Alpha-1-Antitrypsin Deficiency Liver Disease

Dhiren Patel, MD[a], Jeffrey H. Teckman, MD[a,b,*]

KEYWORDS

• Alpha 1 antitrypsin • Autophagy • Proteolysis • ERAD • Protein polymer • siRNA

KEY POINTS

- Homozygous ZZ alpha-1-antitrypsin (AAT) deficiency is a common genetic metabolic liver disease primarily affecting adults but also, rarely, children. The clinical manifestations are highly variable, with many patients remaining healthy or exhibiting only mild biochemical abnormalities.
- Accumulation of the AAT mutant Z protein within hepatocytes activates an intracellular injury cascade of apoptotic liver cell death and compensatory hepatocellular proliferation, leading to end-organ injury.
- There is no specific treatment of AAT-associated liver disease; however, there are treatment options involving supportive measures and liver transplant.
- New technologies aimed at stimulating proteolysis via autophagy, small molecule chaperones, gene therapy, RNA technologies, gene repair, or cell transplantation may hold promise for the treatment of this disease.

INTRODUCTION

The liver is the primary site of synthesis of alpha-1-antitrypsin (AAT) protein, although it is also made in enterocytes and some mononuclear white blood cells.[1] Large quantities of AAT are secreted from the liver on a daily basis, second only to albumin as a mass of a single serum protein. Almost all liver disease is associated with homozygosity for the Z mutant of the AAT gene, although in some circumstances compound

Disclosure Statement: D. Patel has no disclosures. Dr J.H. Teckman is a consultant in the Alpha-1 patient community, and grant reviewer and advocate for the nonprofit Alpha-1 Foundation and the Alpha-1 Project. Dr J.H. Teckman is a consultant, site investigator, and/or grant recipient involved with the following companies: Alnylam Inc, Arrowhead Pharmaceuticals Inc, Dicerna Inc, Editas Pharmaceuticals, Gilead Pharmaceuticals, Intellia Corp, Proteostasis Inc, RestorBio, Third Rock Consulting, Triangle Insights, and Snyder Legal.

[a] Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, Saint Louis University School of Medicine, 1465 South Grand Boulevard, St Louis, MO 63104, USA; [b] Department of Biochemistry and Molecular Biology, Saint Louis University School of Medicine, 1465 South Grand Boulevard, St Louis, MO 63104, USA
* Corresponding author. 1465 South Grand Boulevard, St Louis, MO 63104.
E-mail address: Jeff.teckman@health.slu.edu

Clin Liver Dis 22 (2018) 643–655
https://doi.org/10.1016/j.cld.2018.06.010 **liver.theclinics.com**

heterozygotes involving one Z gene are implicated in liver disease. During biosynthesis, the AAT mutant Z protein is appropriately transcribed and translated, and the nascent polypeptide chain is translocated into the endoplasmic reticulum (ER) lumen of the hepatocyte.[1,2] In the ER, the nascent polypeptide binds with a complex system of chaperone proteins, which not only assist in folding but also perform quality-control functions to identify abnormal proteins. Unlike the wild-type (WT) M, AAT protein, which rapidly folds into its final conformation and is secreted in minutes, the mutant Z form folds inefficiently: 85% of the molecules never reach a secretion-competent conformation and are retained in the hepatocyte. Individual, monomeric mutant Z molecules are held in the ER, which can last more than an hour before being directed to proteolysis pathways in experimental systems.[2] Some new data suggest that the molecules may be routed to the Golgi and then returned to the ER as part of the quality-control process. Some of the mutant Z molecules aggregate, or polymerize, into large masses surrounded by rough ER, although how the destiny of these molecules is determined and how the location in the ER is chosen remains unknown. Often, these inclusions, termed globules, are large enough to be seen by light microscopy as the classically described periodic acid-Schiff (PAS)–positive, digestion-resistant, hepatocellular inclusions characteristic of this disease (**Fig. 1**). It is this accumulation of AAT mutant Z protein in hepatocytes that is the inciting event in liver injury associated with AAT deficiency. Although this accumulation is the primary cause of liver damage, it is not sufficient because not all ZZ individuals develop liver disease despite the presence of mutant Z protein retained in the liver.[1,3] Therefore, there is likely a significant role for genetic and environmental disease modifiers, or second hits, which determine whether a given individual will develop liver injury and at what age this might occur.

CLINICAL PRESENTATION

Liver disease associated with AAT deficiency is highly variable and may have a variety of clinical presentations, including chronic hepatitis, cirrhosis, hepatocellular carcinoma (HCC), or the rare occurrence of fulminant hepatic failure[4–6] The pathogenesis of liver and lung disease seems to be independent and, therefore, it is likely that they are neither protective of each other nor a risk factor for each other. The peak

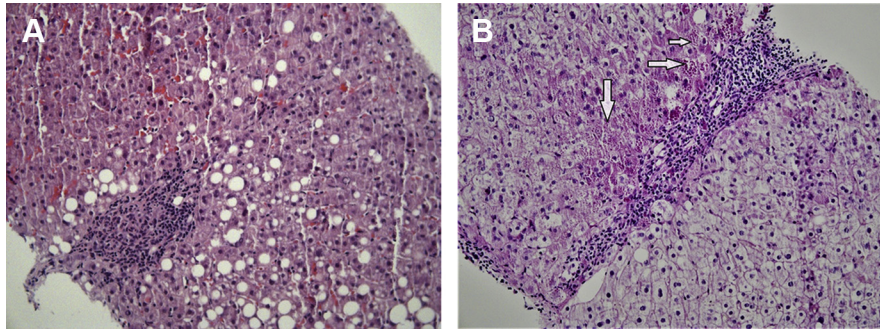

Fig. 1. Photomicrographs of human ZZ liver stained with (*A*) hematoxylin-eosin (H&E) and (*B*) PAS followed by diastase digestion (PASd). PASd stains accumulations of glycoproteins red, which can be easily identified on a neutral background. Normal liver is typically free of large, stainable glycoprotein masses. The globules (some highlighted by *arrows*), are variable in size and are not seen in all hepatocytes for unknown reasons.