Pharmacological Treatment for Non-alcoholic Fatty Liver Disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has become the most frequently encountered chronic liver disease. NAFLD is associated with increased liver-related morbidity and mortality, but also contributes to cardiovascular disease, diabetes and non-liver-related malignancy. Non-alcoholic steatohepatitis (NASH) is considered the more severe subtype of NAFLD that drives most of these adverse outcomes. Lifestyle modification and associated weight loss can improve NASH but are not always sufficient and sustained results are difficult to obtain. There is hence an urgent need for pharmacological treatment. In this review we discuss some of the concepts and challenges in the development of pharmacological treatment. We also briefly summarise what can be achieved with some of the drugs that are currently available for other indications but have demonstrated benefit in the treatment of NASH. Finally we present an overview of some of the main drugs or types of drugs, mainly based on their mode of action, that are now being developed specifically to treat NASH and that might soon result in the availability of drugs licensed for NASH.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of vesicles of fat (mainly triglycerides) in the hepatocytes in the absence of classic causes of steatosis, with alcohol being one of the most frequent of these causes [1]. The latter explains the name that was given to this disease, but other causes, such as the use of steatogenic drugs or viral hepatitis (steatosis has particularly been associated with genotype 3), also need to be excluded to make a diagnosis of NAFLD. This type of steatosis also needs to be distinguished from microvesicular steatosis that is seen in acute fatty liver of pregnancy or in Reye's syndrome, where fat accumulation is mostly micellar and in an acute setting. NAFLD is closely related to overweight, disturbances of glucose homeostasis and metabolic syndrome

(although it can also be present in patients that do not exhibit features of metabolic syndrome, often referred to as "lean NASH") [2, 3]. The current definition tends to reduce NAFLD to a diagnosis of exclusion, but it is important to realise that NAFLD can co-exist with other chronic liver diseases, which often results in synergistic effects in terms of disease progression. An overweight patient with diabetes who also regularly drinks alcohol and presents with steatosis should not simply receive the diagnosis of alcoholic liver disease, but the potential role of both alcohol and the metabolic factors causing NAFLD should be taken into account. When it comes to clinical trials and pharmacological therapy for NAFLD, however, the exclusion of other causes of steatosis before putting forward the diagnosis of NAFLD remains an important issue [4].

NAFLD encompasses a whole spectrum of liver disease. Steatosis can be the only lesion defining non-alcoholic fatty liver (NAFL). Steatosis can, however, be accompanied by chronic low-grade inflammation and features of hepatocellular damage [1]. When lobular inflammation and ballooning of hepatocytes (rounding and enlargement of hepatocytes, not because of fat accumulation but because of degeneration of the cytoskeleton that is responsible for the classic rectangular shape of hepatocytes) are both present, the diagnosis of non-alcoholic steatohepatitis (NASH) can be established [1, 5–7]. Various degrees of liver fibrosis, up to cirrhosis, can be present (but fibrosis is not part of the definition of NASH). Fibrosis can be present without the presence of steatohepatitis at the biopsy, an entity called steatofibrosis [8]. The exact clinical significance of this entity remains to be determined. Furthermore, patients may exhibit histological lesions besides steatosis, but without meeting the formal criteria for the diagnosis of NASH. These borderline cases potentially have a different outcome compared to those with steatosis as the only lesion, but are currently classified within the NAFL group. NAFLD-related cirrhosis can lead to the classic complications of cirrhosis, including the development of a hepatocellular carcinoma (HCC). HCC can also develop on the background of a non-cirrhotic and even non-fibrotic NAFLD, but the exact magnitude of this risk is currently unknown.

It is clear from these definitions (which is of great relevance when it comes to pharmacological treatment of NAFLD) that histology and hence the liver biopsy are the cornerstone of our current understanding of the disease.

In the present review, we will address several questions relevant to the pharmacological treatment of NASH and give a short overview of what is currently available and what is in the pipeline for the near future.

METHODOLOGY

A literature search using the PubMed and Web of Science database was performed. Articles were ranked according to their relevance. First, we performed a MeSH search using the following MeSH terms: "NonAlcoholic Steatohepatitis"[MeSH] OR "Non-alcoholic Fatty Liver Disease"[MeSH]) AND "Therapy"[MeSH]; "Non-alcoholic Fatty Liver Disease"[MeSH] AND "Pathophysiology"[Subheading] AND "Drug"; "Pharmacological therapy"[MeSH] AND "Non-alcoholic Fatty Liver Disease"[MeSH]. Thereafter the abstracts were screened. Books of abstracts from annual meetings of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases were also screened for the years 2015–2018 (NAFLD sections). Finally, the authors used a personal archive of papers. Clinical trials were further identified by consulting ClinicalTrials.gov (latest search on 3 December 2018).

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

WHAT ARE THE CONSEQUENCES OF NAFLD THAT COULD POTENTIALLY BE PREVENTED?

As outlined before, NAFLD can be associated with progressive fibrosis and hence result in liver cirrhosis with decompensation and/or the

development of HCC. The natural history of NAFLD is still largely unknown. Estimates on NAFLD prevalence, mainly based on non-invasive tests such as liver enzymes or ultrasound, tend to show a 25–30% prevalence in the Western adult population, with higher prevalence in populations with risk factors such as obesity or diabetes [9].

As a biopsy is required for accurate diagnosis of NASH, data on large populations using non-invasive tools cannot accurately distinguish between NASH and NAFL, and series of biopsy-proven cases are smaller and tend to be enriched with more severe cases by obvious selection bias. This hampers the quality of the data on prevalence of NAFLD and its subtypes and on their natural history.

A basic concept, looking at NAFLD from an exclusively liver perspective, is that isolated steatosis without any sign of inflammation or hepatocellular damage is considered harmless and probably needs to be considered as an adaptive mechanism to a calorie overload that is insufficiently buffered by the adipose tissue. When there is inflammation and hepatocellular damage, the activation of several pathways potentially leads to extracellular matrix deposition and fibrogenesis. These events will be counterbalanced by fibrinolytic and repair mechanisms, but when there is an imbalance, progressive fibrosis can develop [10]. Hence NASH is considered the more severe form of the disease, with a risk of progression towards advanced fibrosis and cirrhosis. To complete the picture, the occurrence of HCC outside the setting of cirrhosis, as mentioned before, should also be taken into account, but the magnitude of this problem is unknown and specific risk factors are ill defined.

Interestingly, the dogma that isolated steatosis is (almost) harmless and NASH is the culprit has recently been challenged by paired biopsy studies showing that patients with isolated steatosis also exhibit progressive fibrosis [11]. Furthermore, recent data also identified the degree of fibrosis as the most important predictor of not only liver-related but also overall mortality, regardless of the presence of NASH, overruling previous data showing that NASH patients had a worse outcome compared

to patients with isolated steatosis [12]. The fibrosis progression rate in NAFL is, however, only half that compared to NASH. Of note, if looking into the details of the data, most of the patients in the paired biopsy cohorts who progressed had some degree of inflammation or ballooning and/or portal inflammation at baseline and almost all had some degree of NASH on the follow-up biopsy [13]. Furthermore, several reports show a very significant correlation between disease activity and degree of fibrosis.

