Review

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Alcohol-related liver disease: Areas of consensus, unmet needs and opportunities for further study ☆,☆☆

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Summary

A joint meeting of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) was held in London on September 30 and October 1, 2017. The goals of the meeting were to identify areas of broad agreement and disagreement, develop consensus, and determine future directions to ultimately reduce the burden, morbidity, and mortality of alcohol-related liver disease (previously termed alcoholic liver disease). The specific aims of the meeting were to identify unmet needs and areas for future investigation, in order to reduce alcohol consumption, develop markers for diagnosis and prognosis of disease, and create a framework to test novel pharmacological agents with pre-specified treatment endpoints.

Keywords: ALD; Alcohol; Epidemiology; Endpoints; Public health; Unmet needs; Biomarkers; Clinical trials.

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Epidemiology, addiction, diagnosis and disease progression factors in alcohol-related liver disease

Epidemiology

Worldwide, approximately 2.4 billion people consume alcohol, with 1.5 billion (1.4–1.6) current male drinkers and 0.9 billion (0.8–1.0) current female drinkers.[1] Globally, approximately 2 million people die of liver disease each year, and up to 50% of mortality with cirrhosis is attributable to alcohol. Alcohol-related liver disease represents one of the top 30 causes of death in recent studies on the global burden of disease. In 2010, the worldwide rate of alcohol-attributable cirrhosis death was 7.2 deaths per 100,000 people (4.6 in females and 9.7 in males).[2]

Total per capita consumption of alcohol varies from continent to continent, from country to country within a continent, and from region to region within a country. As an example, total per capita annual consumption is at about 10 L/adult in the US, 12–13 L in France, 11–12 L in the UK, 7–8 L in Italy and 11–13 L in Eastern Europe, whereas it is only 0–2 L in North Africa/Middle East.[3]

Regardless of the variation from country to country, liver-related death rates correlate with alcohol consumption in a given country. For example, a decrease in overall alcohol consumption in the wine-drinking countries of southern Europe has driven reductions in cirrhosis mortality rates, whereas a substantial increase has been observed in the UK for both men and women.[4] Despite the high global burden of mortality due to alcohol-related liver disease, both in terms of number of deaths and in terms of years of life lost, the estimates may actually underrepresent the true burden of disease. Because of this, international comparisons of the burden of alcohol-related liver disease are problematic and often unreliable. Indeed, much of this information relies on coding of death certificates. An example of coding errors includes a lack of willingness of many providers to attribute cirrhosis death to alcohol. This may lead to significant under-reporting of alcohol-related liver disease, especially alcohol-related cirrhosis. It is also unknown whether the risk of alcohol-related liver disease depends on the type of alcohol imbibed, whether alcohol is consumed with foods or on an empty stomach, whether certain foods are protective, and whether binge drinking clearly confers a higher risk. The severity of alcohol-related liver disease in all its stages is potentiated by obesity, but genetic risk factors for both alcohol misuse and alcohol-related liver disease are unclear (Table 1).

Public health policy relating to alcohol-related liver disease

Given the link between alcohol consumption and alcohol-related liver disease, it follows that public health policy substantially influences mortality rates. In fact, public policies are more effective than education and approaches at the individual level. The dominant strategies for public intervention include pricing and marketing,[5] with price being the single strongest driver of alcohol use. When pricing rises, alcohol consumption and alcohol-related liver disease commensurately decrease. Conversely, when prices drop, alcohol consumption and alcohol-related death rates increase. The best approach for pricing strategies focusses on taxation. Availability can also be regulated at the government level by determining days and hours of sale and state control over outlets of sale. Simple measures to reduce alcohol consumption have been proposed, such as regular

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☆ This report summarizes the highlights of the first AASLD-EASL Joint Conference on Alcohol-related Liver Disease and Alcoholic Hepatitis. See Appendix for the full list of all speakers from the Conference.

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Table 1. Epidemiology, addiction, diagnosis, and disease progression factors.

Areas of consensus
Public policy: Price availability and marketing are the best tactics to manage alcohol consumption at society level. Government policies are necessary to regulate marketing promotions via sports sponsorship, use of internet and social media, specifically those promotions that target vulnerable populations such as young individuals. Increasing consumption of alcohol amongst younger women is recognised as a public health concern as this population is at increased risk of development of ALD. It is essential that this population be an important focus of alcohol reduction measures
Health policies aiming to reduce per capita consumption should be emphasised to reduce the burden of ALD
As with diabetes, national health policies should not only consider primary intervention to decrease alcohol use but should integrate in their plan secondary or tertiary interventions aiming to prevent development of ALD and its complications in patients with alcohol use disorder
Heavy alcohol consumption alongside obesity leads to adverse consequences.
Alcohol rehabilitation should begin in hospital for patients with AH, while addiction trials should activate at time of discharge
Surveillance for advanced hepatic fibrosis or cirrhosis with non-invasive methods should be promoted in patients with excessive alcohol consumption.
Policies are not uniform regarding early liver transplantation for patients with severe AH not responding to medical therapy. Societies need to establish guidelines for liver transplantation for AH based on local legislation framework
Unmet needs and opportunities for future study
Pharmacologic therapy for AUD in patients with ALD
Define parameters for non-invasive imaging of the liver in patients with AUD
Define subsets, predictors of outcome in patients with combined AH/NASH
Epidemiological studies on the burden of AH
Which team member should primarily manage the patient with AUD/ALD
Ideal endpoints for AUD/ALD addiction trials
Non-invasive staging approach in patients with AUD/ALD
Best serologic nomogram for determining AH disease severity (MDF, MELD, *etc.*)
Role of liver biopsy in AH
Safe level of alcohol consumption in patients with NASH

