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EXPERT OPINION

Treatment options for managing atherogenic dyslipidemia and fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries with up to 30% of the population affected. Since NAFLD is associated with an increased risk of cardiovascular (CV) disease, these patients should be stratified for CV risk factors, including atherogenic dyslipidemia, and managed accordingly. Lifestyle modifications represent an effective treatment for NAFLD, since most patients are overweight or obese. Also, promising, but not conclusive, results are available for current pharmacologic treatment. Drugs potentially effective against NAFLD include insulin sensitisers as well as fibrates and omega-3 polyunsaturated fatty acids, while there is reluctance to use statins in patients with suspected or established chronic liver disease. Several other therapeutic options are potentially available, and more data are expected from new peroxisome proliferator-activated receptor agonists and incretin-based therapies.

Keywords: cardiovascular risk, dyslipidemia, non-alcoholic fatty liver disease, therapy

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) results from an imbalance between lipid availability and lipid disposal resulting in hepatic steatosis, since the liver plays a major role in lipid metabolism, importing free fatty acids and manufacturing, storing and exporting lipids [1]. NAFLD represents the most common cause of chronic liver disease in the Western countries with up to 30% of the population affected, and its prevalence is increasing in parallel with that of obesity and type-2 diabetes [2]. The American Association for the Study of Liver Diseases (AASLD) guidelines have highlighted that NAFLD patients are at increased risk for cardiovascular (CV) disease (their most common cause of death) [2]. Therefore, NAFLD patients should be stratified for CV risk and their risk factors, including atherogenic dyslipidemia, should be managed accordingly [3].

2. Atherogenic dyslipidemia and CV risk

Higher plasma triglyceride (TG) levels and decreased high-density lipoproteins (HDL) concentrations are usually accompanied by the presence of small dense (sd) low-density lipoproteins (LDL) in the so-called 'atherogenic lipoprotein phenotype': this phenotype is highly atherogenic and is associated with abdominal obesity and insulin resistance, thus representing one of the components of the metabolic syndrome [4]. As stated by the National Cholesterol Education Program Adult Treatment Panel III, each component of the atherogenic lipoprotein phenotype is individually atherogenic, but the relative contribution of each component cannot be easily determined. Therefore, it has been suggested to consider this characteristic as a whole as a 'risk factor'. This interpretation is supported by data

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from epidemiological studies on high-risk populations, where the contribution to CV risk of each individual component could not be dissected from the sum of all the factors [5].

LDL are very heterogeneous particles with several distinct subclasses that differ in physicochemical composition, metabolic and oxidative properties as well as atherogenicity, and up to seven distinct LDL subclasses can be identified [6]. Oxidative susceptibility increases and antioxidant concentrations decrease with decreasing LDL size, so that sdLDL particles are those with enhanced susceptibility to oxidation and atherogenicity [7]. More than hundred studies suggest that measuring LDL particle size, sdLDL cholesterol content and LDL particle number provides additional assessment of CV risk [8].

3. Treatment options for atherogenic dyslipidemia and NAFLD

Lifestyle changes represent an effective treatment for NAFLD since most patients are overweight or obese [9]. Drugs potentially effective against NAFLD include the insulin sensitisers, metformin and pioglitazone [10]. Fibrates are potent PPARα agonists and they can significantly increase the hepatic oxidation of free fatty acids; yet, although fibrates are an attractive option to treat hypertriglyceridemia in patients with NAFLD, their effect on liver histology is still unclear [11].

Another option to treat hypertriglyceridemia is omega-3 polyunsaturated fatty acids (PUFA); several studies have shown that PUFA supplementation can improve biochemical and ultrasonographic steatosis [12]. The AASLD guidelines stated that it is premature to recommend PUFA for the specific treatment of NAFLD, but they may be considered as first-line agents to treat hypertriglyceridemia in NAFLD [2]. There is reluctance to use statins in patients with suspected or established chronic liver disease although a *post hoc* analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study showed a significant reduction in CV events and improved transaminase activity with statins in patients with suspected NAFLD [13]. Similarly, a recent *post hoc* analysis of the Incremental Decrease in Events through Aggressive Lipid Lowering (IDEAL) study showed that the CV benefit of intensive lipid lowering with atorvastatin was generally greater in patients with mildly-to-moderately elevated baseline serum alanine aminotransferase (ALT) activity than patients with normal baseline ALT activity [14].

