Targeting Galectin-3 Protein as a Therapeutic Approach in NASH and Liver Fibrosis

Galectin-3 protein has been implicated in the pathogenesis of NASH and liver fibrosis. Galectins are a family of proteins, containing 15 members (11 in humans), with the property of binding avidly to the monosaccharide galactose associated with glycoproteins (reviewed in (1)). Glycoprotein interactions promote cell-cell, cell-matrix, and matrix-matrix interactions and association of membrane receptors that can cause activation, inactivation, or modulation of cell receptor activity leading to modulation of intracellular signaling and subsequent events.

Increased expression of galectin proteins has been implicated in a number of pathological processes associated with inflammation, immune function, organ fibrogenesis, and cancer. Galectin-3 knockout mice have been shown to be resistant to liver fibrosis due to toxin administration (2), lung fibrosis due to bleomycin toxicity (3), and kidney fibrosis due to ureteral ligation (4). Galectin-3 knockout mice have also been used to explore the importance of galectin-3 in NASH. In these experiments, mice were fed a high fat diet to induce the development of NAFLD and NASH (5). Normal mice readily developed fatty liver, inflammatory infiltrates in the liver and liver fibrosis. In stark contrast, the galectin-3 knockout mice did not develop as much fat accumulation and had minimal inflammatory infiltrate and fibrosis. It should be noted that another investigative group has suggested that galectin-3 knockout mice are more prone to develop NASH and neoplastic nodules later in life (6). The different conclusions of these two groups are not resolved, but may be due to mouse strain differences. Taken together, these data suggest that galectin-3 plays a critical role in fibrogenesis in a number of organs, and importantly in two models of liver fibrosis.

To evaluate pharmacological inhibition of galectin-3, animal models of NASH and liver fibrosis were tested with a galectin inhibitor developed by Galectin Therapeutics, GR-MD-02. Experiments focused on NASH were performed in diabetic mice, which develop a highly reproducible NASH with fibrosis pathology after being fed a high fat diet. The mice consistently develop NASH with hepatocyte fat accumulation, evidence of hepatocyte toxicity, portal and lobular inflammatory infiltrates, peri-sinusoidal fibrosis, advanced fibrosis with nodule formation, cirrhosis, and ultimately hepatocellular carcinoma in a percentage of animals.

In this mouse NASH model, therapy with GR-MD-02 was able to reduce development of, and cause regression of, histopathological evidence of NASH, including hepatocellular fat accumulation, hepatocyte ballooning, intra-portal and intra-lobular inflammatory infiltrate, and fibrosis, including, but not limited to, collagen deposition in the peri-sinusoidal space (7). In additional experiments in a toxin-induced model of liver fibrosis in rats, GR-MD-02 demonstrated the ability to reverse established fibrosis and cirrhosis and reduce portal hypertension (8).
In 2013, a clinical development program was initiated which received Fast Track Designation from the FDA. A Phase 1 clinical trial in subjects with NASH with advanced hepatic fibrosis was conducted at 7 US sites to evaluate safety and pharmacokinetics of GR-MD-02 to provide information and support to design a Phase 2 clinical program to assess efficacy of GR-MD-02 in patients with NASH with advanced fibrosis and cirrhosis. The trial was designed as a blinded, placebo controlled, sequential dose escalation trial with three cohorts receiving 2, 4, and 8 mg/kg lean body weight of GR-MD-02 administered by IV infusion over one hour. The subjects enrolled had liver biopsy proven NASH with Brunt stage 3 fibrosis. The primary endpoints were safety and pharmacokinetics. Disease serum biomarkers and FibroScan® (9) were also evaluated as exploratory endpoints. More information on the trial can be found at clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT01899859?term=GR-MD-02&rank=2

The results show that the Phase 1 study was successful in providing information on the design of a Phase 2 clinical trial to demonstrate efficacy. First, and most importantly, GR-MD-02 was safe and well tolerated at single and multiple doses of 2, 4, and 8mg/kg. Pharmacokinetics revealed drug exposure in humans at the 8 mg/kg dose that was equivalent to the upper range of the targeted therapeutic dose determined from effective doses in NASH animal models, thus providing support for the proposed Phase 2 dosing regimen. Additionally, there was evidence of an effect on a relevant disease marker, with a dose dependent reduction in FibroTest® (10) scores due to a reduction in alpha-2 macroglobulin levels. And finally, there was a trend that suggested liver stiffness, which may be related to a reduction in fibrotic tissue, is reduced by GR-MD-02 at the highest dose administered.

Based on the results of the Phase 1 study, two Phase 2 clinical trials will be initiated in Q2 2015. Study GT-026 will evaluate the safety and efficacy of one year of therapy with GR-MD-02 in subjects with portal hypertension due to NASH cirrhosis. The primary endpoint of this study will be portal pressure as measured by hepatic venous pressure gradient, with secondary endpoints of collagen proportional area on liver biopsy, FibroScan®, and 13C-methacetin breath test (Exalenz). Study GT-028 will evaluate the safety and efficacy of 4 months of therapy with GR-MD-02 in subjects with NASH with advanced fibrosis (>Brunt stage 3). The primary endpoint of this study will be liver stiffness as measured by magnetic resonance elastography, with secondary endpoints of FibroScan® and multi-parametric magnetic resonance imaging (LiverMultiScan®, Perspectum Diagnostics).
References