AH, alcoholic hepatitis; ALD, alcohol-related liver disease; AUD, alcohol use disorder; MDF, Maddrey discriminant factor; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.

incremental above inflation tax increases, a minimal price of alcohol, protecting children from alcohol marketing, and clinicians, especially primary care physicians, advising all their patients to reduce alcohol consumption.[5] Finally, government can also regulate a number of marketing features, including the prevention of targeting selected vulnerable populations such as young individuals and banning sports sponsorship. Despite these tools that government possesses to influence alcohol consumption, there are a number of counter-regulatory goals and lobbying initiatives that combat the effectiveness of government regulations. A summary of the goals and aims to reduce alcohol consumption is provided in Table 1.

Alcohol use disorder

Alcohol use disorders represent a chronic and relapsing disease which affects nearly 1 in 10 individuals of the general population in the Western world. Given that continued alcohol consumption after the onset of liver disease increases liver-related morbidity and mortality, the ideal focus of treatment in these patients is long-term abstinence and prevention of relapse. There is strong evidence that the most effective strategy to reduce alcohol intake, promote abstinence, and prevent relapse at the individual level is the combination of psychosocial and pharmacologic intervention.[6] One of the few randomised controlled trials comparing modes of psychosocial therapy specifically in patients with alcohol-related liver disease supported the use of motivational enhancement therapy, although other counselling approaches are also widely utilised.[7,8] A number of medications have been approved for treatment of alcohol use disorders including disulfiram, naltrexone, nalmefene, and acamprosate.[9] Additional drugs are also under intense investigation, including topiramate, ondansetron, and baclofen.[10] However, a major limitation is that most of these drugs have not been tested in patients with alcohol use disorder who also have advanced liver disease. The medication with the strongest evidence for effectiveness and safety in this group of patients is baclofen given that this is the only anti-craving medication formally tested in randomised controlled trials in patients with alcohol use disorder and cirrhosis.[11]

Baclofen has been approved in some countries, but has not received FDA approval for this indication in the US. Thus, a major unmet need is further validation of a pharmacologic intervention for patients with alcohol use disorders and cirrhosis. Further complicating this issue is the lack of proper care models in many parts of the world (*e.g.*, patients with alcohol use disorder and cirrhosis fall in the gap between addiction specialists and hepatologists). Another unmet need is a reliable and discrete remote monitoring and/or digital health solution for ascertaining alcohol consumption. Nonetheless, screening for alcohol-related liver disease in high risk populations is recommended at the primary care level. Based on recent evidence screening strategies have been proposed for alcohol-related liver disease in at-risk populations, although validation is required (Table 1).[12]

Co-factors and genetics

Progression and prognosis of alcohol-related liver disease is influenced by important co-factors, most notably, fatty liver disease due to metabolic syndrome and viral hepatitis. Indeed, there has been

a progressive rise in the prevalence of obesity and of type II diabetes in the general population and alcohol-related liver disease is frequently superimposed on obesity. Recent population-based studies have found that obese individuals who consume alcohol may have a greater likelihood of having hepatic steatosis. Furthermore, obesity may negatively impact alcohol-related liver disease progression and prognosis. These observations suggest that there are additive and/or synergistic interactions of variables associated with non-alcoholic fatty liver disease (NAFLD) in combination with variables associated with alcohol-related liver disease, most notably the amount of alcohol consumption. This has led to recommendations to curtail alcohol use in individuals with non-alcoholic steatohepatitis (NASH) and conversely to manage weight and risk factors for NASH in individuals with alcohol-related liver disease. Though small studies have suggested there may be potential beneficial effects of low levels of alcohol consumption in individuals with NASH, the majority of studies showing a benefit of low levels of alcohol consumption are focused in healthy individuals. In a recent study, alcohol use ≥210 g/week for men and ≥140 g/week for women were associated with a higher risk of severe complications of liver disease in the general population.[13] The interaction between alcohol consumption and obesity is clearly an area that needs further investigation. Another co-variable is non-hepatic comorbidity that is increasing in patients with alcohol-related liver disease.[14] Indeed, a recent analysis of electronic medical records demonstrate that the Charlson comorbidity index has increased substantially over the last decade and that patients in the US presenting with alcoholic hepatitis are older and more likely to have multiple systemic comorbidities such as chronic obstructive pulmonary disease.[14] This may also adversely affect the prognosis of alcohol-related liver disease. However, there are positive co-factors to consider as well. For example, coffee drinking has been shown to be protective in alcohol-related liver disease although this requires much more detailed investigation before application can be proposed.[15] There may also be microbiome characteristics
that afford protection of more severe prognoses in patients with alcohol-related liver disease.

