Review

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Pharmacotherapy for NASH: Current and emerging

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Summary

Non-alcoholic fatty liver disease (NAFLD) has become one of the most prominent forms of chronic liver disease worldwide, reflecting the epidemic of global obesity. Those with the progressive variant of NAFLD, non-alcoholic steatohepatitis (NASH), are at significantly increased risk of multisystem morbidity and mortality. However, there are currently no approved pharmacologic therapies for NASH. Given the disease burden, there is an important unmet need for pharmacologic treatment options for this patient population. The underlying pathophysiologic mechanisms that contribute to the development and progression of NAFLD and NASH are complex and reflected by the myriad of therapies, with different targets, currently under investigation. In broad strokes, drug development has focused on modulation of metabolic pathways, inflammatory cascades, and/or mechanisms impacting fibrosis. Although much progress has been made in enhancing our understanding of NAFLD pathogenesis, development of pharmacologic treatments has been hindered by challenges in clinical trial enrollment and complexities in clinical trial design. The compounds in phase IIa have provided promising results in terms of potential benefits on various aspects of histopathology. Agents in later stages of development have shown fairly modest results in terms of reduction of hepatic steatosis, necroinflammation and fibrosis. If longer term safety and efficacy are established among heterogeneous cohorts, these medications may help mitigate potential morbidity and mortality for this burgeoning patient population.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become one of the most prominent forms of chronic liver disease worldwide, as a direct result of the obesity epidemic. The World Health Organization estimates the prevalence of obesity has more than doubled since 1980 with >600 million people (13%) having a body mass index (BMI) ≥30.[1] In this setting, the global prevalence of diabetes among adults has also increased from 4.7% in 1980 to 8.5% as of 2014.[2] Within the general population, the overall global prevalence of NAFLD (defined using imaging criteria) is estimated to be 25% (95% CI 22.1–28.6%) though substantial variability was noted across geographic regions (peak prevalence in the Middle East [31.8%] and South America [30.4%], with the lowest rates noted in Africa [13.5%]).[3] Prevalence rates of NAFLD among those with metabolic disease are notably higher. Approximately a third of patients with hypertension, half of patients with dyslipidaemia, up to two-thirds of patients with type II diabetes, and >90% of patients undergoing bariatric surgery had evidence of NAFLD.[4–10] Additional variations in prevalence rates are attributable to gender (twice as high in men than pre-menopausal women) and ethnicity (higher rates in Hispanic individuals and significantly lower rates in non-Hispanic black individuals), with ethnic variations partly driven by genetic distributions of *PNPLA3* among other factors.[11–13] Within the broad population of patients with NAFLD, a subset have associated inflammation and hepatocyte injury (with or without accompanying fibrosis) termed non-alcoholic steatohepatitis (NASH). The prevalence of NASH among patients with NAFLD is challenging to assess because of the biopsy-based definition. A review of liver biopsies performed in patients with NAFLD reported NASH prevalence rates ranging from 6.7% to 59% depending on whether the procedure was done in the absence or presence of a specific "clinical indication".[3] Focussing on the only prospective prevalence study of NASH to date, the prevalence of NASH among patients presenting for routine colon cancer screening was 12%.[14]

The public health impact of NAFLD is significant given the worldwide disease burden and the associated morbidity and mortality. Patients with NAFLD are at higher risk of cardiovascular disease, even when accounting for relevant metabolic co-morbidities. In fact, cardiovascular disease represents the leading cause of death for patients with NAFLD.[15,16] When focussing on liver-related morbidity and mortality, NASH represents the third most common cause of cirrhosis within the United States, but it is predicted to become the leading cause over the next few years.[17] NASH cirrhosis is currently the primary aetiology for dual liver-kidney transplantation and is estimated to become the number one indication for liver transplant by 2020.[18–20] Overall, the distinction between those with NAFLD and those with NASH is clinically relevant given that multiple studies have demonstrated that patients with NASH are at higher risk of adverse liver-related outcomes, with the degree of fibrosis contributing most significantly to this increased risk.[3,21,22]