Several factors might explain some of these findings. First, the dichotomy of NAFL/NASH does not capture the borderline cases that have in addition to steatosis some abnormalities (e.g. some ballooning or little lobular inflammation or portal inflammation), not enough to qualify for the diagnosis of NASH according to the current definition, but also not qualifying for the concept of isolated steatosis. Second, the histological criteria for NASH diagnosis potentially do not capture subtle changes in necro-inflammatory cascades that need more granular and sophisticated techniques to be picked up and hence currently remain unrecognised. Third, in a liver biopsy, which is just a snapshot (to some extent comparable to a blood glucose level in a diabetic patient), we tend to look at activity and fibrosis in the same way. The activity component of the disease is, however, probably highly dynamic (influenced by diet, exercise, small fluctuations in weight). By contrast, the fibrosis component (although also not static) probably reflects the activity of the disease over a longer period preceding the biopsy, just as the HbA1c reflects glycaemic control over a longer period. Consequently, activity can show fluctuations between certain levels, whereas fibrosis, by the way we assess and define it, can continue to increase along a broader spectrum. The time point at which the biopsy is taken can hence show quite different pictures in terms of activity whereas the fibrosis shows a more stable picture that is potentially progressive over time [14].

The fluctuating nature of NASH and its dichotomous character as a parameter (NASH vs. no-NASH) compared to the more stable and potentially progressive nature of fibrosis along a

broader scale (0–4) might explain why statistically fibrosis comes out as the most important predictor of outcome, whereas the snapshot assessment of disease activity does not. From there to the conclusion that fibrosis and not disease activity is what we have to look for and what we have to treat seems, at least in our opinion, erroneous. We should consider the possibility, if we assume that disease activity is the driving force of adverse outcomes, that the current definitions of disease activity and/or the tools to assess it are largely imperfect.

Besides the liver-centred approach, evidence is accumulating that NAFLD, beyond the shared risk factors, independently contributes to the development of cardiovascular disease (CVD), chronic kidney disease, diabetes (if not present upfront) and non-liver related or extrahepatic malignancy [15–18]. CVD and non-liver malignancies constitute the most frequent causes of death in patients with NAFLD but the incremental risk attributable to NAFLD, on top of the classic risk factors, is difficult to decipher. Although fibrosis comes out as the most important predictor of long-term liver and non-liver-related outcomes, NASH patients seem to be more at risk than patients with NAFL [15]. Importantly, the impaired prognosis is not restricted to patients with cirrhosis or advanced (i.e. fibrosis stage 3 on a 0–4 scale, F3) fibrosis, but clearly starts to decrease from stage F2 onwards (so-called significant fibrosis) (the fibrosis grades are based on the NASH CRN and FLIP/SAF system ranging from 0 to 4 and not to be confused with the Metavir scoring system for viral hepatitis, which also ranges from 0 to 4 but with different definitions for the stages, as the fibrosis pattern differs) [12].

This all leads to the current concept that fibrosis is the most important predictor of both liver- and non-liver-related adverse outcomes with NASH as the driving force of these outcomes (and hence fibrosis as a marker or read-out of long-standing active disease with an imbalance between damaging and repair mechanisms). This implies that, although regression of fat might be an endpoint in early development of drugs, the target of pharmacological treatment is NASH and/or fibrosis [19]. Although patients with NAFLD suffer from fatigue and impaired quality of life [20], with to date a paucity of data on the exact relation to disease severity, this is currently not considered an indication or target for pharmacological treatment. Data on the last aspects are, however, captured in most of the clinical trials, which might allow for a better understanding of these aspects and for a change in the concepts in the future.

A final consideration is that this approach is also based on the assumption that if we improve NASH and/or fibrosis we will positively influence the long-term outcomes of the disease. Although plausible, this has to date not been proven. It is well known that, although diabetes control lowers the risk of diabetes-related complications, even well-controlled patients may develop significant consequences of their disease. Some studies on the impact of glycaemic control on long-term outcome failed to show a reduction in CV mortality despite good glycaemic control. This has been attributed to the so-called metabolic memory, denoting the persistence of endothelial dysfunction despite correction of glycaemia [21]. Only patients with short duration of diabetes mellitus, low baseline HbA1c and no history of a CVD event benefitted (in terms of improved survival) from good glycaemic control, suggesting that early intervention is needed to improve survival and once vascular damage is well established, improved metabolic control hardly impacts on long-term survival. For all these reasons, histological improvement in NAFLD lesions is, until further data become available, not a validated (only a "reasonably likely") surrogate for clinically meaningful benefit.

ANTI-NASH VS. ANTI-FIBROSIS: THE (NON-)DEBATE

As outlined previously, progressive fibrosis is mainly responsible for the liver-related consequences of the disease in terms of cirrhosis and its complications. Furthermore, fibrosis has been identified as the most important predictor of overall and liver-related mortality (with a decline in prognosis from F2 onwards) [12]. This has led to the concept of an anti-fibrotic

strategy to treat NAFLD in an attempt to prevent these fibrosis-related outcomes.

Fibrosis is, however, not a stand-alone process, but the result of the activation of several complex pathways, including pathways that counteract the damage and try to repair the tissue [10, 14]. Hence, NASH is what drives the disease. In this context, we use NASH not in the sense of its strict histological definition but as the entity that denotes the activation of inflammatory cascades and hepatocyte suffering in relation to the (mainly metabolic) factors that also lead to steatosis. Steatosis is not per se driving the inflammation by lipotoxicity or other mechanisms but can also be an associated, concomitant feature without a strict causal role, hence a marker of metabolic overload or impairment. Locally NASH can result in progressive fibrosis if damage and repair are not balanced; and extra-hepatically it potentially contributes to several deleterious processes (endothelial dysfunction and others) via complex mechanisms, including the release of numerous mediators by the chronically inflamed and metabolically deranged liver [22].

Besides the aforementioned arguments, the role of NASH is further substantiated by the analysis of clinical trial data showing that patients that experience an improvement in NASH are also those that have an improvement in fibrosis, whereas those whose NASH worsens are also more prone to fibrosis progression [23]. Although selonsertib showed fibrosis regression without an impact on NASH, at first sight challenging the role of NASH because of this apparent disconnect, improvement in NAFLD Activity Score (NAS) was amongst the strongest predictors of fibrosis improvement [24].

Hence fibrosis progression is closely linked to NASH and, especially when it comes to the impact on overall mortality, is probably to be considered a marker of long-standing disease activity and damage–repair imbalance rather than it being the fibrosis per se that drives the adverse outcomes.