There is now increasing evidence that supports a genetic basis for alcohol-related liver disease. Since all individuals who drink in excess do not develop liver disease there is clearly a genetic risk in alcohol-related liver disease. The genetic loci that have been best studied and validated include *PNPLA3*, *TM6SF2*, and *MBOAT7*.[16,17] It is important to note that these genetic profiles are distinct from other genetic loci, which may predispose towards alcohol misuse as aforementioned loci focus on liver injury in response to alcohol consumption. The allelic risk conferred by these genetic variants is approximately 2.5-fold, which is surprisingly high for a genetically-complex disorder such as alcohol-related liver disease, and may reflect biases in the choice of the control groups.[16] Interestingly, all 3 of these mutations are also risk factors for NAFLD/NASH and all 3 genes are "lipid genes".[18] For example, PNPLA3 is a triglyceride lipase, while TM6SF2 plays a role in very low-density lipoprotein lipidation, and MBOAT7 is a lysophosphatidylinositol acyltransferase.[18] It may be that PNPLA3 is most relevant for steatosis and hepatocellular cancer in alcohol-related liver disease, while TM6SF2 is relevant for inflammation and fibrosis progression in hepatocellular cancer, and MBOAT7 is most notable for fibrosis progression.[16] However, this hypothesis needs further validation. Most recently, a splice variant encoding a lipid droplet protein was associated with a reduced risk of progression from steatosis to hepatitis.[19] Future studies will hopefully allow us to "individualise" care for patients with alcohol-related liver disease based on genetic predispositions, especially if "druggable" targets can be developed for the phenotypic alterations associated with the genetic profiles (Table 1).

Alcohol-related liver disease

Alcohol-related liver disease covers a spectrum including fatty liver disease, alcoholic hepatitis, and cirrhosis and its complications. The type and severity of steatosis and extent of fibrosis are independent predictive factors of fibrosis progression and the highest risk of disease progression is observed in heavy drinkers with alcoholic hepatitis.[20–23] Approximately 3% of patients with alcoholic hepatitis progress to cirrhosis annually. Epidemiological data show a strong correlation between severity and duration of alcohol abuse and the presence of cirrhosis. Among a cohort of 6,970 adults from a general population, the rate of cirrhosis was significantly higher in patients who consumed ≥30 g/day than among abstinent controls or those with consumption <30 g/day (2.2% *vs.* 0.08%). Individuals with alcohol consumption >120 g/day had the highest risk of cirrhosis (around 13.5%[24]).

Epidemiological data focussing on alcoholic hepatitis are sparse. In Denmark, from 1999 through 2008, the incidence of alcoholic hepatitis increased from 37 to 46 per million for men and from 24 to 34 per million for women. The increase in alcoholic hepatitis paralleled the increase in alcohol consumption.[25] In the US, alcoholic hepatitis-related hospitalisation increased from 249,884 in 2002 to 326,403 in 2010.[26] The cost of each hospitalisation increased by 40.7% in 2010 compared to 2002 after adjustment for inflation over this period.[26] Outside of these studies, information on the burden of alcoholic hepatitis is missing and future epidemiological studies should focus on evolution of the burden of alcoholic hepatitis, including less severe disease.

The most dramatic presentation of alcohol-related liver disease is alcoholic hepatitis which manifests as rapid onset of jaundice and, in severe

forms, may lead to acute-on-chronic liver failure with hepatic and extrahepatic organ failure, and mortality of around 30% at one month. However, a symptomatic form of disease is also recognised where patients may be entirely asymptomatic but laboratory tests and liver biopsy show changes of steatohepatitis.

The currently accepted definition of alcoholic hepatitis is rapid onset of jaundice (bilirubin >3 mg/dl) with aspartate aminotransferase (>50 IU/ml), and aspartate aminotransferase to alanine aminotransferase ratio of >1.5 in patients with heavy alcohol use.[27] Heavy alcohol use is generally defined as more than 3 standard drinks per day for women (approximately 40 g of alcohol), and 4 standard drinks per day for men (approximately 50–60 g of alcohol). It is important to emphasise that standard drinks differ between countries. Liver biopsy remains the standard for making a diagnosis of alcoholic hepatitis though patients may be entered into clinical protocols with a clinical diagnosis, which is defined as heavy alcohol use with typical liver biochemistry and exclusion of other causes of liver disease. However, relying on clinical criteria alone may be associated with a risk of wrongly classifying patients with or without alcoholic hepatitis, while there is also interobserver variation in the assessment of alcoholic hepatitis severity on liver biopsy.

