Nonalcoholic Fatty Liver Disease

Digestive Diseases

Dig Dis 2016;34(suppl 1):27–31
DOI: 10.1159/000447278

Treatment of Non-Alcoholic Fatty Liver Disease

Antonia Scherer[a, b] Jean-François Dufour[a, b]

[a]Department of Clinical Research, Hepatology, and [b]University Clinic for Visceral Surgery and Medicine, Inselspital, University of Bern, Bern, Switzerland

Key Words
Antioxidants · Drug treatments · Lifestyle changes · Non-alcoholic steatohepatitis treatment · Transcription factor agonists

Abstract
Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of conditions from steatosis to cirrhosis and hepatocellular carcinoma. Steatosis is a benign reversible condition, which does not need treatment. Cirrhosis and hepatocellular carcinoma are the end stages of any chronic liver disease and do not have etiology-specific treatments. In this chapter, we will review treatment options for non-alcoholic steatohepatitis, which is the progressive form of NAFLD. Basically there are 2 strategies, the first of which is to address lifestyle and the second to use medication. The first approach is the most physiologic, the least expensive, but is also the most difficult to implement. The second approach, which should help patients who failed the first approach, is at the advanced clinical research stage.

Lifestyle Changes

Non-alcoholic steatohepatitis (NASH) occurs with such frequency because it is the consequence of our physiology being unable to adapt to our new living conditions, that is, the evolution selected for organisms able to store energy to survive famine. Nowadays, it is no longer a necessity for us to move to find food, as it would have been for our ancestors. We are constantly exposed to high energy and high caloric nutrients and overweight concerns a significant proportion of the population. Weight loss improves transaminases. In a prospective, longitudinal cohort study, a correlation between weight changes and modification of transaminases was found [1]. Patients who gained >5% of body weight had increased transaminases, whereas those who lost >5% of body weight saw an improvement in their transaminases. More than 5% weight reduction was also associated with a decrease in serum triglycerides and fasting blood glucose, an increase in HDL cholesterol as well as decreased blood pressure. Harrison et al. [2] reported that losing ≥5% of body weight over 9 months was enough to improve insulin resistance as well

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Prof. Jean-François Dufour
Department of Clinical Research
University Clinic for Visceral Surgery and Medicine
Inselspital, CH–3010 Bern (Switzerland)
E-Mail jean-francois.dufour@ikp.unibe.ch

as steatosis and that a weight loss ≥9% was additionally associated with less hepatocyte ballooning, less inflammation and a decrease in non-alcoholic fatty liver disease (NAFLD) activity score. This was confirmed in a randomized controlled trial where there was a correlation between improvement of NAFLD activity score in the histology and the percentage of weight change [3]. People, who achieved a mean weight reduction of 8.7 kg due to lifestyle interventions during a 48-week period, could reduce their overall NASH activity score by ≥3 points. Huang et al. [4] also showed an improvement in histology for NASH patients due to a 1-year dietary program.

Physical activity reduces steatosis in patients with NAFLD [5] even when it is not enough to change body weight [6] or to improve ALT [7], but according to St. George et al. [8], it does improve gamma GT significantly. Hallsworth et al. [9] also showed an improvement of steatosis in sedentary adults through resistance exercise, even at a level where it does not have an impact on body weight. In a study by Oh et al. [10], 169 obese men were enrolled in a 3-week weight reduction program. Those with physical activity of >4 h per week not only had an improvement of the hepatic steatosis, they also showed an improvement of hepatocellular apoptosis and hepatic stiffness.

With regards to diet, omega-3 polyunsaturated fatty acids have been suggested to improve steatosis and AST, but not ALT [11]. In a phase II randomized controlled trial though, no significant effects of ethyl-eicosapentaenoic acid on histologic features of NASH were reported [12]. Monounsaturated fatty acids have been reported in a controlled randomized study over 8 weeks to improve liver fat significantly, which was measured by proton nuclear magnetic resonance spectroscopy in patients with type 2 diabetes [13]. Regarding the benefit of a Mediterranean diet with a high consumption of monounsaturated fatty acids, Ryan et al. [14] performed a randomized crossover study, which also demonstrated a decrease in liver fat and an improvement in insulin sensitivity. Machado et al. [15] found out that trans- and saturated fatty acids correlate with oxidative stress markers such as 4-hydroxynonenal. In a rather provocative study, Kechagias et al. [16] placed 18 healthy individuals on a high caloric fast food-based diet for 4 weeks. They gained 6.4 kg and most of them had abnormal ALT at the end of the study. This clarifies the negative effects of excessive nutrition.