The pathophysiology of NAFLD/NASH is complex and incompletely understood. It is beyond the scope of this review and we refer the reader to excellent extensive reviews for further reading [10, 25, 26]. It is, however, important to emphasise its extremely complex nature. In contrast to alcohol or viral hepatitis, there is no clearly identifiable external agent (besides perhaps calorie overload and some specifics in food composition) that causes the disease. It is on the contrary an intrinsic disease, driven mainly by metabolic derangements and with a very complex and multidirectional interplay between several other body sites, such as the (several types of) adipose tissue, the gut, the gut microbiome or the CV system (Fig. 1). If we focus on the liver, numerous pathways are involved in the several liver cell types (hepatocytes, stellate cells, Kupffer cells, infiltrating monocytes/macrophages and other inflammatory cell types, endothelial cells etc.) (Fig. 1). Not only does this imply that potential therapeutic targets are numerous, it also implies that, up to a certain level, the separation of inflammation-related pathways and fibrosis-related pathways is artificial. Many drugs that target metabolic pathways or inflammatory pathways (hence anti-NASH drugs) not only indirectly (by reducing mediators or mechanisms that promote fibrogenesis downstream) but in many cases also directly interfere with fibrogenesis. The direct role of nuclear receptors like peroxisome proliferator-activated receptor (PPAR) or farnesoid receptor X (FXR) in fibrogenesis illustrate this complexity [27, 28].

It is obvious that the more downstream in the process of fibrogenesis a drug interferes, the more purely anti-fibrotic its strategy will be. Simtuzumab, a lysyl oxidase homolog 2 (LOX-L2) antibody interfering with collagen cross-linking, is an example of this approach. It, however, failed to show clinical efficacy [24, 29]. The reasons for this failure can be several, including insufficient suppression of LOX-L2, but a plausible one is that a pure anti-fibrotic strategy (which means with a target very close to the final steps of fibrosis) is far too downstream to be efficient if the upstream driving force is left untouched. Interestingly, cenicriviroc, a C–C motif chemokine receptor (CCR) 2 and 5 dual antagonist mainly influencing macrophage recruitment and activation and hence having an anti-inflammatory profile, appeared to have anti-fibrotic properties despite the absence of a clear effect on steatohepatitis
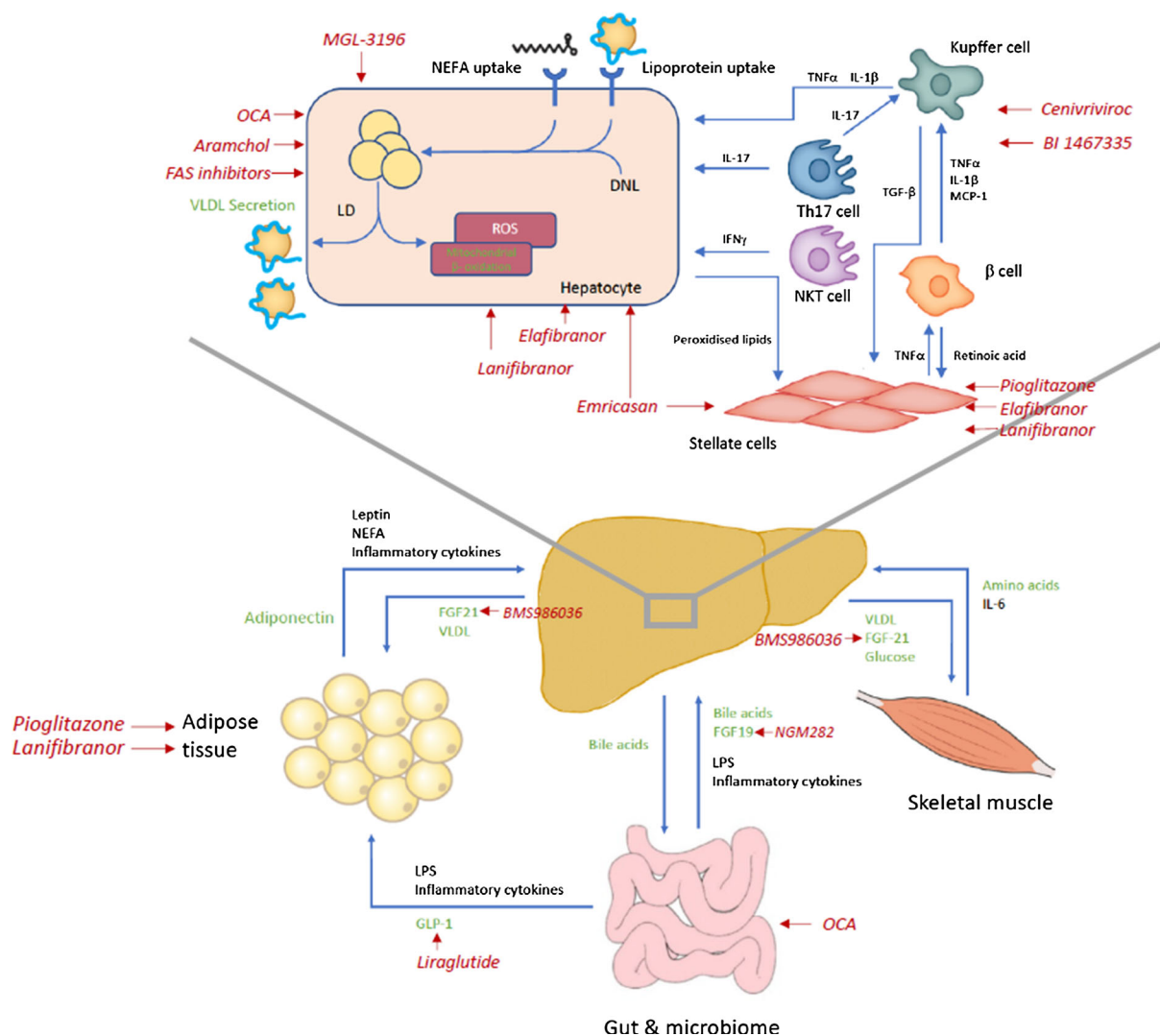
Fig. 1 Current therapeutic targets in the complex pathophysiology of NASH. NASH is the result of a complex interplay of metabolic, inflammatory and fibrogenic processes. Within the liver, hepatocytes and several of its intracellular organelles, most notably mitochondria, play an important role, alongside the stellate cells and several resident and infiltrating immune cells of different populations. NASH furthermore results from and impacts on an important crosstalk between the liver, the adipose tissue, the gut (including the gut microbiome) and the muscle. The cardiovascular system is even so implicated (not depicted, see ref. [22]). Numerous mediators are involved. Drugs that have been tested in NASH or that are under development have differential targets inside and outside the liver to ultimately result in an improvement of the steatohepatitis and/or fibrosis. DNL de novo lipogenesis, FAS fatty acid synthase, FGF19 fibroblast growth factor 1, FGF21 fibroblast growth factor 21, GLP-1 glucagon-like peptide 1, IFN interferon gamma, IL1-β interleukin 1 beta, IL-6 interleukin 6, IL-17 interleukin 17, LD lipid droplets, LPS lipopolysaccharide, MCP-1 monocyte chemoattractant protein 1, NEFA non-esterified fatty acids, NKT cell natural killer T cell, OCA obeticholic acid, ROS reactive oxygen species, Th17 T helper 17 cell, TGFβ tumour growth factor beta, TNF tumour necrosis factor alpha, VLDL very low density lipoproteins. Reproduced with permission from the Annual Review of Physiology, Volume 78 © 2016 by Annual Reviews, http://www.annualreviews.org [10] (courtesy of J. Haas)

