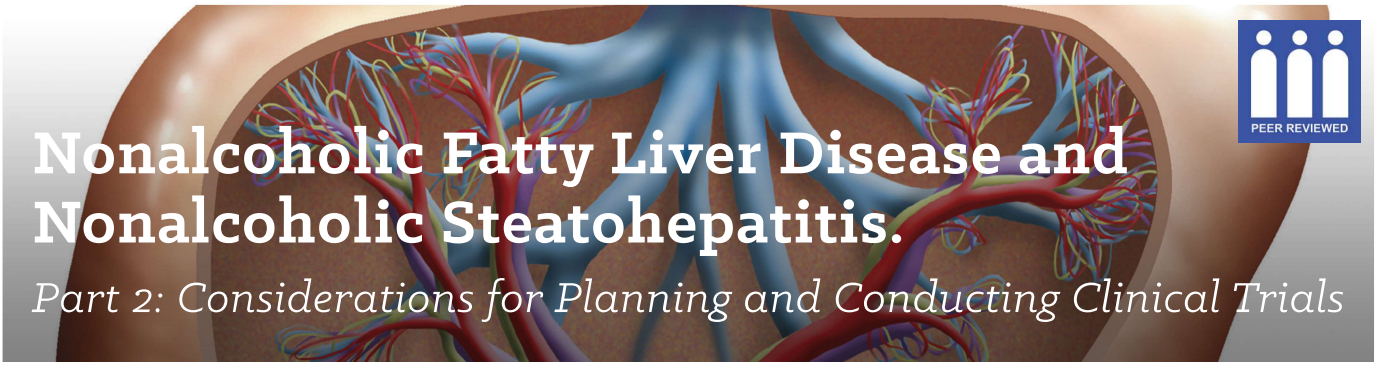

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis.

Part 2: Considerations for Planning and Conducting Clinical Trials

PEER REVIEWED

Editor's Note: This paper is the second in a two-part series addressing non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. In Part 1, Dr Mark Delegge provided an overview of these important diseases. In Part 2, he discusses considerations when planning and conducting clinical trials for new treatments in these therapeutic areas.

Introduction

As indicated in the Editor's Note, this paper is the second in a two-part mini-series addressing nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. After introducing these diseases in Part 1 in the previous issue of this journal, this paper addresses considerations for the future of clinical trials in these therapeutic areas. Topics covered include trial design, biomarker and liver biopsy considerations, and efficacy outcome endpoints.

Clinical Trials

A multitude of new molecular entities have been evaluated for the treatment of NASH. A few will be reviewed here. Insulin resistance is nearly universal in patients with NASH, and some studies have therefore evaluated insulin sensitisers in humans: these employed biguanides (metformin) and thiazolidinediones (pioglitazone and rosiglitazone). Metformin's anti-diabetic action is likely related to decreased hepatic gluconeogenesis, decreased glucose absorption, and increased insulin sensitivity by facilitating glucose uptake and utilisation.[1] In addition, its stimulatory effect on AMP-activated protein kinase or modulation of hepatic TNFα expression may offer benefits. A Cochrane database analysis showed that metformin leads to normalisation of serum aminotransferases in a significantly greater proportion of patients with NAFLD compared with dietary modification.[2]

The NASH Clinical Research Network performed the Treatment of NAFLD in Children (TONIC) trial, which evaluated the impact of metformin, vitamin E, or placebo on liver function, testing abnormality improvement and histology in a multicentre trial of paediatric patients diagnosed with NAFLD by biopsy. Neither liver function test abnormality nor histology were improved with the use of metformin or vitamin E as compared with placebo.[3,4]

Thiazolidinediones

Thiazolidinediones (TZDs) are a class of oral anti-diabetic medications that improve insulin resistance by acting as selective peroxisome proliferator-activated receptor (PPAR)-γ agonists. Rosiglitazone and pioglitazone are the second generation TZDs that are currently available for clinical use. They redistribute fat from muscle and liver to adipose tissue and thereby improve peripheral (skeletal muscle) and hepatic insulin sensitivity.[5] In addition, they increase circulating levels of adiponectin, which is produced exclusively by the adipose tissue and has insulin sensitising properties.[6]

