Journal of Complementary Medicine And Alternative Healthcare
ISSN: 2572-1232

Juniper Publishers key to the Researchers

Opinion
Volume 10 Issue 2 - August 2019
DOI: 10.19080/JCMAH.2019.10.555781

J Complement Med Alt Healthcare

Angiogenesis as A Potential Therapeutic Target for NASH Treatment

Min Young Kim*

AngioLab, Korea

Submission: July 11, 2019; **Published:** August 08, 2019

***Corresponding author:** Min Young Kim, AngioLab, Inc., Hanshin S mecca Suite 159, 65 Techno 3ro, Yuseong gu, Daejeon, Korea

Key Facts About NASH

Non-alcoholic fatty liver disease (NAFLD) - the most common type of chronic liver disease - encompasses a histological spectrum of disorders including simple fat accumulation (steatosis), non-alcoholic steatohepatitis (NASH) and cirrhosis. NASH is a chronic and silent liver disease characterized histologically by the presence of hepatic inflammation and cell injury (hepatocellular ballooning) due to hepatic steatosis equal or superior to 5% of hepatocytes [1]. NASH develops in the absence of excessive alcohol consumption but is linked to unhealthy eating habits and lack of physical activity [1]. It is often referred to as metabolic disease of the liver. NAFLD patients with obesity and metabolic syndrome features such as insulin resistance, type 2 diabetes mellitus, hypertension and dyslipidemia, are at higher risk of progression to NASH. NASH is associated with higher cardiovascular risk and increased fibrosis leading to cirrhosis and liver cancer when serious [2].

Currently no approved pharmacotherapy exists for the treatment of NASH. Mainly sustained weight loss by a calorie-restricted diet, eating habit and lifestyle modification, and increased exercise are the top priorities and recommendations for patients. Final goal is to achieve and sustain weight loss of 7% to 10% of bodyweight, as this has been shown to improve the majority of histopathological features of NASH [1]. The past decade has been an explosive interest in drug development targeting pathologic pathways in NASH, with numerous phase 2 and 3 trials currently in progress.

Drugs in Phase 2 And 3 Trials

The development fever of NASH treatment called 'golden egg' has not cooled down. Currently, 'Ocaliva, Obeticholic acid (OCA)' of Intercept Pharmaceuticals (USA) is the only treatment that has finished phase 3 of clinical trial. However, there are still labels for safety and efficacy issues. This means that the NASH cure, which in turn has a higher efficacy and a more safety, is strongly needed. Currently developing drugs in phase 2 and 3 trials have different mechanism each. The most leading player is OCA, a potent agonist of the farnesoid X nuclear receptor (FXR) that is just being evaluated in the phase 3 study REGENERATE (NCT02548351) for the treatment of NASH after being studied in the phase 2b FLINT trial (NCT01265498), where 283 patients with non-cirrhotic NASH were randomized 1:1 to receive OCA 25mg or placebo for 72 weeks [3].

The next launching candidate is Elafibranor (GFT505). Elafibranor is a dual PPAR-α/δ agonist produced by GENFIT (France) that is currently undergoing evaluation in the phase 3 RESOLVE-IT trial (NCT02704403). Elafibranor was tested in the phase 2b GOLDEN-505 trial (NCT01694849) which randomized 276 patients with NASH without cirrhosis to Elafibranor 80mg, 120mg or placebo groups for 52 weeks [4]. Estimated primary completion date is December 2021. Cenicriviroc (CVC) is a dual CCR2/CCR5 inhibitor owned by Tobira Therapeutics (USA). In animal fibrosis models it is demonstrated to have anti-inflammatory and anti-fibrotic properties. CVC is being evaluated in phase 2 and phase 3 trials. However, big pharmas have experienced continuing failures in developing NASH treatments and terminated clinical trials such as Selonsertib (P3, Gilead, ASK-1, apoptosis signal-regulating kinase 1 inhibitor), Liraglutide (P3, Novo Nordisk, GLP-1, glucagon-like peptide-1 analogue), Metadoxine (P3, General de Mexico, Antioxidant, glutathione source), hydroxytyrosol and vitamin E (P3, Bambino Gesù Hospital and Research Institute, Antioxidant), Emricasan (P2, Novartis, Caspase Inhibitor), NGM282 (P2, NGM Bio, Variant of FGF-19), BMS-986036 (P2, Bristol-Myers Squibb, Pegylated FGF-21), Simtuzumab (P2, Gilead, LOXL2 antibody), Volixibat (P2, Shire Pharmaceuticals, ASBT, apical sodium–bile acid transporter inhibitor) and Saroglitazar (P2, Zydus Discovery, PPAR-α/γ agonist) [5].

Multi Target

The pathogenesis of NASH is still unclear. Until recent years, a 'two-hit' theory has been thought to drive NASH pathogenesis (steatosis of more than 5 % of hepatic fat, as a first hit and other factors such as inflammatory cytokines, mitochondrial dysfunction, and oxidative stress, as a second hit) [6]. However,

this view is not generally recognized because NASH can be developed by many other molecular pathways and the driving factors may be different among patients. Thus, 'multiple-hit' model is widely accepted now [7]. The presumable multiple factors are as follows: lipid accumulation by excessive delivery from adipose tissue such as visceral fat, insulin resistance, inflammation, gut-liver axis dysfunction, genetic factors associated with inflammation, lipid metabolism and oxidation. These factors affect to liver function to treat energy sources such as carbohydrate and lipid and result in the accumulation of toxic lipid species, leading to stress, damage, death in hepatocyte and following fibrosis, cirrhosis and hepatocellular carcinoma. Based on these hypotheses, it is considered that the development of therapeutic regulating multiple target may be more effective rather than that of specific one target.

