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Review

Perspectives of Drug Therapy for Non-Alcoholic Steatohepatitis-Related Liver Fibrosis

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ABSTRACT: Liver fibrosis (LF) is an adverse event of the natural course of non-alcoholic steatohepatitis (NASH) since its progression leads to the development of liver cirrhosis, which is associated with poor prognosis. In addition, there is evidence that the presence of advanced LF may be a strong independent predictor and risk factor for cardiovascular disease in NASH patients, which is the main cause of their death. Based on the severity of the problem, the study and implementation of drugs for the treatment of NASH-related LF is extremely necessary. The purpose of this review was to describe phase II and III randomized controlled trials (RCTs) evaluating the efficacy and safety of drug therapy for NASH-related LF. To date, the possibilities for pharmacological treatment of NASH-related LF are very limited. However, in recent years, several drugs have been evaluated in NASH patients with LF (F2–3), and in some cases with compensated liver cirrhosis, in large phase II and III RCTs, and they have shown promise. It can be assumed that drugs that have shown efficacy and safety in phase II and III RCTs will be recommended for testing and confirming practical benefits in phase IV RCTs. Besides, an in-depth study of the cellular and molecular mechanisms of NASH-related LF will contribute to the development of new medications, the introduction of which will expand the possibilities of its drug therapy.

Keywords: Non-alcoholic fatty liver disease; Nonalcoholic steatohepatitis; Liver fibrosis; Liver cirrhosis; Drug therapy

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the main liver diseases that currently affects 25–30% of the world's adult population. In most cases, NAFLD has a non-progressive course. However, over 20% of patients may develop non-alcoholic steatohepatitis (NASH), which is characterized by both steatosis and hepatocellular ballooning, lobular inflammation, and various liver fibrosis (LF) stages [1]. LF is a response to hepatic insults, which is an adverse event of the natural course of most chronic liver diseases, including NAFLD, since its progression leads to the development of liver cirrhosis, which is associated with poor prognosis [2]. In addition, there is evidence that the presence of advanced LF may be a strong independent predictor and risk factor for cardiovascular disease in NASH patients, which is the main cause of their death [3]. Based on the severity of the problem, the study and implementation of drugs for the treatment of NASH-related LF is extremely necessary. This review describes phase II and III randomized controlled trials (RCTs) evaluating the efficacy and safety of drug therapy for NASH-related LF.

2. Literature Search

PubMed, Google Scholar, Web of Science platform, Reference Citation Analysis, and Cochrane Systematic Reviews were searched for literature published between 2005 and 2024. The articles relevant to the review topic were identified using the following keywords: "non-alcoholic fatty liver disease", "non-alcoholic steatohepatitis", "liver fibrosis", "liver cirrhosis", "drug therapy". The reference lists of articles identified were also searched for other relevant publications. Phase II and III RCTs were the inclusion criterion for evaluating the efficacy and safety of drug therapy for NASH-related LF. Eighty articles were found in the databases that were relevant to the review topic, of which forty were phase II and III RCTs evaluating the efficacy and safety of drug therapy for NASH-related LF. When searching

for literature, it was taken into account that since June 2023, the terms "non-alcoholic fatty liver disease" and "non-alcoholic steatohepatitis" were officially replaced by "metabolic dysfunction–associated steatotic liver disease" and "metabolic dysfunction–associated steatohepatitis", respectively.

3. Basic Principles of Conducting Clinical Trials Evaluating the Efficacy and Safety of Drug Therapy for Non-Alcoholic Steatohepatitis-Related Liver Fibrosis

The implementation of drugs for the treatment of NASH-related LF directly depends on the conduct of adequate and well-planned controlled clinical trials. They must establish that the selected drug affects surrogate endpoints, which either directly reflect the results of treatment or predict the outcome of the disease with sufficient probability. Finally, the clinical benefits of the drug should be confirmed by post-marketing studies, taking into account information about how the patient "feels, functions or survives" (U.S. Food and Drug Administration (FDA) criteria) [4].

In many studies, non-invasive biomarkers of NASH-related LF are used as the primary and/or secondary endpoints. However, it should be borne in mind that none of them is absolutely accurate in determining the success of antifibrotic therapy. Currently, the Enhanced Liver Fibrosis (ELF) score is the first and only FDA-approved non-invasive outcome measure for disease prognosis in NASH patients [5]. Despite known limitations, in clinical trials of new drugs in NASH patients with moderate or severe (bridging) LF (F2–3), the "gold standard" confirming their efficacy is liver biopsy [6]. The Pathology Committee of the NASH Clinical Research Network (NASH CRN) has developed and approved a histological signs assessment system that takes into account the entire spectrum of NAFLD lesions and proposed the NAFLD Activity Scale (NAS) for use in clinical trials, in particular, to assess the efficacy of NAFLD treatment. An improvement in histological signs correlates with a decrease in NAS values [7]. In NASH patients with moderate or severe (bridging) LF (F2–3), surrogate histological endpoints in phase II and III clinical trials may be:

- NASH resolution (on overall histological signs) without worsening of LF (according to the NASH CRN fibrosis score);
- LF improvement by ≥1 stage (according to the NASH CRN fibrosis score) without worsening of NASH;
- NASH resolution and LF improvement by ≥1 stage (according to the NASH CRN fibrosis score).

These surrogate histological endpoints were based on the Kaplan-Meyer curve, demonstrating a decrease in overall survival and an increase in liver-related mortality that occurred with more advanced LF [4]. Indeed, liver cirrhosis (F4) accurately predicts the highest mortality compared to moderate or severe (bridging) LF (F2–3), which turned out to be higher than in LF (F0–1). The severity of LF also makes it possible to predict liver-related clinical outcomes effectively. In addition, a strong correlation was found between the histological NASH resolution and LF improvement [8,9].

In accordance with FDA recommendations, in pre-marketing studies of NASH patients, the validation of surrogate histological endpoints is usually planned after 12–18 months of treatment. However, given the slow, gradual progression, or *vice versa*, an improvement in inflammation and LF can be determined after two years or more. In addition, it is necessary to ensure long-term follow-up of patients who receive treatment for NASH-related LF in RCTs in order to determine clinical results in post-marketing settings.