In past clinical trials, TZDs improved hepatic histology in patients with NASH, although their favourable effect on steatosis was greater than their impact on other histological variables such as inflammation, ballooning, or fibrosis. Their favourable effect on liver histology and liver biochemistries disappeared upon their discontinuation, suggesting that long-term treatment is needed to maintain therapeutic benefits.[7]

The PIVENS trial compared the impact of vitamin E, pioglitazone or placebo on the diagnosis of biopsy-proven NASH. Vitamin E therapy compared with placebo was associated with a significantly higher rate of improvement in NASH (43% vs. 19%; P = 0.001) after 96 weeks. However, the difference in the rate of NASH improvement with pioglitazone compared with placebo did not reach the pre-specified 0.025 level of significance (34% vs. 19%; P = 0.04).[8]

Vitamin E (RRR-α-tocopherol) is a lipid-soluble antioxidant that is able to scavenge free radicals and avoid lipid peroxidation. A meta-analysis reported that vitamin E supplementation might improve transaminase levels in patients with NASH, which confirms the therapeutic potential of vitamin E.[9] The potential benefit of vitamin E was demonstrated in the PIVENS trial described in the previous paragraph.[8] Conversely, the TONIC trial failed to demonstrate any impact of vitamin E on paediatric patients diagnosed with NASH.[3]
The bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid [OCA]) is a potent activator of the farnesoid X nuclear receptor that reduces liver fat and fibrosis in animal models of fatty liver disease. The Phase II FLINT trial evaluated the impact of OCA on the diagnosis of biopsy proven NASH.[10] OCA was statistically significantly superior to placebo for the primary outcome of improved liver histology, as well as the secondary endpoint of fibrosis improvement by at least one stage. Additionally, statistically significant OCA treatment effects were demonstrated on the major histological features of NASH, including steatosis, lobular inflammation, and hepatocellular ballooning. Post-hoc subgroup analyses found that the histological improvements were consistently greater in patients with more advanced disease and at greatest risk of progressing to liver failure and death. A large Phase III trial is currently underway, with completion forecast for 2021.

Elafibranor is an agonist of the peroxisome proliferator-activated receptor-alpha and receptor-gamma that play key roles in fatty acid transport, oxidation, glucose homeostasis, and anti-inflammatory activities. A Phase II international, randomised, placebo-controlled, multicentre study evaluated the efficacy of elafibranor for treating NASH. A total of 276 patients with biopsy-proven NASH but not cirrhosis were randomised to elafibranor 80 mg, elafibranor 120 mg, or placebo. Patients were followed every two months for a year, and an end-of-treatment biopsy was performed.[11] There was no difference between the elafibranor groups and placebo in the primary outcome (reversal of NASH). A post-hoc analysis used a more stringent

outcome where NASH resolution was defined as disappearance of ballooning and either no or mild inflammation. In this analysis, the 120-mg elafibranor group had a significantly higher resolution of NASH without fibrosis progression than did placebo (19% vs 12%). Elafibranor was well tolerated, with the only significant side-effect being a mild, reversible increase in serum creatinine. A large Phase III trial is currently underway, with completion forecasted for 2021.

Other new molecular entities are focused specifically on the inflammatory cascade and/or inhibiting fibrosis. Cenicriviroc is a chemokine blocker impacting receptors 2 and 5. In a Phase II study, Cenicriviroc was able to show an improvement in fibrosis with no worsening of inflammation. A Phase III clinical trial looking specifically at fibrosis improvement in NASH has begun. Selonsertib is an apoptosis signal regulating kinase inhibitor (ASK-1 inhibitor). In a Phase II study, this new molecular entity was shown to inhibit fibrosis. Selonsertib is currently enrolling in a Phase III trial. A thyroid receptor hormone B-agonist has recently completed a Phase II trial where it achieved its primary outcome. A Phase III trial is planned. There are numerous other compounds in pre-clinical, Phase I, and Phase II trials that are beyond the scope of this paper.

