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Comment - The devotion to surrogate outcomes in drug development for patients with liver disease

Ian A Rowe

Leeds Institute for Data Analytics
University of Leeds
Leeds, UK

Address for correspondence:

Dr Ian A Rowe MBChB, MRCP(UK), PhD
Leeds Institute for Data Analytics,
Room 6.1, Clinical Sciences Building,
University of Leeds,
St. James's Hospital,
Leeds.
LS9 7TF
Email i.a.c.rowe@leeds.ac.uk
Telephone: +44 (0)113 206 5667
Twitter: @IanARowe

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Tables 1

Standfirst

Surrogate endpoints are often used in clinical trials where the time to clinical outcomes is long. In patients with liver disease these surrogate outcomes are rarely validated. Without validation, there are predictable consequences to patients participating in the clinical trials and those exposed to drugs after licensing.

Surrogate outcomes are often used to identify the benefits of treatment without the need to wait for an improvement in clinical outcomes.(1) The development and validation of surrogate outcomes requires two steps: first, identification of an association between the surrogate and a relevant clinical outcome; and second, confirmation that the treatment intervention's effect on the proposed surrogate accurately predicts the treatment's effect on the relevant clinical outcome in a clinical trial setting. It has been argued that for patients with liver disease, the interval between treatment and clinical outcomes of liver disease (i.e. liver failure or the development of hepatocellular carcinoma) is too long and surrogate endpoints must be used instead.

Perhaps the best-known surrogate in hepatology is the sustained virological response in the treatment of hepatitis C virus (HCV) infection. Seemingly straightforward since it indicates cure of infection, even this outcome measure has been criticised. This has prompted a debate regarding the effectiveness of directly acting antivirals (DAAs) for the treatment of HCV and has highlighted the issues surrounding the use of surrogate endpoints in clinical trials for patients with liver diseases.(2) These issues include difficulties in defining the magnitude of clinical benefits with treatment, determining the impact of confounding variables in the analysis of benefit of uncontrolled studies of antiviral treatments, and the impact of competing causes of mortality in the extended follow-up that would otherwise be required to identify benefit. This final issue is of relevance in trials of DAAs where a significant proportion of liver disease mortality is driven by alternative causes of liver disease, most notably alcohol. It is also of paramount importance in trials of novel therapeutics for patients with non-alcoholic fatty liver disease (NAFLD) where there is the ongoing risk of mortality due to coronary heart disease mortality and non-liver cancer, even if liver disease progression is halted.

Surrogate outcome measures in drug development for non-alcoholic fatty liver disease

Early drug development

In early phase drug development, clinical studies have often focused on improvements in aspects of the NAFLD activity score (NAS).(3) This score identifies the histological severity of non-alcoholic steatohepatitis (NASH) and an improvement in NAS has been seen as a key signal in the progression of treatments to Phase 3 clinical trials (**TABLE 1**). Whilst it is biologically plausible that the degree of liver injury defined by the presence and severity of NASH is associated with fibrosis progression, the weight of epidemiological evidence supports the severity of fibrosis as being the principal driver of clinical events.(4, 5) Most importantly of all however, there

are no data that suggest that an improvement in NAS following treatment predicts improvements in clinical outcomes for patients.

More recently there has been a move to assessing improvements in liver fibrosis in relatively short duration (compared with the natural history of liver disease) studies ranging from 24 to 48 weeks.(6, 7) This seems a more direct surrogate of likely clinical benefit since it is liver fibrosis that is the greatest risk factor for liver-related mortality. The reliability of assessing changes in liver fibrosis over short periods remains to be proven in the context of NAFLD but in the rush to reach the market, several phase 3 studies (**TABLE 1**) are now using that abbreviated time frame to expedite reporting.

Late stage clinical trials

There is a perception that pharmacological treatments are urgently required for patients with NAFLD/NASH. Consequently, there is agreement with the Food and Drug Administration (FDA) that treatments developed for NASH might receive conditional approval if they meet early endpoints that assess resolution of NASH using NAS or if they show improvements in liver fibrosis.(8)

To gain final regulatory approval treatments must show clinically relevant benefits. Liver related events will be most frequent in patients with cirrhosis at baseline however only one of the ongoing phase 3 studies includes that patient population (**TABLE 1**). The selected endpoint in the remaining ongoing Phase 3 studies is a composite of overall mortality, the development of cirrhosis, and liver related events including hepatic decompensation and the development of hepatocellular carcinoma. Of these three events that comprise this composite endpoint, the development of cirrhosis is likely to be the most frequent by far since overall mortality will likely be low in a highly-selected trial population and liver related events by and large will follow the diagnosis of cirrhosis in the trial setting. For this reason, cirrhosis is itself still a surrogate endpoint. Critically, patients with NAFLD and NASH are at substantial risk of mortality from other causes. Whilst individuals with advanced fibrosis and cirrhosis carry the greatest risk of complications of liver disease, even amongst patients developing cirrhosis during follow-up, liver related death is less frequent than death from coronary heart disease and non-hepatic malignancy.(5, 9)

