EDITORIALS

Non-Alcoholic Steatohepatitis (NASH): Approaching more Tailored and Effective Therapies

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Nonalcoholic fatty liver disease (NAFLD) is a form of liver disease resembling the histological changes of alcoholic liver disease but found in subjects who do not abuse alcohol (1). Subjects are often carriers of metabolic conditions such as insulin resistance, overweight, obesity, dyslipidemia, and diabetes (2). NAFLD is becoming a major emerging clinical problem worldwide and attention has been focused in Eastern European countries, too (3-5). Its more aggressive form, the nonalcoholic steatohepatitis (NASH) has an estimated prevalence of 2-3% in adults (6), and is now among the leading causes of cryptogenic cirrhosis in Western Countries. The enormous interest of researchers for NAFLD is documented by the impressive number of publications in both basic and clinical research appearing in the past few years in Pubmed (check at http://www.ncbi.nlm.nih.gov/entrez/query. fcgi? db=PubMed).

The relevance of NAFLD/NASH, which is now deemed as an example of a complex and multifactorial health problem, requiring a meticulous diagnostic and therapeutic interdisciplinary approach, has also been emphasized by our group (2,7) employing innovative breath tests labeled with ^{13}C substrates for unravelling different metabolic pathways in NASH (8). Whereas NAFLD/NASH is becoming such a worrysome health problem, there is no proven effective therapy, so far (9). Current strategies point to the identification and treatment of associated metabolic conditions such as diabetes and hyperlipidaemia, insulin resistance, and are encouraging weight loss even by bariatric surgery (10), when indicated. Also, regular aerobic physical exercise or hepatoprotective agents might play a role to protect the liver from secondary insults. Few medications have shown promising results in preliminary pilot studies, but few agents have been tested rigorously (9). Liver transplant is feasible in NAFLD patients with end-stage liver function, but the outcome can be poor if metabolic abnormalities persist after transplantation.

In the March issue of the *Journal of Gastrointestinal and Liver Diseases,* Georgescu EF and Georgescu M (5) have tested four different potentially effective drugs in NASH. In this interesting prospective study the authors have challenged biopsy-proven NASH patients with treatments logically targeted to the most prominent "metabolic" disorder, *i.e.* using the methylxanthine agent pentoxifylline or the hydrophilic di-hidroxy bile salt ursodeoxycholic acid (UDCA) (diabetes mellitus, n=17), the angiotensin-converting enzyme (ACE) inhibitor losartan (hypertension, n=12), and the potent inhibitor of HMG-CoA reductase atorvastatin or UDCA (obesity/dyslipidaemia, n=19) for a mean duration time of 37.8 weeks. Despite the fact that the study was uncontrolled, non randomized, and the number of patients in each group was limited, a significant improvement of biochemical markers was observed with all four treatments (ALT normalization in 30-46% of the patients), while liver histology improved with atorvastatin (steatosis) and losartan or pentoxyfilline (steatosis/necroinflammation). Of note, none of the four treatments reversed the already ongoing liver fibrosis.

Data from this clinical trial in NASH carried out in Romania are encouraging and need to be compared with results available from other countries. As far as lipid-lowering agents are concerned, pilot trials showed improvement of liver enzymes with atorvastatin (11, 12). Six months pravastatin 20 mg, moreover, normalised liver enzymes and improved hepatic inflammation in five patients with NASH (13). In line with such promising results, the study by Georgescu points to a positive effect of atorvastatin on biochemistry and histology in obese, dyslipidemic NASH patients.

The effect of angiotensin-converting enzyme inhibitors is currently being investigated, as the renin-angiotensin system plays a role in the development of the metabolic syndrome-associated conditions. Such agents have antihypertensive properties and display stoichiometric similitude with ligands of the peroxisomal proliferation-