Considerations for the Future of NAFLD/NASH Clinical Trials

The majority of multicentre, interventional clinical trials in NAFLD/NASH have been conducted in the past 15 years, starting with the landmark PIVENS trial in 2003 that was funded by the US National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).[8] However, as of 2017, of the approximately 87 interventional trials that have been conducted or are currently active, over 80% have been initiated in the past five years alone, which is indicative of the increased attention being paid to the unmet medical needs and growing incidence and awareness of NAFLD and NASH globally. Overall study initiation trends are shown in Figure 1.

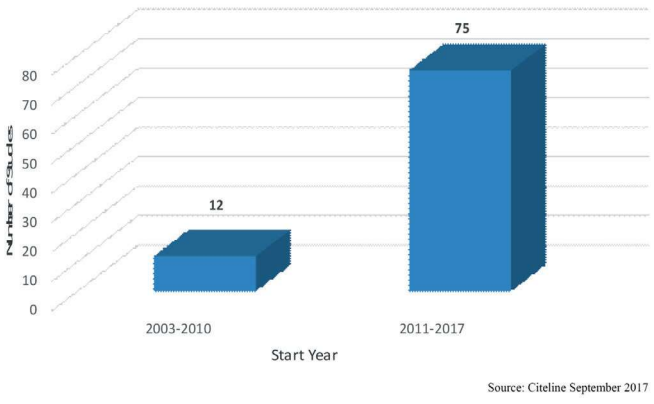

Figure 1: Initiated Industry-sponsored NASH/NAFLD Trials by Start Year (n=87)

Many of these trials, 16 of which are in Phase II, are actively enrolling with a target accrual of over 13,000 patients. The three largest trials are in Phase III, aiming to recruit over 12,000 patients combined at over 1200 sites globally. Because of the size of Phase III trials needed to show a statistically significant treatment effect and the time over which this effect can be seen, it is expected that future Phase III trials in this space will be equally large in terms of site and patient volumes.

Study Design Considerations: Adaptive Trials

Clinical trials are designed with regulatory milestones in mind regarding safety and efficacy outcomes, while being mindful of cost and ultimate acceptability by both principal investigators and patients who become clinical trial participants. Many drug and device development pathways follow a standard Phase I-III process. Although traditionally this has provided successful drug approval pathways and robust data production, the time and cost of these pathways can be prohibitive and may not meet the needs of new molecular entities in certain disease spaces, such as NASH.

Adaptive designs may be useful when developing NMEs for NASH. This approach, which has become acceptable within clinical trials, evaluates a medical device or drug by observing participant outcomes (and possibly other measures, such as side-effects) on a prescribed schedule, and allows modification of the trial protocol based on those observations.[12] The adaptation process continues throughout the trial, as pre-determined in the trial protocol. Modifications may include drug dosage, sample size, and patient selection criteria. The aim of an adaptive trial is to identify drugs or devices more quickly that have a therapeutic effect, and to zero in on patient populations for whom the drug is appropriate. When adaptive designs are used properly, efficiencies can include a smaller sample size, a more efficient treatment development process, and an increased chance of correctly answering the clinical question of interest. However, improper adaptations can lead to biased studies.[13] The adaptive design model works well within the NASH clinical space where multiple new molecular entities are hypothesised to work on one or more of the pathophysiologic pathways.

