

## Combination drug treatment in patients with non-alcoholic fatty liver disease

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### Abstract

Non-alcoholic fatty liver disease (NAFLD) includes simple steatosis, a benign condition, and non-alcoholic steatohepatitis, a condition that beyond TG accumulation also includes necroinflammation and fibrosis. An association between NAFLD and cardiovascular disease (CVD) has been recently suggested. NAFLD patients usually have an increased CVD risk profile. NAFLD is also associated with metabolic syndrome (MetS) and is considered as the hepatic component of MetS by some authors. Currently, the only established treatment of NAFLD is gradual weight loss. However, multifactorial treatment of NAFLD risk factors may be needed to reduce the increased CVD risk of NAFLD patients. Drug combinations that include antiobesity drugs (such as orlistat and sibutramine) and target CVD risk factors may be a good approach to NAFLD patients. Our group has investigated the orlistat-fenofibrate combination treatment in obese patients with MetS and the orlistat-ezetimibe and sibutramine-antihypertensive combination treatment in obese patients with hyperlipidaemia with promising results in CVD risk factor reduction and improvement of liver function tests. Small studies give promising results but double-blind, randomized trials examining the effects of such multifactorial treatment in hard CVD endpoints in NAFLD patients are missing.

### INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) ranges from pure fatty liver alone, a benign condition characterized by triglyceride (TG) accumulation in hepatocytes, to non-alcoholic steatohepatitis (NASH), a condition that beyond TG accumulation also includes necroinflammation and fibrosis, and to end stage liver disease and liver cancer<sup>[1,2]</sup>. Insulin resistance (IR) is considered to play central role in the pathogenesis of NAFLD<sup>[3-7]</sup>. IR results in hyperinsulinaemia and high levels of plasma free fatty acids which enter into the hepatocyte cytoplasm to produce TGs. TG accumulation in hepatocytes results in hepatic steatosis<sup>[1]</sup>. Natural history studies show that up to 16% of patients with NASH may progress to cirrhosis and some of these patients will develop end-stage liver disease and/or possibly hepatocellular carcinoma necessitating liver transplant<sup>[8]</sup>.

An association between NAFLD and cardiovascular disease (CVD) has been recently suggested<sup>[9,10]</sup>. NAFLD patients have increased subclinical atherosclerosis compared with non-steatotic individuals<sup>[9]</sup>. NAFLD is also

associated with an increased CVD risk profile<sup>[11]</sup>. In NAFLD, the liver overproduces several atherogenic factors such as inflammatory cytokines, glucose, lipoproteins, coagulation factors and factors that increase blood pressure<sup>[11]</sup>. Furthermore, in Koreans it has been shown that elevated alanine aminotransferase (ALT) levels are independently associated with increased CVD or diabetes-related mortality<sup>[12]</sup>. Thus, elevated ALT levels, as a marker for NAFLD, may serve as a surrogate predictor of CVD or diabetes-related mortality.

NAFLD is also associated with metabolic syndrome (MetS) and is considered as the hepatic component of MetS<sup>[6,13-15]</sup> by some authors. In a recent study of 1003 people of whom 225 (22.6%) had NAFLD, the prevalence of MetS was significantly greater (47%) among cases compared with control subjects (23%)<sup>[16]</sup>.

The prevalence of NAFLD is expected to rise owing to the increasing prevalence of obesity and MetS world-wide. Currently the only established treatment of NASH is gradual weight loss. Many studies show that dietary intervention or bariatric surgery in patients with biopsy-confirmed NASH can be effective in improving not only liver function tests (LFTs) but also liver histology<sup>[17-19]</sup>. Multifactorial treatment of NAFLD risk factors may be needed to achieve the best results. In a prospective, open-label, randomized study, 186 non-diabetic patients with MetS and both biochemical and ultrasonographic evidence of NAFLD received lifestyle advice and treatment for hypertension (mainly inhibitors of the renin-angiotensin system), impaired fasting glucose (metformin), obesity (orlistat) and dyslipidaemia [randomly allocated to atorvastatin 20 mg/d or micronised fenofibrate 200 mg/d or both drugs] for 54 wk<sup>[20]</sup>. At the end of the treatment, 67% of patients on atorvastatin, 42% on fenofibrate and 70% on combination treatment did not have biochemical plus ultrasonographic evidence of NAFLD ( $P < 0.05$  *vs* baseline for all comparisons)<sup>[20]</sup>. In this context, drug combinations that include antiobesity drugs (such as orlistat and sibutramine) and target CVD risk factors may be a good approach for NAFLD patients.

There is evidence that weight loss induced by orlistat reverses fatty infiltration and improves hepatic fibrosis in obese patients with non-alcoholic steatohepatitis<sup>[21]</sup>. Moreover, in another study, 50 overweight subjects with non-alcoholic steatohepatitis (proven with biopsy) were randomized to receive a 1 400 Kcal/d diet plus vitamin E (800 IU) daily with or without orlistat (120 mg tid) for 36 wk<sup>[22]</sup>. Subjects who lost  $\geq 5\%$  of their body weight experienced an improvement in insulin resistance and steatosis whereas those who lost  $\geq 9\%$  experienced an improvement in hepatic histologic findings<sup>[22]</sup>.

