

Novel Pharmacotherapy Options for NASH

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Abstract While simple to recommend, diet and lifestyle measures as a first-line therapy for nonalcoholic steatohepatitis (NASH) are hardly a model of successful therapy, as most clinicians can testify. They can be complex to implement, hard to sustain, and of limited efficacy in advanced stages of the disease. The need for specific pharmacotherapy is now acknowledged by practitioners, the pharmaceutical industry, and regulators and is largely expected by patients. The result is a clear move away from products developed second hand for NASH (such as pioglitazone or metformin) or from generic, non-specific hepatoprotectors (such as pentoxifylline, ursodeoxycholic acid, or antioxidants) toward molecules developed and tested specifically for NASH that aim to correct one or several of the pathways of liver injury in this disease. The two most advanced molecules, obeticholic acid and elafibranor, have shown encouraging data on improving hepatic histology. Both compounds appear to clear NASH, with obeticholic acid improving liver fibrosis and elafibranor improving the glycemic and lipid profile. Much larger trials, currently ongoing, will need to confirm these preliminary data and better characterize the safety and tolerability profile. Meanwhile, other compounds are being tested, a few in phase 2b studies (cenicriviroc, aramchol for NASH, and simtuzumab for NASH fibrosis) and many more in earlier, smaller trials. Most of these drug candidates target

different pathways, which speaks to the diversity and dynamism of the NASH pipeline.

Keywords Nonalcoholic steatohepatitis · Elafibranor · Obeticholic acid · Cenicriviroc · Aramchol · Liraglutide

Nonalcoholic steatohepatitis (NASH) is becoming the leading cause of chronic liver disease and a major health issue owing to its close association with the worldwide epidemics of obesity and diabetes [1]. A significant proportion of patients can experience disease progression with the occurrence of cirrhosis, hepatocellular carcinoma, and end-stage liver disease [2]. This results in an increase in the overall and liver-related mortality [3, 4]. Patients at risk of disease progression need to be identified as not all individuals with metabolic risk factors will experience disease progression [5]. Prognostic markers have mostly been derived from histological studies and found that the degree of inflammation is the strongest and independent predictor for fibrosis progression [6].

Is There a Need for Pharmacological Therapy?

As NASH is a disease that is closely linked to overweight and resulting insulin resistance, the need for pharmacological therapy has been questioned. The mere correction of the predisposing condition through diet and lifestyle measures could be deemed sufficient for treating the ensuing hepatic disease. Weight loss not only corrects the underlying condition that promoted the occurrence of NASH but also improves liver injury itself [7, 8]. Reports from bariatric surgery provided the proof of principle that massive and gradual weight loss improves steatosis and inflammation, clears steatohepatitis, and reverses fibrosis, occasionally

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even at the cirrhotic stage [9, 10]. Dietary changes and lifestyle modifications are therefore the first-line therapy for patients with NASH. Unfortunately, in many patients, these measures cannot be implemented efficiently or maintained in the long run. Also, many NASH patients have already tried diet and lifestyle modifications repeatedly but unsuccessfully before being referred to the hepatologist. Others have advanced liver disease that would warrant targeted therapy in addition to the treatment of the underlying condition. For these reasons, pharmacological options should be made available at least for some patients with NASH.

Who Should Be Treated with Pharmacological Agents?

Pharmacological therapy for NASH should be restricted to those individuals with advanced liver disease or at high risk of progression to cirrhosis [11, 12]. Similar to other chronic liver diseases, advanced liver disease can be defined by advanced (i.e., bridging) fibrosis or cirrhosis. What defines high risk of progression is less consensual. Studies with sequential liver biopsies have shown that necroinflammation is the best predictor of progression to fibrosis, a finding corroborated by numerous observations showing that steatohepatitis, and not steatosis, can progress toward advanced liver disease [13]. Thus, patients with NASH and marked hepatocyte injury (ballooning) and inflammation could have a higher risk of disease progression, especially if they already have a moderate amount of fibrosis (peri-portal and portal fibrosis) and clinical risk factors for fibrosis, such as age >50 years, male sex, and type 2 diabetes. At the opposite end of the spectrum, patients with isolated steatosis or steatosis and non-specific inflammation are considered at very low risk of fibrosis progression. These patients are not candidates for pharmacological therapy that specifically targets the liver condition.

What Are the Relevant Pharmacological Targets?

