Review

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Endpoints and patient stratification in clinical trials for alcoholic hepatitis

Philippe Mathurin[1], Mark Thursz[2,*]

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Summary

In some areas of medicine the clinical development pathway through phase II and III clinical trials has been well mapped out and refined through extensive experience. In contrast, a number of key questions remain unanswered in the development of novel therapeutics for alcoholic hepatitis. The use of mortality as an endpoint in phase II clinical trials will potentially restrict the appeal of this therapeutic area for pharmaceutical companies, as the number of patients required for adequately powered clinical trials becomes impractical. Herein, we discuss alternative endpoints and conclude that dynamic assessment of liver function is the most pragmatic option in early stage studies. Stratification based on disease severity should be applied to avoid uneven distribution of patients with substantially differing mortality risks. Consensus on early phase trial design would help to facilitate new therapeutic development in this area of high unmet medical need.

[1]*Service des Maladies de l'Appareil Digestif, PU-PH, Hôpital Claude Huriez, 1er étage- Aile Est, Rue Michel Polonovski, 59037 Lille Cedex, France*;
[2]*Digestive Diseases Division, Department of Surgery & Cancer, Imperial College, London W2 1NY, United Kingdom*

Introduction

Alcoholic hepatitis is the most florid presentation of alcohol-related liver disease characterised by recent onset jaundice and hepatic failure.[1] Alcoholic hepatitis invariably develops after prolonged periods of alcohol excess and often occurs after a recent bout of increased consumption. Severe alcoholic hepatitis, characterised by a discriminant function score (DF) ≥32, carries a high short-term mortality risk: 15–20% at 1 month and 30% at 3 months.[2]

Current options for specific treatment of alcoholic hepatitis are inadequate. Corticosteroids, the only class of drug currently recommended, are associated with a modest reduction in mortality at 28 days but no therapeutic benefit at 3 months or beyond.[3] Furthermore, corticosteroids are not indicated in patients with unresolved infection or gastrointestinal haemorrhage. Therefore, whilst there is a clear unmet need for new drug therapy in alcoholic hepatitis there is relatively little pharmaceutical investment in this therapeutic area. One of the major disincentives to pharmaceutical drug development is the lack of a clear clinical evaluation pathway and lack of consensus around endpoints and stratification in clinical trials.

Key points

The endpoints currently being used or considered for trials in alcoholic hepatitis are mortality, improvement in liver function and histological resolution.

Endpoints

Endpoint selection in clinical trials in alcoholic hepatitis is not as obvious as it may seem at first glance. The endpoint contenders include mortality, improvement in liver function or histological resolution.

Mortality

In many areas of medicine generally, and hepatology specifically, the endpoints in clinical trials are frequently surrogates for clinically meaningful outcomes such as survival or cure. The choice of endpoints is made around practical considerations such as the duration of a study. As many hepatological conditions progress to cirrhosis, decompensation or death over decades, trials lasting months or years cannot be expected to compare the event rates for these clinical endpoints. Surrogate endpoints which accurately predict future clinical events are frequently accepted as trial outcomes and this is well exemplified in primary biliary cholangitis where trial endpoints based around changes in serum alkaline phosphatase measurements have been accepted by regulatory authorities.[4]

In alcoholic hepatitis we have the opposite problem as short-term mortality rates are relatively high, but there is no acceptable surrogate which could realistically replace mortality. The reason this is important is that as mortality rates in severe alcoholic hepatitis fall the number of patients required to give trials adequate statistical power is potentially too high for phase II studies. In recent trials the mortality rate in patients with severe alcoholic hepatitis has been around 20% at 1 month (or 28 days) and 30% at 3 months.[2] If a new drug has a reasonable effect size (measured as the odds ratio) of 0.80, then in a double-blind trial with standard of care as the comparator, 300 patients would need to be recruited in each arm. Larger estimates for effect sizes would reduce the number of patients required to achieve the statistical power, but these are unlikely to be realistic. Large scale trials of this magnitude are undoubtedly required in phase III trials but cannot be justified at earlier phases.