In order to decrease the risk of misclassification for future studies evaluating drugs, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) consortium has proposed 3 groups[27]: a) the most definitive diagnosis requires both clinical and histological documentation and has been referred to as *definite alcoholic hepatitis*;[27] b) in the absence of histologic confirmation but typical liver biochemistry and exclusion of confounding variables, the diagnosis is referred to as *probable alcoholic hepatitis*;[27] and c) in the absence of histology and in the presence of potential confounding variables, the diagnosis is *possible alcoholic hepatitis*.[27]

Alcoholic hepatitis may be stratified as mild, moderate, and severe. Severe alcoholic hepatitis has traditionally been defined by a Maddrey Discriminant Function (MDF) score of ≥32 that predicts mortality of up to 30% at 30 days.[28–30] Other scorings such as the model for end-stage liver disease (MELD) score, ABIC (age, serum bilirubin, international normalized ratio, serum creatinine) score,[28–30] and the Glasgow alcoholic hepatitis score[31] have also been used and may be superior to the MDF score.[32] It is unclear whether changes in any of these scores can be used as a surrogate endpoint for survival, especially with less severe alcoholic hepatitis. Since patients with an MDF ≤ 32 still have a significant risk of mortality, it has been proposed that the MELD score be used to stratify severity of alcoholic hepatitis. An MELD score ≥20 is used to define severe alcoholic hepatitis, which is associated with mortality rates of approximately 20%–40% at 90 days.[33,34] MELD scores of 11 to 20 define a group with moderately severe alcoholic hepatitis; and MELD scores ≤10 define mild hepatitis. The natural history of the mild and moderately severe groups is unclear. It is also not known whether patients with moderately severe alcoholic hepatitis who do have a mortality risk have survival benefit from abstinence alone or if pharmacological therapy is required in addition.

The Lille score is used to determine response to steroid therapy at 1 week.[35] Corticosteroids can be stopped at day 7 in non-responders (*i.e.*, those with a Lille score ≥0.56) as these patients do not benefit from continued treatment.[36] It is unknown whether the Lille score is a valid marker of treatment outcome for therapies other than corticosteroids. A combination of MELD score at baseline and Lille score at 7 days may be used to assess mortality at 2 months and 6 months and seems to be more accurate, compared with either model alone.[37]

Invasive and non-invasive diagnosis of alcohol-related liver disease

Biopsy is required to make a definitive diagnosis of alcoholic hepatitis,[38–41] but use of liver biopsy as a standard of care for diagnosis varies throughout the world. Histology is also helpful for the short-term prognosis of alcoholic hepatitis[41] and alcohol-related acute-on-chronic liver failure.[42] For example, morphological evidence of bile accumulation (*i.e.*, bilirubinostasis) is associated with the development of septic complications. Importantly, the degree of fibrosis is the main predictor of outcome in patients with compensated alcohol-related liver disease.[40] The characteristic histological findings of severe alcoholic hepatitis include macrovesicular steatosis, parenchymal inflammation with mononuclear cells and neutrophils, hepatocellular injury in the form of ballooning with abundant Mallory-Denk bodies, necrosis, and canalicular and/or ductular cholestasis. Hepatocellular ballooning is associated with deposition of collagen fibres resulting in pericellular and peri-sinusoidal fibrosis.[43,44] Most patients with symptomatic alcoholic hepatitis have underlying cirrhosis. When cirrhosis is established, histological features of alcoholic hepatitis and even pericellular fibrosis may not be prominent. While there is no "NAFLD Activity Score (NAS)" equivalent for histology of alcoholic hepatitis as has been described for NASH, the histologic features are interchangeable in the 2 conditions in most cases. However, there is usually a greater disease severity with severe ballooning, necroinflammation and neutrophils surrounding hepatocytes (satellitosis) and bilirubinostasis in patients with alcoholic hepatitis as opposed to NASH.[41] This may simply reflect the sicker nature of patients who undergo liver biopsy for alcoholic hepatitis as opposed to NASH. In addition, fibro-obliterative venous lesions and sclerosing hyaline necrosis are typical for alcohol-associated liver injury and have not been described in NAFLD/NASH to date.[43]

Given the risks, cost, and inconvenience of invasive liver biopsy there is a large focus on non-invasive efforts to diagnose and determine prognosis in patients with alcohol-related liver disease (Table 2). Non-invasive methods rely on 2 different but complementary approaches: serum biomarkers and the measurement of liver stiffness, using elastography modalities, either ultrasound- or magnetic resonance (MR)-based.[45] Among ultrasound-based approaches, transient elastography, a relatively inexpensive and widely used point-of-care test, is the most validated for detection of advanced fibrosis, better at ruling out than ruling in the diagnosis of cirrhosis.[46] However, there is no consensus on cut-offs for cirrhosis in the literature and there is a risk of false positive results in non-abstinent patients. Serum biomarkers have also been validated,[47] but do not increase diagnostic performance when combined with transient elastography.[47,48] MR-based elastography is expensive, less available, and time consuming, but possibly more accurate for steatosis and fibrosis assessment.[49] In general, unlike in patients with other aetiologies of liver disease, such as viral hepatitis, non-invasive methods are much less well validated in patients with alcohol-related liver diseases, especially in at-risk populations.[12]