Our current understanding of the pathophysiology of NASH is that excessive fat accumulation coexisting with overweight, particularly when localized to visceral adipose tissue, promotes insulin resistance. Uninhibited lipolysis, a consequence of insulin resistance, increases delivery of free fatty acids to the liver [14]. In addition, hyperinsulinemia and the subsequent increase in serum glucose will enhance a maladaptive hepatic lipogenic response and inhibit lipid disposal through beta-oxidation [15]. The resulting increase in intrahepatic flux of numerous lipid species promotes liver damage through multiple lipocytotoxic pathways: oxidative stress, mitochondrial dysfunction, apoptosis, free cholesterol

toxicity, and endoplasmic reticulum stress [16]. The resulting cell injury and accompanying inflammation (part of which is modulated by cross talk with the inflamed adipose tissue) sets the stage, in the long run, for liver fibrosis to occur.

This brief description suggests that the relevant mechanisms of action for NASH drugs could be: (1) weight loss agents; (2) insulin sensitizers; (3) antidiabetic drugs with antihyperglycemic properties; (4) hepatoprotectants with broad antiinflammatory properties; and (5) antifibrotic drugs. These drugs can therefore be classified into two broad categories: drugs that improve the underlying metabolic conditions that promoted the emergence of NASH and hepatoprotectants that specifically target the mechanisms of hepatic cell injury. As some pathways can be involved in both hepatic inflammation and insulin resistance, some drugs might belong to both categories. Alternatively, combination therapy with molecules that act on distinct metabolic and hepatoprotective pathways could also be envisioned. Depending on how vast the NASH drug pipeline will be, tailored therapy for particular patients could thus become a reality in the near future.

Where Do We Stand with Pharmacological Therapies?

An ideal drug candidate for NASH should reduce hepatic inflammation and liver cell injury, should correct the underlying insulin resistance, and should have antifibrotic effects. However, primarily “anti-NASH” drugs that have no direct antifibrotic effect could, theoretically, result in a subsequent reduction in fibrosis if a sustained resolution of NASH is achieved. Conversely, purely antifibrotic drugs with no anti-NASH activity and no interference with insulin resistance will leave the triggers for fibrogenesis intact. Therefore, even if an antifibrotic is effective, efforts to curb the underlying pro-fibrotic condition must be considered [11]. We will here review some of the novel anti-NASH agents that are now in late stages of drug development. Many other agents are in preclinical phases of development or in early human studies and will not be reviewed here. These agents that target fibrotic pathways, hepatic lipogenesis, endothelial adhesion molecules, apoptosis, miRNA, endotoxin, nuclear receptors, among others, are part of a very diverse and rich pipeline for NASH.

FXR Agonists and Obeticholic Acid

Recent discoveries have identified bile acids as key regulators of liver and metabolic homeostasis. Their action is mediated through nuclear hormone receptors such as the

farnesoid X receptor (FXR) and TGR5 [17]. FXR activation results primarily in a reduction in bile acid synthesis from cholesterol by altering expression of a host of genes but mainly by downregulating CYP7A1 [18]. This limits the size of the circulating bile acid pool and promotes choleresis, thus protecting against the toxic accumulation of bile acids. Obeticholic acid (OCA), a first-in-class FXR agonist, is a synthetic bile acid with picomolar agonistic activity on FXR [18]. The bile acid effects have translated into clinical efficacy in patients with primary biliary cirrhosis [19] with a reduction in phosphatase alkaline, a biochemical surrogate for clinical events in the natural history of the disease [20]. Based on these results, it is expected that OCA will be approved for this indication. FXR activation also has a wide range of metabolic effects: inhibition of hepatic neoglucogenesis and hepatic glucose production, reduction in lipogenesis, enhancement of beta-oxidation, and improvement in peripheral insulin sensitivity [21]. Interestingly, FXR activation has also anti-inflammatory actions [22] with resultant protection against liver inflammation and fibrosis in experimental models of NASH [23].

