of causing complications and requiring liver transplantation, could help liver organ shortages by decreasing the need for liver transplantation, and could provide a different therapeutic approach for patients who are not ideal candidates for liver transplantation. One interesting avenue of research involves carbamazepine, a drug that is currently approved by the US Food and Drug Administration (FDA) for the treatment of epilepsy and neuropathic pain. In 2010, my colleagues and I reported that this drug could stimulate intracellular degradation of misfolded alpha-1 antitrypsin, and oral administration of this drug was found to decrease the proteotoxic effects of the deficiency and reverse fibrosis in a mouse model.

The exciting part of investigating this drug for the treatment of alpha-1 antitrypsin deficiency is that it is the first of a pipeline of drugs that work by stimulating autophagy, the cellular process that destroys misfolded proteins, in the liver. My colleagues and I believe that other drugs may also produce this type of biological effect and, thus, could be examined for efficacy in animal models of alpha-1 antitrypsin deficiency. This is important to note because several autophagy-enhancing drugs have been approved by the FDA for other diseases and, thus, are currently being used in clinical practice; therefore, these drugs could immediately jump to phase 2/3 trials for investigation in the setting of alpha-1 antitrypsin deficiency.

### **G&H** Have there been any clinical trials on the use of carbamazepine in patients with alpha-1 antitrypsin deficiency?

**DP** My colleagues and I are currently conducting a phase 2/3 pilot, double-blind, placebo-controlled, randomized, clinical trial on the safety and efficacy of carbamazepine in the setting of severe liver disease and alpha-1 antitrypsin deficiency. The study population consists of patients who have the ZZ or SZ phenotype of alpha-1 antitrypsin deficiency as well as portal hypertension. This trial is still ongoing, so we do not yet know the outcomes of this

potential treatment; in fact, we still need to recruit additional patients to complete the trial. Patient recruitment has been challenging due to the rare nature of the disease.

In addition, my colleagues and I are planning to start a new trial to determine whether the use of other autophagy-enhancing drugs can help stop the progression of alpha-1 antitrypsin deficiency to portal hypertension.

### **G&H** Is carbamazepine the only drug currently undergoing clinical investigation for treatment of this deficiency?

**DP** As far as I know, there are no other clinical trials of drugs or therapeutic strategies for alpha-1 antitrypsin deficiency, although various strategies have undergone discussion and animal study. For example, antisense oligonucleotides have been shown to be efficacious in an animal model of alpha-1 antitrypsin deficiency. However, I do not know whether there are phase 1 trials yet on this treatment strategy.

Another therapeutic approach that has caused some excitement involves the use of clustered regularly interspaced short palindromic repeats (CRISPR) technology to correct the gene defect for alpha-1 antitrypsin deficiency.

### **G&H** How is the gene corrected using this technology?

**DP** CRISPR is a relatively new technology in which a certain type of enzyme can change a single DNA base. This has been an explosive development in biology, and researchers have begun to try to develop the technology for in vivo use in an animal. There have been published reports of correcting the gene defect in a mouse model of Duchenne muscular dystrophy using CRISPR techniques for genomic editing. Recently, it was announced that the company Intellia would target alpha-1 antitrypsin deficiency using this technology. However, this treatment approach is not yet in any clinical trials.

### **G&H** Are any other therapeutic strategies being investigated for alpha-1 antitrypsin deficiency?

**DP** A number of other research groups are working on cell-based therapies. Cells are taken from a person in whom the gene is correct and then differentiated into liver cells and transplanted into an animal with alpha-1 antitrypsin deficiency.

### **G&H** What are the next steps for research?

**DP** My colleagues and I will be continuing to pursue clinical trials of autophagy-enhancing drugs as well as

high-throughput drug discovery efforts that have the potential to identify other pharmacologic approaches. It will also be important to determine whether gene correction strategies, using the new genome editing technologies, can be performed effectively and safely.

*Dr Perlmutter has no relevant conflicts of interest to disclose.*

## Suggested Reading

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