Current management and treatment of alcoholic hepatitis

Management of patients should be standardised in clinical trials for optimal assessment of the impact of novel agents. Lack of standardisation may result in differences in clinical trial outcomes that are unrelated to the investigational agent. Current strategies and future directions in the management of alcoholic hepatitis are summarized in Table 2. It has been difficult to stipulate that a liver biopsy be performed to confirm the diagnosis of alcoholic hepatitis prior to starting therapy. Biopsy could also potentially enable the study of molecular pathways of hepatic injury that may inform future novel therapies. In the absence of liver biopsy, patients with "probable" alcoholic hepatitis may be treated in a similar way to those patients with biopsy-confirmed alcoholic hepatitis.

There is broad agreement that management of severe alcoholic hepatitis requires treatment of the alcohol use disorder, treatment of the risks of alcohol withdrawal and treatment of the liver disease. Management of the liver disease in turn requires reversal of the alcoholic hepatitis and treatment of complications of alcohol-related cirrhosis including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal bleeding.

Treatment of alcoholic hepatitis includes nutritional supplementation to provide adequate protein and calories. Enteral supplementation is the preferred route because of safety and the lower risk of infections. Patients only require transfer to the intensive care unit if organ support is required. The role of routine antibiotic therapy is unclear and the results of ongoing clinical trials are awaited. Since sepsis is difficult to diagnose in patients with alcoholic hepatitis, if sepsis is strongly suspected, and certainly when infection is diagnosed, broad-spectrum antibiotics should be initiated within 1 hour. The only pharmacological agents recommended for treatment of severe alcoholic hepatitis in the absence of contraindications are corticosteroids, namely prednisolone 40 mg daily or methylprednisolone, 32 mg daily

Table 2. Current management and treatment of alcoholic hepatitis.

Areas of consensus
Patients with AH and MELD <20 or MDF <32 have a mortality rate of 10% at 90 days and, therefore, cannot be considered as non-severe. It is proposed to use the term "moderate alcoholic hepatitis" for patients with AH and MELD 11–20; and mild AH with MELD ≤10
The 3-month natural history of moderate AH (MELD score 11–20) needs to be defined. It is also necessary to define whether pharmacological therapy is required for patients with moderate AH
A team approach with hepatologist, addiction specialist, nutritional expert and social work is desirable for treatment of patients with severe AH
Liver biopsy is advised prior to treatment for severe AH but is not mandatory
Inpatient management of severe AH includes:
• Nutritional assessment and optimal replacement of protein and calories
• Transfer to the intensive care unit for organ support
• Meticulous investigation for infection. When infection is diagnosed or strongly suspected, broad spectrum antibiotics should be started within 1 h
• Steroid therapy if there are no contraindications
• Lille score should be the preferred tool to access response to steroid therapy
• Liver transplantation should be offered to highly selected patients who fail medical management
Steroid therapy reduces 1-month mortality but does not impact medium term mortality. The absence of impact on medium term survival emphasises the need for newer therapies
Living donor liver transplantation should be carried out only after approval of local ethics committees and in centres with large experience and where deceased donor transplantation is not available
Unmet needs and opportunities for future study
Validation of histological endpoints as a surrogate for a clinical event
Non-invasive methods for the diagnosis of AH when considering the limitations of liver biopsy
Studies comparing long-term alcoholism behaviour of patients with early transplantation to patients undergoing transplantation after abstaining from alcohol for a 6-month period
Routine use of antibiotics in all patients with severe AH
Specific contraindications to steroids
Criteria for "futility" to exclude patients from studies

AH, alcoholic hepatitis; MDF, Maddrey discriminant factor; MELD, model for end-stage liver disease.

for 28 days. Pentoxifylline is not recommended as therapy for severe alcoholic hepatitis.

Corticosteroids are only associated with a 1-month survival benefit in about 60% of treated patients with severe alcoholic hepatitis and the benefit is not sustained over the intermediate- or long-term. Therefore, physicians may consider early liver transplantation in highly-selected patients with alcoholic hepatitis.[50–52] The United Network for Organ Sharing (UNOS),[53] the American College of Gastroenterology (ACG) Clinical Guideline[54] and the EASL Clinical Practice Guidelines on alcohol-related liver disease[45] suggest that listing a patient for transplantation should not be based only on the 6-month abstinence rule. When liver transplantation has been carried out in these highly-selected patients, survival has been excellent.[50–52,55] In terms of public opinion, a vast majority of the population of donors was not against early liver transplantation for alcoholic hepatitis.[56] Early liver transplantation should be considered in the context of ethical principles recommending active treatment of patients, without discrimination, and according to the best available scientific knowledge.[57] However, due to organ shortage and the stringency of the selection process limiting transplant availability, novel pharmacological agents to decrease mortality and progression of disease need to be developed for most non-responders to medical therapy. Living-donor transplantation has been carried out in parts of the world where deceased-donor liver transplantation is unavailable. Such an approach requires discussions on the ethics of subjecting a donor to risk for an indication of liver transplantation that is still under investigation.[57]