(albeit with a reduction in systemic inflammatory markers). This again illustrates the complex entanglement of inflammation and fibrosis and the difficulties with the "anti-NASH" or "anti-fibrosis" concept [30]. Finally, although halting fibrosis progression or reversing fibrosis will most likely reduce the liver-related outcomes and are hence potentially beneficial in a purely liver-centred view, their impact on the presumed systemic consequences of the disease (which are substantially larger in terms of events to prevent) might be limited if they have little or no impact on NASH. This might reduce their target population to those with a high risk of evolving towards cirrhosis or with already established cirrhosis to prevent decompensation.

In conclusion, many targets for pharmacological treatment potentially have an effect on both necro-inflammatory and also directly or indirectly on fibrogenic mechanisms, making the concepts of anti-fibrotic or anti-inflammatory or anti-metabolic drugs somewhat artificial and irrelevant in many cases. A more purely anti-fibrotic approach implies targeting downstream mechanisms and might be difficult if the driving force of NASH persists and might, if efficient, have a more restricted target population who could potentially benefit.

COMPLEXITY OF THE PATHOPHYSIOLOGY: CONSEQUENCES

As numerous and sometimes closely entangled pathways are involved, the fact that a certain step in a particular pathway has been shown to impact on disease pathophysiology does not necessarily mean that targeting this step will result in benefit. First, several escape routes are usually present to circumvent a specific blockade or stimulation, neutralising the effect. The step that is targeted should be crucial enough or rate-limiting and the agonism or antagonism powerful enough to have a net impact. Second, although a specific step might be altered and have an impact on disease occurrence, this might not be enough to cause disease regression; so, an impact on a combination of several

pathways might be required to induce cure. Consequently, targeting only one of these pathways might be insufficient to restore the tissue. Furthermore, the mechanism or the combination of mechanisms that explain the occurrence and severity of the disease are presumably not identical in all patients. We know that the patient population is heterogeneous, probably reflecting this potential heterogeneity in underlying pathophysiological mechanisms. Whether this is a continuous spectrum or whether different subtypes exist is currently unknown, and we currently do not have tools to identify and classify patients on these grounds [31]. Nevertheless, these factors might explain the non-responders in the trials conducted so far. They also provide the rationale for combined treatments. Furthermore, they strengthen the need to develop tools to identify the mechanisms at play in a given patient, so that response or non-response can be predicted and a patient-tailored or personalised treatment can be proposed [32]. For the time being, however, no tools exist to guide pharmacological treatment in this respect.

WHICH PATIENTS QUALIFY FOR PHARMACOLOGICAL TREATMENT?

Lifestyle modification, if it results in sustained weight loss, can improve the histological lesions of NASH [33]. Sufficient and sustained weight loss is, however, not obtainable in all patients for several reasons, including important osteoarticular problems limiting the possibility to increase the level of physical activity (which is, in conjunction with caloric restriction, crucial to achieve and maintain a substantial reduction in fat mass). Furthermore, even diabetic patients who are well treated for a long time with optimal metabolic control still may exhibit features of NASH. Genetic factors might influence not only the risk of having NASH and progressive fibrosis but also the responsiveness to weight loss and lifestyle modifications [34]. This might help explain why even lifestyle modification, if successful, does not always result in the desired endpoints. Hence for many

patients, pharmacological treatment will be required.

Indications and goals for pharmacological treatment can be debated. As outlined before, fibrosis is the best predictor of prognosis, with a clear decline from F2 onwards, and NASH is to be considered the driving force of the disease. Hence, in our current understanding, pharmacological therapy should be restricted to patients who have NASH and some degree of fibrosis. Generally, a steatohepatitis with a NAS of 4 of higher (there is currently no equivalent definition based on the Steatosis Activity Fibrosis (SAF) scoring system, but A ≥ 3 could be proposed) with a fibrosis of F2 onwards is considered an indication for pharmacological treatment [4, 19]. F1 patients with a NAS of at least 5 and/or severe (mostly metabolic) co-morbidities (persistently elevated ALT, diabetes, metabolic syndrome) should, however, also be considered as they have a high risk of fibrosis progression. As a biopsy is still needed to accurately diagnose these different aspects of the disease, a liver biopsy is currently considered mandatory before initiating a pharmacological therapy specifically for NASH [6, 7, 35]. Exceptions can be made for some of the early phase proof-of-concept clinical trials that try to pick up a signal of efficacy of a drug based on non-invasive parameters, but in general a pharmacological treatment for NAFLD should not be started without a liver biopsy showing the aforementioned criteria. As non-invasive biomarker research progresses, this principle is likely to change in the near future.

WHAT ARE THE GOALS OF THERAPY?

In terms of the goals to achieve, several possibilities can be considered. Most of the definitions of endpoints in clinical trials, which can serve as a basis for routine clinical practice, focus on the resolution of NASH (which is defined as the specific prerequisite of a complete disappearance of ballooning) and/or regression of fibrosis, but stable disease and hence halting progression might also be a valuable target [36]. The goals mentioned are currently the outcome measures approved by the regulatory authorities as acceptable surrogate markers that "reasonably likely" predict clinically meaningful benefit in the long run and that can serve as the basis for conditional approval of drugs in phase 3. Besides these endpoints, reduction in activity of the steatohepatitis or other criteria of improvement might also be considered beneficial, as well as stabilising the disease and halting disease progression.

Furthermore, the impact of drugs on the cardiometabolic co-morbidities is also an important aspect, both in terms of safety and efficacy. As CVD is the most important cause of death in these patients who already frequently accumulate several CV risk factors, these drugs, which probably need to be taken for a long time, need to be safe from a CV point of view. Impacts on lipid profile, glycaemic control, body weight, blood pressure, renal function and other related parameters need to be carefully assessed and negative effects might hamper long-term applicability if a certain potentially negative side effect cannot be properly managed. On the other hand, a drug that not only improves NASH and/or fibrosis but also reduces body weight, improves lipid profile, improves glycaemic control or results in any other cardiometabolic improvement might represent a substantial additional benefit that influences its position within the future therapeutic landscape.