For the final approval of drugs for the treatment of NASH-related LF, a phase IV clinical trials is required. To this end, randomized, double-blind, placebo-controlled trials examine events indicating stabilization or improvement of the course of NASH, as well as slowing the progression of associated liver cirrhosis, weakening the severity of signs of its decompensation (gastroesophageal variceal bleeding, ascites, hepatic encephalopathy, *etc*.), improvement in Child-Pugh and MELD scales, decline in mortality from liver diseases and all causes, reducing the need for liver transplantation, *etc*. [4].

4. Phase II and III Randomized Controlled Trials Evaluating the Efficacy and Safety of Drug Therapy for Non-Alcoholic Steatohepatitis-Related Liver Fibrosis

To date, the possibilities for pharmacological treatment of NASH-related LF are very limited. However, in recent years, several drugs have been evaluated in NASH patients with LF (F2–3), and in some cases with compensated liver cirrhosis, in large phase II and III RCTs. They have shown promise [10] (Figure 1).

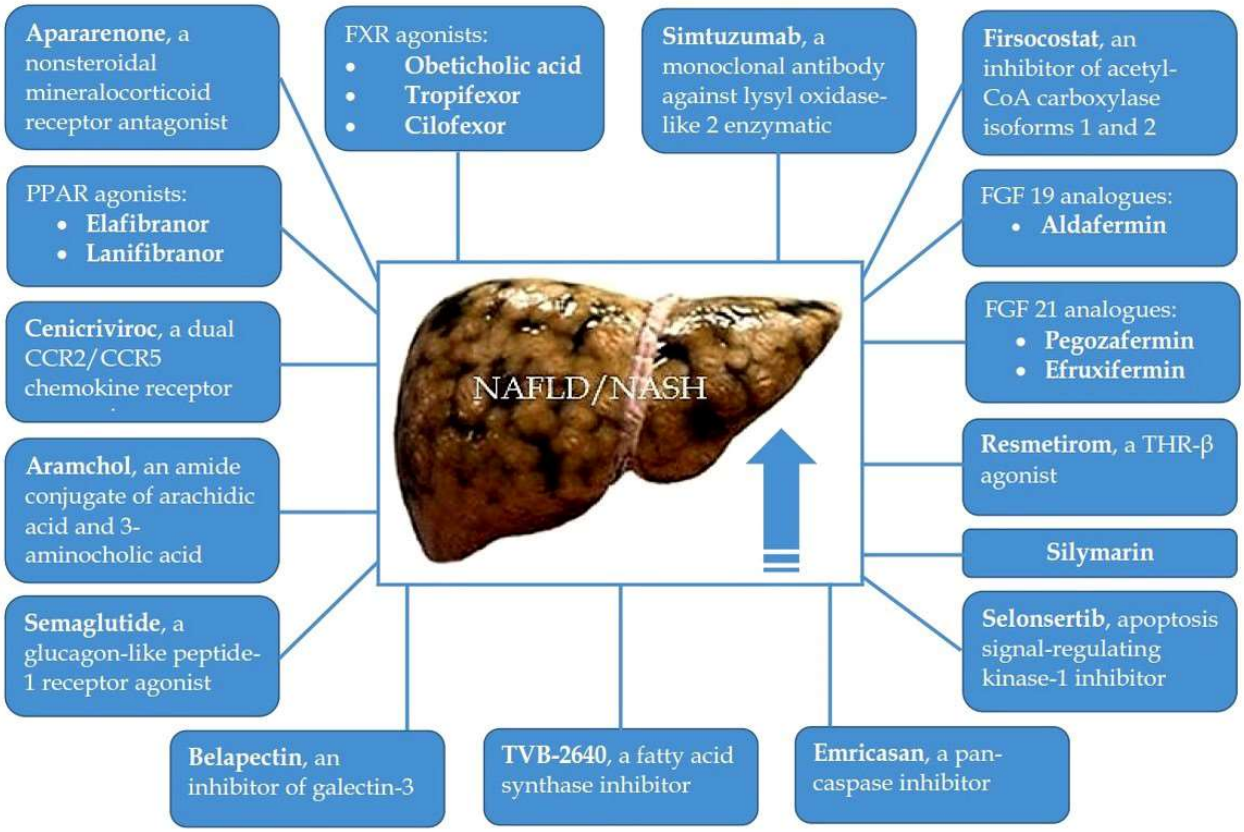

Figure 1. Drugs whose efficacy and safety have been evaluated in phase II and III randomized controlled trials. Legend to Figure 1. NAFLD-Non-alcoholic fatty liver disease; NASH-Non-alcholic steatohepatitis; FXR-Farnesoid X receptor; PPAR-Peroxisome proliferator-activated receptor; FGF-Fibroblast growth factor; THR-Thyroid hormone receptor.

4.1. Farnesoid X Receptor Agonists

The farnesoid X receptor (FXR) is an important player in the pathogenesis of NASH. It participates in the synthesis of bile acids and enterohepatic circulation, glucose and lipid metabolism, liver fibrosis and inflammation, and also induces genes that affect intestinal permeability, preventing bacterial translocation [11].

Obeticholic acid (OCA) is a semisynthetic modified bile acid derived from chenodeoxycholic acid that represents the first-in-class selective FXR agonist proposed for the treatment of NASH-related LF [12]. In a multicentre, double-blind, placebo-controlled, parallelgroup, randomized, phase IIb trial (FLINT), the efficacy of treatment with OCA (orally 25 mg per day) for 72 weeks was evaluated in 219 NASH patients without liver cirrhosis (110 in the OCA group and 109 in the placebo group). 50 (45%) patients in the OCA group had improved liver histology (≥2 points decrease in NAS, without worsening of LF) compared with 23 (21%) of patients in the placebo group (relative risk [RR] 1.9, 95% CI: 1.3–2.8; $p = 0.0002$) [13]. The most significant predictors of histological response in OCA-treated NASH patients during the first 24 weeks of treatment in the FLINT trial were baseline NAS > 5, baseline triglyceride ≤ 154 mg/dL, baseline international normalized ratio ≤ 1, baseline aspartate aminotransferase (AST) ≤ 49 U/L, and a decline in alanine aminotransferase (ALT) by 17 U/L or more (AUROC, 0.83; 95% CI: 0.77–0.89; $p < 0.0001$) [14].