A small randomized trial in type 2 diabetic patients with NAFLD showed an improvement in hepatic and muscle insulin sensitivity as measured by the euglycemic clamp, a modest but dose-related weight loss, and a reduction in ALT levels [24]. This study provided the proof of principle of an improvement in insulin sensitivity and possibly NAFLD in humans. It was followed by a much larger trial that tested the oral administration of 25 mg OCA QD versus placebo over 72 weeks of therapy in non-cirrhotic NASH patients [25]. The therapeutic phase of the FLINT trial was stopped early, partly because a preplanned interim analysis showed improved histology in more patients on OCA than on placebo (45 vs. 21 %). The primary endpoint was a two-point reduction in the composite nonalcoholic fatty liver disease score (NAS) without worsening of fibrosis. However, beyond this composite endpoint, OCA was able to significantly improve all histological lesions constitutive of NASH including liver fibrosis. Although the trial was not designed for fibrotic endpoints, there was a significant reduction in the fibrosis score (one stage) in 35 % of OCA-treated patients versus 19 % in the placebo arm. The reduction in fibrosis was observed regardless of the baseline fibrosis stage. The study included patients at high risk of progression (half of the participants had type 2 diabetes) and “non-responders” to vitamin E (20 %). The primary endpoint was reached in secondary analyses of all subgroups of patients. There was a trend in favor of a higher rate of resolution of NASH in the OCA group (22 vs. 13 % in the placebo group) which became significant (19 vs. 8 %, $p < 0.05$) in a subgroup analysis restricted to patients with well-characterized NASH at baseline. All these data are

very encouraging but need to be confirmed in much larger trials as the FLINT trial only included 110 patients per arm. As far as safety and tolerability two issues emerged: pruritus and an increase in LDL cholesterol. Pruritus occurred in 23 % of OCA-treated patients versus 6 % in the placebo group, but discontinuation was very rare (only one patient). It is, however, a concern as the NASH population is overwhelmingly asymptomatic. Further studies will test whether lower doses of OCA reduce the incidence of pruritus. An increase in LDL cholesterol occurred early on therapy, plateaued with continued therapy, and then reversed once the drug was discontinued. Post hoc analyses showed that statins, when initiated during the trial, were able to mitigate the excursion in LDL. Future studies are needed to better characterize alterations in lipid profile and to determine whether this results in an increase in cardiovascular risk, if any. Interestingly, in animal models of atherosclerosis, FXR agonists reduce atherosclerosis and vascular cholesterol load and inflammation. OCA is a very promising molecule for the treatment of NASH, and a large phase 3 trial, the REGENERATE trial (NCT02548351), is ongoing. It is not yet known whether OCA will be effective at the cirrhotic stage. Animal data have shown that in rodents, OCA reduces bacterial translocation by increasing the expression of intestinal tight junction proteins which resulted in a normalization of the endotoxin-TLR4 signaling [26]. Other studies have shown that OCA can reduce the intrahepatic vascular resistance and improving endothelial vasorelaxation by restoring hepatic e-NOS activity [27]. This suggests beneficial effects on portal hypertension which together with reduced risk of infections due to reduced bacterial translocation could result into clinical benefit in cirrhotic patients. This hypothesis will be tested in future trials in cirrhotic patients.

PPAR Alpha/Delta Agonists and Elafibranor

Another innovative insulin sensitizer is elafibranor, a dual PPAR α/δ agonist. PPARs (α , β , and γ) are fatty acid-activated nuclear receptors that have a wide range of physiological actions. PPAR δ activation emerged as a potent metabolic regulator that induces hepatic fatty acid β -oxidation, inhibits hepatic lipogenesis [28], reduces hepatic glucose production, and improves hepatic inflammation [29, 30]. PPAR α is a major regulator of fatty acid disposal through mitochondrial beta-oxidation, but also has anti-inflammatory actions as it inhibits inflammatory genes induced by NF- κ B and acute phase response genes induced by IL6 [31]. Combining these two modes of action can thus improve many of the pathways of injury involved in NASH. Animal data confirmed the hepatoprotective effects of GFT505 in dietary models of NASH or fibrosis with, in particular, a reduction in steatosis,

hepatic inflammation, and pro-inflammatory genes [32]. Importantly, this compound exhibited antifibrotic properties in fibrosis models that were independent of metabolic and insulin resistance abnormalities [32], thereby suggesting a universal antifibrotic potency in rodents. Elafibranor is a PPAR modulator with preferential activity on PPAR α and additional activity on PPAR δ , but no PPAR γ actions [33]. It undergoes extensive enterohepatic cycling and is liver targeted with little or no muscle action [34]. Human studies performed in abdominally obese, insulin-resistant patients, with or without diabetes, have shown that GFT505 improves hepatic and peripheral insulin sensitivity, dyslipidemia, inflammatory markers, and liver function tests [33, 35].