CURRENTLY AVAILABLE PHARMACOLOGICAL TREATMENT OPTIONS

Several drugs that are not specifically licensed for the treatment of NASH but with a potential benefit based on their mode of action have been tested.

Ursodeoxycholic acid (UDCA), a bile acid that has hepatoprotective effects and showed benefit in cholestatic disease, improved liver tests and some histological features, mainly inflammation, but failed to show histological benefit in two long-term trials [37] and hence is not recommended.

Drugs that impact on insulin sensitivity and glycaemic control have for obvious reasons attracted some attention as they are of potential benefit in NASH.

Metformin improves insulin resistance, a key pathophysiological mechanism in NASH, but failed to show histological benefit [37]; hence, despite data suggesting that metformin improves the risk of cancer (including HCC) [38], it should not be used with the intent to treat NASH but only if there is an approved indication.

Dipeptidyl peptidase 4 (DPP4) rapidly degrades incretins like glucagon-like peptide (GLP)-1, which plays an important role in glycaemic control, and hence DPP4 inhibitors, which are used in the treatment of diabetes, have also been tested. A recently published small trial with sitagliptin was negative but further studies are awaited [39].

Sodium/glucose co-transporter 2 (SGLT2) inhibitors or gliflozins that inhibit glucose reabsorption from the urinary ultrafiltrate effectively improve glycaemic control and hence are licensed for the treatment of diabetes. Preclinical data suggest benefit in NASH. A small trial of 50 patients with type 2 diabetes randomised to empagliflozin vs. placebo on top of their treatment showed significant reduction in liver fat content and liver enzymes, but no results of randomised controlled trials (RCTs) including histological endpoints have been published so far, so their clinical utility in NASH has not yet been established [40].

GLP-1 analogues or incretin mimetics improve glycaemic control and reduce weight. They have been approved for the treatment of type 2 diabetes and several molecules for that indication are available on the market. In 2015 liraglutide in a dose up to 3 mg QD was also approved for the treatment of obesity [41]. Liraglutide, used on top of a hypocaloric diet and increased physical activity, has been shown to reduce body weight by more than 5% in 63% of treated individuals after 1 year [42]. Liraglutide (at a dose of 1.8 mg QD) has been reported to beneficially affect liver histology in a small RCT with 23 patients in each arm [43]. The induced weight loss is likely one of the main drivers of the histological benefit, although

other hormonal effects also might contribute to the overall effect on liver histology. Side effects include nausea and diarrhoea. Until further data become available (several other GLP-1 analogues are currently being studied, including semaglutide), its use should be restricted to the approved indications, with the only extension being that we propose to add NASH to this list of co-morbidities of obesity that justify pharmacological treatment of obesity.

Thiazolidinediones or glitazones are agonists of PPAR, a nuclear receptor that has a key role in glucose and lipid homeostasis, but also impacts on inflammation and fibrogenesis [27]. PPAR is expressed in adipose tissue and to a certain extent in other cell types, including non-activated stellate cells (PPAR expression decreases upon activation), whereas it is poorly expressed in hepatocytes. Glitazones have been approved for the treatment of diabetes but were also shown to be effective in improving histological lesions of NASH in several trials [37, 44, 45]. The improvement in liver histology is probably driven by both extrahepatic effects that subsequently benefit the liver (especially improvement in adipose tissue dysfunction) and by direct intrahepatic effects. The safety profile is not alike for all molecules and some harbour safety concerns. There is some weight gain, but with a shift from visceral to subcutaneous adipose tissue, implying that the weight gain is not deleterious from a medical point of view. Pioglitazone clearly improved CV outcomes in diabetic patients and has a more favourable safety profile [46], but is nevertheless not frequently used. There are some concerns regarding the possibility of eliciting heart failure in predisposed individuals, although, as mentioned, an overall significant CV benefit has been recently demonstrated [46, 47].

Also for lipid-lowering drugs there was a good rationale to explore their potential utility in the treatment of NASH. Fibrates, which are agonists of the PPAR isoform that is mainly expressed in hepatocytes, were only tested in small trials, showing no benefit, but probably merit further study [37]. Ezetimibe, a cholesterol uptake inhibitor, showed no effect on imaging-assessed liver fat content [48]. The

same holds true for the bile acid sequestrant colesevelam [49].

Although statins might have pleiotropic beneficial effects, they have not been tested properly [37]. A few small open-label studies suggested some histological improvement [50, 51]. They have also been shown to reduce the risk of HCC and to reduce the progression towards cirrhosis and decompensation of cirrhosis [38, 52]. In preclinical models they showed a beneficial impact on fibrogenesis and angiogenesis and specifically impacted on insulin resistance, endothelial function and portal pressure in an animal model of steatosis [53, 54]. Given the role of endothelial dysfunction and increased intrahepatic resistance in the early development of NASH, these findings hold promise for statins as adjuvant drugs in NASH treatment [55]. The potential for hepatic toxicity has withheld physicians from the use of statins in NAFLD patients with elevated transaminases, but recent studies have shown that there is no increased risk of drug-induced liver injury with statins in NAFLD patients [56, 57], so they should be used if there is an indication in the context of dyslipidaemia treatment.

As highlighted above, these hypolipidaemic drugs should be used to appropriately treat dyslipidaemias according to their proper guidelines, but should not be prescribed for the sole indication of treating NAFLD until more data become available. Omega-3 fatty acids showed some promise in initial trials, but more recent trials did not show a clear benefit. Although probably not of harm, they should currently not be prescribed as a NASH treatment [6, 7, 35].

Vitamin E has also shown beneficial effects on liver histology in non-diabetic and non-cirrhotic NASH patients, so its use can be recommended in this patient category [58]. Vitamin E is hence not to be recommended in patients in whom NASH was not histologically documented and in diabetic or cirrhotic patients. Although a recent large meta-analysis did not confirm earlier safety issues [59], the potential for increased prostate cancer in men is an unresolved issue of concern. The dose that proved efficacy in the PIVENS trial is 800 IU/day [58].

For glitazones, vitamin E and liraglutide, evidence on efficacy has been demonstrated by histology. There is, however, no clear guidance on how to assess efficacy of treatment in routine clinical practice. Improvement in liver enzymes has been shown to be in line with histological improvement in several trials [23, 60], regardless of baseline values, but there are no clear rules on how to interpret liver enzyme changes in individual patients. In a subanalysis of the FLINT trial (vide infra) a reduction in ALT of 17 U/L was an independent predictor of histological response (defined as a reduction in NAS of 2 points), but this needs further validation.

There is hence currently no pharmacological treatment that has NASH on its label. There is, however, a large pipeline of drugs that are being tested, some of them already in phase 3. The first to come on the market, if the registration trials are positive, will presumably do so by 2020.

Meanwhile, patients with significant disease eligible for pharmacological treatment as defined above can be offered treatment in the context of a clinical trial. Given the potential benefit for the patients, the possibility of participating in a clinical trial should systematically be considered and offered to the patient, reinforcing also the recommendation to screen and adequately diagnose patients at risk.

