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Steatotic Liver Disease with Alcohol Drinking Working Group Update

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Disclosures

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- Nikhil Vergis
  - GSK Employee and shareholder
- Maja Thiele
  - Speaker's fee from Siemens Healthcare, Echosens, Norgine, Madrigal, Takeda, Tillotts Pharma. Advisory fee from Boehringer Ingelheim, Astra Zeneca, Novo Nordisk and GSK.
  - Co-founder and board member for Evido.
  - Board member for Alcohol & Society (non-governmental organisation).

Since last Liver Forum meeting

1. New evidence:
   - EASL position paper
   - New evidence on MetALD & ALD prevalence
2. From MetALD to MetALD-ALD working group
3. Working group position papers defined

Alcohol Consumption and Metabolic Dysfunction: EASL Position statement by an expert panel on alcohol-associated liver disease

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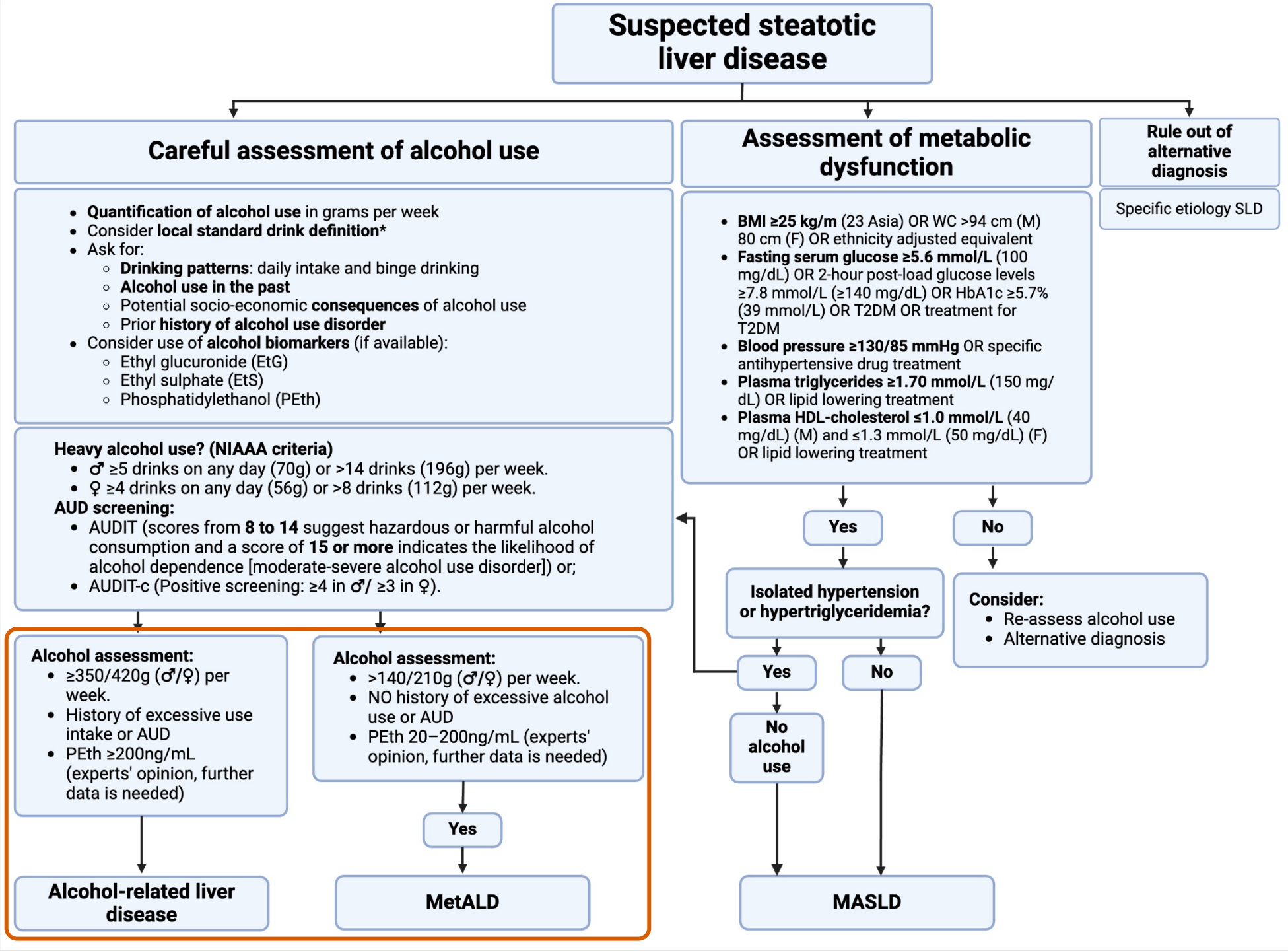
- Recent and lifetime alcohol consumption should be accurately assessed in all patients with SLD for adequate classification.
- The use of only 1 metabolic dysfunction criteria to diagnose MASLD should be applied cautiously in individuals with alcohol consumption, especially hypertension and dyslipidemia.
- It is necessary to consider re-appraising metabolic dysfunction and alcohol consumption over time, especially after periods of cessation or reduction.
- Standardized surveys, electronic health records, and input from collateral sources can improve accuracy in obtaining an accurate alcohol history. Biomarkers like phosphatidylethanol (PEth) can also aid in the detection and quantification of alcohol use.