Next steps for future trials

There are a number of reasons for the paucity of clinical trials in alcohol-related liver disease. Recruitment to clinical trials in this group of patients can be challenging whilst endpoints such as mortality require large numbers of participants to achieve meaningful levels of statistical power. Abstinence or recidivism inevitably affect patient outcomes but cannot be predicted. Nonetheless, clinical trials in early alcohol-related liver disease are urgently needed to avoid the usual late presentation with decompensated liver disease. In order to achieve this end, patients could be selected in alcohol rehabilitation clinics. There is also evidence that universal screening for alcohol misuse in acute medical admissions is feasible and identifies patients at high risk of liver disease.[58] Inclusion criteria should be defined and endpoints may include prevention of liver-related mortality and complications of liver disease. The next steps for future trials are summarized in Table 3.

Patients with alcoholic hepatitis are highly susceptible to infection and systemic inflammatory response syndrome which may be exacerbated by immunomodulatory drugs used to control hepatic inflammation. Finally, there is a lack of consensus around the design of clinical trials, particularly for the early phases of therapeutic development.

In alcoholic hepatitis there is a higher level of consensus around the type of patients who should be recruited into trials defined by inclusion and exclusion criteria. Patients with severe alcoholic hepatitis, defined by an MDF ≥32, MELD ≥20 or Glasgow alcoholic hepatitis score ≥9, are considered a priority for therapeutic drug trials but it is now acknowledged that patients with milder disease states may also benefit from treatment given that the mortality in this group at 90 days may be as high as 15–20%. Patients who have recently suffered a significant gastrointestinal haemorrhage where haemodynamic instability may have caused hepatic ischaemia should be excluded. Similarly, patients with significant renal impairment (serum creatinine >3 mg/dl) at the time of randomisation should be excluded as acute kidney injury is

Table 3. Next steps for future trials.

Areas of consensus
The optimal time frame of survival endpoint for studies testing new molecules in the setting of severe AH should be 90 days
Liver biopsy is recommended for patients entering phase I-II studies and may be informative for phase III studies
Calculation of sample size in future phase III studies without liver biopsy should integrate the risk of misclassification based on NIAAA classification as also interobserver agreement in liver biopsy interpretation
Use of NIAAA classification of AH is recommended for design of studies without liver biopsy. Only patients with probable or definite AH should be candidates in future studies testing new drugs
Lille and other scores should be recorded at different time points to determine response to treatments such as regenerative therapies
There is the need for surrogate endpoints for survival. We propose a combined endpoint of survival and decrease in MELD score as an endpoint for efficacy of a treatment. That is, either mortality or patient who is alive but without a decrease in MELD score is study drug failure
Unmet needs and opportunities for future study
Validation of histological endpoints as a surrogate for a clinical event
Developing specific stage/fibrosis scoring systems for ALD
The concordance between the clinic syndrome of AH and histological lesion of steatohepatitis needs formal definition
The impact of sarcopenia and frailty on outcome and selection of treatment should be explored
Criteria of drug-induced liver injury and drug-induced kidney injury adapted to patients with severe AH should be established
Markers of futility for pharmacological therapy are required to exclude patients from clinical trials (example MELD score >35 which is associated with 80% risk of 90-day mortality)
Consensus for endpoints for phase I and II studies

AH, alcoholic hepatitis; ALD, alcohol-related liver disease; MELD, model for end-stage liver disease.

established as a poor prognostic factor. The need for ventilator or vasopressor support is also an exclusion criterion. Patients with viral hepatitis and active viral replication (HBV surface antigen positive or HCV RNA positive) may be excluded as candidate immunomodulatory drugs might adversely affect the course of the viral infection. Active infection at the time of evaluation should not be considered an exclusion criterion, assuming the infection is controlled prior to randomisation, as treated infection has been shown not to adversely influence mortality rates.