Use of mortality as an endpoint is further complicated by selection of the timepoint at which mortality is measured. For over 40 years mortality at 28 days or 1 month has been the 'gold standard' for trials in severe alcoholic hepatitis. There is now a widely held consensus that 28 days is too early to assess the impact of intervention.[5] Concern about this early timepoint is based on the lack of resolution of alcoholic hepatitis at 28 days in many patients despite enforced abstinence from alcohol. In addition the adverse effects of treatment may persist and influence mortality after this time.[6] Measuring mortality rates at 6 or 12 months is appealing, as these timepoints represent a medium-term survival. However, a number of studies have now demonstrated that return to alcohol consumption is the greatest determinant of mortality at these timepoints.[7] Mortality measured at 3 months is therefore recommended as the optimal endpoint in phase III clinical trials.

Improvement in liver function

The goal of treatment in patients with alcoholic hepatitis is to restore liver function in order to avoid the risks of infection, acute kidney injury and acute-on-chronic liver failure, which may lead to death. Assessment of residual liver function is readily achieved using individual biochemical or coagulation parameters or by using combinations of laboratory and clinical parameters in scoring systems such as Maddrey's discriminant function (mDF), model for end-stage liver disease (MELD), ABIC (age, serum bilirubin, international normalized ratio, serum creatinine), United Kingdom end-stage liver disease or Glasgow alcoholic hepatitis score.[8] A change in serum bilirubin over the course of the first week of admission with alcoholic hepatitis or in response to treatment with prednisolone is strongly associated with the risk of mortality; an early reduction in bilirubin predicts survival.[9] Dynamic scoring systems, exemplified by the Lille score which combines baseline variables with the change in bilirubin at 7 days therefore provide a good prognostic system.[10] Using the Lille system, a score of <0.45 identifies a group of patients with a 3-month survival of 80% and a score of >0.56 predicts a mortality rate of 70%. This level of discrimination is not sufficient to be considered as a surrogate endpoint for phase III trials but might be considered as an endpoint in phase II studies. Combining the MELD and Lille scores is an interesting approach to improve prediction of survival. Indeed, combining static (Maddrey, MELD, ABIC) and dynamic scores is more discriminating than each score alone and is also more accurate in predicting survival in patients treated with placebo.[11] Combining static and dynamic models provides a continuum for the prediction of mortality risk with more useful information for study design.

Development and evaluation of new molecules targeting liver regeneration is an additional rationale for using changes in liver function as an endpoint in clinical trials. Regeneration of functional hepatocytes is recognised as a key process in the recovery from alcoholic hepatitis and is markedly impaired in patients who die from the disease. Targeting regeneration using IL-22 is already under evaluation in clinical trials.[2,12]

There are a number of reasons why patients with a good Lille score may subsequently die. Improvement of liver function does not immediately restore the immune paresis which characterises patients with alcoholic hepatitis. Furthermore, treatment with corticosteroids increases susceptibility to infection.[6] An episode of sepsis is inevitably followed by a rapid deterioration in liver function and other complications. Similarly, as alcoholic hepatitis is frequently accompanied by portal hypertension, an episode of variceal haemorrhage may rapidly change an apparently good prognosis.

Evaluation of novel therapeutics for alcoholic hepatitis is likely to require a high degree of sophistication. Whilst restoration of liver function is an important objective, in order to achieve survival improvements candidate drugs should not increase the risk of complications. As we consider alcoholic hepatitis to be an inflammatory condition, the use of drugs which suppress immune responses is inevitable and the risk of increased susceptibility to infection is high.

At present there is no readily accessible test to measure immune paresis or how it changes in response to treatment apart from measuring the incidence of infection. We already recognise a number of defects in the immune system of patients with alcoholic hepatitis and inevitably more will emerge. Therefore, it is unlikely that a single test for immune paresis will emerge in the foreseeable future. Thus, it is worth considering that in early phase trials endpoints focussed on restoration of liver function should take priority and strategies to address susceptibility to infection may develop independently. For instance, the approach of using prophylactic antibiotics in combination with prednisolone is currently being evaluated in the Anti-BioCor trial in France (NCT02281929).

Whilst strategies may emerge to counteract increased susceptibility to infection, it is inconceivable that a drug which failed to improve liver function would influence mortality or progress to phase III trials.

Development plan of future drugs from phase I to phase III studies

A consensus between experts and health agencies is required to propose and validate the requirements of study designs for phase I to phase III trials. Such consensus needs a clear definition of

Key points

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* Corresponding author.
Address: Digestive Diseases Division, Department of Surgery & Cancer, Imperial College, London W2 1NY, United Kingdom.
E-mail address: m.thursz@imperial.ac.uk (M. Thursz).

