Novel Approaches in Drug Designing & Development

Juniper Publishers key to the Researchers

Mini Review
Volume 4 Issue 4 - January 2019
DOI: 10.19080/NAPDD.2019.04.555644

Nov Appro Drug Des Dev

New Pharmacological Therapies for Non-Alcoholic Fatty Liver Disease

Marco A López Hernández

Universidad Autonoma del Estado de Mexico, Ecatepec General Hospital, Mexico

Received Date: December 06, 2018; **Published Date:** January 09 , 2019

***Corresponding author:** Marco A López Hernández, Universidad Autonoma Del Estado De Mexico, Ecatepec General Hospital, Division of Internal Medicine, Mexico

Introduction

The Non-alcoholic Fatty Liver Disease (NAFLD) is the liver disorder most common in western countries, has a global prevalence of approximately 25% and is strongly associated to obesity and metabolic syndrome. According to the Third National Health and Nutrition Examination Survey (NHANES III) the prevalence of NAFLD is more common in obese individuals with a prevalence of 39.4% than in lean individuals with a prevalence of 7.7%. NAFLD is the hepatic manifestation of the metabolic syndrome and is defined as the accumulation of fat in the liver.

The high calories diet with an excess of saturated fats, refined carbohydrates, has been associated with weight gain and obesity, and more recently with NAFLD [1,2]. The "multiple hit" hypothesis considers multiple insults acting together on genetically predisposed subjects to induce NAFLD and provides a more accurate explanation of NAFLD pathogenesis [3].

Dietary habits, genetic and environmental factors can lead to insulin resistance, obesity with adipocyte proliferation and changes in the gut microbiota. The insulin resistance is a key factor in the pathogenesis of NAFLD, the insulin resistance results in a hepatic de novo lipogenesis and impaired inhibition of adipose tissue lipolysis, with consequent increased flux of fatty acids to the liver [4]. Insulin resistance also promotes adipose tissue dysfunction that results in an impaired secretion of adipokines and inflammatory cytokines [5]. In the 2018 Annual Meeting of the American Association for the Study of Liver Diseases were presented phase II data in therapies with drugs for NAFLD and NASH.

Farnesoid X Receptor Agonists

Farnesoid X receptors (FXRs) are nuclear hormone receptors expressed in high amounts in body tissues that participate in bilirubin metabolism including the liver, intestines, and kidneys. Bile acids are the natural ligands of the FXRs. XRs play a critical role in carbohydrate and lipid metabolism and regulation of insulin sensitivity. FXRs also modulate live growth and regeneration during liver injury.

The farnesoid X receptor agonist GSK-9674 was compared with placebo at doses of 30 and 100 mg and showed ≥ 30% relative reduction in liver fat and improving markers of fibrosis also improved [6] Obeticholic acid (OCA), is a semi-synthetic bile acid analogue which has the chemical structure 6α-ethyl-chenodeoxycholic acid. The natural bile acid, chenodeoxycholic acid, was identified in 1999 as the most active physiological ligand for the farnesoid X receptor, which is involved in many physiological and pathological processes. In a double-blind, placebo-controlled, phase II study, the OCA was compared with placebo, at the week 16, patients with vs without cirrhosis (F4 vs F1-F3) showed no trend for differences in ALT, bilirubin, platelets, and INR [7]. Tropifexor (TXR) in the study FLIGHT a 3-part randomized, placebo-controlled, double-blind, dose-ranging phase IIb study in adults with NASH, weighing 40-150 kg with liver fat ≥ 10%, showed reduction in liver fat, ALT and GGT compared with placebo [8].

Fibroblast Grow Factor (FGF) Analogues

NGM282 is a non-tumorigenic analogue of human FGF19 demonstrating significant reductions in hepatic steatosis, liver transaminases and fibrosis markers after 12 weeks of treatment at doses of 3 mg and 6 mg. Treatment with NGM282 at doses of 1mg and 3mg for 12 weeks results in clinically meaningful improvements in all components of the NAS and fibrosis in NASH patients, and is preceded by rapid and significant improvements in imaging-based parameters and liver transaminases [9].

