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Research Progress of Multi-Target Drugs in the Treatment of Non-Alcoholic Steatohepatitis

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Abstract: *Non-alcoholic steatohepatitis is a clinical syndrome with pathological changes similar to alcoholic steatohepatitis without a history of excessive alcohol consumption, and is a key stage of reversible progression to liver fibrosis, which can further develop into malignant diseases such as cirrhosis or even liver cancer if preventive measures are not taken. The pathogenesis of NASH is complex, and there are no any effective drugs for NASH. It is difficult for single-target drugs to achieve good therapeutic effects, and are accompanied by strong side effects, and many of them are terminated in the clinical trial stage. Multi-target drugs are not easy to produce drug resistance, and can exert synergistic effects on multiple targets to maximize drug efficacy and minimize adverse side effects, and has a good effect on the treatment of complex diseases. This article summarizes the multi-target drugs for the treatment of NASH, and provides a reference for finding new drugs for the treatment of NASH.*

Keywords: *Non-alcoholic Steatohepatitis, Multi-target Drugs, Multi-target Agonists, Dual Antagonists*

1. Introduction

Non-alcoholic steatohepatitis is a chronic inflammatory disease of the liver characterized by the non-history of excessive alcohol intake (or men < 30 g/day, females < 20 g/day) and pathological features, such as hepatocyte loss, steatosis, ballooning, mild inflammation of diffuse hepatic lobules and collagen deposition in the central hepatic vein and around the hepatic sinusoids [1-3]. It is commonly found in patients with metabolic syndrome including obesity, insulin resistance, type II diabetes mellitus, and hyperlipidemia [4-5]. In recent years, with the change in people's lifestyles and drug abuse, the incidence of NASH is gradually increasing, and the age of patients with NASH is showing a trend of younger age [6-8]. Without intervention, NASH will further develop into malignant diseases, such as liver fibrosis, cirrhosis, and liver cancer [9]. The pathogenesis of NASH is complex, which is affected by diet, lifestyle, drug therapy, environment, metabolism, genetics, gene polymorphism and other factors, and the therapeutic targets are diverse [10-12]. An often overlooked is the complexity and robustness of the disease as a system in multi-target drugs therapy, we believed that highly selective drugs can reduce the toxic side effects due to binding to other targets of the disease. However, like other molecular networks, disease networks also suffer from redundancy and alternative compensatory signaling pathways. Therefore, highly selective drugs have certain limitations, which are usually difficult to achieve the desired effect or produce serious adverse side effects during the treatment of complex diseases. This is also the reason that clinical candidates fail to meet the observed endpoints in phase II or phase III clinics [13-14]. There are some NASH-related agonists and antagonists have been reported, and some of them have entered clinical trials, but the efficacy and safety of long-term drug use still need to be further observed and analyzed [15]. Multi-target drugs can simultaneously regulate multiple targets and produce synergistic effects and have been successfully used in the treatment of diabetes, Alzheimer’s disease, hypertension, depression, asthma, cancer, HIV, and infectious diseases. Together, multi-target drugs demonstrated the superiority in simultaneous modulation of multiple links in the disease network system for complex diseases.

2. Classification and mode of action of multi-target drugs

Multi-target drugs can be divided into three categories according to different drug components. (1) Multi-drug combination: this kind of drug is the most widely used, which can play a synergistic effect, delay the tolerance of the body or the resistance of pathogens, and improve the efficacy, but may also produce antagonism, increase the occurrence of adverse reactions, so attention should be paid to the

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incompatibility contraindications when using them. (2) Multi-component drugs: multiple active components in a single dosing unit, such as a tablet or injection. This kind of drug makes up for the defects of multi-drug combination, which has higher safety and more convenient to use. (3) Single-component drugs: a single-component drug can selectively act on multiple molecular targets at the same time [16]. The pharmacodynamics and pharmacokinetics of single-component drugs can be predicted, and are superior to the multi-drug combination and multi-component drugs in drug metabolism. However, there are some great challenges that need to be considered during the design and development of single-component drugs, such as the balance of drug activity, pharmacokinetic properties, and safety.