In a multicentre, double-blind, placebo-controlled, randomized, phase III trial (REGENERATE), 1968 NASH patients with LF (F1–3; 931-F2–3) and NAS ≥ 4 were randomized in a 1:1:1 ratio to get oral placebo, OCA 10 mg, or OCA 25 mg daily. The primary endpoints for the intermediate analysis after 18 months were LF improvement by ≥1 stage without worsening of NASH or NASH resolution without worsening of LF. The primary endpoint LF improvement was achieved by 12% of patients in the placebo group, 18% in the OCA 10 mg group ($p = 0.045$) and 23% in the OCA 25 mg group ($p = 0.0002$). The primary endpoint NASH resolution was not met in 8% of patients in the placebo group, 11% in the OCA 10 mg group ($p = 0.18$) and 12% in the OCA 25 mg group ($p = 0.13$). This intermediate analysis showed a clinically significant histological improvement, which, with sufficient probability, allows for the prediction of the benefit of OCA in NASH patients when evaluating long-term results [15]. Subsequent histology data in a larger population of NASH patients confirmed the original results of the REGENERATE trial on the antifibrotic effect of OCA 25 mg, which was superior to placebo in improving LF by ≥1 stage without worsening of NASH. Besides

regression of LF, OCA 25 mg in NASH patients is able to halt LF progression, sustain improvements in biochemical markers of liver injury and oxidative stress, and measure liver stiffness [16]. Non-invasive biomarkers of NASH-related LF were evaluated in the REGENERATE trial. Rapid, sustained reductions from baseline in ALT, AST, and gamma-glutamyltransferase (GGT) levels, as well as in Fibrosis-4 (FIB-4), FibroMeter, FibroScan-AST, and FibroTest scores were noticed in OCA-treated *vs.* placebo-treated patients. A decrease in liver stiffness measured by vibration-controlled transient elastography was noticed in the OCA 25 mg group *vs.* the placebo group. Non-invasive biomarker changes were associated with shifts in the histologic LF stage. The greatest effect was noticed in patients with LF improvement by ≥1 stage; however, improvements in ALT, AST, FIB-4, and FibroTest were also observed in OCA-treated patients whose histologic LF remained stable [17]. It should be added that NASH patients in the REGENERATE trial have impaired quality of life and underlying mild to moderate pruritus at baseline, which did not worsen over time [18].

Tropifexor is a highly potent, non-bile acid FXR agonist, the efficacy of which has been shown in preclinical NASH models [19]. In a multicentre, double-blind, placebo-controlled, three-part adaptive design, randomized, phase IIa/b trial, the efficacy and safety of tropifexor were evaluated in NASH patients. In Parts A + B, 198 patients were randomized to get tropifexor (10–90 μg) or placebo for 12 weeks. In Part C, 152 patients were randomized to get tropifexor 140 μg, tropifexor 200 μg, or placebo (1:1:1) for 48 weeks. There were no notable differences among the treatment groups at week 48 in the proportion of patients who achieved LF improvement by ≥1 stage without worsening of NASH in the placebo (21%), tropifexor 140 μg (26%), and 200 μg (26%) groups. The NASH resolution without worsening of LF at week 48 was seen in a few patients in the tropifexor 140 μg (5%) and 200 μg (6%) groups versus none in the placebo group. At week 48, the decrease in mean total NAS was −0.9, −1.0 and −1.2 in the placebo, tropifexor 140 μg, and tropifexor 200 μg groups, respectively. There was no meaningful change in liver stiffness measured by FibroScan from baseline to end-of-treatment in any tropifexor dose group compared with placebo. A notable change in ELF score was observed from baseline to end-of-treatment in the tropifexor 60 μg group (−0.25 versus +0.12 (placebo)) and tropifexor 140 μg and 200 μg groups only (−0.28 and −0.23, respectively, versus −0.07 (placebo)). Decreases in mean fibrosis biomarker test scores from baseline to end-of-treatment in tropifexor 10–90 μg groups were not notably different compared with placebo, and neither were the least squares mean decreases observed in the tropifexor 140 μg and 200 μg groups. In this study, pruritus was the most commonly adverse event with tropifexor, with a dose-dependent incidence. The cases were usually of mild severity and led to low treatment discontinuation rates [20].

In a double-blind, placebo-controlled, randomized, phase II trial, the efficacy and safety of *cilofexor*, a small-molecule nonsteroidal FXR agonist, was evaluated in 140 NASH patients. Magnetic resonance imaging-proton density fat fraction (MRI-PDFF), liver stiffness by magnetic resonance elastography (MRE) and transient elastography, and serum markers of LF were measured at baseline and week 24. Cilofexor was well-tolerated and provided significant reductions in hepatic steatosis, serum GGT, 7α-Hydroxy-4-cholesten-3-one (C4), and primary bile acids, whereas significant changes in ELF scores and liver stiffness were not observed [21].

4.2. Peroxisome Proliferator-Activated Receptor Agonists

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors that are involved in a wide range of physiological processes and play an important role in regulating cellular differentiation, development and metabolism (affecting lipid and carbohydrate metabolism). There are three main isotypes of PPARs: PPAR-α, PPAR-β/δ and PPAR-γ, each of which has a distinct tissue-specific expression pattern [22].

Elafibranor, a dual agonist for PPAR-α and -δ, has been shown to improve insulin sensitivity, glucose homeostasis, and lipid metabolism and reduce inflammation in preclinical NASH models and early clinical trials [23]. In a multinational, double-blind, placebo-controlled, randomized, phase II trial, the efficacy and safety of elafibranor were evaluated in 276 NASH patients with LF (F1–3). Patients were randomly assigned (1:1:1) to groups that received elafibranor 80 mg (n = 93), elafibranor 120 mg (n = 91), or placebo (n = 92) each day for 52 weeks. The primary endpoint was NASH resolution without worsening of LF. The NASH resolution without worsening of LF was higher in the group that received elafibranor 120 mg vs. the placebo group (p = 0.045). In patients with NAS ≥ 4 (n = 234), elafibranor 120 mg resolved NASH in larger proportions than placebo (p = 0.018). Patients with NASH resolution after receiving elafibranor 120 mg had reduced LF stages compared with those without NASH resolution (mean reduction of 0.65 ± 0.61 in responders for the primary outcome vs an increase of 0.10 ± 0.98 in nonresponders; $p < 0.001$). Elafibranor was well tolerated and did not cause weight gain or cardiac complications, but contributed to a moderate, reversible increase in serum creatinine [24].