The results of a large, international, phase Ib trial, the GOLDEN505 trial, have been reported [36]. In this randomized trial, 274 NASH patients received elafibranor 80, 120 mg/day, or placebo for 1 year. While the lower, 80 mg dose did not improve histology, the higher dose was more effective than placebo at inducing NASH resolution without fibrosis worsening. The optimal definition for this histological outcome is still under debate, but these positive results were obtained with a modified, more stringent definition that is consensually emerging. There was no effect on fibrosis (1-year trial duration only) although patients who cleared steatohepatitis (responders) had an improvement in fibrosis after 1 year of therapy, while non-responders did not. This validates the concept that resolution of NASH will be followed by a reversal of fibrosis, a cornerstone of the current surrogate endpoints used in drug development. As anticipated from earlier phase 2 trials, elafibranor improved lipid parameters, glucose homeostasis, and insulin sensitivity as well as systemic inflammatory markers. Remarkably, the cardiometabolic improvement was achieved on top of standard of practice management of the comorbidities in these patients with metabolic syndrome. The drug was well tolerated although a few patients had an increase in creatinine, which was reversible after discontinuation of elafibranor. The increase was less than that observed with fibrates, and similarly to fibrates, it is not expected to be associated with renal insufficiency. This promising molecule needs to be tested in large, phase 3 trials.

Chemokines and Cenicriviroc

Chemokines are chemotactic cytokines specialized in leukocyte recruitment at sites of tissue injury, inflammation, and fibrosis. Chemokines and their receptors form a complex network of redundant ligand complex binding as one receptor may bind different chemokines, but their overall effect is the promotion of local inflammatory and fibrotic response [37]. CCL2 (a.k.a. monocyte chemoattractant protein-1, MCP1) and CCL5 (RANTES) are

particularly involved in liver and adipose tissue inflammation and hepatic fibrosis [38–40]. Cenicriviroc (CVC) is a selective inhibitor of CCR2 and CCR5 with nanomolar potency. It was developed initially as an anti-HIV agent as CVC blocks the use of CCR5 as a co-receptor for entry into host cells by HIV. CVC blocks the binding of MCP-1 to CCR2 and of RANTES, macrophage inflammatory protein-1 α (MIP-1 α), and MIP-1 β to CCR5. There is a strong rationale for the use of CVC in NASH. CVC decreases recruitment, migration, and infiltration of pro-inflammatory monocytes to the site of liver injury mainly via CCR2 antagonism, thereby having the potential to reduce chronic liver inflammation. CVC also disrupts co-receptor and cytokine signaling pathways or “cross talk” of intrahepatic immune cells within the inflamed liver via CCR2 and CCR5 antagonism, resulting in decreased Kupffer cell and hepatic stellate cell activation and migration, and therefore reduced fibrogenesis. CVC demonstrated significant antifibrotic effects in diet-induced (mouse model of NASH with streptozotocin and high-fat diet [41]) and chemically induced (rat thioacetamide [TAA] [42]) models of liver fibrosis, as well as in a model of kidney fibrosis. It also reduced lobular inflammation and hepatocyte ballooning in the dietary NASH model. Studies in up to 48 weeks in HIV-infected individuals did not show any safety concern.

Currently, a large randomized phase 2b trial in NASH, the CENTAUR trial (NCT02217475), is ongoing. This trial tests CVC versus placebo over a 2-year period in patients with fibrotic NASH or NASH at high risk of progression [43]. An interim histological analysis at year one will be performed and will allow to understand the benefit of short-term versus prolonged exposure to cenicriviroc both on NASH and on fibrosis.

Fatty Acid–Bile Acid Conjugates and Aramchol

Aramchol is a first-in-class, novel synthetic small molecule produced by conjugating two natural components, a fatty acid, arachidic acid, and a bile acid, cholic acid linked by a stable amide bond. It was initially synthesized to treat gallstones as the saturated fatty acid has cholesterol-solubilizing properties and the bile acid enabled secretion into the bile and entry into the enterohepatic circulation [44]. However, empirical observations of animals fed a high-fat, lithogenic diet documented a strong reduction in liver fat that occurred much earlier than did gallstone dissolution [45]. The antisteatogenic mechanism is probably related to the inhibition of *stearoyl-CoA desaturase-1* (SCD1) activity well documented in human liver [46]. This results in decreased synthesis of monounsaturated fatty acids and of triglyceride stores. Moreover, aramchol activates cholesterol efflux by stimulating the ABCA1 transporter, a