The modes of action of multi-target drugs can be divided into three categories as follows: (1) Combining effects by affecting different targets, which can exist in the same or different signal transduction pathways in specific tissues, cells, or intercellular fluid; (2) The effect of the drug on the first target can have an impact on the second target, such as altering drug metabolism, inhibiting efflux pumps, or blocking other resistance mechanisms; (3) Acting on different active sites of one drug target or molecular complex to exert combined effects and improve pharmacological activity.

3. Main targets of NASH treatment and clinical candidates under development

Through in-depth studies, it was found that metabolic disorders, oxidative stress, inflammation, apoptosis, intestinal microbiota disorders, and fibrosis are the main pathogenesis of NASH. In order to better understand the molecular targeted therapy of NASH, the main targets of NASH therapy and clinical candidates under development were summarized in this study [17-18]. (1) The main targets and corresponding clinical candidates based on metabolic regulation: peroxisome proliferator-activated receptor (PPAR) agonists, including pioglitazone, pemafibrate, elafibranor, saroglitazar, IVA337. Farnesol X receptor (FXR) agonists, including obeticholic acid, GS-9674, LJN452, LMB763. Acetyl-CoA carboxylase (ACC) agonists, including NDI-010976, PF-05221304. Glucagon-like peptide-1 (GLP-1) agonists, including liraglutide, somarlutide. Sodium-glucose cotransporter-2 (SGLT-2) agonists, including remogliflozin and LIK066. (2) Based on the main targets of oxidative stress regulation and clinical candidates, such as vitamin E and cysteamine. They exert some anti-NASH efficacy by scavenging reactive oxygen species and increasing glutathione reserves. (3) The main targets and clinical candidates are based on the anti-inflammatory principle, such as CCR2/CCR5 agonist cenicriviroc. (4) The main targets and clinical candidates based on apoptosis regulation: the tumor necrosis factor-α (TNFα) receptor agonist, such as pentoxifylline. The caspase inhibitor, such as emricasan. The apoptosis signal-regulated kinase 1 (ASK-1) inhibitor, such as selonsertib. (5) The main targets and clinical candidates based on the regulation of gut microbiota disorders: an inhibitor of intestinal lipases, such as orlistat. (6) Targets and clinical candidates based on hepatic fibrosis regulation: the lysyl oxidase-like protein 2 (LOXL2) monoclonal antibody, such as simtuzumab. The galectin-3 inhibitor, such as GR-MD-02. The liver X receptor α (LXRα) agonist, such as oltipraz. The transforming growth factor-β (TGF-β) inhibitor, such as pirfenidone.

4. Multi-target drugs for clinical application

NASH refers to a clinical syndrome with pathological changes similar to alcoholic steatohepatitis but without a history of excessive alcohol consumption. It is a critical stage in the reversible progression to liver fibrosis, and can further develop into liver cirrhosis or even liver cancer if preventive measures are not taken. The early diagnosis and treatment of NASH have become an important public health issue. The pathogenesis of NASH is complex, and there are no any effective drugs for NASH. It is difficult for single-target drugs to achieve good therapeutic effects, and are accompanied by strong side effects, and many of them are terminated in the clinical trial stage. Multi-target drugs have good effect on the treatment of complex diseases. Currently, there are several new multi-target drugs therapy options for NASH that are being evaluated at various clinical stages, such as the PPARα/γ agonist saroglitazar magnesium; PPARα/γ agonist elafibranor; PPARα/δ/γ agonist lanifibranor; GLP-1/FGF21 agonist GLP-1-FC-FGF21D1; CCR2/CCR5 dual antagonist cenicriviroc.

4.1. Multi-target Agonists

4.1.1. PPARα/γ agonist Saroglitazar Magnesium

Saroglitazar magnesium is a PPARα/γ agonist that targets hypertriglyceridemia by activating