Efficacy Outcome/Endpoint Measures

The 2012 guidelines from the American Association for the Study of Liver Disease and the 2009 European Association for the Study of Liver Disease position statement on liver biopsy recommend liver biopsy as an endpoint for all clinical trials.[14,15] Therefore, to date, liver biopsy has been the mainstay for monitoring NAFLD progression when repeated biopsies are performed.[16] A more recent (2016) publication from the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) noted that "the resolution of the histological lesions defining NASH is now accepted as a surrogate endpoint, particularly in clinical trials."[17]

Histology findings are an accepted surrogate for hard clinical endpoints such as mortality, but the most relevant histological features are a matter of debate.[18,19] The US Food and Drug Administration (FDA) recently endorsed endpoints for clinical trials of potential NASH therapies. Reversal of NASH without evidence of progression to advanced fibrosis is now defined as the endpoint for Phase IIb and Phase III trials in individuals with NASH and early-stage fibrosis.[20] While a reduction in the nonalcoholic fatty liver disease activity score could be used as an endpoint in clinical trials, it is unclear whether patients with lower scores have a reduced risk of developing advanced fibrosis. Endpoints for clinical trials involving NASH cirrhosis are currently based on the model for end-stage liver disease and Child-Turcotte-Pugh scores (for classification of the severity of cirrhosis), in addition to the hepatic venous pressure gradient.[20] These approaches offer a starting point to develop treatments.

Liver Biopsy Considerations

To achieve consistency in histology interpretation in NASH clinical trials, a central reading process consisting of a pathologist specifically experienced in NASH histology assessment is recommended. The same pathologist should be evaluated over time to ensure interpretation consistency. A formal adjudication process should be in place to resolve any inconsistencies in interpretation: similar adjudication processes have been used for other disease states such as central reading of endoscopy for inflammatory bowel disease.[21] Some limitations of liver biopsy are due to variability of the disease process itself, as with all other forms of chronic liver disease. This

is compounded by the sampling limitations of biopsy with only 1/50,000 of the liver volume captured at biopsy. NAFLD, while a diffuse process of the liver, can have differences due to the location of the samples under evaluation. It is important that pre- and post-study biopsies are done in a similar fashion and from the same region of the liver.[22]

Transport of tissue slides and blocks between multiple sites can make tissue sample management complex. In addition, slide preparation can vary between local pathologists. The ideal situation is to have tissue samples be sent in 'block' form to a central site for slide preparation. These slides are digitally imaged for review by the central readers.

Biomarkers in Clinical Studies

Probably the most urgent need in the field of NASH is the discovery of biomarkers that would help diagnose and monitor disease progression.[23] To date, the FDA has not endorsed any biomarker as an alternative for liver biopsy histology as the primary outcome for NASH clinical trials. Therefore, biomarkers and scoring systems are usually considered secondary or exploratory endpoints in clinical trials. Attempts have been made to create algorithms to predict which patients with NASH as a potential diagnosis should receive a liver biopsy for definitive diagnosis.[24]

Serum biomarkers for staging of fibrosis include combinations of either direct markers, which are mainly complex proteins from myofibroblasts and extracellular matrix remodelling, or indirect markers, which are detectable via simple biochemical tests and can be used to estimate the severity of disease. These diagnostic algorithms (scoring systems) have also been adapted to take account of risk factors for metabolic syndrome, helping to provide more accurate estimates of the severity of NAFLD.[25]

A combination of serum biomarker and bedside transient elastography (bedside liver stiffness text) analyses appears to offer initial approaches to assessing NASH, but their applicability for follow-up analyses has yet to be established. Most imaging methods are unable to directly visualise the combination of fibrosis and inflammation, or accurately assess liver disease progression. Promising exploratory results have been recorded from molecular and targeted magnetic resonance imaging studies of small molecules that bind to fibrillary collagen, or other extracellular matrix proteins. These may have potential in tracking changes in fibrosis, offering promising new and non-invasive tools for quantitative measurement of fibrogenesis. This may enable validation of next-generation biomarkers, helping in assessment of the efficacy of potential anti-fibrotic therapies.[26]