Lanifibranor is a pan PPAR agonist for PPAR-α, -β, and -γ. It modulates key metabolic, inflammatory, and hepatic fibrotic pathways in NASH [25]. In a multinational, double-blind, placebo-controlled, randomized, phase IIb trial, the efficacy and safety of lanifibranor was evaluated in 247 NASH patients, of whom 103 (42%) had type 2 diabetes mellitus and 188 (76%) had moderate or severe (bridging) LF (F2–3). Patients were randomly assigned (1:1:1) to receive 1200 mg or 800 mg of lanifibranor or placebo once daily for 24 weeks. The percentage of patients who had a decrease of at least 2 points in the SAF-A score (the activity part of the Steatosis, Activity, Fibrosis [SAF] scoring system) without worsening of LF was significantly higher among those who received the 1200 mg of lanifibranor than with placebo. Diarrhea, peripheral edema, nausea, weight gain, and anemia occurred more frequently with lanifibranor than with placebo [26].

4.3. Cenicriviroc, a Dual CCR2/CCR5 Chemokine Receptor Antagonist

Cenicriviroc is a novel, orally administered, chemokine receptor type 2 and 5 antagonist that showed antifibrotic potential in preclinical NASH models [27]. In a multinational, double-blind, placebo-controlled, randomized, phase IIb trial (CENTAUR), the efficacy and safety of cenicriviroc 150 mg for the treatment of 289 NASH patients with LF (F1–3) and NAS ≥ 4 were evaluated over 2 years. The primary endpoint was ≥2-point NAS improvement without worsening of LF at year 1. Key secondary endpoints were: NASH resolution without worsening of LF; LF improvement by ≥1 stage without worsening of NASH at year 2. After 1 year of cenicriviroc treatment, twice as many NASH patients achieved LF improvement without worsening of NASH compared with placebo [28]. Cenicriviroc was well tolerated, and year 2 data confirmed antifibrotic findings from year 1. The majority of patients treated with cenicriviroc, who achieved a fibrosis response at year 1 maintained it at year 2, with greater effect in advanced LF [29]. At the same time, a double-blind, placebo-controlled, two-part, randomized, phase III trial (AURORA) including 1778 NASH patients with histologically confirmed LF (F2–3) did not demonstrate the efficacy of cenicriviroc 150 mg for the treatment of LF [30]. In open-label rollover phase II trial, a total of 167 NASH patients who completed the CENTAUR trial or reached a predefined endpoint in the AURORA trial were rolled over and received cenicriviroc 150 mg once daily with a median treatment duration of 33.6 months. Treatment-related adverse events were detected in 28 patients (16.8%). The most frequent of these were 4 cases of diarrhea (2.4%) and 2 cases each (1.2%) of abdominal pain. In addition, nausea, hypertriglyceridemia, myalgia, pruritus, rash, and increases in ALT, AST were observed [31].

4.4. Fibroblast Growth Factor 19 and 21 Analogues

The fibroblast growth factors (FGFs) family consists of 22 members performing various biological functions in cells, from cellular development to metabolism. In particular, FGF19 and FGF21 are endocrine FGFs that act in a hormone-like/endocrine manner to regulate various metabolic processes [32]. Currently, FGF19 and FGF21 analogues are in clinical development for the potential treatment of NASH-related LF [33].

In a multicentre, double-blind, placebo-controlled, randomized, phase II trial, the efficacy and safety of *aldafermin*, an engineered FGF19 analogue, was evaluated in 78 NASH patients with LF (F2–3) and NAS ≥ 4. Compared with placebo, treatment with aldafermin daily for 24 weeks produced significant improvements in liver fat content, LF regression and NASH resolution. The drug was discontinued due to adverse events in 4% of patients in the placebo group and none in the aldafermine group [34]. In a multicentre, double-blind, placebo-controlled, randomized, phase IIb trial (ALPINE 2/3) involving 171 NASH patients with LF (F2–3) and NAS ≥ 4, treatment with aldafermin was generally well tolerated but did not produce a significant dose response on LF improvement by ≥1 stage without worsening of NASH, despite positive effects on a number of secondary endpoints [35]. In a multicentre, double-blind, placebo-controlled, randomized, phase IIb trial involving 160 NASH patients with biopsy-confirmed compensated liver cirrhosis (F3–4) and NAS > 5, treatment with aldafermin at a dose of 3 mg resulted in greater reductions in ELF score than placebo (p = 0.0003) over 48 weeks, meeting the primary outcome. Furthermore, mean ALT, AST, N-terminal propeptide of type III collagen (PRO-C3) values were reduced in a dose-dependent manner to a greater extent with aldafermin than with placebo. All secondary outcomes, including the percentage of patients who had LF improvement by ≥1 stage without worsening of NASH, reductions in liver stiffness, and pharmacodynamic markers C4 and serum bile acids, generally favored aldafermin. In addition, aldafermin was generally well tolerated in NASH patients with compensated liver cirrhosis [36].

Clinical trial data have shown that *pegbelfermin*, a human FGF21 analogue, can reduce hepatic fat and improve metabolic factors and biomarkers of NASH-related LF. The FALCON trials were planned to evaluate the efficacy of pegbelfermin for treatment in NASH patients with advanced LF [37]. In a multicentre, double-blind, placebo-controlled,

randomized (1:1:1:1), phase IIb trial (FALCON 1), 197 NASH patients with biopsy-confirmed LF (F3) received weekly subcutaneous pegbelfermin (10, 20, or 40 mg) or placebo injections for 48 weeks. The week 24 primary endpoint was LF improvement by ≥1 stage without worsening of NASH or NASH resolution without worsening of LF. The secondary/exploratory endpoints included histological and non-invasive measures of liver steatosis, fibrosis, and injury/inflammation. At week 24, the primary endpoint was met by 14% in the placebo group *vs*. 24–31% in the pegbelfermin group ($p = 0.134$). At weeks 24 and 48, more patients who received pegbelfermin had ≥30% relative reductions in MRI-PDFF *vs*. placebo without statistical significance differences. In the pegbelfermin groups, LF improvement (MRE and PRO-C3) and liver injury/inflammation (ALT, AST) were observed vs placebo. Adverse events occurred at similar frequencies across groups. There were no treatment-related serious adverse events [38]. In a multicentre, double-blind, placebo-controlled, randomized (1:1:1:1), phase IIb trial (FALCON 2), 155 NASH patients with biopsy-confirmed compensated liver cirrhosis (F4) received weekly subcutaneous pegbelfermin (10, 20, or 40 mg) or placebo injections for 48 weeks. The primary endpoints were LF improvement by ≥1 stage without worsening of NASH at week 48. Additional endpoints included histologic and non-invasive measures of steatosis, fibrosis, and liver injury/inflammation. At week 48, 24% to 28% of the pegbelfermin groups had primary endpoint responses *vs*. 31% of the placebo group ($p = 0.361$). NAS improvements were more frequent with pegbelfermin *vs.* placebo and were driven primarily by reduced lobular inflammation. Numerically, higher proportions of the pegbelfermin groups had improvements of liver stiffness (MRE) and steatosis (MRI-PDFF) *vs*. the placebo group; these differences were not statistically significant. Mean PRO-C3, ALT, and AST values were numerically lower in the 20- and/or 40-mg pegbelfermin groups compared with the placebo group. Serious adverse events were more frequent with pegbelfermin vs placebo, although none were treatment-related. One patient (40 mg pegbelfermin group) discontinued treatment because of a treatment-emergent adverse event (worsening ascites) [39].