Thyroid Hormone Receptor Beta Selective (THR-b)

The THR-b VK2809 in a Randomized, multicenter, placebo-controlled phase IIa study at the week 12 showed an higher proportion of patients with liver fat > 30% compared placebo [10]. MGL-3196 is a liver-directed, orally active, highly selective THR-β agonist which may reduce lipotoxicity in NASH by increasing hepatic fat metabolism. At Week 36, MGL-3196 treatment compared with placebo resulted in significant and sustained reductions in hepatic fat on MRI-PDFF, liver enzymes, fibrosis biomarkers, atherogenic lipids and improvement in NASH

on liver biopsy. In MGL-3196 treated patients, ≥30% fat reduction (MRI-PDFF) at Week 12 predicted an improved NASH histologic response at Week 36 [11].

Acetyl-CoA Carboxylase (ACC) Inhibitor

Elevated plasma levels of medium and long chain acylcarnitines are markers of impaired mitochondrial beta oxidation of fatty acids. GS-0976 inhibits cytoplasmic ACC1 and mitochondrial ACC2 thereby reducing fatty acid synthesis and augmenting beta oxidation, respectively. NASH patients who responded to GS-0976 with reduction of liver fat by MRI-PDFF also demonstrated a reduction in plasma acylcarnitine species. This effect is consistent with an improvement in the efficiency of mitochondrial beta oxidation. These reductions in plasma acylcarnitine species provide further evidence to support the therapeutic targeting of ACC1 and ACC2 in patients with NASH [12].

Stearoyl-coenzyme A Desaturase-1. (SCD-1) Modulator

Aramchol (arachidyl amido cholanoic acid) is a novel fatty acid bile acid conjugate, inducing beneficial modulation of intra-hepatic lipid metabolism. The ARREST study enrolled 247 NASH patients who were overweight/obese and had prediabetes or diabetes with HbA1C at baseline of 6.6%. More than 50% were hypertensive and had dyslipidemia. Baseline histology demonstrated a population with advanced disease, with 60% having stage 2 and 3 fibrosis and 70% having NAS≥5.

The study ARREST, a randomized, global phase IIb study with aramchol in patients with NASH and diabetes or prediabetes, compared armachol at doses of 400 and 600 mg versus placebo, in the aramchol patients the proportion with >5% of reduction in liver fat by MRI, the resolution of NASH than in the placebo group [13].

Glucagon Like Peptide Type 1 (GLP-1) Receptor Agonist

The glucagon-like peptide 1 analogs semaglutide and liraglutide improve glycemic control and reduce elevated liver enzymes in subjects with type 2 diabetes and reduce body weight in subjects with or without diabetes. In subjects with obesity and high ALT, semaglutide 0.2–0.4 mg daily reduced ALT to an extent that was broadly comparable across weight loss categories and resulted in dose-related ALT normalization in up to 46% of subjects after 52 weeks. These data suggest a potential role for semaglutide in the treatment of NAFLD with elevated liver enzymes [14].