DRUGS IN DEVELOPMENT

Numerous drugs are currently being tested for the treatment of NASH. The development is complex, as different endpoints can be defined and a variety of targets proposed. When it comes, however, to drug licensing, drugs have to show a proven clinically meaningful benefit. What is currently accepted by the regulatory authorities is that efficacy must be proven on clinical endpoints that are mainly restricted to the concept of NASH as a liver disease: development of cirrhosis or cirrhosis-related complications (although all-cause mortality is also included) [61]. As these phase 3–4 trials will take a long time, drugs can be granted conditional

approval based on histological benefit, which is considered a reasonably likely surrogate for later clinical outcomes, and which has been defined as resolution of NASH without worsening of fibrosis or improvement in at least one stage of fibrosis without worsening of NASH [61]. The last two endpoints are in line with the aforementioned dichotomous concept, tending to discern two approaches: an anti-NASH approach or an anti-fibrotic approach. As NASH drives fibrosis, this dichotomy is in our opinion rather artificial and not very useful, although some drugs might preferentially fall into one or other category.

A consequence of these regulatory considerations is that phase 3 trials rely on serial biopsies. Also phase 2 trials that should provide data to justify progression to a phase 3 trial need a histological proof of efficacy. Earlier phase 2 trials can use other endpoints and other efficacy assessments besides biopsy. In the subsequent paragraphs we will briefly discuss most of the classes of drugs currently under investigation. As a multitude of mechanisms are potentially involved and targeted by a long list of compounds in early development, an extensive review of all potential targets is beyond the scope of this article. The most important pathways are depicted in Fig. 1. An overview of the molecules currently in phase 2 (without or with histological endpoints) and phase 3 trials is given in Tables 1, 2, 3 and 4.

PPAR Agonists

Three isoforms of PPAR exist [27]. PPAR is mainly expressed in hepatocytes but also in many other cell types, including muscle cells. PPAR agonists like fibrates have not been extensively studied, but the small studies performed failed to show a histological benefit [37]. We demonstrated previously that PPAR expression is inversely correlated to the severity of NASH and that NASH improvement is associated with increased PPAR expression, giving rationale to a PPAR-targeted treatment despite the negative data with fibrates [62]. Elafibranor is a hepatotropic dual PPAR agonist, hence targeting not only PPAR but also PPAR that is

expressed in stellate cells and several other cell types. In a large phase 2b trial including 276 patients (GOLDEN), elafibranor was able to induce resolution of NASH without worsening of fibrosis in significantly more patients compared to placebo if baseline NASH was sufficiently severe [23]. Fibrosis regression was also noted in those that responded to treatment, highlighting again the link between NASH and fibrosis. The drug had a very good safety profile and also improved serum lipids and glycaemic control, reducing the calculated overall CV risk. Elafibranor is now in phase 3 and the first part of the cohort needed for the interim analysis has been fully recruited.

Several other PPAR drugs are in development, including lanifibranor (a pan-PPAR agonist potentially combining positive effects of the glitazones with PPAR agonism and currently in phase 2b) [63] as well as saroglitazar (a PPAR dual agonist) and seladelpar (a PPAR agonist).

FXR Agonist

FXR plays in important role in bile acid metabolism but also impacts on several metabolic, inflammatory and fibrogenic pathways. FXR is present in the liver and the intestine, with some differences in effect according to the site [28].

Bile acids are the natural ligands of FXR. UDCA has no FXR agonistic effect, but the bile acid obeticholic acid (OCA) is a potent FXR agonist and resulted in a significant response compared to placebo as defined by a 2-point reduction in NAS in the FLINT trial in 110 treated vs. 109 placebo patients eligible for paired biospies (there was also a beneficial effect on fibrosis, a secondary endpoint) [64]. There was a trend for resolution of NASH, which was another secondary endpoint. Because of the significant benefit in terms of the primary endpoint, the study was stopped prematurely and the drug went on to phase 3. Pruritus is a known side effect of OCA, which is currently already licensed for the treatment of primary biliary cholangitis. Furthermore, OCA decreased HDL cholesterol levels and did not improve glycaemic control. The first part of the cohort needed for the interim analysis was fully

Table 1 Phase 2 placebo-controlled trials with histology as a primary endpoint (Source: clinicaltrials.gov)

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
Semaglutide	GLP-1 Receptor agonist	SC	NASH resolution without worsening of fibrosis	72 w	
Lanifibranor (IVA337)	PanPPAR	PO	≥ 2 points decrease from baseline in activity score (SAF)	24 w	
MSDC 0602K	PPARγ-independent (?) regulator of mitochondrial pyruvate entry	PO	≥ 2 points decrease in NAS without worsening of fibrosis	12 w	
Emricasan	Pan-caspase inhibitor	PO	≥ 1 stage improvement in fibrosis without worsening of steatohepatitis	72 w	Also in phase 2 with composite clinical endpoint without histology and trial in cirrhotic patients with effect on HVPG as outcome measure
BMS-986036	Pegylated FGF21 analogue	SC	≥ 1 stage improvement in fibrosis without worsening of steatohepatitis or NASH improvement without worsening of fibrosis	24 w	
SAR 425899	Dual GLP-1 receptor/ GCGR agonist	SC	Resolution of NASH	52 w	

FGF fibroblast growth factor, *GCGR* glucagon receptor, *GLP-1* glucagon-like peptide, *HVPG* hepatic venous pressure gradient, *NAS* NAFLD activity score, *NASH* non-alcoholic steatohepatitis, *PO* per os, *PPAR* peroxisome proliferator-activated receptor, *SAF* steatosis-activity-fibrosis scoring system, *SC* subcutaneous

recruited by the end of 2017. Recently positive results on liver fibrosis have been reported resulting from the interim analysis that should be the basis of registrational approval in a press release, but the full data have not been presented so far.