It has been shown that *pegozafermin*, a glycoPEGylated FGF21 analogue, is well tolerated and leads to a clinically significant decrease in liver fat content, circulating lipid levels, and improved liver function in NASH patients [40]. In a multicentre, double-blind, placebo-controlled, randomized, phase IIb trial involving 222 NASH patients with biopsy-confirmed LF (F2–3), treatment with pegozafermin at doses of 30 mg once weekly and 44 mg every 2 weeks for 24 weeks led to significant improvements, as compared with placebo, in LF without worsening of NASH. The most common adverse events associated with pegozafermin therapy were nausea and diarrhea [41].

Efruxifermin is an engineered Fc-FGF21 fusion protein with an optimized pharmacokinetic and pharmacodynamic profile that has beneficial metabolic effects, reducing obesity, hepatic fat fraction, and insulin resistance in NASH patients with an acceptable safety profile [42]. In a multicentre, double-blind, placebo-controlled, randomized, phase IIb trial (HARMONY) involving 128 NASH patients with biopsy-confirmed LF (F2–3) and NAS ≥ 4, treatment with efruxifermin at doses of 28 mg and 50 mg subcutaneously once weekly for 24 weeks improved LF and resolved NASH in a significantly higher proportion of patients compared with placebo, resulting in histological improvements that are reasonably likely to predict clinical benefit [43]. In a multicentre, double-blind, placebo-controlled, randomized, phase IIa trial, the safety and tolerability of efruxifermin were evaluated in 30 NASH patients with biopsy-confirmed compensated liver cirrhosis (F4). Patients were randomized 2:1 to groups given efruxifermin 50 mg ($n = 20$) or placebo ($n = 10$) once-weekly for 16 weeks. The primary endpoint was the safety and tolerability of efruxifermin. The secondary and exploratory endpoints included the evaluation of non-invasive markers of liver injury and fibrosis, glucose and lipid metabolism, and changes in histology in a subset of patients who consented to end-of-study liver biopsy. Efruxifermin was safe and well-tolerated. The most frequent adverse events were transient, mild to moderate diarrhea, and/or nausea. At week 16, treatment with efruxifermin was associated with significant reductions in non-invasive markers of LF, including Pro-C3 (−9 μg/L in the efruxifermin group *vs.* −3.4 μg/L in the placebo group; $p = 0.0130$) and ELF score (−0.4 in the efruxifermin group *vs.* +0.4 in the placebo group; $p = 0.0036$), with a trend towards reduced liver stiffness (−5.7 kPa in the efruxifermin group *vs.* −1.1 kPa in the placebo group; n.s.). Of 12 efruxifermin-treated patients with liver biopsy after 16 weeks, 4 (33%) achieved LF improvement by ≥1 stage without worsening of NASH, while an additional 3 (25%) achieved NASH resolution, compared to 0 of 5 placebo-treated patients [44].

4.5. Selonsertib, Apoptosis Signal-Regulating Kinase-1 Inhibitor

The apoptosis signal-regulating kinase-1 (ASK1) pathway is upregulated in NASH patients and correlates with the LF stage [45]. ASK1 inhibition has been demonstrated as an antifibrotic effect in preclinical NASH models [46]. To evaluate the antifibrotic effect and safety of *selonsertib*, a selective ASK1 inhibitor, two multicentre, double-blind, placebo-controlled, randomized, phase III trials were conducted in 802 NASH patients with severe (bridging) LF (F3,

STELLAR-3) and compensated liver cirrhosis (F4, STELLAR-4). Patients received selonsertib at doses of 18 mg and 6 mg once daily for 48 weeks. Selonsertib had no significant effect on liver biochemistry, non-invasive tests of LF, progression to liver cirrhosis, or adjudicated clinical events. The rates and types of adverse events were similar among selonsertib and placebo groups [47].

4.6. Simtuzumab, a Monoclonal Antibody against Lysyl Oxidase-like 2 Enzymatic Activity

Lysyl oxidase-like 2 (LOXL2) is a secreted, copper-dependent amine oxidase that plays a central role in fibrosis by catalyzing the cross-linkage of collagen and elastin [48]. In NASH patients, increased LOXL2 levels in serum correlate with more advanced LF and the severity of portal hypertension [49]. *Simtuzumab*, a humanized monoclonal antibody directed against LOXL2, binds to and inhibits LOXL2 enzymatic activity [50]. In two multicentre, double-blind, placebo-controlled, randomized, phase IIb trials involving 477 NASH patients with biopsy-confirmed LF (F3–4), treatment with subcutaneous injections of simtuzumab (75 or 125 mg) once weekly (219 NASH patients with LF (F3)) or intravenous infusions of simtuzumab (200 or 700 mg) every other week (258 NASH patients with LF (F4)) for 96 weeks did not lead to decreasing hepatic collagen content or reducing hepatic venous pressure gradient (HVPG), respectively [51].

4.7. Belapectin, an Inhibitor of Galectin-3

Belapectin is a complex carbohydrate molecule derived from a natural plant compound that contains oligosaccharide chains containing galactose residues and binds to galectin-3 and, to a lesser extent, galectin-1. It has demonstrated high efficacy in preclinical NASH models with LF and has also been safe and well tolerated in human phase 1 trials [52]. In a multicentre, double-blind, placebo-controlled, randomized, phase IIb trial involving 162 NASH patients with liver cirrhosis and portal hypertension, treatment with biweekly infusions of belapectin 2 mg/kg or 8 mg/kg for 52 weeks was safe but not associated with significant reduction in HVPG or LF, compared with placebo. However, in a subgroup of patients without gastroesophageal varices, 2 mg/kg belapectin did reduce HVPG and development of gastroesophageal varices [53].

