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Drugs Needed for Treatment of Liver Cirrhosis

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A number of chemicals including most commonly used and abused agent, alcohol,are the cause of progression of liver from hepatosteatosis, steatohepatitis, and fibrosisto cirrhosis [1]. The earliest symptoms of alcohol toxicity are treatable involvingcessation of drinking and modifications of diet. The initial exposure of liver after either binge or chronic alcohol drinking, results in liver injury especially hepatocytes death. Due to death of hepatocytes, the level of enzymes, transaminases, glutamic pyruvic transaminase (GPT) and glutamate oxaloacetate transaminase (GOT) in serum is elevated and biosynthesis of bile salts and its derivatives are affected. The rise in the blood level of alkaline phosphatase is the indicator of affected bile acid biosynthesis and its secretion from liver. The dead hepatocytes are replaced with scarring tissues resulting in loss of liver functions, including drug metabolism, secretions of proteins from liver, decreased albumin level and changes in the blood clotting time. The metabolism of drugs like acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) could also be affected. The bilirubin metabolism occurs in liver and due to affected liver function, its clearance is also affected. In alcohol mediated hepatitis, the level of bilirubin is increased in the blood and is an indicator of jaundice. Liver cirrhosis mediated death is linked to usage of alcohol. According to the several published reports, the highest number of deaths due to alcohol mediated cirrhosis occurs in countries like Spain, France and Italy where highest amount of alcohol is consumed compare to many other industrialized western countries including USA. It is difficult to estimate the incidence of liver cirrhosis as it remains silent till patients develops the symptoms of liver failure. It is estimated that liver cirrhosis occurs in 2 individuals per 100,000 individuals.

Chronic alcohol drinking leading liver to cirrhosis has a genetic component as well. Not all alcohol abusers and chronic alcoholics progress to liver cirrhosis. Some of likely genetic markers of alcohol mediated liver toxicity to end stage liver cirrhosis have been studied. However, predicting an individual of progression from hepatosteatosis, steatohepatitis, and fibrosisto cirrhosis is still difficult. Liver cirrhosis is an irreversible condition and goals for the available treatments are slowing the progression of disease and further complications. There are no drugs that can reverse and treat liver cirrhosis. Researchers are investigating the efficacy of several antifibrotic agents which can block the fibrosis of liver, a condition before the scarring of liver tissue. Fibrosis is associated with excessive deposition of extracellular matrix (ECM) and fibroblasts have been the excessive source of ECM. Counteracting the synthesis and secretion of ECM molecules is the focus of antifibrotic agent. Transforming growth factor β (TGFβ) is implicated in fibrosis and blocking TGFβ ameliorates the experimental fibrosis. However, TGFβ independent fibrosis mediated by cytokines can also occur in liver. Two humanized antibodies against TGFβ, one by Genzyme (GC1008) and Lilly (LY2382770) are under clinical trials at phase I and Phase II respectively for non-liver fibrosis (ClinicalTrials.gov). Antibodies against other important molecules are targeted for many other organ fibrosis [2]. Another approach of the treatment could be degradation of ECM molecules.Collagen, a component deposited during fibrosis can be degraded by matrix metalloproteinases and experimentally increasing the expression of such metalloproteinases like MMP-8 has been shown to ameliorate the symptoms of fibrosis in experimental models [3]. Another approach could be application of microRNAs (miRNA) or miRNA mimetics but delivery of such agents is a challenging task for the current scientists. Patients with liver cirrhosis are recommended for screening of liver cancer and one of the markers of liver cancer; α-fetoprotein in blood [4] in addition to imaging test which includes ultrasound, magnetic resonance imaging (MRI), or computerized tomography (CT) scan can be employed. In spite of development, there are not that many options for the treatment of liver cirrhosis; transplant of the liver is the only solution. There is an immediate need for the development of drugs which can block the progression of liver from fibrosis to cirrhosis and reverse the process for the growth of hepatocytes which can replace the scarred tissue thus restoring the liver function.

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