Several other bile acid FXR agonists are being investigated, *nor*-UDCA being the most advanced (currently in phase 2) and promising. Furthermore, several non-bile acid FXR agonist are being developed. According to their differential effects on intestinal or hepatic FXR and other pharmacokinetic and pharmacodynamic properties, the net effects on the liver as well as on the metabolic parameters and their safety and side effect profile should be waited for

Table 2 Placebo-controlled trials with non-invasive primary endpoint (Source: clinicaltrials.gov)

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
Aparenone (MT-3995)	Non-steroidal mineralocorticoid receptor antagonist	PO	ALT change	24 w	
Tropifexor (LNJ452)	Non-steroidal FXR agonist	PO	Change in transaminase levels	12 w	
			Change in liver fat (MRI)		
Seladelpar (MBX-8025)	Selective PPARδ agonist	PO	Relative change in MRI-PDFF	12 w	Study continues for 52 weeks including histology as secondary outcome measure
Namodenoson (CF102)	A3 adenosin receptor inhibitor	PO	Mean % change in ALT levels	12 w	
LIK 066	Dual SGLT1/2 inhibitor	PO	Change from baseline ALT	12 w	
BI 1467335	AOC3 (VAP1) inhibitor	PO	AOC3 activity relative to baseline	12 w	ALT change from baseline as a secondary outcome measure
Foralumab	Oral anti-CD3 antibody	PO	Safety	30 d	Change in ALT as a secondary outcome measure
SNP-610	Enzyme modulator at several steps of TG metabolism and lipid peroxidation (CYP2E1 pathways)	PO	Absolute change from baseline in serum ALT	12 w	
Emricasan	Pan-caspase inhibitor	PO	Event-free survival based on composite clinical endpoint	48–120 w	In patients with decompensated cirrhosis. Compound also phase 2 with histological endpoint
Emricasan	Pan-caspase inhibitor	PO	Mean change in HVPG	28 d	In cirrhotic patients

Table 2 continued

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
Saroglitazar	Dual PPARαγ agonist	PO	% change in ALT levels	16 w	Also trial of 24 w in women with PCOS and with changes in liver fat by MRI-PDFF as primary outcome
Pemafibrate	PPARα agonist	PO	% change in liver fat measured by MRI-PDFF	24 w	
HTD1801	Lipid modulator (2 moities)	PO	% change in liver fat content measured by MRI	18 w	
PF-5521304	ACC inhibitor	PO	% change in liver fat content measured by MRI PDFF	16 w	
SGM-1019	Small molecule modulator of inflammasome activity	PO	Safety	12 w	Monitoring of ALT as secondary outcome measure
EDP-305	Non-steroidal FXR agonist	PO	Change in ALT	12 w	
Tesamorelin	Growth hormone releasing hormone analogue	SC	Liver fat content by MR spectroscopy	12 months	
MGL-3196	TRHβ agonist	PO	Change from baseline in hepatic fat fraction measured by MRI-PDFF	12 w	Study continues for a total of 36 weeks with histology as secondary outcome measures; study has been completed and results presented (EASL 2018, AASLD 2018). Will enter Phase 3

Table 2 continued

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
DS102	Anti-inflammatory and anti-fibrotic lipid	PO	Change in serum ALT	12 w	
ISIS703802	ANGPTL3 protein inhibitor	SC	% change in fasting TG	6 months	Changes in liver fat measured by MRI PDFF in secondary outcome measures
AZD4076	GalNAc-conjugated anti-miRNA-103/107 oligonucleotide	SC	Reduction in liver fat content measured by MRI	54 days	

ACC acetyl-CoA carboxylase, *ALT* alanine aminotransferase, *ANGPTL3* angiopoietin 3, *AOC3* amine oxidase copper-containing 3, *CYP* cytochroom P, *FXR* farnesoid receptor X, *GalNAc* N-acetylgalactosaminyl, *miRNA* microRNA, *HVPG* hepatic venous pressure gradient, *MRI-PDFF* magnetic resonance imaging proton density fat fraction, *PO* per os, *PPAR* peroxisome proliferator-activated receptor, *PCOS* polycystic ovary syndrome, *SGLT* sodium glucose transporter, *TG* triglycerides, *THR* thyroid hormone receptor, *VAP1* vascular adhesion protein 1, *W* week

before any claims can be made. Meanwhile the non-bile acid FXR agonist tropifexor has entered a phase 2 trial in combination with cenicriviroc (vide infra).

Cenicriviroc

Cenicriviroc is a CCR2 and CCR5 dual antagonist. CCR2 and CCR5 play an important role in macrophage recruitment and polarisation and have been implicated in NASH pathogenesis. A large 2-year phase 2 trial (CENTAUR) including 289 patients has recently been completed and reported [30]. Year 1 analysis demonstrated a significant decrease in systemic inflammation, but this did not translate into a clear effect on NASH. By contrast, there was a significant benefit of cenicriviroc over placebo in terms of regression of fibrosis. Therefore, the drug is now in phase 3 with reduction in fibrosis as the primary endpoint.

Selonsertib

Selonsertib is an apoptosis signal-regulating kinase 1 (ASK1, involved in response to various stresses) inhibitor that was tested in a 6-month trial in combination with or without simtuzumab in an anti-fibrotic strategy in 72 patients [24]. When the other simtuzumab trials turned out negative, simtuzumab was considered as placebo and the patients in the different arms were regrouped. In this new setting, selonsertib was superior to placebo in terms of fibrosis regression, without an effect on steatohepatitis or on the metabolic features. Two phase 3 trials have been initiated, one for F3 patients and one for cirrhotic patients, with an interim analysis planned after one year of treatment. The trial in cirrhotic patients did not meet its primary endpoint and was stopped, whilst the trial in F3 patients is currently ongoing.

Besides the four molecules currently in phase 3, several other molecules are under investigation. Some have already been mentioned.

Table 3 Phase 2 randomised combination trials (not all placebo-controlled) (Source: clinicaltrials.gov)

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
Selonsertib	ASK-1 inhibitor	PO	≥1 stage improvement in fibrosis without worsening of NASH	48 w	Placebo-controlled; multiple combination arms
GS-0976	ACC inhibitor				
GS-9674	Non-steroidal FXR agonist				
Selonsertib	ASK-1 inhibitor	PO	Safety	12–24 w according to the different arms	No placebo-arm
GS-0976	ACC inhibitor				
GS-9674	Non-steroidal FXR agonist				
Fenofibrate	PPARα agonist				
Tropifexor (LNJ452)	Non-steroidal FXR agonist	PO	Safety	48 w	No placebo-arm; histology as secondary outcome measures
Cenicriviroc	CCR2-CCR5 dual antagonist				

ACC acetyl-CoA carboxylase, *ASK-1* apoptosis signal-regulating kinase 1, *CCR* C-C motif chemokine receptor, *FXR* farnesoid recpeptor X, *NASH* non-alcoholic steatoHepatitis, *PO* per os, *PPAR* peroxisome proliferator-activated receptor

Aramchol is another compound for which the phase 2 ARREST study data in 247 patients have recently been presented [65]. The full data set is hence still to be published. Aramchol is a bile acid–fatty acid conjugate acting as a stearyl-CoA desaturase 1 (the rate-limiting enzyme in the synthesis of unconjugated fatty acids) inhibitor and showed some efficacy in mice [66]. The primary endpoint of the trial was reduction in the amount of liver fat (with overall no significant reduction in liver fat, but a significantly greater percentage of patients with 5% reduction of liver fat according to magnetic resonance (MR) spectroscopy was observed in the high dose aramchol arm). Also, on secondary endpoints, especially resolution of NASH, a

Table 4 Phase 3 randomised placebo-controlled trials. Two more compounds have announced entering phase 3 (Aramchol and MGL-3196) (Source: clinicaltrials.gov)