References

1. Barrera F, George J (2014) The role of diet and nutritional intervention for the management of patients with NAFLD. Clin Liver Dis 18(1): 91–112.
2. Chiu S, Sievenpiper JL, de Souza RJ, Cozma AI, Mirrahimi A, et al. (2014) Effect of fructose on markers of non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of controlled feeding trials. Eur J Clin Nutr 68(4): 416-423.
3. Buzzetti E, Pinzani M, Tsochatzis EA (2016) The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism 65(8) :1038-1048.
4. Bugianesi E, Moscatiello S, Ciaravella MF (2010) Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des 16: 1941-1951.
5. Guilherme A, Virbasius JV, Puri V (2008) Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol 9: 367-377.
6. Patel K, Harrison SA, Trotter JF (2018) The Non-Steroidal FXR Agonist GS-9674 Leads to Significant Reductions in Hepatic Steatosis, Serum Bile Acids, and Liver Biochemistry in a Phase 2, Randomized, Placebo-Controlled Trial of Patients with NASH. Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases; 9-13, Abstract 736 San Francisco, California.
7. Halegoua De Marzio D, Thuluvath PJ, Abdelmalek MF (2018) Obeticholic Acid Was Safe and Well Tolerated in Patients with Nonalcoholic Steatohepatitis and Compensated Cirrhosis: A Secondary Analysis of the Control Study. Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases. 9-13, Abstract 71. San Francisco, California, USA.
8. 8.-Sanyal A, Lopez P, Lawitz E (2018) Tropifexor (TXR), an FXR Agonist for the treatment of Nash - Interim Results from First Two Parts of Phase 2b Study Flight-FXR. Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases; 9-13, Abstract LB 23, San Francisco, California, USA.
9. Harrison FA, Trotter JF, Paredes AH (2018) NGM282 Rapidly Improves NAFLD Activity Score (NAS) and Fibrosis in 12 Weeks in Patients with Biopsy-Confirmed Nonalcoholic Steatohepatitis (NASH): Results of a Phase 2 Multi-Center Dose Finding Study. Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases; 9-13, Abstract 104, San Francisco, California, USA.
10. Loomba R, Neutel J, Bernard D (2018) K2809, a Novel Liver-Directed Thyroid Receptor Beta Agonist, Significantly Reduces Liver Fat in Patients with Non-Alcoholic Fatty Liver Disease: A Phase 2 Randomized, Placebo-Controlled Trial. Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases; November 9-13. San Francisco, California, USA.
11. Harrison FA, Guy CD, Bashir M (2018) In a Placebo-Controlled 36-Week Phase 2 Trial, Treatment with Mgl-3196 Compared to Placebo Results in Significant Reductions in Hepatic Fat (MRI-PDFF), Liver Enzymes, Fibrosis Biomarkers, Atherogenic Lipids, and Improvement in Nash on Serial Liver Biopsy Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases; November 9-13, Abstract 14, San Francisco, California, USA.
12. Charlton MR, Lai M, Noureddin M (2018) GS-0976, a Liver-Targeted Acetyl-CoA Carboxylase (ACC) Inhibitor, Reduces Plasma Acylcarnitines in Patients with Nonalcoholic Steatohepatitis (NASH). Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases; November 9-13, Abstract 1741, San Francisco, California, USA.
13. Ratziu O, Ladron-De-Guevara L, Safadine R (2018) One Year Results of the Global Phase 2b Randomized Placebo-Controlled Arrest Trial of Aramchol, a Stearoyl CoA Desaturase Inhibitor, in Patients with Nash Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases; November 9-13, 2018; Abstract LB 5, San Francisco, California, USA.
14. Newsome PN, Harrison SA, Rasmussen S (2018) The Effect of Semaglutide on Liver Enzymes in Subjects with Obesity and Elevated Alanine Aminotransferase: Data from a Randomized Phase 2 Trial. Program and abstracts of the 2018 Annual Meeting of the American Association for the Study of Liver Diseases. 9-13 Abstract 105, San Francisco, California, USA.

How to cite this article: Marco A López Hernández. New Pharmacological Therapies for Non-Alcoholic Fatty Liver Disease. Nov Appro Drug Des Dev 2019; 4(4): 555644. DOI: 10.19080/NAPDD.2019.04.555644.

DOI: 10.19080/NAPDD.2019.04.555644

How to cite this article: Marco A López Hernández. New Pharmacological Therapies for Non-Alcoholic Fatty Liver Disease. Nov Appro Drug Des Dev 2019; 4(4): 555644. DOI: 10.19080/NAPDD.2019.04.555644.