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PPARα (mainly in the heart, muscle, kidney, and liver) and hyperglycemia by activating PPARγ (mainly in the adipose tissue) [19]. Results of the saroglitazar clinical trial in 2018 showed that it can remarkably reduce low alanine aminotransferase, liver fat, total cholesterol, low-density lipoprotein cholesterol, triglyceride, and apolipoprotein B, and increase the cholesterol level in patients with high-density lipoprotein in type II diabetes mellitus [20-23]. Saroglitazar magnesium is safe and well tolerated [24], and can improve the biochemical and histological features (hepatic steatosis, ballooning degeneration, inflammation, and fibrosis) of NASH [25]. The results of a study of saroglitazar magnesium for the treatment of non-alcoholic fatty liver disease (NAFLD) and NASH were published by the American Association for the Study of Liver Diseases in 2019, showing that saroglitazar magnesium remarkably reduced Alanine aminotransferase levels (by 44.4%) and hepatic fat content in patients with NASH, but the study is not complete and needs to be validated in subsequent clinical trials. Saroglitazar magnesium was approved by the Indian Medicines Board for the treatment of NASH in March 2020. However, the indication for NASH has not yet been approved by the United States Food and Drug Administration and European Medicines Agency. There is no doubt that saroglitazar magnesium should be further evaluated in NASH patients of different races, and elucidated its role in global NASH treatment [26].

4.1.2. PPARα/δ agonist Elafibranor

Elafibranor (GFT505) is a PPARα/δ agonist, which can effectively improve insulin sensitivity, glucose homeostasis, and lipid metabolism, reduce inflammation, and has been considered a potential drug for NASH [27]. Cariou confirmed that elafibranor has significant effects in reducing triglycerides, fasting blood glucose, increasing high-density lipoprotein, and improving insulin resistance. Elafibranor can be used for the treatment of lipid and glucose metabolism abnormalities related to metabolic syndrome [28]. Subsequently, the phase II clinical trial of elafibranor was conducted, the results showed that NASH resolved without fibrosis worsening in a higher proportion of patients in the 120-mg elafibranor group vs the placebo group and the 80-mg elafibranor group [29]. Adult NASH patients with remarkable liver fibrosis treated with elafibranor 120 mg/day for 72 weeks failed to achieve the primary endpoint of NASH remission without worsening fibrosis, possibly due to its weak PPARα/δ agonist activity and poor metabolic stability. Finally, elafibranor failed in phase III clinical trial [30].

4.1.3. PPAR α / δ / γ agonist Lanifibranor

Lanifibranor (IVA377) is a non-selective PPAR agonist, which can simultaneously activate PPARα, δ, and γ receptors [31]. PPARβ/δ is highly expressed in the liver, which is involved in lipid and carbohydrate metabolism, inflammatory reaction, and other processes. PPARδ, similar to PPARα, can both reduce the risk of cardiovascular diseases, and also promote hepatic gluconeogenesis and glucose utilization, reduce the expression of inflammatory factors and endoplasmic reticulum stress in the liver, reduce the activation of kupffer cells and macrophages, and improve the inflammatory response in the liver [32]. The results of phase IIb clinical trials showed that lanifibranor could inhibit the inflammatory response and fibrosis due to its receptor non-selectivity, and also regulates abnormal glucolipid metabolism. The primary endpoints were a reduction in Steatosis Activity Fibrosis activity score ≤2 points and no deterioration in Clinical Research Network fibrosis score, and the histological improvement of NASH and serological indicators (serum inflammatory markers, glucose metabolism, and blood lipids) were the secondary endpoints. Finally, only the lanifibranor 1200 mg group achieved the primary observation endpoint (the 800 mg group and the placebo control group did not achieve the endpoint), confirming that lanifibranor can delay or even reverse the histological progression of NASH to a certain extent. Currently, phase III clinical trials are underway to observe the efficacy of lanifibranor in patients with NASH complicated with grade 2/3 liver fibrosis. The primary endpoints are delay or reversal of NASH progression and improvement of liver fibrosis, and the secondary endpoints are improvement of histological features of liver NASH, liver function indexes, and serum indexes of glucose and lipid metabolism. Lanifibranor has a good safety profile and expected to be a promising drug for the treatment of NASH.

4.1.4. GLP-1 /FGF21 dual agonist GLP-1-FC-FGF21 D1

GLP-1-Fc-FGF21 D1 dual agonist produced by the potential synergy of fibroblast growth factor 21 (FGF21) and the incretin glucagon-like peptide 1 (GLP-1), which provided potent and sustained glucose lowering effect in diabetic mice models. Moreover, GLP-1-Fc-FGF21 D1 exhibited strong anti-NASH effect in the high-fat diet-induced ob/ob mice due to its improved liver function, serum, and hepatic lipid profile and reduced NAFLD activity score with an efficacy superior to either FGF21 or GLP-1 analogs alone. This novel GLP-1/FGF21 dual agonist is worth developing for the treatment of

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T2D, obesity, and NASH [33].