Predictable outcomes of the use of surrogates for drug development in NAFLD

The devotion to surrogate outcomes has four main predictable adverse outcomes in drug development in NAFLD. Firstly, the reliance on NAS, an unvalidated surrogate outcome, may have led to the advancement of therapeutics to late stage clinical trials that have no impact on the clinical outcomes of patients with NASH. These development false positives are costly both to industry as well as to patients enrolled in later phase 3 clinical trials that require repeated interventions that carry risk, including liver biopsy. Secondly, the use of this surrogate may also have led drug developers to discard drugs that may have been useful if a more appropriate

outcome measure had been used in clinical trials. Thirdly, if a drug in phase 3 trials does reach the composite clinical endpoint and identify a benefit to treatment largely through a reduction in the incidence of cirrhosis, inevitably the real clinical benefit of treatments for NAFLD will be less, and likely substantially less, than those predicted as a consequence of the competing mortality risk. Finally, selection of an endpoint that includes progression to cirrhosis denies the possibility of treatment to those with cirrhosis, those who are in greatest need of treatment and will question the applicability of treatment to that important patient group post-licensing.(10)

Clinical trial design for the future

It is imperative that hepatology learns from the lessons of surrogate endpoint use in drug development for HCV. Surrogate outcome measures in drug development in NAFLD need to be validated, and the role of the development of cirrhosis as a surrogate measure needs to be evaluated. It may be that the ongoing phase 3 trials will begin to address validation of these surrogates and extended follow-up studies of the trial populations should be mandated to maximise the natural history data that are collected.

In many ways however, trials of therapeutics in NAFLD are more analogous to primary prevention studies in cardiovascular disease than they are to antivirals for hepatitis infections. Given the estimated population prevalence of NAFLD resembles that of coronary heart disease it should be possible to recruit to large scale clinical trials of patients at high risk of liver related events that do not rely on improvements in liver histology or the development of cirrhosis as the primary outcomes but rather identify the patient relevant benefits of treatment, such as prevention of hepatic decompensation, hepatocellular carcinoma, and ultimately improvement in survival. This is what was required for licensing of treatments for primary prevention of cardiovascular disease and this should be the standard for assessing proposed treatments for NAFLD and NASH.

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Drug	clinicaltrials.gov identifier	Phase 2 signal	Key inclusion criteria	Conditional licensing		Full licensing		Number to be enrolled
				Primary endpoint	Timeframe	Primary endpoint	Timeframe	
Obeticholic acid	NCT02548351	Primary endpoint >2 point reduction in NAS Secondary endpoint Improvement in fibrosis by 1 stage	NASH + stage 2 or 3 fibrosis	Co-primary: Improvement in fibrosis ≥ 1 stage without worsening of NASH OR resolution of NASH without worsening of fibrosis	18 months	Composite including all-cause mortality, progression to cirrhosis and liver-related morbidity	Pre-specified number of events, estimated 6 years	2000
Elafibrinor	NCT02704403	Primary endpoint Resolution of NASH in a subgroup with NAS $\geq 4^a$	NASH (NAS ≥ 4) + stage 1-3 fibrosis	Resolution of NASH without worsening of fibrosis	72 weeks	Composite including all-cause mortality, progression to cirrhosis and liver-related morbidity	Pre-specified number of events, estimated 4 years	2000
Cenicriviroc	NCT03028740	Secondary endpoint Improvement in fibrosis without worsening of NASH	NASH + stage 2 or 3 fibrosis	Improvement in fibrosis ≥ 1 stage without worsening of NASH	12 months	Composite including all-cause mortality, progression to cirrhosis and liver-related morbidity	Pre-specified number of events, estimated 5 years	2000
Selonsertib	NCT03053050	Safety endpoints only May reduce liver fibrosis ^b	NASH + stage 3 fibrosis	Improvement in fibrosis ≥ 1 stage without worsening of NASH	48 weeks	Composite including all-cause mortality, progression to cirrhosis and liver-related morbidity	240 weeks	800
Selonsertib	NCT03053063	Safety endpoints only May reduce liver fibrosis, ^b not tested in cirrhosis	NASH + cirrhosis	Improvement in fibrosis ≥ 1 stage without worsening of NASH	48 weeks	Composite including all-cause mortality and liver-related morbidity	240 weeks	800

^a Per protocol analysis.

^b Trial designed to identify possible efficacy of selonsertib, directionality of effects only described using 95% confidence intervals.

Table 1. Characteristics of ongoing placebo controlled phase 3 trials for treatments for NASH.