4.8. Emricasan, a Pan-Caspase Inhibitor

Emricasan is an oral pan-caspase inhibitor that suppresses excessive apoptosis and inflammation, as well as reduces liver damage and LF in preclinical NASH models [54]. In a multicentre, double-blind, placebo-controlled, randomized, phase II trial involving 318 NASH patients with biopsy-confirmed LF (F1–3), treatment with twice-daily emricasan (5 mg or 50 mg) for 72 weeks did not improve liver histology but, on the contrary, aggravated LF and hepatocellular ballooning. Overall, no adverse event was clearly associated with emricasan treatment [55]. In a multicentre, double-blind, placebo-controlled, randomized, phase III trial involving 318 NASH patients with liver cirrhosis and clinically significant portal hypertension (HVPG $\geq$ 12 mmHg), despite a reduction in biomarkers of NASH-related LF, treatment with twice-daily oral emricasan (5 mg, 25 mg, 50 mg) for 48 weeks was not associated with improvement in HVPG or clinical outcomes. Compensated patients with higher baseline HVPG had evidence of a small treatment effect. Emricasan treatment appeared safe and well-tolerated [56].

4.9. Aramchol, an Amide Conjugate of Arachidic Acid and 3-Aminocholic Acid

Aramchol (arachidyl amido cholanoic acid), which is formed as a result of the connection of cholic acid and arachidic acid, inhibits stearoyl coenzyme A desaturase, which leads to a direct anti-steatosis effect by reducing fat synthesis and enhancing its oxidation, contributing to a decrease of liver fat accumulation. Aramchol has played a significant role in the improvement of NASH and LF in preclinical NASH models and early clinical trials [57]. In a multicentre, double-blind, placebo-controlled, randomized, phase IIb trial (ARREST) involving 247 NASH patients, treatment with aramchol 600 mg (n = 98) once daily for 52 weeks contributed to NASH resolution without worsening of LF was achieved in 16.7% of patients and LF improvement by $\geq$1 stage without worsening of NASH in 29.5% of patients. Early termination due to adverse events was <5%. Aramchol were safe and well tolerated [58].

4.10. Semaglutide, a Glucagon-like Peptide-1 Receptor Agonist

A glucagon-like peptide-1 (GLP-1) receptors activation has been demonstrated reduce hepatic fat content by improving insulin resistance, *de novo* lipogenesis, mitochondrial function and lipotoxicity in preclinical NASH models

[59]. In a double-blind, placebo-controlled, randomized, phase II trial involving 320 NASH patients with biopsy-confirmed LF (F1–3; 230-F2–3), treatment with once-daily subcutaneous GLP-1 receptor agonist *semaglutide* at a dose of 0.1 mg, 0.2 mg, 0.4 mg for 72 weeks resulted in a significantly higher percentage of patients with NASH resolution without worsening of LF than placebo ($p < 0.001$ for semaglutide 0.4 mg *vs.* placebo). However, the trial did not show a significant between-group difference in the percentage of patients with LF improvement by ≥1 stage. The incidence of nausea, constipation, and vomiting was higher in the 0.4 mg group than in the placebo group (nausea, 42% *vs.* 11%; constipation, 22% *vs.* 12%; and vomiting, 15% *vs.* 2%) [60].

In a multicentre, double-blind, placebo-controlled, randomized, phase II trial, the efficacy and safety of semaglutide was evaluated in 71 NASH patients with compensated liver cirrhosis. Patients were randomly assigned (2:1) to groups that received either once-weekly subcutaneous semaglutide 2.4 mg ($n = 47$) or placebo ($n = 24$) for 48 weeks. The primary endpoint was the proportion of patients with LF improvement by ≥1 stage without worsening of NASH after 48 weeks. Safety was assessed in all patients who received at least one dose of semaglutide. There was no statistically significant difference between the two groups in the proportion of patients with LF improvement by ≥1 stage without worsening of NASH (11% patients in the semaglutide group *vs.* 29% patients in the placebo group (odds ratio [OR], 0.28; 95% CI: 0·06–1·24; $p = 0·087$). There was also no significant difference between groups in the proportion of patients who achieved NASH resolution ($p = 0.29$). Similar proportions of patients in each group reported adverse events (89% of patients in the semaglutide group vs 79% of patients in the placebo group) and serious adverse events (13% of patients in the semaglutide group *vs.* 8% of patients in the placebo group). The most common adverse events in the semaglutide group and in the placebo group were nausea (45% *vs.* 17%), diarrhea (19% *vs.* 8%), and vomiting (17% *vs.* none), respectively. Hepatic and renal function remained stable. There were no decompensating events or deaths [61].

4.11. Resmetirom, a Thyroid Hormone Receptor β Agonist

A thyroid hormone receptor β (THR-β) agonists, which are mainly found in the liver, can promote lipophagy, mitochondrial biogenesis, and mitophagy, stimulating increased hepatic fatty acid β-oxidation, and thus reducing the burden of lipotoxic lipids while promoting low-density lipoprotein uptake and favorable effects on lipid profiles. Currently, a number of THR-β agonists are being investigated for the treatment of NASH [62]. On 14 March 2024, the FDA announced the conditional approval of *resmetirom*, a THR-β agonist, for the treatment of NASH/metabolic dysfunction–associated steatohepatitis with LF (F2–3) [63]. In a double-blind, placebo-controlled, randomized, phase II trial involving 31 NASH patients with biopsy-confirmed LF (F1–3) and MRI-PDFF of at least 10% at baseline, treatment with resmetirom (MGL-3196) 80 mg or 100 mg orally once daily for 36 weeks resulted in hepatic fat reduction ($p < 0.0001$) and improvement in LF markers, including liver stiffness measured by transient elastography ($p = 0.015$) and PRO-C3 ($p = 0.0004$). Resmetirom was well-tolerated with no serious or severe adverse events [64]. In a multicentre, double-blind, placebo-controlled, randomized, phase III trial involving 966 NASH patients with biopsy-confirmed LF (F1–3) treatment with resmetirom 80 mg or 100 mg orally once daily for 52 weeks were superior to placebo with respect to NASH resolution without worsening of LF ($p < 0.001$) and LF improvement by ≥1 stage without worsening of NASH ($p < 0.001$). Diarrhea and nausea were more frequent with resmetirom than with placebo. Serious adverse events occurred in 10.9% of patients in the 80 mg resmetirom group, in 12.7% of patients in the 100 mg resmetirom group, and in 11.5% of patients in the placebo group [65].