More recently, work in multiparametric MRI scanning has been provocative and impressive. The sensitivity of this technology to both fibrosis and inflammation offers a non-invasive approach with the potential to enrich the population of NASH patients volunteering for NASH trials and reducing the number of unnecessary biopsies.[27,28] It has been reported that 50–60% of patients who have liver biopsy for NASH trial inclusion are subsequently excluded from clinical trial participation based on the biopsy results. This is a significant inconvenience and medical risk for patients and a substantial cost burden to any clinical trial. As noted earlier, given that it is an invasive procedure with a 0.5% complication rate and a 0.01% mortality rate, liver biopsy is not suitable as a screening test.[29] There is also a mounting body of evidence that a needle liver biopsy that results in a tissue sample that is a tiny portion of the liver (as mentioned previously, around 1/50,000 of the total mass of the liver) may be subject to significant sampling variability. In a cost assessment model, multiparametric MRI was superior to transient elastography in predicting the presence of NAFLD prior to liver biopsy.[30] Multiparametric MR has also been shown to be predictive of future liver-related outcomes.[27]

Feasibility Considerations: Competition for Study Participants

Although the number of potential NAFLD and NASH clinical trial participants is theoretically large enough to support such trials, it is expected to become increasingly difficult to enroll these patients. The burden on sites is expected to increase since there will likely be greater competition from pharmaceutical companies to recruit principal investigators at the most experienced sites, and a need to expand into geographic regions and sites that have patients but less direct experience in NAFLD/NASH clinical trials.

One potential and paradoxical advantage for clinical trial participant recruitment in this therapeutic area is the lack of currently available pharmacological treatments: clinical trial participation therefore offers considerable benefit to patients in allowing access to potential new therapies. Investigational sites with NAFLD/NASH expertise generally have clinical trial experience in this area dating back to the PIVENS trial and, more recently, the FLINT trial, in addition to the influx of pharma-sponsored trails over the last five years. As the research landscape grows more crowded, studies will become more complex and targeted with regard to patient eligibility: patient populations that are most likely to show benefit will be of great interest.

Figure 2 shows geographic regions that have some experience of participation in these trials. As can be seen, to date the US has accumulated the bulk of the experience in NASH/NAFLD clinical trials. However, it is unlikely that the experienced US-based investigational sites will be able to accommodate all future trials, due to limited availability of patients and site resources. This presents an opportunity for other physicians with patient populations and clinical interests in NASH/NAFLD around the world to participate in clinical trials that have the potential to offer novel treatments to patients while also increasing understanding of the disease itself.

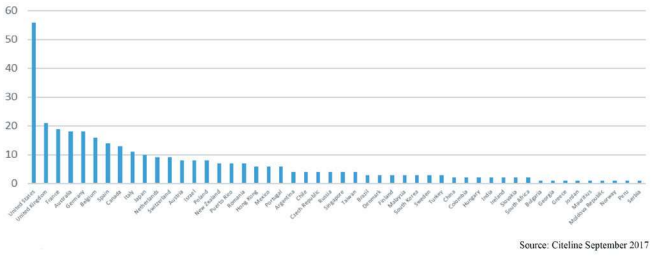

Figure 2: NASH/NAFLD Trials to Date by Country

Anonymised Patient Data Mining

Diverse methodologies exist for anonymised patient data mining. These include electronic medical records (EMR), prescription data, and direct information from patients. The EMR is a timetable recording of patient health information, generated by multiple encounters in a multitude of healthcare settings (e.g., clinic, hospital, and emergency room visits). The dramatic advancement and availability of health information technologies offers tremendous opportunities for clinical research.[31–33] EMR is fairly well established in the US, but many countries have yet to adopt this approach. Prescription data may be of value to identify concentrations of NASH patients, especially as treatment options expand.

Linking EMRs with clinical trials has been demonstrated to increase the recruitment rate of patients.[34] The ability to access

EMR information can allow very precise questions to be asked about a disease state including disease prevalence in a region, physicians caring for patients with these diseases, current therapies, hospitalisations as a result of the disease, and procedures performed. A funnel plot can be created that allows the overall incidence of a disease in a region to be captured and further analysed by a study's inclusion and exclusion criteria to generate a more reliable estimate of how many patients are truly available for participation in a given clinical trial.

