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Pentoxifylline for Steatohepatitis: Magic Bullet Or Smoking Gun?

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Nonalcoholic steatohepatitis (NASH) is the most common chronic liver disease in North America.[1,2] It is characterized by the presence of predominantly macrovesicular steatosis along with scattered inflammation, hepatocellular ballooning, and varying degrees of pericellular fibrosis, usually with a predominantly centrilobular distribution.[3] NASH is commonly associated with obesity, type 2 diabetes mellitus, hypertension, and dyslipidemia, which are features of the metabolic syndrome.[4]

Much of the data regarding the prevalence of NASH have either come from focused biopsy-based studies in a hospital environment or from population-based studies where the presence of NASH has been inferred from the presence of either elevated liver enzymes and/or presence of excessive fat in the liver as assessed by an imaging study.[5,6] Despite the variability of sources of the data and their methodologic limitations, the data indicate that approximately 4%–5% of the general population has NASH, whereas up to 30% of the population has hepatic steatosis.[5,7,8] It has also recently been shown that in subjects attending an outpatient medical clinic who were all screened with an ultrasound and offered a liver biopsy if they were found to have an echogenic liver, up to 12% of subjects had NASH.[9] Even conservatively estimating the prevalence of NASH at 4%, there are 1.2 million individuals in the United States with NASH.

There are only limited prospectively collected data on the natural history of NASH. Retrospective data indicate that 15%–20% of subjects will progress to cirrhosis.[10,11] NASH also increases overall mortality with cardiovascular death and liver-related deaths dominating as causes of the excess mortality.[10,12,13] Although direct high-quality evidence of increased mortality due to cirrhosis and cardiovascular disease remain to be published,[14] there is a large body of indirect evidence by which to make a compelling case that NASH increases both liver-related and cardiovascular mortality. The widespread prevalence and the effect of NASH on all-cause mortality in general and liver and cardiovascular mortality in particular are the principal determinants of the public health burden of the disease and provide the rationale for treating it with all means possible.

Several drugs have been used in an attempt to treat NASH. The largest amount of data relate to the efficacy of thiazolidinediones such as pioglitazone (an insulin sensitizer) and vitamin

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E. Insulin resistance is a common pathophysiologic denominator in conditions associated with the metabolic syndrome, and thiazolidinediones are potent insulin sensitizers.[15,16] Several studies (Table 1) indicate that this class of drugs is effective in decreasing the severity of individual histologic features of NASH. A recent meta-analysis also suggests that pioglitazone improves hepatic fibrosis.[31] However, the use of these drugs is associated with weight gain, which continues as long as the subject is on treatment.[31] This weight is not lost after discontinuation of therapy, although the benefits of treatment rapidly reverse after stopping treatment.[30,31] Moreover, as a class, these drugs are associated with volume overload and congestive heart failure as well as an increased risk of osteopenia and fractures.[32]

Vitamin E (tocopherols) is a potent antioxidant and has also been used for the treatment of NASH. Vitamin E exists in eight forms: α-, β-, γ-, and Δ-tocopherol and α-, β-, γ-, and Δ-tocotrienol. All feature a chromanol ring, with a group that can donate an atom to reduce free radicals and a side chain that allows for penetration into biological membranes. There are substantial differences in the biological properties of these compounds. The natural form of vitamin E (rrr α-tocopherol) has been shown to improve the histological features of NASH in a large, prospective, controlled trial.[30] These data are corroborated by several smaller studies. It is, however, important to note that vitamin E is not a panacea and only improves histological features in 43% of subjects.[30] There is considerable controversy over whether vitamin E produces a small but significant increase in all-cause mortality when taken as a health supplement.[33–36] Therefore, there is room for additional therapies for NASH. In this issue of Hepatology, Zein et al.[37] provide evidence of improvement of NASH following pentoxifylline administration.

The rationale for the use of pentoxifylline is based on its reported ability to inhibit the synthesis/release of tumor necrosis factor-α (TNF-α) and its ability to inhibit TNF- and eicosanoid-induced inflammatory responses.[38] TNF-α is a proinflammatory, proapoptotic cytokine that is activated as part of the innate immune system and has been implicated as a key player in the development of hepatic steatosis and steatohepatitis. The development of hepatic steatosis has also been shown to increase the susceptibility of hepatocytes to TNF-mediated apoptosis.[39] Prior small trials have also shown the promise of efficacy of pentoxifylline for treatment of NASH.[40,41] The data from Zein et al.[37] further corroborate these early data.