4.12. Firsocostat, an Inhibitor of Acetyl-CoA Carboxylase Isoforms 1 and 2

Acetyl-CoA carboxylase is a key enzyme in the synthesis of fatty acids since it catalyzes the carboxylation of acetyl-CoA to form malonyl-CoA. This is an important step in *de novo* lipogenesis, which significantly contributes to the accumulation of triglycerides in hepatocytes in NASH patients. Thus, pharmacological inhibition of acetyl-CoA carboxylase represents an attractive approach to the treatment of NASH [66]. GS-0976 (*firsocostat*) is an inhibitor of acetyl-CoA carboxylase isoforms 1 and 2 (ACC1/2), which improved NASH and LF in preclinical NASH models and early clinical trials [67,68]. In a multicentre, double-blind, placebo-controlled, randomized, phase II trial, the efficacy, safety, and tolerability of GS-0976 (firsocostat) was evaluated in 126 NASH patients with biopsy-confirmed LF (F1–3). Patients were randomly assigned (2:2:1) to groups that received GS-0976 20 mg ($n = 49$), GS-0976 5 mg ($n = 51$), and placebo ($n = 26$) once daily for 12 weeks. Treatment with GS-0976 at a dose of 20 mg daily for 12 weeks was safe. It led to a significant decrease in hepatic fat content according to MRI-PDFF data and a reduction in serum levels of tissue inhibitor of metalloproteinases-1, an endogenous regulator of matrix metalloproteinases that is considered to

promote LF. Adverse events were experienced by 71% of patients receiving both 20 mg and 5 mg of GS-0976 and by 62% of patients receiving placebo. The most common adverse events among patients receiving GS-0976 were nausea, abdominal pain, diarrhea, and headache [69].

4.13. Apararenone, a Nonsteroidal Mineralocorticoid Receptor Antagonist

Apararenone (MT-3995) is a novel, highly selective, potent, nonsteroidal mineralocorticoid receptor antagonist that showed anti-inflammatory and antifibrotic potential in preclinical NASH models [70]. In a multicentre, double-blind, placebo-controlled, randomized, phase II trial involving 48 NASH patients with biopsy-confirmed LF (F2–3) and NAS ≥ 4 treatment with apararenone 10 mg once daily for 72 weeks was effective in decreasing ALT levels, in improving biomarkers of NASH-related LF (type IV collagen 7S and PRO-C3) and non-invasive tests of LF (ELF score and FIB-4 index). The percentage of patients with LF improvement by ≥1 stage without worsening of NASH was 41.7% with apararenone and 26.1% with placebo ($p = 0.203$). Treatment with apararenone was safe and well tolerated [71].

4.14. TVB-2640, a Fatty Acid Synthase Inhibitor

TVB-2640 is a selective, potent, reversible inhibitor of human fatty acid synthase enzymatic activity that showed anti-inflammatory and antifibrotic potential in preclinical NASH models and early clinical trials [72]. In a multicentre, single-blind, placebo-controlled, randomized, phase II trial (FASCINATE-1) involving 99 NASH patients with biopsy-confirmed LF (F1–3) treatment with TVB-2640 25 mg or 50 mg orally once-daily for 12 weeks significantly decreased liver fat and improved biochemical, inflammatory, and biomarkers of NASH-related LF. TVB-2640 was well tolerated; adverse events were mostly mild and balanced among the groups [73].

4.15. Silymarin

Silymarin is a complex mixture of six major flavonolignans and other minor polyphenolic compounds derived from the milk thistle plant. Silymarin has been shown to have anti-inflammatory, antioxidant, and antifibrotic effects on the liver in preclinical NASH models and early clinical trials [74]. However, in a multicentre, double-blind, placebo-controlled, randomized, phase II trial involving 78 NASH patients with biopsy-confirmed LF (F1–3) and NAS ≥ 4 treatment with silymarin 420 mg or 700 mg daily for 48 weeks did not lead to histological improvement of LF and NAS [75].

4.16. Combination Drug Therapy for Non-Alcoholic Steatohepatitis-Related Liver Fibrosis

The relatively low response rate when using drugs proposed as monotherapy for the treatment of NASH-related LF is largely due to the complexity and diversity of the underlying pathophysiological mechanisms. Therefore, in order to increase their efficacy and safety, combination therapy schemes are proposed, which allow the influence of different links of hepatic fibrogenesis [76].

In a multicentre, double-blind, randomized, phase II trial, 72 NASH patients with biopsy-confirmed LF (F2–3) were randomly assigned (2:2:1:1:1) to groups that received 6 mg or 18 mg of *selonsertib* alone, 6 mg or 18 mg of selonsertib with 125 mg of *simtuzumab*, or 125 mg of simtuzumab alone for 24 weeks to evaluate efficacy and safety of combination therapy compared with the monotherapies. It turned out that the addition of simtuzumab to selonsertib had no discernible benefit. There were no significant differences in adverse events between the treatment groups [77].

In a multicentre, double-blind, randomized, phase IIb trial (TANDEM) 193 NASH patients with biopsy-confirmed LF (F2–3) were randomly (1:1:1:1) to groups that received once-daily *tropifexor* (TXR) 140 μg, *cenicriviroc* (CVC) 150 mg, TXR 140 μg + CVC 150 mg, or TXR 90 μg + CVC 150 mg for 48 weeks. The primary endpoint was to evaluate the safety and tolerability of combination therapy compared with the monotherapies. The secondary endpoints were to evaluate the proportion of patients who had LF improvement by ≥1 stage without worsening of NASH and the proportion of patients with NASH resolution without worsening of LF. The safety profile of TXR + CVC combination was similar to the respective monotherapies. TXR monotherapy showed sustained ALT and decreased body weight. No substantial incremental efficacy was observed with TXR + CVC combination on ALT, body weight, or histological endpoints compared with monotherapy [78].