Where sodas are concerned, fructose reduces the satiety sensation; it is taken up into hepatocytes where it increases lipogenesis as well as the production of reactive oxygen species and reduces lipid oxidation [17]. Additionally, fructose has been shown to promote fibrosis as well as inflammation and hepatocyte ballooning in subjects older than 48 years [18].

There are more and more epidemiology studies showing the beneficial effects of coffee. In a large survey and multivariate analysis, low caffeine intake was found to be an independent predictor for NAFLD, after adjustment for race, gender and metabolic syndrome components [19]. Coffee consumption was lower in patients with more fibrosis, which allows the assumption of regular coffee having a protective role against NAFLD [20].

Provocatively, no alcohol is worse than a little bit of alcohol. In a study conducted by the NASH Clinical Research Network, it was discovered that NASH, fibrosis, ballooning, Mallory bodies and inflammation in histology occurred more frequently in non-drinkers than moderate drinkers [21].

Smoking has also been associated with NAFLD [22] and there are data showing that cannabis promotes liver fibrosis in patients with chronic hepatitis C [23]. Finally, sleep duration is also important. Less than 5 h of sleep elevates the risk of NAFLD in middle-aged people significantly and insufficient sleep has also been associated with an elevated risk for a fatty liver index ≥60 [24].

Based on this evidence, it is clear that the first approach for patients with NASH is to review their habits and to discuss strategies with them that improve their lifestyles. Unfortunately, changing habits is difficult and even if it is the least expensive, the safest and the most effective treatment option for NASH, it is one of the least successful in practice. Recommendations to perform exercise, eat differently and lose weight often remain wishful thinking.

Drug Treatments

Antioxidants

In the past, antioxidative medication was discussed as a treatment of NASH. In randomized controlled trials, however, ursodeoxycholic acid was unconvincing as it was ineffective as monotherapy at the usual dose [25]. Thiazolidinediones, which function as PPARγ agonists, did show positive effects in patients with NASH in randomized controlled trials, but unfortunately, they result in significant weight gain [26].

The systematic review of the network meta-analysis comparing the effectiveness of pharmacologic interventions for NASH found that pentoxifylline, which is an inhibitor of TNF-α, may have an anti-fibrotic effect [27]. A

meta-analysis confirmed possible advantages of pentoxifylline in patients with NASH [28].

A randomized controlled trial performed with nondiabetic adults with NASH found that vitamin E for about 2 years led to a significant improvement in histologic lesions [29]. These results were duplicated in a pediatric trial [30], showing less hepatocellular ballooning in children who were treated with vitamin E. Singh et al. [27] also reported a positive effect on ballooning by vitamin E. In a pooled analysis, it was suggested that vitamin E might also have a positive effect on histology in patients with diabetes and NASH (K. Kowdley et al. AASLD 2015, Abstract 107). However, they could neither confirm an association between vitamin E and changes in serum lipids nor an association with cardiac events. In other trials, however, vitamin E has been reported to be associated with cardiovascular events [31]. This is an issue in patients with NASH since they are already at risk of cardiovascular events. In addition, the extended follow-up of the SELECT trial demonstrated a significant association between vitamin E and an increased risk of developing prostate cancer among healthy men [32]. These aspects unfortunately decrease the attractiveness of an otherwise inexpensive, safe, well-tolerated and (probably) effective NASH treatment. It emphasizes the need for further trials on vitamin E, especially on its efficacy in diabetic patients as well as other possible treatments for NASH.