Box 1. Secondary endpoints in clinical trials. MELD, model for end-stage liver disease.

- Drug safety
- Incidence of ascites, encephalopathy or variceal haemorrhage
- Incidence of infection
- Incidence of acute kidney injury
- Changes in liver function (*e.g.* using MELD)
- Changes in performance status and/or quality of life
- Duration of hospitalisation
- Abstinence after discharge

Key points

It is important to stratify patients based on the factors which are most likely to influence survival and therefore confound the study results.

disease, a rational evaluation of severity to calculate sample size, the choice and validation of endpoints, the development and the correct assessment of surrogate markers of outcome.[5] It may be assumed that the study design of phase I-II trials would need to focus on patients with a minimal competitive risk of mortality to ensure sufficient exposure time of the tested drugs. The issue of histological diagnosis of disease will need to be considered, at least in proof of concept studies (phase I or II studies), when considering the risk of false positive inclusions that may impact the statistical hypothesis by increasing the risk of type I and type II errors, because the outcomes of patients without alcoholic hepatitis may not be affected by molecules targeting the pathways driving alcoholic hepatitis. For phase III studies, as many experts do not consider liver biopsy as a prerequisite, a strategy aiming to decrease the risk of misclassification as proposed by the NIAAA consortium is mandatory. For future phase III studies, experts may propose to include only patients with definite alcoholic hepatitis (both clinical and histological documentation) or patients with probable alcoholic hepatitis (typical liver biochemistry in the absence of confounding variables).[5]

It therefore seems reasonable to propose that phase II trials use a measure of liver function as a primary endpoint. At present we would recommend either the early change in bilirubin, the Lille score or the joint-effect model combining MELD and the Lille scores that may be used in future trials irrespective of the use of corticosteroids. Study design may consist of the administration of the tested molecule during a leading phase of 7 days, after which patients identified with a low predicted risk of death may be maintained on the tested molecule. Conversely, therapeutic strategies involving a switch to or add-on of corticosteroids may be proposed for those with a higher predicted risk of death than that planned in the study design.

Table 1. The association between disease severity scores and mortality in the STOPAH study.

Score	Cut-off	28-day mortality	90-day mortality
MELD	<25	9.3%	16.0%
	≥25	25.5%	40.4%
ABIC	<6.71	2.3%	5.8%
	≥6.71	17.8%	29.5%
GAHS	<9	7.6%	15.1%
	≥9	25.1%	38.4%

ABIC, (age, serum bilirubin, serum creatinine, international normalized ratio); GAHS, Glasgow alcoholic hepatitis score; MELD, model for end-stage liver disease.

Histological improvement

Alcoholic hepatitis characteristically develops on the background of steatohepatitis with additional histological features such as mega-mitochondria and bilirubinostasis.[13] Successful resolution of alcoholic hepatitis is therefore expected to involve marked improvement in the histological features of the disease. It could also be envisaged that an effective treatment could result in histological improvement even if blood-based tests fail to show improvements because of complications such as infection. To date no trial has relied on histological changes as a primary endpoint, but the histological response, correlated with other outcome measures, would be highly informative for the evaluation of novel therapeutic agents. Histological improvement cannot currently be linked directly to reduction in mortality, so this endpoint should only be considered in phase II trials.

Secondary endpoints

A number of outcomes are important to assess in trials of alcoholic hepatitis irrespective of whether mortality is selected as a primary endpoint. Key secondary endpoints are listed (Box 1).

Stratification

Stratification is a method used in clinical trials to avoid uneven distribution of patients with strong positive (or negative) prognostic features between trial arms. Age is one of the factors influencing survival in alcoholic hepatitis. Consequently, it could be envisaged that if all the elderly patients were accidentally randomised to the treatment arm of a placebo-controlled trial then the trial might erroneously report that the treatment was ineffective. From a statistical perspective it is difficult to consider more than 3 stratification factors, even in large clinical trials. In smaller trials, 2 stratification factors are the maximum that can be realistically considered. In practical terms, the selection of stratification factors should therefore be based on the strength of prognostic impact.[14]

Disease severity scores

In the STOPAH trial, which recruited patients with a DF ≥32 the mortality rates varied substantially depending on the baseline disease severity score as demonstrated in Table 1.[15]

Randomisation could theoretically generate an adverse distribution of disease severity, which would markedly influence the outcome of the trial. Stratification by disease severity would reduce, though not completely eliminate this risk.