The ideal treatment for NASH should be one that decreases overall mortality, including liver-related and cardiovascular deaths, while remaining safe, widely available, and relatively inexpensive. Demonstration of an improvement of all-cause mortality would require a very large study followed over an extended period of time. These considerations make it impractical to use this as a primary endpoint in clinical trials, and instead has led to the use of surrogate endpoints to determine the efficacy of a drug for NASH. Because liver-related mortality is associated mainly with cirrhosis, prevention of cirrhosis or reversal of the disease associated with cirrhosis, i.e., steatohepatitis, is often considered acceptable as an endpoint for NASH. Because steatohepatitis may disappear with disease progression, it is further imperative to combine this endpoint with “at least no worsening of fibrosis” to make it clinically relevant.[42]

In the study by Zein et al., the primary endpoint was a decrease in the NAFLD activity score (NAS) of 2 or greater. This score was developed as a relatively quantifiable way to evaluate the impact of drug treatment on the severity of key histological features of NASH.[43] It must, however, be emphasized that changes in NAS have not been validated to correlate with alteration in the natural history of the disease. Also, the clinical significance of the relative contribution of individual features to the decrease in NAS remains unknown. Thus, given these gaps in knowledge, changes in NAS are inferior to reversal of steatohepatitis as an endpoint that reflects an improvement in the natural history of the disease.

Although the authors provide a justification for their sample size estimations, given the variability in the severity of the individual parameters included in the NAS and the variability due to sample size estimation, the study is somewhat underpowered to make definitive conclusions about treatment efficacy in NASH. Also, several subjects did not complete the study or or did not receive an end-of-treatment biopsy. Finally, only 5 of 55 subjects had type 2 diabetes; diabetes is a major risk factor for disease progression to cirrhosis. These factors limit the ability to draw definitive conclusions about the efficacy of pentoxifylline for NASH or the generalizability of the data to those at greatest risk of developing progressive disease.

It is interesting to note that pentoxifylline did not meet the proof of concept sufficient to demonstrate biological effect, i.e., a decrease in circulating TNF-α levels or markers of insulin sensitivity (adiponectin, insulin sensitivity index). These would suggest that either the assays were inaccurate or there are alternate mechanisms underlying the observed decrease in NAS. Our view is that the latter is more likely. Notably, the improvement in NAS was driven by a decrease in steatosis. This could reflect changes in diet and exercise; however, these data were not collected or provided. Also, the clinical implications of a major decrease in steatosis are unknown. It is also possible that pentoxifylline has novel, hitherto unknown, mechanisms of action. This remains to be experimentally verified. So, is pentoxifylline a magic bullet or a smoking gun in the treatment of NASH?

In conclusion, the list of drugs that can improve histological characteristics of NASH seems to be growing. Although Dr. Zein's study provides impressive evidence of improvement in steatosis and inflammation, pentoxifylline did not significantly improve hepatocellular ballooning. Although a trend for improved fibrosis was noted, it is critically important not to overinterpret the data in a study with a small sample size. However, these data show enough preliminary evidence for a potential ability of pentoxifylline to improve NASH to set the stage for future, fully powered, phase 3 clinical trials.

Abbreviations

NAS	NAFLD activity score
NASH	nonalcoholic steatohepatitis
TNF	tumor necrosis factor

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Table 1

Controlled Trials of the Effects of Vitamin E and Insulin Sensitizers in Patients with Nonalcoholic Fatty Liver Disease

Author (Year)	Design	Intervention	Comparator	Duration (Months)	Histologic Improvement	ALT Improvement	Reference
Lavine (2001)	OL	Vitamin E	–	4–10	NA	+	17
Hasegawa et al. (2001)	OL	Vitamin E	–	12	+	+	18
Harrison et al. (2003)	RCT	Vitamin E and vitamin C	Placebo	6	–	–	19
Sanyal et al. (2004)	RCT	Vitamin E + pioglitazone	Vitamin E	6	+	–	20
Uygun et al. (2004)	RCT	Metformin	Diet	12	–	+	21
Bugianesi et al. (2005)	RCT	Metformin	Vitamin E or diet	12	+	+	22
Belfort et al. (2006)	RCT	Diet + pioglitazone	Diet + placebo	6	+	+	23
Dufour et al. (2006)	RCT	Vitamin E + UDCA	UDCA + placebo	24	+	+	24
Yakaryilmaz et al. (2007)	OL	Vitamin E	–	6	+	+	25
Ratziu et al. (2008)	RCT	Rosiglitazone	Placebo	12	+	–	26
Aithal et al. (2008)	RCT	Diet/exercise + pioglitazone	Diet/exercise + placebo	12	+	+	27
Nar and Gedik (2009)	RCT	Metformin	Lifestyle modification	6	NA	+	28
Omer et al. (2010)	RCT	Metformin	Rosiglitazone or rosiglitazone + metformin	12	+	NA	29
Sanyal et al. (2010)	RCT	Pioglitazone or vitamin E	Placebo	24	+	+	30

NA, not applicable; OL, open label; RCT, randomized controlled trials; UDCA, ursodeoxycholic acid.

For improvement columns, “+” indicates improvement and “−” indicates no improvement.