Transcription Factor Agonists

Obeticholic acid is a semi-synthetic bile acid analog and a ligand for the farnesoid X receptor (FXR) [33]. When bound to the FXR, it suppresses bile acid synthesis from cholesterol as well as hepatic lipid synthesis [34]. It increases peripheral clearance of VLDL and accelerates reverse cholesterol transport [34, 35]. In a randomized controlled trial [36], obeticholic acid (25 mg/day) was given to patients with NASH for 72 weeks. Eight centers in the US participated. The trial was halted when an interim analysis based on 140 of the 280 planned end of treatment biopsies found superiority of obeticholic acid compared with placebo for the primary outcome. The primary outcome was determined by a decrease in NAFLD activity score of 2 points without worsening of fibrosis. This was met by 45% of patients on obeticholic acid compared with 21% in the placebo group. Moreover, a greater number of patients assigned to obeticholic acid had an improvement in fibrosis, hepatocellular ballooning, steatosis and lobular inflammation. The mean change in NAFLD activity score was greater in patients treated with obeticholic acid. There was a significant reduction in the liver tests (such as ALAT, ASAT and γ-GT) except for alkaline phosphatase. Obeticholic acid treatment was also associated with weight loss. However, in patients with NASH, obeticholic acid led to higher cholesterol, higher LDL and decreased HDL cholesterol. Moreover, pruritus occurred in 23% of patients treated with obeticholic acid as compared with only 6% in the placebo group. Therefore, the long-term safety of obeticholic acid needs to be addressed for further clarification.

Elafibranor is a dual PPARα and PPARδ agonist. This drug has been tested in an international, phase II, randomized controlled trial [39]. It enrolled patients with a NAFLD activity score >3 from a large number of centers (n = 56) in Europe and the US. In an intention-to-treat analysis using the protocol definition of the primary end point, the study was negative. Using a new definition of the primary end point as a resolution of NASH without worsening of fibrosis, the result was statistically significant; 12% of patients in the placebo group achieved this new primary end point and 19% in the elafibranor group. The effect was stronger in patients with a NAFLD activity score >4 and in those with fibrosis. Importantly, this drug had beneficial effects on lipids with improvement of triglycerides, decrease in total cholesterol, decrease in non-HDL cholesterol and increase in HDL cholesterol. Furthermore, an improvement in insulin sensitivity was detected, suggesting that elafibranor may be safe in patients with NASH. Clearly, a larger study needs to duplicate these findings.

Other Targets

Other targets might be considered in the treatment of patients with NASH. Hepatocellular apoptosis is important for the progression of fibrosis. Anti-apoptotic drugs might prove useful in the treatment of NASH. Emricasan targets apoptosis through inhibition of caspases, and it is currently being evaluated in non-cirrhotic patients with NASH [37]. However, long-term safety of such suppression of apoptosis needs to be evaluated, as cancer is the second most frequent cause of death in NASH patients.

Patients with NASH are at risk of developing cirrhosis, which comes from deposition of fibrotic tissues in the liver. Therapeutic strategies aimed at preventing fibrosis might also work in patients with NASH. Simtuzumab is an antibody against lysine oxidants and its efficacy is currently being tested [37]. As an anti-fibrotic treatment, it may have a place in the future NASH treatment algorithm.

Some chemokine ligands and their receptors, such as CCR2 and CCR5, are upregulated during NASH, which results in liver inflammation, fibrosis and steatosis [38]. Cenicriviroc is a dual antagonist of CCR2 and CCR5,

which is currently being tested [37]. By targeting chemokines, this approach may also have potential in the treatment of NASH.

Conclusion

What the field desperately needs is a positive definition of NASH. NASH implies that alcohol has been excluded as a cause of the disease and that one has a histology showing the typical lesions of the disease. It is crucial that we better understand the pathophysiologic mechanisms underlying this disease in order to have a positive non-invasive definition, which will allow the selection of more homogenous groups of treatments as well as better definitions of end points for clinical trials.

Disclosure Statement

Advisory committees: Abbvie, Bayer, BMS, Genfit, Gilead Science, Intercept, Merck, Novartis, Sillagen. Speaking and teaching: Abbvie, Bayer, Gilead Science. Unsrestricted research grant: Bayer.

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