Angiogenesis and Liver Fibrogenesis

Angiogenesis is closely associated with NASH, especially in pathogenic liver as well as in adipose tissue. Fatty acids primarily delivered into liver come from adipose tissue such as visceral fat. Adipose tissue accumulates lipids by the remodeling process including adipocyte differentiation and angiogenesis, and supplies lipid to liver in the form of free fatty acids through lipolysis [8]. Inflammation and excessive free fatty acids due to dysregulation of lipolysis in adipose tissue can induce the NASH pathogenesis [6]. In normal liver, fibrogenesis initiate under acute liver injury but the process is transient and easily recovered. In pathogenic status of chronic liver disease, for example, fibrotic liver, normal oxygen delivery is persistently reduced due to the increase of portal venous resistance by the deposition of extracellular matrix (ECM) [9,10]. Hepatic stellate cells (HSCs), which produce collagen and pro-inflammatory cytokines, are a major culprit of fibrosis. Hypoxia in liver upregulates angiogenic factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) in hepatocyte and HSCs and induce immature angiogenesis. The incomplete vessels cannot overcome hypoxia and furthermore maintain chronic inflammatory condition by infiltrating inflammatory cells secreting pro-inflammatory cytokines tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), nitric oxide (NO). These conditions again stimulate HSCs and induce the deposition of ECM, leading to liver fibrosis. Therefore, hypoxia, pathologic angiogenesis, and liver fibrogenesis are all interconnected events.

Conclusion

Although the causes of NASH are not well defined, we now know the presences of many factors and multiple targets in NASH. Angiogenesis inhibitors have the potential to treat NASH targeting liver fibrogenesis. Studies examining antiangiogenic therapy in rodent models of chronic liver disease were undertaken. However, NASH therapeutics that are able to control multiple factors at a time and to treat for a long term are required. Recently, herbal extracts of Melissa [11] and stevia [12] showed the alleviation of NASH pathogenesis through multiple pathways including angiogenesis. Herbal medicine may be a desirable alternative due to its multiple action, long-term safety, cost-effectiveness and good compliance for NASH treatment.

References

1. Chalasani N, Younossi Z, Lavine JE, Charlton M, Kenneth Cusi, et al. (2018) The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the AASLD. Hepatology 67(1): 328-357.
2. Torres DM, Williams CD, Harrison SA (2012) Features, Diagnosis, and Treatment of Nonalcoholic Fatty Liver Disease. Clin Gastro Hepatol 10(8): 837-858.
3. Neuschwander Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, et al. (2015) Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 385(9972): 956-965.
4. Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, et al. (2016) Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α and -δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 150(5): 1147-1159.
5. James J Connolly, Kohtaro Ooka, Joseph K Lim (2018) Future Pharmacotherapy for Non-alcoholic Steatohepatitis (NASH): Review of Phase 2 and 3 Trials. J of Clinical and Translational Hepatology 6(3): 264-275.
6. Friedman SL, Neuschwander Tetri BA, Rinella M (2018) Sanyal AJ Mechanisms of NAFLD development and therapeutic strategies. Nat Med 24(7): 908-922.
7. Fang YL, Chen H, Wang CL, Liang L (2018) Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: From "two hit theory" to "multiple hit model". World J Gastroenterol 24(27): 2974-2983.
8. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB (2016) Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders Front Endocrinol (Lausanne) 7: 1-16.
9. Park S, Kim JW, Kim JH, Lim CW, Kim B (2015) Differential Roles of Angiogenesis in the Induction of Fibrogenesis and the Resolution of Fibrosis in Liver. Biol Pharm Bull 38(7): 980-985.
10. Bocca C, Novo E, Miglietta A, Parola M (2015) Angiogenesis and Fibrogenesis in Chronic Liver Diseases. Cell Mol Gastroenterol Hepatol 1(5): 477-488.
11. Kim J, Lee H, Lim J, Lee H, Yoon S, et al. (2017) The lemon balm extract ALS-L1023 inhibits obesity and nonalcoholic fatty liver disease in female ovariectomized mice. Food Chem Toxicol 106(Pt A): 292-305.
12. Ramos Tovar E, Flores Beltrán RE, Galindo Gómez S, Vera Aguilar E, Diaz Ruiz A, et al. (2018) Stevia rebaudiana tea prevents experimental cirrhosis via regulation of NF-κB, Nrf2, transforming growth factor beta, Smad7, and hepatic stellate cell activation. Phytother Res 32(12): 2568-2576.

How to cite this article: Min Young Kim. Angiogenesis as A Potential Therapeutic Target for NASH Treatment. Amateur Soccer Players. J Complement Med Alt Healthcare. 2019; 10(2): 555781. DOI: 10.19080/JCMAH.2019.10.555781

DOI: 10.19080/JCMAH.2019.10.555781

How to cite this article: Min Young Kim. Angiogenesis as A Potential Therapeutic Target for NASH Treatment. Amateur Soccer Players. J Complement Med Alt Healthcare. 2019; 10(2): 555781. DOI: 10.19080/JCMAH.2019.10.555781