4.2. CCR2/CCR5 dual Antagonists Cenicriviroc

Liver inflammation is coordinated by chemokines, a family of chemokines produced by hepatocytes, kupffer cells, hepatic stellate cells, endothelial cells, and vascular smooth muscle cells [34]. Cenicriviroc is a novel oral dual antagonist of potent chemokine receptors (CCR2/CCR5) involved in inflammatory and fibrotic pathways. Cenicriviroc was initially used as an antiviral drug for AIDS, and the indication was expanded to NASH after similar immune signaling pathways were found. Cenicriviroc was associated with improvements in serum markers of fibrosis in clinical trials of HIV-infected patients without liver disease. Cenicriviroc is currently in development for the treatment of liver fibrosis in adults with NASH. Cenicriviroc can effectively exert anti-inflammatory and anti-hepatic fibrosis effects in the mouse model of NASH. Retrospective clinical studies have shown that cenicriviroc can effectively improve insulin resistance, liver triglyceride level, liver inflammation, and liver fibrosis progression in patients with NASH. The phase IIb clinical trial showed that some subjects with improvement in liver fibrosis and no worsening in NASH increased twofold after one year of treatment with cenicriviroc. The subsequent phase III clinical trial was conducted to evaluate the efficacy and safety of cenicriviroc in patients with NASH and liver fibrosis has been completed, but the relevant results have not yet been published [35].

4.3. Other

In addition, a new class of GPBAR1/CysLT1R dual-target regulator REV5901 derivatives with cysteinyl leukotriene receptor 1 (CysLT1R) antagonism and G protein bile acid receptor 1 (GPBAR1) agonism have been identified in recent studies. It effectively prevents the development of weight gain, hepatic steatosis, and hepatocyte injury in NASH mouse model experiments, which needs to be verified in subsequent clinical experiments and shows the prospect of further development [36].

5. Problems and challenges for multi-target drugs for NASH

Multi-target drugs have shown superiority in the treatment of complex diseases like NASH, but still little multi-target drugs are developed for the treatment of NASH in clinical. Currently, only saroglitazar magnesium, a PPARα/γ dual agonist, has been approved for the treatment of NASH in the world. The development of multi-target drugs faces the following three problems and challenges. (1) The balance of multi-target drugs activity: the density distribution of receptors or enzymes in different tissues in the human body, with different expression levels, can cause a loss of balance in the use of drugs, affecting the optimal balance of multi-target drugs in the body [37]. (2) The pharmacokinetic properties of multi-target drugs: the multi-target drugs molecules obtained by pharmacophore combinations usually have large relative molecular masses and complex structures, with poor oral absorption and solubility [38]. Therefore, the pharmacokinetics, therapeutic effects, adverse reactions, and physicochemical properties should be taken into account during the design and optimization process of the lead compound, and multiple parameters should be optimized simultaneously. (3) The safety of multi-target drugs: the safety of multi-target drugs with large molecular weight and complex structure is often difficult to be judged by the traditional rules of drug-likeness properties and empirical parameters. It is necessary to find patterns in a large number of basic and clinical experiments and to establish targeted guidelines.

6. Conclusion

Human diseases caused by a single gene or target account for only a small number of cases. In a large number of clinical trials, it has been found that highly selective drugs have certain limitations, which are usually difficult to achieve the desired effect or produce serious adverse side effects during the treatment of complex diseases. This is also the reason why so many clinical candidates fail to meet the observed endpoints in phase II or phase III clinics trials. Multi-target drugs can simultaneously regulate multiple targets and produce synergistic effects and have been successfully used in the treatment of diabetes, Alzheimer’s disease, hypertension, depression, asthma, cancer, HIV, and infectious disease. Currently, saroglitazar magnesium, the world's first and only drug approved for the treatment of NASH, is a PPAR α/γ agonist. Another promising drug with a good safety profile, lanifibranor, is also a multi-target agonist for the treatment of NASH. The success of the multi-target

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drugs above mentioned confirms the superiority of multi-target drugs for NASH treatment to some extent. It is believed that more and more safe and efficient multi-target drugs will be used for the treatment of NASH in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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