The AASLD statement suggests that statins can be used to treat dyslipidemia in patients with NAFLD [2]. Several other therapeutic options are potentially available, and more data are expected from the new PPAR agonists [15] and incretin-based therapies [16,17].

4. Conclusions

In conclusion, patients with NAFLD have several alterations in lipid metabolism that are associated with atherogenic dyslipidemia, including increased levels of TGs and sdLDL and decreased HDL-cholesterol concentrations. Such lipid and lipoprotein alterations contribute to the increased CV risk of NAFLD patients. It may therefore be useful to select treatment options able to manage both atherogenic dyslipidemia and fatty liver disease.

5. Expert opinion

Management of atherogenic dyslipidemia and NAFLD is somewhat challenging since many prescribers will have reservations about using statins in patients with liver diseases. Statins have relatively little impact on hypertriglyceridemia (especially at low doses), while fibrates and PUFA are more indicated for raised plasma TG concentrations. In addition, sdLDL, another component of atherogenic dyslipidemia, can be significantly decreased by treatment with fibrates and PUFA [18]. A European Consensus Document has reviewed the pathophysiology, atherogenicity and clinical significance of LDL subclasses [19].

As recently discussed [20], therapies for NAFLD should ideally not only reverse the accumulation of TG in hepatocytes (i.e., hepatic steatosis) but also effectively suppress hepatic inflammation, thereby preventing progression of simple steatosis to non-alcoholic steatohepatitis, fibrosis and cirrhosis. Current treatment modalities, including fenofibrate, can target the risk factors of NAFLD, such as dyslipidemia, insulin resistance, oxidative stress and inflammation [21].

Clinical outcome studies have shown that fenofibrate, a PPARα agonist, can significantly reduce CV events in patients with atherogenic dyslipidemia [22,23]. In addition, newer agents are being developed that have less potential for adverse pharmacokinetic interactions with statins as well as greater specificity and balanced activation of PPAR subtypes [20]; such new agents would improve the beneficial lipid-modifying effects of PPAR activation while minimizing off-target adverse effects.

It seems that novel anti-diabetic incretin-based therapies may improve NAFLD. Although studies in humans are still scarce, available evidence suggests that dipeptidyl peptidase IV inhibitors and glucagon-like peptide-1 analogues may improve NAFLD by weight reduction, improvement of hepatic insulin sensitivity and fatty acid oxidation, as well as by inhibition of fibroblast growth-factor-21 [24]. For example, in 82 Japanese NAFLD patients with type-2 diabetes, the administration of liraglutide improved glycemic control and also had beneficial effects on liver inflammation, liver fibrosis and body weight [25].

In conclusion, lifestyle changes represent an effective treatment for NAFLD and atherogenic dyslipidemia; in addition, promising, but not conclusive, results are available for current pharmacologic treatment, including fibrates. Several other therapeutic options are potentially available, and more data are expected from the new PPAR agonists and incretin-based therapies.

Declaration of interest

M Rizzo has given lectures, received honoraria or research support, and participated in conferences and clinical trials sponsored by AstraZeneca, Bracco, Bristol Myers Squibb, Bromatech, Chiesi Farmaceutici, Novartis, Novo Nordisk, Rikrea and Servier. G Montalto has given lectures, received honoraria or research support, and participated in conferences sponsored by Roche, Bristol Myers Squibb and Gilead. K Al-Rasadi has given lectures, received honoraria or research support, and participated in conferences and clinical trials sponsored by AstraZeneca, Pfizer, MSD, Abbott and Aegerion. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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