universal cholesterol efflux pump [47] which can explain the antiatherogenic effects in some animal models [46]. Since liver-specific SCD1 inhibition in rodents reversed hepatic insulin resistance and reduced neoglucogenesis [48], several SCD1 inhibitors were tested as a treatment of diet-induced metabolic complications. However, systemic inhibition of SCD1 resulted in severe skin and eye side effects, and most of them have been discontinued [49]. Aramchol does not induce these side effects possibly because of the liver *targeting* or the partial and not complete inhibition of SCD1. A small phase 2a study performed in patients with biopsy documented NAFLD tested two doses of aramchol versus placebo over a 3-month period and did not raise any significant safety concern [50]. The higher, 300 mg daily, dose resulted in significant reduction in liver fat as measured by magnetic resonance spectroscopy (MRS). There was also a trend toward an increase in serum adiponectin and an improvement in flow mediated dilation [50], an early marker of *endothelial* dysfunction in patients with NASH [51].

A large international phase 2b trial is ongoing in patients with histologically documented NASH, high liver fat content measured by MRS, and several features of the metabolic syndrome (NCT 02279524). This trial of one-year duration tests still higher doses of daily aramchol, 400 and 600 mg. The main endpoint is a reduction in liver fat content measured by MRS and histological improvement as secondary endpoints.

Incretin Mimetics and Liraglutide

Among existing therapies for type 2 diabetes, incretin mimetics which are glucagon-like peptide-1 receptor (GLP-1R) agonists hold promise for the treatment of NASH. GLP-1, a peptide product of the L cells of the small intestine and proximal colon, stimulates insulin secretion from the β cells and inhibits glucagon secretion from the α cells in a glucose-dependent manner [52]. GLP-1 also enhances satiety and delays gastric emptying [52]. However, because of their short half-life due to rapid degradation by specific enzymes (such as dipeptidyl peptidase, DPP-IV), native GLP-1 cannot be used as a pharmacological agent. GLP-1R agonists have a much longer half-life than natural GLP-1 allowing either a daily or a once-weekly administration [53]. There seems to be some controversy over the presence of receptors for GLP-1 in hepatocytes and stellate cells. Some studies have shown the presence of a cognate receptor for GLP-1 on human hepatocytes [54]; signaling through these receptors improves hepatic insulin sensitivity [55] by inducing phosphorylation of key signaling pathways [54]. GLP-1 R binding in hepatocytes results in an induction of PPAR α and γ expression, which increases disposal of hepatocyte fatty acids by

beta-oxidation and lipid export [55, 56]. In vivo studies have confirmed an antisteatogenic effect of exendin in mice [55, 57]. Several potentially beneficial effects have been demonstrated in humans by metabolic studies including the euglycemic clamp: Patients with NAFLD had decreased de novo lipogenesis, decreased adipose tissue lipolysis, and reduced hepatic glucose production upon administration of 1.8 mg liraglutide daily [58]. Moreover, because it induces weight loss, liraglutide at the dose of 3 mg/day [59] is now approved for treatment of obesity or overweight with comorbidities. Other GLP-1R agonists are approved for glycemic control in diabetic patients.

Data from large registration trials have shown that diabetic patients treated with liraglutide improved ALT levels and possibly steatosis, measured by CT scan imaging [60]. Taken together, all the above data form a compelling rationale for testing liraglutide in patients with NASH. A British study randomized 52 NASH patients and analyzed 23 of them treated with liraglutide, 1.8 mg/day, and 22 with placebo, in a randomized controlled trial of a 1-year duration [61]. Patients treated with liraglutide experienced more often reversal of NASH (39 vs. 9 %, $p < 0.02$) and less often progression of fibrosis. There was no significant effect on lobular inflammation and ALT and only a marginally significant effect on hepatocyte ballooning, an indication of the very small sample size of this trial. Hence, these results, although encouraging, especially in the light of the pre-clinical data and the weight loss effect, clearly need further confirmation before any recommendations can be made.