In a multicentre, double-blind, placebo-controlled, randomized, phase IIb trial (ATLAS) 392 NASH patients with severe (bridging) (F3) or compensated liver cirrhosis (F4) received placebo, selonsertib (SEL) 18 mg , cilofexor (CILO) 30 mg, or firsocostat (FIR) 20 mg, alone or in two-drug combinations, once daily for 48 weeks. LF improvement by ≥1 stage without worsening of NASH was achieved in 11% of placebo-treated patients versus CILO/FIR (21%; $p = 0.17$),

CILO/SEL (19%; $p = 0.26$), FIR/SEL (15%; $p = 0.62$), FIR (12%; $p = 0.94$), and CILO (12%; $p = 0.96$). In addition, CILO/FIR led to improvements in NASH activity, had an antifibrotic effect, and was well tolerated [79].

In a randomized, open-label, proof-of-concept, phase II trial, 108 NASH patients with biopsy-confirmed LF (F2–3) or MRI-PDFF ≥ 10% and liver stiffness measured by transient elastography ≥ 7 kPa received *semaglutide* 2.4 mg once weekly as monotherapy or combined with once-daily *cilofexor* 30 mg, combined with once-daily cilofexor 100 mg, combined with once-daily *firsocostat* 20 mg or combined with once-daily cilofexor 30 mg and firsocostat 20 mg for 48 weeks. Semaglutide with firsocostat and/or cilofexor was generally well tolerated. Combination treatments resulted in greater improvements in liver steatosis, liver biochemistry, and several biomarkers of NASH-related LF, than achieved with semaglutide alone [80].

5. Ongoing Trials Evaluating the Efficacy and Safety of Drug Therapy for Non-Alcoholic Steatohepatitis-Related Liver Fibrosis

Literature search on ClinicalTrials.gov identified three ongoing phase II RCTs evaluating the efficacy and safety of drug therapy for NASH-related LF. In a placebo-controlled, randomized, phase II trial (ClinicalTrials.gov Identifier: NCT05327127), the efficacy and safety of combination therapy with *K-877-ER* and *CSG452*, a sodium-glucose transporter 2 inhibitors, compared with placebo will be evaluated in NASH patients with LF (F1–3) and NAS ≥ 4. The primary endpoint will be NASH resolution without worsening of LF at week 48. The secondary endpoint will be a number of patients with treatment-related adverse events at week 52 [81].

In a multicentre, double-blind, placebo-controlled, parallel group, randomized, phase II trial (ClinicalTrials.gov Identifier: NCT04065841), the efficacy, safety, and tolerability of oral *tropifexor*, a non-bile acid FXR agonist, and *licogliflozin*, a sodium-glucose transporter 2 inhibitor, combination therapy and each monotherapy, compared with placebo will be evaluated in NASH patients with LF (F2–3) and NAS ≥ 4. Combination therapy includes administration of tropifexor 140 μg capsule + licogliflozin 30 mg tablet, once daily. Tropifexor monotherapy includes administration of: tropifexor 140 μg capsule (+placebo matching licogliflozin tablet), once daily. Licogliflozin monotherapy includes administration of licogliflozin 30 mg tablet (+placebo matching tropifexor capsule) once daily. Placebo includes administration of placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily. The primary endpoints will be the number and percentage of patients who responded at week 48 compared with baseline, and number and percentage of patients with NASH resolution without worsening of LF at week 48. The secondary endpoints will be number and percentage of patients who achieved NASH resolution without worsening of LF or LF improvement by ≥1 stage without worsening of NASH at week 48, number and percentage of patients with LF improvement by ≥1 stage at week 48, number and percentage of patients with LF improvement by ≥2 stage without worsening of NASH at week 48, number and percentage of patients achieving ≥5% reduction in body weight at week 48 compared with baseline, change from baseline to week 48 in percent liver fat content based on MRI-PDFF, change from baseline in ALT, AST, GGT over time (up to 62 weeks) [82].

In a prospective, multicentre, double-blind, placebo-controlled, randomized, phase IIb trial (ClinicalTrials.gov Identifier: NCT05011305), the efficacy and safety of *saroglitazar magnesium*, a novel dual agonist for PPAR-α and -γ, will be evaluated in NASH patients with LF (F2–3) and NAS ≥ 4. Saroglitazar magnesium 2 mg tablet orally is administered once daily in the morning before breakfast without food for the duration of treatment. Saroglitazar magnesium 4 mg tablet orally is administered once daily in the morning before breakfast without food for the duration of treatment. Placebo tablet orally is administered once daily in the morning before breakfast without food for the duration of treatment. The primary endpoint will be NASH resolution without worsening of LF at week 52. The secondary endpoints will be proportion of patients achieving LF improvement by ≥1 stage without increase in NAS values for ballooning, inflammation or steatosis at week 52, proportion of patients with ≥2 points improvement in NAS values at week 52 with ≥1 point improvement in either ballooning or inflammation and without worsening of LF, proportion of patients with ≥1 point improvement in steatosis, ballooning, inflammation and fibrosis at week 52, proportion of patients with decrease in SAF score (steatosis, activity, and fibrosis) ≥2 combining hepatocellular inflammation and ballooning without worsening of LF at week 52, change from baseline in steatosis, ballooning, inflammation, and fibrosis at week 52, change from baseline in liver enzyme parameters (ALT, AST, alkaline phosphatase, GGT, total bilirubin, albumin) at week 52, change from baseline in non-invasive markers of steatosis (ELF score, FIB-4, AST to Platelet Ratio Index (APRI), NFS [NAFLD Fibrosis Score], PRO-C3) at week 52, change from baseline in lipid parameters (triglycerides, low density lipoprotein cholesterol, total cholesterol, high-density lipoprotein-cholesterol, non–high-density lipoprotein cholesterol, very low density lipoprotein cholesterol) at week 52,

change from baseline in body weight at week 52, change from baseline in insulin resistance marker (HOMA-IR) at week 52, change from baseline in inflammatory markers (cytokeratin-18, interleukin-6, C-reactive protein) at week 52, change from baseline in glucose homeostasis markers (hemoglobin A1c, fasting plasma glucose) at week 52 [83].

6. Conclusions

Despite the lack of approved protocols for antifibrotic therapy for NASH, there are a number of drugs that, in phase II and III RCTs have demonstrated an adequate efficacy and safety profile in patients with LF (F2–3), and some cases with compensated liver cirrhosis. It can be assumed that some of them will be recommended for testing and confirming practical benefits in phase IV RCTs. Besides, an in-depth study of the cellular and molecular mechanisms of NASH-related LF will contribute to the development of new medications, the introduction of which will expand the possibilities of its drug therapy.

Author Contributions

D.V.G. contributed to the conception, design, acquisition, analysis, interpretation of data, wrote the manuscript and approved the final version.

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