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The striking prevalence of NAFLD paired with its profound complications underscores the critical need for safe, effective, and broadly applicable therapy. Presently, there are no medications approved by the Federal Drug Administration (FDA) or European Medicines Agency (EMA) for the treatment of NAFLD or NASH, though as this review will detail, many agents are currently being studied in clinical trials. In current clinical practice, vitamin E is the most commonly used medication, though evidence of efficacy is limited in those with diabetes and cirrhosis and current AASLD and EASL guidelines recommend its use be restricted to patients with NASH in the absence of diabetes and cirrhosis.[23,24] This recommendation is largely based on data from the PIVENS trial where subjects randomised to 800 IU/day of vitamin E for 96 weeks demonstrated improvements in steatosis ($p = 0.005$), lobular inflammation ($p = 0.02$) and ballooning ($p = 0.01$), as well as resolution of NASH (43% *vs.* 19% in placebo arm, $p = 0.001$), but no improvement in fibrosis ($p = 0.24$).[25] There have also been subsequent safety concerns regarding the use of vitamin E, as data suggest a possible increased risk of overall mortality and higher rates of prostate cancer, though this remains controversial.[26–28]

The insulin sensitiser pioglitazone, a thiazolidinedione, has been well studied and prescribed by some for the treatment of NASH, usually in line with diabetic practice guidelines. Pioglitazone has been extensively evaluated in clinical trials with fairly consistent improvements in various features of NASH and less consistently fibrosis. When evaluated in a meta-analysis, there was an overall improvement in the histopathologic components of NASH (ballooning RR 1.62 and OR 2.11, steatosis RR 2.03 and OR 3.39, and inflammation RR 1.71 and OR 2.58), with improvements in fibrosis (RR 1.38 and OR 1.68).[29–31] The major downside to the use of pioglitazone is patient and physician acceptance, given its propensity to induce weight gain (average 4.4 kg).[25] It should not be used in patients with clinically evident heart failure and may promote post-menopausal bone loss.[32,33] Given the increasing disease burden and limited efficacy and safety of current treatment options, the development of additional pharmacologic therapies to treat NASH is critical. This review will highlight the process of therapeutic clinical trial design, challenges in clinical trial recruitment, metabolic and antifibrotic agents under investigation, and an overview of the future landscape of pharmacologic design once initial agents are approved.

Endpoints in clinical trials on NAFLD and NASH

Determining optimal yet feasible endpoints for clinical trials evaluating pharmacologic agents for NAFLD and NASH is complex, because of the chronic nature of the disease, with typically slow progression to clinically significant outcomes.[34] Subsequently, relevant and acceptable surrogate endpoints need to demonstrate efficacy before the onset of long-term complications. In addition, the interconnected and dynamic nature of metabolic, inflammatory and fibrotic aspects of the disease, in response to an intervention, add to the difficulty in identifying clear and precise endpoints. Although the presence of NASH has been clearly linked with fibrosis development, an individual treatment can have different impacts on these two endpoints (*i.e.* treatment with drug X can improve NASH but worsen fibrosis and *vice versa*). Moreover, during disease progression fibrosis may worsen, while features of steatohepatitis resolve or "burnout". As a result, NASH and fibrosis need to be evaluated independently to ensure a beneficial impact on one parameter does not simultaneously result in a negative impact on another endpoint of interest, particularly given that individual treatments tend to focus on one primary mechanism of action (*i.e.* metabolic or NASH disease modifier *vs.* antifibrotic). Moreover, many of the outcomes of interest involve histological parameters, which pose a unique set of barriers and limitations. This includes inherent limitations of liver biopsy such as interobserver reliability and sampling error. Early phase trials are investigating whether relevant or predictive information can be derived from shorter-term endpoints to inform future trials. The challenge remains with long-term registration trials, which are required to demonstrate that clinically beneficial outcomes are in line with FDA and EMA requirements. This has led to the use of surrogate endpoints for accelerated approval in the US and conditional approval in Europe.

Histological endpoints

Histological endpoints to assess response to a therapeutic intervention can be broadly divided into those meeting a numerical reduction in one of two accepted scoring systems: NAFLD Activity Score (NAS) or Steatosis Activity and Fibrosis (SAF) score or the resolution of NASH as determined by a qualified hepatopathologist.[35,36] When change in the NAS is used as a primary outcome, it is recommended that ≥2 point improvement in total score be achieved with contribution from multiple parameters of the NAS, alongside no worsening of fibrosis.[37] For trials evaluating resolution of NASH, this is defined as a complete resolution of hepatocyte ballooning, with inflammation scores of 0 or 1, in addition to no worsening of fibrosis, though there is no specific requirement regarding change in steatosis. Clinical trials with a focus on improvement in fibrosis must similarly require no worsening in NASH.

Key point

Determining optimal yet feasible endpoints for clinical trials evaluating pharmacologic agents for NAFLD and NASH is complicated by slow progression of clinically significant outcomes.

Biomarkers as potential surrogates for histology

Because of the limitations and concerns regarding histological endpoints, there is mounting interest