Our group assessed the effect of orlistat and fenofibrate, alone or in combination, in overweight and obese patients ( $n = 89$ ) with MetS<sup>[23]</sup> in an open-label randomised study (the FenOrli study). At the end of the 6 mo treatment period, only 54% of patients in the orlistat group, 46% in the fenofibrate group and 29% in the

combination group still met the MetS diagnostic criteria ( $P < 0.01$  *vs* baseline in all treatment groups)<sup>[24]</sup>. Furthermore, after 6 mo of treatment, significant in-group changes were observed for body weight, body mass index (BMI) and waist circumference in all treatment groups but these reductions were more pronounced in groups receiving orlistat<sup>[24]</sup>. There were significant in-group reductions in plasma lipid levels. Specifically, the reductions of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels were significantly greater in the combination group compared with monotherapy. Furthermore, glucose, insulin and homeostasis model assessment (HOMA) index levels were improved after the 6 mo treatment significantly more in groups receiving orlistat compared with fenofibrate administration. Aspartate aminotransferase and ALT activities were not significantly altered in either group. However, gamma-glutamyl transpeptidase (GGT) activity was significantly reduced in all 3 groups. This effect may be clinically relevant since GGT activity, even within its reference range, is associated with CVD risk factors<sup>[25]</sup>. Furthermore, an increase in serum GGT activity may predict the onset of MetS, incident CVD and death<sup>[26]</sup>. Furthermore, at 6 mo, fenofibrate and combination treatment groups experienced a greater reduction in small dense LDL-C (sdLDL-C) levels (-63% and -77% respectively)<sup>[24]</sup>, which are considered the most atherogenic LDL particles<sup>[27]</sup>.

Our group also investigated, in an open-label randomised trial, the effects of orlistat and ezetimibe, alone or in combination, in 86 overweight and obese patients with hypercholesterolemia (TC  $> 200$  mg/dL)<sup>[28]</sup>. Reductions in BMI, waist circumference, and body weight at 6 mo were significantly greater in groups receiving orlistat compared with ezetimibe monotherapy. At the end of the 6 mo treatment period, a significant improvement in lipid profile was observed in all groups which was significantly greater in the combination group compared with either monotherapy<sup>[28]</sup>. Glucose, insulin and HOMA index levels were improved after the 6 mo treatment significantly more in groups receiving orlistat compared with ezetimibe administration. ALT and GGT activities improved in all treatment groups. The reduction in GGT activity was significantly greater in the combination group compared with either monotherapy<sup>[28]</sup>. There were also significant reductions in sdLDL-C concentration in all treatment groups which were more pronounced in the combination group<sup>[28]</sup>.

Another antiobesity drug useful for NAFLD is sibutramine<sup>[29]</sup>. In a recent study we examined the effect of sibutramine together with verapamil slow release/trandolapril (VeTra) combination tablet *vs* VeTra alone in obese hypertensive patients<sup>[30]</sup>. The combination treatment resulted in greater reductions of BP (significant only for diastolic BP) compared with the antihypertensive treatment alone at 6 mo, with no significant change in heart rate in any group<sup>[30]</sup>. The combination treatment led to significant improvements in the lipid and carbohydrate metabolism variables. ALT activity was significantly

decreased only in the combination group in our study. This may be associated with a decrease in liver fat content<sup>[31]</sup>.

We also showed successful results in reversing metabolic syndrome in obese patients with MetS receiving combination of fenofibrate and the recently withdrawn rimonabant<sup>[32]</sup>. The combination treatment resulted in a significant reduction in the number of metabolic syndrome criteria compared with that of fenofibrate monotherapy ( $P < 0.05$ )<sup>[32]</sup>.

These results are promising for patients with obesity and MetS of whom a significant percentage has NAFLD. However, it should be mentioned that, although modest elevation of LFTs may raise the suspicion of NASH, none of these tests are sensitive enough to establish the diagnosis of NASH with great accuracy<sup>[33]</sup>. Furthermore, liver CT or MRI, although sensitive, are not specific enough<sup>[34]</sup>. Hence, biopsy remains the “gold standard” for the diagnosis of NASH despite several limitations such as cost, the skill required, associated mortality and morbidity as well as sampling variation<sup>[1,34]</sup>.

In summary, patients with NAFLD usually have visceral obesity and present with increased CVD risk. These patients need a multifactorial treatment targeting excess body weight, hyperlipidaemia and hypertension, to reduce CVD risk factors and possibly improve hepatic histology. Small studies give promising results, but double-blind, randomized trials examining the effects of such multifactorial treatment in hard CVD endpoints in NAFLD patients are missing.

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