Recent progress in the understanding of outcomes in patients with alcoholic hepatitis has allowed experts to propose a more evidence-based approach that will help health agencies validate endpoints adapted to the specific stages of disease. Short-term outcome is mainly driven by severity of liver injury at baseline and early improvement in hepatic function, whereas the most important determinant of longer term outcome is abstinence.[59] As a consequence, study designs testing therapeutic strategies that target the acute insult should focus on short-term liver-related endpoints. Three months seems to be the optimal endpoint as 80% of short-term deaths occur within 3 months. Additionally, relapse to alcoholism starting at around 2–3 months does not significantly affect mortality at 3 months but is a contributing factor to long-term mortality. As a consequence, there is clear consensus that the primary outcome in phase III trials for patients with severe alcoholic hepatitis should be mortality rate at 90 days. Future study designs may propose a 3-month duration of drug exposure in order to maintain improvements in liver injury over this period and avoid the potential bias of analysing outcomes at 3 months, long after short treatment durations are finished. It is also clear that pharmacological interventions may cause adverse events affecting mortality at earlier time points. Criteria need to be developed to ascertain drug-induced liver injury and drug-induced kidney injury in this population of patients who may have worsening of liver and kidney function as a result of the underlying disease alone. The number of patients required to show mortality benefit with a reasonable study power is high and new primary outcomes are required for phase II trials. Unfortunately, there is no consensus on the ideal surrogate primary endpoint. Changes in bilirubin levels at day 7 or the Lille score may be good indicators for some investigational agents but are unlikely to be appropriate for drugs with slower onset of activity or late side effects.

Only drugs that target either the key pathways involved in liver injury or the main mechanisms of early deaths demonstrated in clinical studies, translational research and animal models should be tested. Endpoints for phase I and II studies will be different from those proposed for phase III studies. An agreement of experts and health agencies is urgently required on the different primary endpoints for phase I, II and III studies, so that pharmaceutical companies and scientific societies can plan development of future clinical trials. Characteristics of patients included in phase I-II trials will also differ from those in phase III trials. The optimal candidates for phase I-II studies should be patients with low risk of mortality to ensure sufficient exposure to study drugs. Up to now, short-term mortality has been the only validated primary endpoint for testing drug efficacy in phase III studies. However, there is an urgent need to validate surrogate markers strongly associated with short-term mortality that may be used in the future as primary endpoints for phase III studies.

Unfortunately, there is no strong consensus on the treatment of patients randomised to the control arm of future studies. Survival at 28 days is improved by prednisolone but the drug has no beneficial effect beyond this point. Therefore, it makes sense to use prednisolone in the control arm in studies where the endpoint is 28-day survival and placebo when longer endpoints are being considered. Heterogeneity in the risk of adverse outcomes is widely recognised in patients with alcoholic hepatitis and stratification at the time of randomisation might be usefully deployed in trials to minimise differences between active and control arms. Consensus is evolving towards using the MELD score for mortality stratification. Other potential stratification factors include treatment centres and risk of infection, which might be estimated based on bacterial 16S ribosomal DNA levels in whole blood samples.

A consistent reporting system should include the incidence of physician initiated courses of antibiotics (or antifungal agents), incidence of systemic inflammatory response syndrome (SIRS) and the incidence of infection defined by the clinical criteria as recently proposed.[60]

Translational science and evolving biomarkers in alcohol-related liver disease

New translational research approaches that cross from bench to bedside and from bedside to bench are promising. Basic science and clinical experts agree that translational science can aid the diagnosis and management of alcoholic hepatitis by identifying biomarkers and/or developing prediction models. There is a need for biomarkers that predict disease outcomes and response to therapy, early detection of infections, identify drug (steroid) resistance, or detect alcohol relapse. Areas of consensus and future directions in transitional science and biomarkers in alcohol related liver disease are summarized in Table 4.

Basic science observations from *in vitro* studies and from different animal models have greatly contributed to the increasing understanding of the pathogenetic mechanism of alcohol-related liver disease. However, there are limitations of the currently used animal models because none of them result in the full clinical spectrum of

Table 4. Translational science and evolving biomarkers.

Areas of consensus
Translational science can aid the diagnosis and management of AH by developing biomarkers to:
• Predict disease outcomes
• Predict response to therapy
• Detect infection early
• Predict steroid resistance
• Identify drug resistance
• Detect alcohol use recidivism
Clinical criteria to be used in the diagnosis of ALD and AH in biomarker studies should be defined by:
• Biopsy proven ALD or AH
• Clinical diagnosis
• MELD score to determine severity of disease
Recommended control patient groups:
• Chronic alcoholics without liver disease
• Age & sex matched healthy controls
• Patients with cirrhosis
• Patients with other liver disease
Large scale studies in large populations should take advantage of "omics" technologies in biomarker discovery
Genetic markers should be used in evaluation, prognosis and management of AH
Animal models should be used to assess potential biomarkers to establish proof-of-concept for human studies
Unmet needs and opportunities for future study
Animal models that accurately model human disease are needed where cholestasis, inflammation, and fibrosis are present together:
• Alcohol associated liver fibrosis (current models for ALD do not exhibit significant fibrosis)
• Alcoholic hepatitis
• Alcoholic-related cirrhosis
Need for new biomarkers to:
• Assess ongoing alcohol use in patients with AH after hospital discharge
• Assess inflammation (cytokines, chemokines, PAMPs/DAMPs)
• Differentiate between infection mediated inflammation and sterile inflammation
• Predict organ failure
• Assess liver regeneration

