Pentoxifylline: not just for alcoholic hepatitis anymore?

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Non-alcoholic fatty liver disease (NAFLD) has seen a significant increase in prevalence worldwide, associated with the increase in obesity and the metabolic syndrome in the general population [1, 2]. NAFLD is the hepatic manifestation of insulin resistance. Non-alcoholic steatohepatitis (NASH) is the subset of NAFLD in which steatosis of the liver is accompanied by inflammation and progressive fibrosis. NASH is felt to be a major etiology of cryptogenic cirrhosis [1]. Approximately 10–20% of patients with NASH may progress to cirrhosis [3], and many patients with cryptogenic cirrhosis have been found to have risk factors for NASH including obesity and type II diabetes mellitus [4]. The pathophysiology of NASH is complex and current prevailing theories of pathogenesis involve the overlay of insulin resistance with oxidative stress and/or impaired mitochondrial function [5]. Classically, it has been felt that the presence of obesity-induced insulin resistance leads to the conversion of fatty acids and glucose-3-phosphate to intrahepatic triglycerides, while there is simultaneous suppression of hydrolysis of intrahepatic triglycerides by high circulating levels of insulin, although ongoing research has contributed significant complexity to the understanding of the pathogenesis of NASH [5]. Theories regarding additional factors that contribute to the progression of inflammation and fibrosis in NASH have centered on

oxidative stress. Oxidative stress is mediated by the generation of reactive oxygen species that induce hepatocyte damage/apoptosis which in turn stimulate an inflammatory response. The fibrotic response to inflammation may, in turn, be mediated by induction and activation of TGF- β that activates hepatic stellate cells [6].

As the burden of NAFLD increases, there have been efforts to identify means of modulation of liver injury in this condition. Weight loss through diet and exercise has been shown to result in improved insulin resistance and improvement of markers of liver inflammation [7–9]. Unfortunately, patients in whom significant obesity and insulin resistance have developed over many years oftentimes experience difficulty with efforts at lifestyle modification. Patients with severe obesity and in whom portal hypertension has not developed may be candidates for surgical weight-loss procedures, such as the Roux-en-Y gastric bypass that has been demonstrated to result in improvement of hepatic steatosis and mediators of hepatic fibrosis [10].

The medical therapy of NAFLD and NASH is an arena of significant research. There have been multiple studies of therapeutic agents to impact the evolution of inflammation and fibrosis in patients with NASH. The thiazolidinediones, which function as PPAR- γ agonists have been shown to improve hepatic transaminases and to improve hepatic histology [11, 12], but the long-term safety and effectiveness of these medications have not been demonstrated. In the only placebo controlled trial of a thiazolidinedione for treatment of NASH, while significant histological improvements were noted in patients receiving pioglitazone, a significant improvement in hepatic fibrosis was not observed in this group compared to those receiving placebo [13]. Metformin has been shown to improve hepatic transaminases and may improve hepatic inflammation and

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fibrosis [14] but its long-term effectiveness has not been demonstrated. Anti-oxidants such as vitamin E have not demonstrated convincing effectiveness in improvement of markers of hepatic inflammation or steatosis [15].

The modulation of cytokines associated with hepatic steatosis and its associated inflammation and fibrosis has become a recent focus of study. Circulating levels of TNF- α have been demonstrated to be elevated in patients with NASH compared to control patients [16]. TNF- α has previously been demonstrated to be an important target for modulation in alcoholic liver disease, a condition that shares identical histopathological findings to the spectrum of NAFLD [17, 18]. In a study by Arkiviadis, the short-term use of pentoxifylline was associated with significant improvement in mortality in patients treated for severe acute alcoholic hepatitis [19]. In this group of patients with predicted high mortality, 28 days of standard dose pentoxifylline improved mortality, with the greatest impact being seen in the prevention of hepatorenal syndrome.

As TNF- α has been shown to be a mediator of insulin resistance [20], as well as participate in the development of oxidative stress within the liver, it is a likely contributor to the pathogenesis of NASH. Pentoxifylline has been shown to block the activation of hepatic stellate cells in culture [21]. Animal studies of pentoxifylline in NASH models have shown significant improvement in hepatic steatosis, inflammation, and improvement of hepatic transaminases with the use of pentoxifylline [22, 23]. In addition, in cultured peripheral blood mononuclear cells taken from human patients with NASH, treatment with pentoxifylline significantly decreases TNF- α production after stimulation of cells with lipopolysaccharide [24].

There have been two previous studies of the use of pentoxifylline in human populations. Adams et al. evaluated the effects of pentoxifylline in 20 patients with biopsy-confirmed NASH over a period of 12 months [25]. Improvement of hepatic transaminases was demonstrated after therapy with pentoxifylline, but the study was limited in that almost half of the patients treated were unable to tolerate the medication with side-effects, and there was no placebo arm of the study. The high rate of side effects in this study may have been due to the high doses of pentoxifylline used. In the other study, Satapathy et al. demonstrated improvement in hepatic transaminases, steatosis, inflammation, and fibrosis by serial biopsies in 9 patients treated for 12 months with standard doses of pentoxifylline [26]. In addition, of the patients with measured insulin resistance, the majority of these had significant improvement in insulin resistance with pentoxifylline therapy despite an insignificant improvement in body mass index over the course of the study.

In the present study, Lee et al. compared the use of standard doses of pentoxifylline with placebo in patients

with biopsy-proven NAFLD [27]. Most patients had both inflammation and fibrosis in addition to steatosis. In both groups, weight loss was achieved through the use of a monitored calorie restricted diet as well as regular exercise. The administration of study medications was performed in a double-blind manner. Both groups of patients demonstrated weight loss of similar magnitudes. Both groups of patients had significant improvement of hepatic transaminases. The patients who received pentoxifylline however, experienced a significant reduction in measured AST compared to those who received placebo. While the reduction in measured ALT was greater in those who received pentoxifylline compared to those patients who received placebo, the difference between these groups did not quite meet statistical significance. The authors conclude that the use of pentoxifylline is associated with reduction in hepatic transaminases in patients with biopsy-proven NAFLD. There was no significant difference in measured levels of TNF- α and IL-6 between the two groups.

The results of these three studies offer hope of pentoxifylline as a therapeutic agent in the treatment of patients with NASH. All three studies involved small groups of patients, and only the study by Lee et al. included a control group. NASH is a chronic condition and effective therapy with any medication will have to be demonstrated over multiple years. The long-term safety of pentoxifylline, or any proposed medical therapy for NASH, will have to be demonstrated in patients with chronic liver disease. The prevalence of NASH and the projected forthcoming burden on the health care industry that will be seen if end-stage liver disease from NASH progresses as projected will mandate continued research regarding medical therapies for fatty liver disease. As the roles of cytokines in the pathogenesis of NASH become more understood, it is hoped that efforts at targeting specific cytokines will result in improved management of NASH and prevention of progression of liver disease. The present study by Lee et al., in the context of other small studies, is promising and may be an early step towards improving the clinical course of NASH through the modulation of TNF- α . There are currently no drugs that have demonstrated convincing benefit for the management of NASH. Long-term, adequately powered, placebo controlled trials with histological endpoints will be required of pentoxifylline before its role in the management of NASH will be clarified.

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