Antifibrotic Agents: Simtuzumab and Galectin-3 Inhibitors

Since the overall objective when treating NASH patients is to reduce the progression to cirrhosis, antifibrotic drugs that would specifically block liver fibrosis would be an important addition to anti-NASH drugs. There are very few well-conducted trials of antifibrotic agents and those that are available are negative [62–65]. There are very few well-conducted trials of antifibrotic agents and those that are available are negative. Lysyl oxidase and lysyl oxidase like (LOXL) are a family of enzymes expressed and secreted by fibrogenic cells and catalyze oxidative deamination of lysyl and hydroxylysine residues in collagen precursors and elastin [66]. This results in covalent cross-linking of the extracellular matrix, a phenomenon that is believed to greatly contribute to the deposition and stabilization of the hepatic scar [67]. LOXL2, a member of the LOXL family, is upregulated in hepatocytes, and its expression is correlated with collagen deposition in various hepatic fibrotic diseases [68] including steatohepatitis in humans [69]. LOXL2 regulates fibroblast activation, TGF- β signaling,

and latent TGF- β activation [69]. Experimental studies have shown that inhibition of LOXL2 with an inhibitory monoclonal antibody results in a reduction in liver and lung fibrosis [69]. Simtuzumab is a humanized monoclonal IgG4 antibody with a long half-life of 10–20 days and can be administered either IV or subcutaneously. It is currently tested in two large, 2-year phase 2b clinical trials in patients with NASH and bridging fibrosis and cirrhotic NASH (NCT01672866 and NCT01672879, respectively). The main endpoint of the non-cirrhotic trial is a reduction in the area of fibrosis assessed by micromorphometry, while that of the cirrhotic study is a reduction in hepatic venous pressure gradient. Both studies are followed by several year extension periods for clinical outcomes.

Galectins are a family of proteins that bind to galactose residues present on glycoproteins from extracellular matrix components (collagens, laminin, fibronectin, integrins, elastin) but also on cell surface proteins such as CD4, CD8, or TGF-beta receptors [70]. Galectin-3, a member of the galectin family expressed at high levels on macrophages, regulates multiple cellular processes including cell adhesion and migration, immune cell function, and inflammation [71]. It is upregulated in hepatic human fibrosis and promotes fibrosis in vitro and in vivo [72]. GR-MD-02, a complex polysaccharide polymer (a galactoarabino-rhamnogalacturonan) is a pharmacological inhibitor of galectin-3 that reduces liver fibrosis and portal hypertension in a thioacetamide model of fibrosis/cirrhosis [73]. The antifibrotic effects were confirmed in a dietary NASH model in diabetic mice where GR-MD-02 prevented accumulation of collagen and reduced stellate cell activation [74]. Remarkably, the drug also improved hepatocyte ballooning and lobular inflammation and reduced fat accumulation; these anti-NASH effects are probably related to a reduction in iNOS, a marker of inflammation, and in CD-36 expressing pro-inflammatory macrophages [74]. A phase I dose-ranging study has shown good safety and tolerability in humans receiving this compound intravenously (NCT01899859). A larger, phase 2a study in NASH patients with cirrhosis and portal hypertension testing intravenous infusions of GR-MD-02 every 2 weeks for 1 year is ongoing (NCT 02462967).

Conclusion

Drug development for NASH has accelerated strongly over the past few years. Earlier studies such as the PIVENS trial have provided the proof of principle that histological improvement and even NASH *resolution* is possible with drugs such as insulin sensitizers (glitazones) or antioxidants (vitamin E) [75]. Retrospective studies have documented the prognostic significance of histological lesions in NAFLD [76, 77], suggesting that these lesions could be

acceptable surrogates of disease control on therapy. Tools for a precise histological description and classification have been refined from the NASH CRN classification [78] to the FLIP/SAF algorithm [79]. Major advances also occurred in the regulatory field. Both the European and the American drug agencies now agree that NASH is a valid indication for therapy and as such it can follow a regulatory path for drug approval. Trial outcomes with clinical and regulatory value have been defined and are currently being used in several large trials of new drugs in NASH [11]. What remains to be done is the discovery and validation of biomarkers that would help diagnose patients at risk of advanced or progressive NASH but also monitor disease progression. Renewed and sustained efforts for drug discovery and dedication from physicians to recruit and complete clinical trials will be key to providing patients with NASH with safe and effective drugs in the near future.

Key Messages

- NASH is now an established indication for therapy irrespective of the control of associated metabolic comorbidities. Patients with histologically confirmed steatohepatitis and fibrosis are candidates for pharmacotherapy, in association with diet and lifestyle modifications.
- As current treatment options are limited, new and innovative pharmacological agents are being developed. Obeticholic acid and elafibanor are the most advanced drugs that induced resolution of NASH and for obeticholic acid, an overall improvement in fibrosis.
- Many other drugs such as chemokine blockers, inhibitors of lipogenesis, and antifibrotics are in various stages of development.
- New and effective pharmacological agents that improve insulin resistance but also hepatic inflammation and fibrosis need to be identified.

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Compliance with ethical standards

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