Selection of patients for treatment based on discriminant function may now be outdated as recent studies suggest that MELD, ABIC and GAHS provide a more accurate prediction of mortality.[8] Trials of steroid therapy using 'modern scoring systems' to define moderate alcoholic hepatitis have not yet been conducted, whereas trials guided by discriminant function showed no benefit of treating moderate alcoholic hepatitis with prednisolone. Nevertheless, a consensus is now building to guide therapy based on an MELD cut-off >20.

Risk of infection

Infection is one of the key complications of alcoholic hepatitis.[6,16] Approximately 30% of patients will have evidence of infection at the time of presentation with alcoholic hepatitis – classified as baseline infection. In addition, a further 25–30% of patients will develop infection after admission or initiation of treatment – classified as incident infection. Baseline infections, assuming they are well treated, do not influence survival probability. However, incident infections, particularly in patients taking corticosteroids, are associated with rapid clinical deterioration and increased risk of mortality.[6] Prediction of incident infection is challenging. The main risk factor is disease severity, which is therefore covered by stratification based on severity scores. In addition it has been shown that markers of bacterial translocation or circulating bacteria such as 16S-ribosmal DNA (16S-DNA) and lipopolysaccharide (LPS) are associated with the risk of incident infection, systemic inflammatory response syndrome and multi-organ failure.[6,17] Further studies on the sensitivity and specificity of 16S-DNA and LPS are required before these biomarkers are ready for deployment as stratification variables.

Centre

It is a widely held and rational belief that the survival from alcoholic hepatitis is influenced by the hospital and clinicians who provide the patient care. This is true of a number of different conditions and whilst it may be true in alcoholic hepatitis, there is currently no published data to support this assertion. Furthermore, perceived variation in patient outcomes may be determined by the distribution of disease severity observed in the hospital admissions rather than by the standard of care provided. Although stratification by centre is frequently advocated in clinical trials in liver disease it is not necessarily justified by currently available data.

Trials in patients with moderate alcoholic hepatitis

Although severe alcoholic hepatitis is, by consensus, defined by a discriminant function ≥32 there is no formal definition of moderate alcoholic hepatitis. Nevertheless, patients who are admitted to hospital with alcoholic hepatitis who have a discriminant function <32 may still be subject to a mortality risk of around 6% in the subsequent 3 months.[18–19] Furthermore, the exacerbation of the inflammatory liver disease associated with an episode of alcoholic hepatitis is likely to aggravate liver fibrosis and portal hypertension, leading to increased risk of decompensation in the medium to long term. This group of patients is rarely considered for inclusion in clinical trials as the efficacy of corticosteroids was ruled out in a number of clinical trials more than 3 decades ago. Currently these patients are offered best supportive care and treatment of the underlying alcohol use disorder. Whilst corticosteroids clearly provide no benefit for this group, novel therapeutic interventions might be expected to reduce the length of hospital stay, progression of fibrosis, complications of portal hypertension and mortality.

It is not realistic to design trials in moderate alcoholic hepatitis where the endpoint is mortality as the number patients required to demonstrate benefit is unfeasibly large. In this group of patients, the most pragmatic endpoint for clinical trials would be improvement in liver function measured using change in bilirubin, MELD, ABIC or Lille. Long term follow-up of these patients should be undertaken to document whether treatment influences the risk of decompensation.

Conclusion

Progress in the development of new therapeutics for alcoholic hepatitis will be impaired unless the design of future clinical trials is refined. It is clear that the mortality rate at 3 months is now accepted as the choice of primary endpoint in phase III clinical trials, but this endpoint should not be considered a requirement in phase II studies. Stratification according to disease severity should help to control for the large variation in observed mortality between groups. Alternative stratification variables will need further validation prior to deployment in trial design. Developing a consensus on how best to approach early phase trial design will help to facilitate therapeutic development in alcoholic hepatitis, which is crucial to tackling the high unmet medical need of patients.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Both authors contributed equally to the design and content of this manuscript.

Supplementary data

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