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
Elafibranor (GFT 505)	PPARαδ dual agonist	PO	Resolution of NASH without worsening of fibrosis	72 w	Study continues for composite long-term outcome (progression to cirrhosis, all-cause mortality, liver-related clinical outcomes)
Obeticholic acid	Steroidal FXR agonist	PO	1 stage improvement in fibrosis without worsening of NASH or NASH resolution without worsening of fibrosis	18 m	Study continues for long term outcome (all-cause mortality and liver-related clinical outcomes)
Selonsertib	ASK-1 inhibitor	PO	≥1 stage improvement of fibrosis without worsening of NASH	48 w	Study continues for long term outcome (Event free survival at 240 w)
Cenicriviroc	CCR2-CCR5 dual antagonist	PO	≥1 stage improvement of fibrosis and no worsening of NASH	12 m	Study continues for long term outcome (composite endpoint of all-cause mortality, histopathological progression to cirrhosis or liver-related outcomes)

ASK-1 apoptosis signaling kinase 1, *CCR* C-C motif chemokine receptor, *FXR* farnesoid receptor X, *NASH* non-alcoholic steatohepatitis, *PO* per os, *PPAR* peroxisome proliferator-activated receptor, *W* week

significant effect of aramchol was noted. On the basis of these results, the compound will enter phase 3. An Israeli study in 60 patients with NAFLD (only few had NASH) already previously showed a reduction in liver fat content as measured by MR spectroscopy in the 300 mg dose [67]. Aramchol is an example of an approach that initially is more oriented towards lipid accumulation in the liver (and subsequent composition of the bile) and hence a more purely metabolic approach. Other attempts like ezetimibe have failed in that regard. Different approaches, like fatty acid synthase inhibition and other targets of cholesterol and triglyceride

metabolism are tested in earlier phases of clinical development.

Fibroblast growth factor (FGF) 19 is released by the intestinal cells upon FXR stimulation and, after reaching the liver via the portal vein, exerts its actions on bile acid metabolism via the FGF receptor 4/β-klotho complex and also impacts on lipid and glucose metabolism. Via the IL-6/STAT3 pathway, however, it also drives tumorigenesis [68]. NGM282, a recently engineered FGF19 analogue that lacks the effect on the STAT3 pathway and hence most likely lacks the tumorigenic effect of FGF19, demonstrated a significant reduction in liver fat content in a phase 2 study including 82 patients NASH [68].

Data from single-arm studies have also been released recently and report histological benefit. This injectable drug appeared to have an acceptable safety profile and will be further studied.

Thyroid hormones increase energy expenditure and have catabolic properties, acting via the thyroid hormone receptor (THR), a nuclear receptor with different isoforms. An intrahepatic hypothyroidism has been shown to be present in NASH and potentially contributes to its pathophysiology [70]. This intrahepatic hypothyroidism is potentially attributable to alterations in hepatic deiodinase expression because of repair-related Hedgehog activation [70]. The THR agonist MGL-3196 has selectivity for THR β1 receptor that is mainly expressed in the liver and the kidney and therefore most likely lacks some potentially important side effects, amongst others on bone metabolism. MGL-3196 reduced liver fat significantly at 12 weeks of treatment as assessed by MRI proton density fat fraction (MR-PDFF), with concomitant beneficial effects on liver enzymes and markers [71]. The study of 107 patients went on for a total of 36 weeks and results were recently provided, showing a beneficial effect of the compound over placebo in improving NASH severity and NASH resolution [72], but the data still need to be published before any firm conclusion can be drawn. Based on the provided data, this compound will also enter phase 3.

FGF21 is a so-called hepatokine, a peptide hormone produced by the liver (but also by multiple other organs; circulating levels are, however, mainly determined by the hepatic production) that regulates sugar intake, glucose homeostasis and energy expenditure. Interestingly, in view of the PPAR drugs in the pipeline, its expression in the liver is regulated by PPAR. Animal data suggest enhanced NASH and associated metabolic derangements upon FGF21 deficiency and improvement upon administration [73]. Human data are conflicting, with increased FGF21 levels in NASH patients suggesting FGF21 resistance [74]. Recent data [75] demonstrated a beneficial effect on MR-PDFF-measured liver fat content of BMS986036, an injectable pegylated analogue of human FGF21, along with a reduction in biomarkers of liver injury and fibrosis in a placebo-controlled trial including 74 patients.

The Takeda G-protein-coupled membrane bile acid receptor (TGR5) present on numerous cells, including intestinal epithelium, biliary epithelium, adipocytes and stellate cells, is an important mediator of the influence of bile acids on metabolism, including conversion of free thyroxine FT4 to the active thyroid hormone FT3 (again linking thyroid hormone function to NASH) [76]. Dual FXR-TGR5 agonists have been tested in preclinical models. Recently FXR-TGR5 crosstalk has been identified and this might be implicated in the OCA-associated pruritus [77]. It is hence not clear what the role of TGR5 agonism in NASH treatment will be.

As with cenicriviroc, some drugs that mainly target inflammatory mechanisms are even tested. BI 1467335, an oral small molecule inhibitor of amine oxidase copper-containing 3 (AOC3), also called vascular adhesion protein 1 (VAP-1), is currently in phase 2. AOC3 plays an important role in the recruitment of various inflammatory cell types to a site of inflammation and was shown to play a role in NASH pathogenesis in preclinical models. Its soluble variant showed a correlation with NAFLD severity [78]. Furthermore VAP-1 has been implicated in atherosclerosis and cardiovascular prognosis [79], reinforcing the link between NAFLD and CVD and the rationale for AOC3 antagonists in NASH.

Inhibition of caspases to interfere with inflammatory and apoptotic processes is another of the many pathways that are targeted. Emricasan, a pan-caspase inhibitor, showed efficacy in a preclinical animal model [80]. Interestingly, it was reported to lower liver enzymes in chronic hepatitis C patients a decade ago [81]. The compound is currently in phase 2.

Whilst we are still waiting for a phase 3 proof of efficacy of single drugs, several combinations of drugs are being tested. As outlined before, disease pathophysiology is heterogenous and complex, offering a rationale for combining drugs with different modes of action that can have additive or even synergistic effects. Besides testing combinations of individual drugs (e.g.

tropifexor and cenicriviroc, Table 3), several molecules that combine different structures are being engineered and tested (e.g. a molecule that combines a GLP-1 receptor agonist and a glucagon receptor agonist).

CONCLUSION

Pharmacological treatment for NASH focuses on patients with some activity of the steatohepatitis component combined with already some degree of fibrosis. Definitions, concepts and designs are evolving, and a large number of drugs are currently being evaluated. As pathophysiology is complex, the patient population heterogenous and diagnosis and therapy monitoring difficult, this area of drug development is particularly challenging. Some drugs currently approved for other indications have shown some efficacy and can be used, but new treatments are eagerly awaited.

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