J Gastrointestin Liver Dis
June 2007 Vol.16 No 2, 167-169
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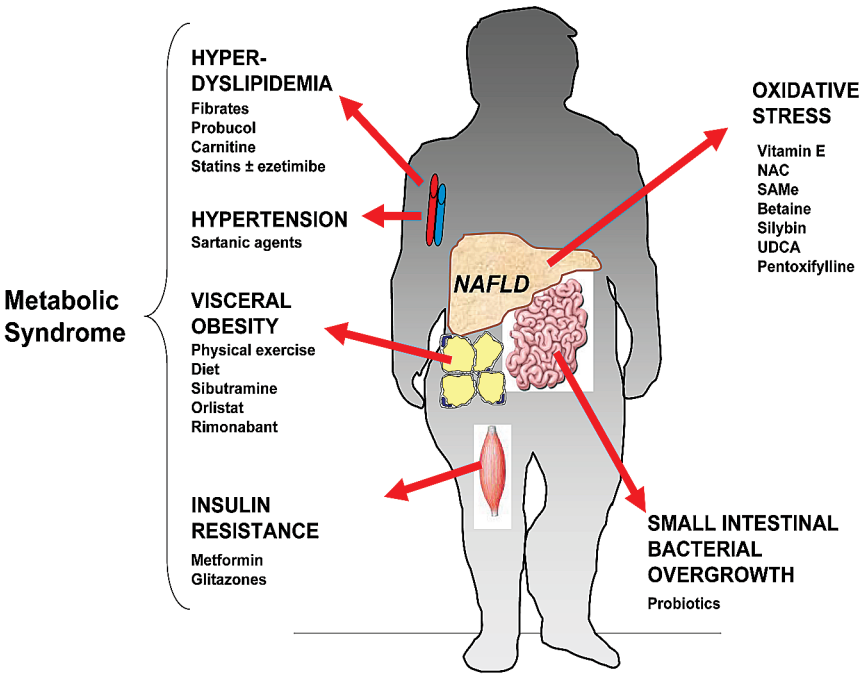
activator nuclear receptors g (PPARg) and might hasten the activation and proliferation of hepatic stellate cells. Therefore, angiotensin-converting enzyme inhibitors have been also employed in hypertensive NASH patients. The study by Georgescu confirms a previous observation by Yokohama *et al.* in which losartan at a similar dosage (50 mg/daily) for 48 weeks decreased hepatic fibrosis, biochemical markers of liver damage and resulted in partial improvement of liver histology (14).

Data for pentoxifylline, with a known inhibitory effect on the production of TNFα (15) are available from a previous study (16). Biochemical improvement was seen in NASH patients with 1.2–1.6 g/daily of pentoxifylline, but data on liver histology were not available and gastrointestinal side effects resulted in high-rate withdrawal. In the study by Georgescu, however, definitive conclusions cannot be drawn due to the low dosage used (400 mg b.i.d.).

Data for UDCA by Georgescu are partly in line with a previous study (17) which found a significant improvement in transaminase levels and in the grade of steatosis at liver biopsy in patients with NASH after one year. However, two years UDCA therapy at high doses (13-15 mg/kg/daily) was not better than placebo for patients with NASH as assessed by liver histology at baseline and after treatment (18). Even more recently, two years UDCA in combination with vitamin E, a potent antioxidant, appeared to improve laboratory values and hepatic steatosis of patients with NASH (19). Vitamin E alone has recently been reported to induce similar effects in NASH (20), but caution is needed, since high-dose vitamin E may not be totally innocuous and may be associated with an increased risk of death and heart failure (21). Certainly, further studies are required for UDCA alone or in combination in NASH patients, and possibly at even higher doses.

The study by Georgescu is interesting in that it is an example of multiple therapeutic approaches in NASH patients. It underscores that the ultimate diagnosis of NASH requires liver biopsy (and this procedure is essential when designing therapeutic trials), and suggests that medical therapies should be tailored to the prominent associated metabolic condition of NASH.

Is this the end of the story for the therapy of NASH? Certainly not. Firstly, knowing that the rate of progression in most NASH patients is slow, a crucial role is currently played by the control of risk factors such as hyperlipidemia, diabetes, and obesity, bearing in mind that weight reduction should be gradual, since rapid weight loss might worsen liver disease (22). This approach will also decrease the overall cardiovascular risk which is usually high in these patients. Secondly, as for the study of Georgescu, further data on the efficacy of several therapies should appear in the near future (Fig.1), hopefully collected within large, randomized, controlled and prolonged trials employing liver histology, which still remains the gold standard to assess subtle liver



Legend: NAC, n-acetyl-L-cysteine; SAMe = S-adenosyl-L-methionine; UDCA, ursodeoxycholic acid. (Adapted from Portincasa *et al.* (24), with permission by Bentham Science Publishers Ltd., Pakistan).

Fig.1 Major sites of action and type of pharmacological management in nonalcoholic fatty liver disease. Several therapeutic strategies are currently being investigated, and the key role of the metabolic syndrome in the pathogenesis of NAFLD/NASH needs to be acknowledged. A rational approach to be tested in the future is that of employing targeted approaches, depending on the most prevalent metabolic/pathophysiologic condition.

changes in morphology (steatosis, necroinflammation, fibrosis). Last but not least, the research agenda for NAFLD/NASH should point to identify ultimate mechanisms governing the balance between liver steatosis/hepatocellular injury and insulin resistance (the former condition might even precede the latter)(23), abnormal lipoprotein metabolism, and inflammation-oxidative stress. In this respect, better knowledge of noninvasive predictors and markers of evolution for NAFLD/NASH are urgently required.

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