Gastroenterol Hepatol. 2018;41(2):128–142

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

REVIEW

New therapeutic perspectives in non-alcoholic steatohepatitis☆

Javier Ampuero[a], Yolanda Sánchez-Torrijos[a], Virginia Aguilera[a], Francisco Bellido[b], Manuel Romero-Gómez[a,*]

[a] *Unidad Aparato Digestivo, CIBERehd, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío, Universidad de Sevilla, Sevilla, Spain*
[b] *Hospital Universitario Virgen de la Macarena, Sevilla, Spain*

Received 20 March 2017; accepted 16 July 2017
Available online 23 February 2018

KEYWORDS
Body mass index;
Visceral obesity;
Obeticolic acid;
Peroxisome proliferator-activated receptor;
Glucagon-like peptide-1 receptor agonists

Abstract Management of non-alcoholic steatohepatitis is focused on restitution of metabolic derangement, weight loss and drugs able to improve steatosis, ballooning and fibrosis. Life-style interventions based on Mediterranean diet and increasing physical activity are the first line therapy. In patients with unsuccessful life-style intervention several drugs are under development: agonist PPAR, agonist GLP-1R and agonist FXR together with drugs focussing on inflammation, ballooning, apoptosis and fibrosis. Bariatric surgery or advanced endoscopy are reserved for morbid obese without response to life-style intervention and weighting loss drugs.

PALABRAS CLAVE
Índice de masa corporal;
Obesidad visceral;
Ácido obeticólico;
Peroxisome proliferator-activated receptors;

Nuevas perspectivas terapéuticas en la esteatohepatitis no alcohólica

Resumen El manejo terapéutico de la esteatohepatitis no alcohólica se basa en la restitución de las alteraciones metabólicas, la pérdida de peso y los fármacos capaces de mejorar la esteatosis, la inflamación, la degeneración balonizante y la fibrosis. Las intervenciones sobre el estilo de vida basadas en dieta mediterránea e incremento de la actividad física configuran la primera línea del manejo de esta enfermedad. En pacientes en los que fracasa la intervención de estilo de vida se han de utilizar fármacos. Existen numerosos fármacos en desarrollo, entre

☆ Please cite this article as: Ampuero J, Sánchez-Torrijos Y, Aguilera V, Bellido F, Romero-Gómez M. Nuevas perspectivas terapéuticas en la esteatohepatitis no alcohólica. Gastroenterol Hepatol. 2018;41:128–142.

* Corresponding author.
E-mail address: mromerogomez@us.es (M. Romero-Gómez).

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Agonistas *glucagon-like peptide-1 receptor*

los que destacan los agonistas FXR, los agonistas PPAR y los agonistas GLP-1R. Terapias dirigidas a las diferentes lesiones histológicas están también en desarrollo para mejorar la esteatosis, la inflamación, la degeneración balonizante, la apoptosis y la fibrosis. La cirugía bariátrica y la endoscopia terapéutica avanzada de la obesidad están reservadas a pacientes con obesidad mórbida en los que fracasan todas las opciones terapéuticas disponibles.

Introduction

The importance of non-alcoholic fatty liver disease (NAFLD) has increased considerably over the last few years, to such an extent that it is now the most prevalent liver disease and one of the main causes of liver transplant in the Western world.[1] It is estimated that NAFLD is detected in between 20% and 30% of the population. The prevalence of NAFLD gradually increases with age and is higher in men than in women (these differences are more pronounced in individuals under the age of 50).[2] Since it is a highly prevalent disease, there are many more patients with benign disease with little impact on prognosis; however, the small percentage of patients with more advanced forms of disease account for the primary cause of liver disease in the Western world. There is an increased risk of liver disease progression in patients with non-alcoholic steatohepatitis, especially in those with fibrosis; there is also an increased risk of cardiovascular disorders and solid tumours. Therefore, treatment is indicated in those patients at risk of disease progression (steatohepatitis, fibrosis, age >60 years, male or presence of type 2 diabetes mellitus). NAFLD has 4 associated phenotypes: obesity, diabetes, metabolic syndrome and NAFLD in metabolically healthy non-obese patients. In brief, there is significant overlap between the disease pathways seen in NAFLD. NAFLD is triggered by a high influx of free fatty acids to the liver, which is especially pronounced in obesity due to insulin resistance (both in liver and in muscle and adipose tissue). NAFLD also sees an increase in de novo lipogenesis, especially due to hyperinsulinaemia, which is characteristic of metabolic syndrome and type 2 diabetes mellitus, resulting in insufficient secretion of triglycerides in the form of very-low-density lipoproteins (VLDL) and fat accumulation. Lipotoxicity is responsible for oxidative stress, with increased production of oxygen-derived free radicals, and endoplasmic reticulum stress, triggering mechanisms of apoptosis, impaired immune response and hepatic stellate cell activation which induces fibrosis progression. These pathogenic phenomena occur in the context of interactions between the patient's exposome, microbiome and genome. Gut microbiota can affect the liver through a number of mechanisms: a) intestinal barrier dysfunction, which allows bacterial translocation and the migration of bacterial products such as lipopolysaccharides; b) impaired metabolism of short-chain fatty acids and intestinal alcohol production; c) impaired metabolism of bile acids, causing gut microbiota to inhibit primary bile acid synthesis in the liver by inhibiting the farnesoid X receptor (FXR).[3]

Therapeutic recommendations in patients in whom lifestyle interventions have failed have been designed to tackle the patient's obesity, diabetes or metabolic disorders. Drugs are also being designed to directly treat steatosis, steatohepatitis (inflammation and ballooning degeneration) and fibrosis (Table 1). Drugs that have shown beneficial effects are pioglitazone and vitamin E, but both the FDA and the EMA do not currently recommend any drug therapy and the AASLD-EASL-EASD guidelines only recommend the use of such drugs for patients with a histological diagnosis of non-alcoholic, non-diabetic and non-cirrhotic steatohepatitis.[15]

Finally, there is a growing interest in this disease, as can be seen from the number of reviews published over recent months on the drug and non-drug treatment of non-alcoholic steatohepatitis.[16–21]

Diet, physical activity and exercise for the management of non-alcoholic steatohepatitis

The first line of treatment involves a change in lifestyle to promote a Mediterranean diet, avoid sedentary behaviour and increase physical activity and moderate aerobic exercise in order to induce weight loss, which in turn improves the patient's liver disease (Fig. 1). A low-calorie diet promotes weight loss, but no differences have been observed between a low-fat and a low-carb diet. In patients following isocaloric diets, ingestion of monounsaturated (such as olive oil) or polyunsaturated fatty acids (such as sunflower oil) promotes the elimination of fat accumulated in the liver (assessed by magnetic resonance spectroscopy). The Mediterranean diet which is characterised by a high intake of olive oil, fibre, nuts, omega-3-rich fish oil, fruits and vegetables and a low intake of refined sugars, saturated fats and processed red meat prevents the development of hepatic steatosis and steatohepatitis.[22] However, a low-calorie, low-fat diet with a reduction of 500 kcal/day (<30%) has been shown to induce resolution of steatohepatitis and regression of fibrosis in patients with weight loss, and, therefore, the percentage of patients showing improvement is directly proportional to the percentage of weight lost. Sedentary behaviour (assessed as the number of hours spent watching television without a break) and