Safety-related Assessments

Lastly, but certainly not of least importance, attention must be paid to safety considerations and assessments. It was noted previously that there is a correlation between the presence of NASH and hypertension, hyperlipidaemia, and obesity, which alerts us to the need for specific safety assessments: in addition to being efficacious, it is imperative that any drug developed for NASH does not increase cardiovascular risk, and, ideally, reduces it.[35] One important goal in Phase IIb and Phase III trials, therefore, is to demonstrate that important cardiovascular parameters (e.g., LDL-cholesterol, HDL-cholesterol, triglicerides, apolipoprotein, coronary calcification scores) are not negatively impacted. It is also important to demonstrate stability of metabolic parameters (HbA1C, fasting insulin and glucose, fasting free fatty acids) during Phase IIb and Phase III trials. Cancer risk is best monitored during longer-term Phase IV post-marketing studies. Monitoring should also occur for drug-induced liver injury, behavioural adverse events such as depression (depression scores should be tracked during treatment), and other off-target unexpected effects.

Concluding Comments

NAFLD and NASH are being diagnosed globally with increasing frequency. The global prevalence of NAFLD is estimated to be 25% – 30%. It is predicted that approximately one-third of patients with NAFLD will ultimately be diagnosed with NASH.

NAFLD and NASH often present clinically as incidental findings on laboratory (elevated liver function tests) or radiographical (steatosis or fibrosis) testing without specific clinical symptoms. The definitive diagnosis of NASH requires a liver biopsy with specific histologic findings of steatosis, fibrosis, inflammation, and hepatocyte ballooning and degeneration.

From a demographic perspective, there are certain patient characteristics which are risk factors for developing NASH, e.g., type 2 diabetes, obesity, hypertriglyceridemia and polymorphism in the PNPLA3 gene. However, we do not have a reliable non-invasive biomarker of NASH including serum and/or imaging biomarkers. Multiparametric MRI appears to be very promising in achieving this goal. Liver biopsy, with its associated cost, morbidity, and mortality, does not allow it to serve as a reasonable screening tool for NAFLD or NASH.

There are currently no commercially available, regulatory-approved pharmacologic agents available for the treatment of NASH. There are some therapies being used off-label. As of writing this paper, four Phase III trials are ongoing or getting ready to begin, and a number of Phase I and Phase II trials and pre-clinical work in progress. These clinical trials face similar challenges for enrolment. Patients are usually asymptomatic and may be reluctant to participate in a clinical trial. The lack of a sensitive and specific biomarker to diagnose NASH or to monitor its response to therapy has led to the requirement of one or multiple liver biopsies over the course of a clinical trial. Patients with elevated liver function tests or abnormal imaging studies suspicious for NASH are subject to a liver biopsy only to have a > 50% likelihood of not having a histologic diagnosis of NASH which would allow them to enter a given clinical trial. This is disappointing and frustrating for both patients and primary investigators.

Most patients with NAFLD and NASH are not currently receiving their medical care from hepatologists but rather from endocrinologists and primary care physicians. Anonymised patient data-mining can determine where patients with NASH or risk factors associated with NASH are located and who are their treating institutions and physicians. This can monumentally improve the identification of productive NASH geographic locations and investigators. Raising the awareness of NASH with these physician groups and encouraging early diagnosis and referral to hepatologists is critical for appropriate patient treatment and monitoring, and for creating a large enough pool of patients for clinical trials involving NMEs. Given the significant impact of NAFLD and NASH on the long-term health of patients, development of NMEs is imperative. Pharmaceutical companies, contract research organisations, clinicians, researchers, and patients need to partner at a very high level to ensure the timely development of approved NMEs for commercialisation and treatment of these diseases.

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