AH, alcoholic hepatitis; ALD, alcohol-related liver disease; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; MELD, model for end-stage liver disease.

human acute alcoholic hepatitis. Animal models can be used to establish proof-of-concept with the caveat that different animal models may need to be used for different stages of alcohol-related liver disease. For example, the Lieber DeCarli chronic alcohol diet model results in fatty liver and very mild alcohol-induced liver injury.[61] The acute-on-chronic alcohol administration in the NIAAA model shows some features of early alcoholic hepatitis including neutrophil infiltration and mild liver fibrosis.[62] An acute binge in animals with chronic alcohol feeding increases liver damage and neutrophil infiltration.[63] The continuous intragastric alcohol feeding model with weekly binge achieves most features of alcoholic hepatitis[64–66] including unique activation of the pyroptotic caspase 4/11-gasdermin-D pathway and its association with liver bacterial load, as validated in patients with severe alcoholic hepatitis, but is expensive and requires special surgical expertise to develop.[66] The salient features of human acute alcoholic hepatitis such as hyperbilirubinemia and fibrosis are not induced significantly in current murine models of alcohol-related liver disease. Combining a high-fat diet with continued alcohol administration results in features of human alcoholic hepatitis; however, this models the combination of NASH and alcoholic hepatitis.[67]

The evolution of alcohol-related liver disease into cirrhosis does not always include distinct episode(s) of alcoholic hepatitis. Little is known about early alcoholic hepatitis when liver inflammation is ongoing, but the patient is asymptomatic. Since these patients may eventually develop severe disease, clinical and translational studies should also focus on low grade alcoholic hepatitis to better understand the natural history of disease and impact a larger, currently neglected patient population.

Biomarker discovery is hampered by the lack of well-defined stages of alcohol-related liver disease. Therefore, it remains to be determined whether liver biopsy is required in clinical studies of biomarker discovery. Some argue that clinical parameters and/or MELD scores are sufficient for identification of biomarkers for disease progression and response to therapy. Additional consideration is related to selection of controls and references for biomarkers. Biomarker studies will likely need control groups including patients with alcohol use disorder without liver disease, patients with liver disease or cirrhosis due to factors other than alcohol, and normal healthy controls. Biomarker discovery and translational research may not only help in understanding the pathogenesis of disease but may also be incorporated into clinical prediction models.

There are many candidate biomarkers that have been identified in discovery phases and await validation in large well-defined patient populations. Some of these include circulating indicators of gut microbial translocation (endotoxin, bacterial DNA), markers of systemic inflammation (cytokines, chemokines), sterile danger molecules (ST2, HMGB1), markers of apoptosis and cell death (fragments of keratin 18) and fibrosis markers[68–72] including cytochrome P4502E1. In addition to blood-based biomarkers, there are new potential biomarkers in exhaled breath and urine. Finally, the composition of the microbiome in the gut and oral cavity may also represent useful sources of biomarkers in alcohol-related liver disease.

Conflicts of interest

M.T. reports grants from Novartis, Gilead and Vital Therapeutics, and personal fees from Affimune outside the submitted work. P.M. reports personal fees from Verlyx and Gilead during the study, and personal fees from Gilead, Abbvie, MSD, Bayer Healthcare, Intercept, Sanofi and Verlyx outside the submitted work. V.S. reports personal fees from Enterome, France; Vital Therapies, USA; Novartis Pharma, Switzerland; Durect Corporation, USA; Merck Research Laboratories, USA; Afimmune Ltd., Ireland outside the submitted work. G.S. consults for Terra Firma, Carlos Foundation, Glympse Bio, Quest Diagnostic, Arrow Diagnostic, GLG, Salix, Tobira and Allergan. G.S. has received funding from NIH-NIAAA, Gilead, Genfit,

University of Florida, Intercept, Allergan, Novartis, SignaBlok and Shire. P.K. has no conflicts of interest in relation to this manuscript.

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

EASL-AASLD Joint Meeting: *Definition, therapeutic advances and clinical endpoints in alcoholic liver disease and alcoholic hepatitis*

London, United Kingdom – September 30–October 1, 2017

Conference speakers (in alphabetical order): Giovanni Addolorato, Ramon Bataller, Patrizia Burra, Laurent Castera, Helena Cortez Pinto, Anna Mae Diehl, Bin Gao, Sir Ian Gilmore, Jochen Hampe, Rehm Jürgen, Patrick S. Kamath, Michael Karin, Alexander Krag, David Leon, Christopher Leptak, Alexandre Louvet, Michael Lucey, Philippe Mathurin, Craig McClain, Laura Nagy, Georges-Philippe Pageaux, Arun Sanyal, Bernd Schnabl, Vijay H. Shah, Gyongyi Szabo, Mark Thursz, Dina Tiniakos, Christian Trautwein, Hidekazu Tsukamoto.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.041.

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Author names in bold designate shared co-first authorship

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