J.P. Arab, Philippe Mathurin, and a global expert group, in revision


Suspected steatotic liver disease
Careful assessment of alcohol use
Assessment of metabolic dysfunction
Rule out of alternative diagnosis
Specific etiology SLD
Quantification of alcohol use in grams per week
Consider local standard drink definition*
Ask for:
Drinking patterns: daily intake and binge drinking
Alcohol use in the past
Potential socio-economic consequences of alcohol use
Prior history of alcohol use disorder
Consider use of alcohol biomarkers (if available):
Ethyl glucuronide (EtG)
Ethyl sulphate (EtS)
Phosphatidylethanol (PEth)
BMI ≥25 kg/m (23 Asia) OR WC >94 cm (M) 80 cm (F) OR ethnicity adjusted equivalent
Fasting serum glucose ≥5.6 mmol/L (100 mg/dL) OR 2-hour post-load glucose levels ≥7.8 mmol/L (≥140 mg/dL) OR HbA1c ≥5.7% (39 mmol/L) OR T2DM OR treatment for T2DM
Blood pressure ≥130/85 mmHg OR specific antihypertensive drug treatment
Plasma triglycerides ≥1.70 mmol/L (150 mg/dL) OR lipid lowering treatment
Plasma HDL-cholesterol ≤1.0 mmol/L (40 mg/dL) (M) and ≤1.3 mmol/L (50 mg/dL) (F) OR lipid lowering treatment
Heavy alcohol use? (NIAAA criteria)
♂ ≥5 drinks on any day (70g) or >14 drinks (196g) per week.
♀ ≥4 drinks on any day (56g) or >8 drinks (112g) per week.
AUD screening:
AUDIT (scores from 8 to 14 suggest hazardous or harmful alcohol consumption and a score of 15 or more indicates the likelihood of alcohol dependence [moderate-severe alcohol use disorder]) or;
AUDIT-c (Positive screening: ≥4 in ♂/ ≥3 in ♀).
Yes
No
Isolated hypertension or hypertriglyceridemia?
Consider:
Re-assess alcohol use
Alternative diagnosis
Yes
No
No alcohol use
Alcohol assessment:
≥350/420g (♂/♀) per week.
History of excessive use intake or AUD
PEth ≥200ng/mL (experts' opinion, further data is needed)
Alcohol assessment:
>140/210g (♂/♀) per week.
NO history of excessive alcohol use or AUD
PEth 20–200ng/mL (experts' opinion, further data is needed)
Yes
Alcohol-related liver disease
MetALD
MASLD

MetALD and ALD make up ~10-20% of all SLD patients

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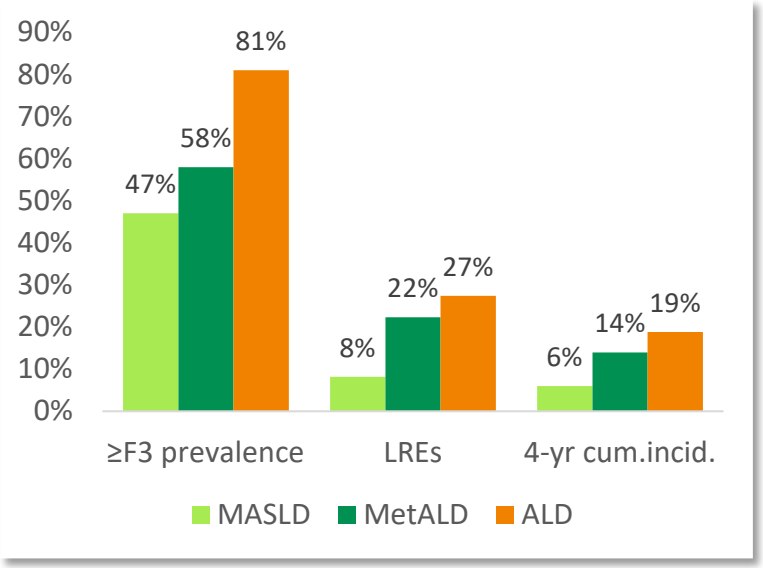
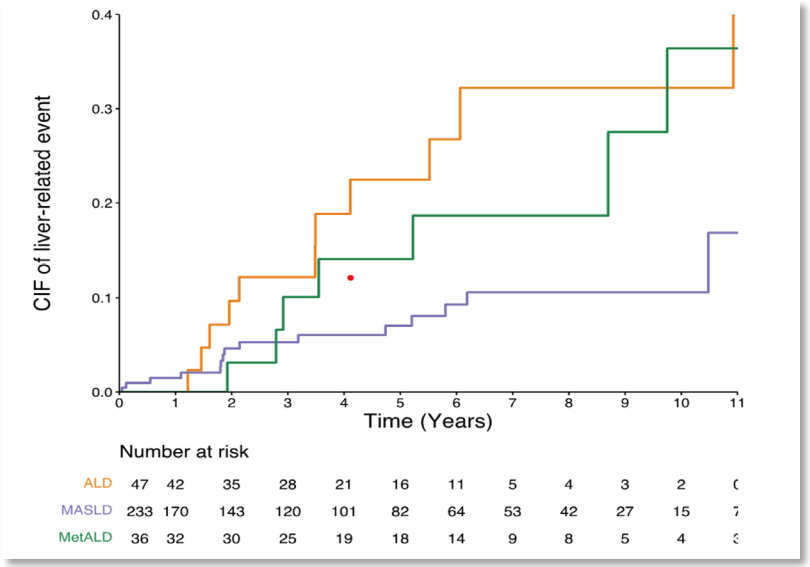
- MetALD 14% and ALD 7% of all SLD in South Korea primary care health checks (MRI-PDFF)
- MetALD 8% and ALD 1% of all SLD in UK Biobank (MRI-PDFF)
- MetALD 7% and ALD 2% in NHANES (FibroScan)
- MetALD and ALD both exhibit high LRE and mortality in secondary care patients





EASL poster THU-335 , Adrien

Change in SLD group over time

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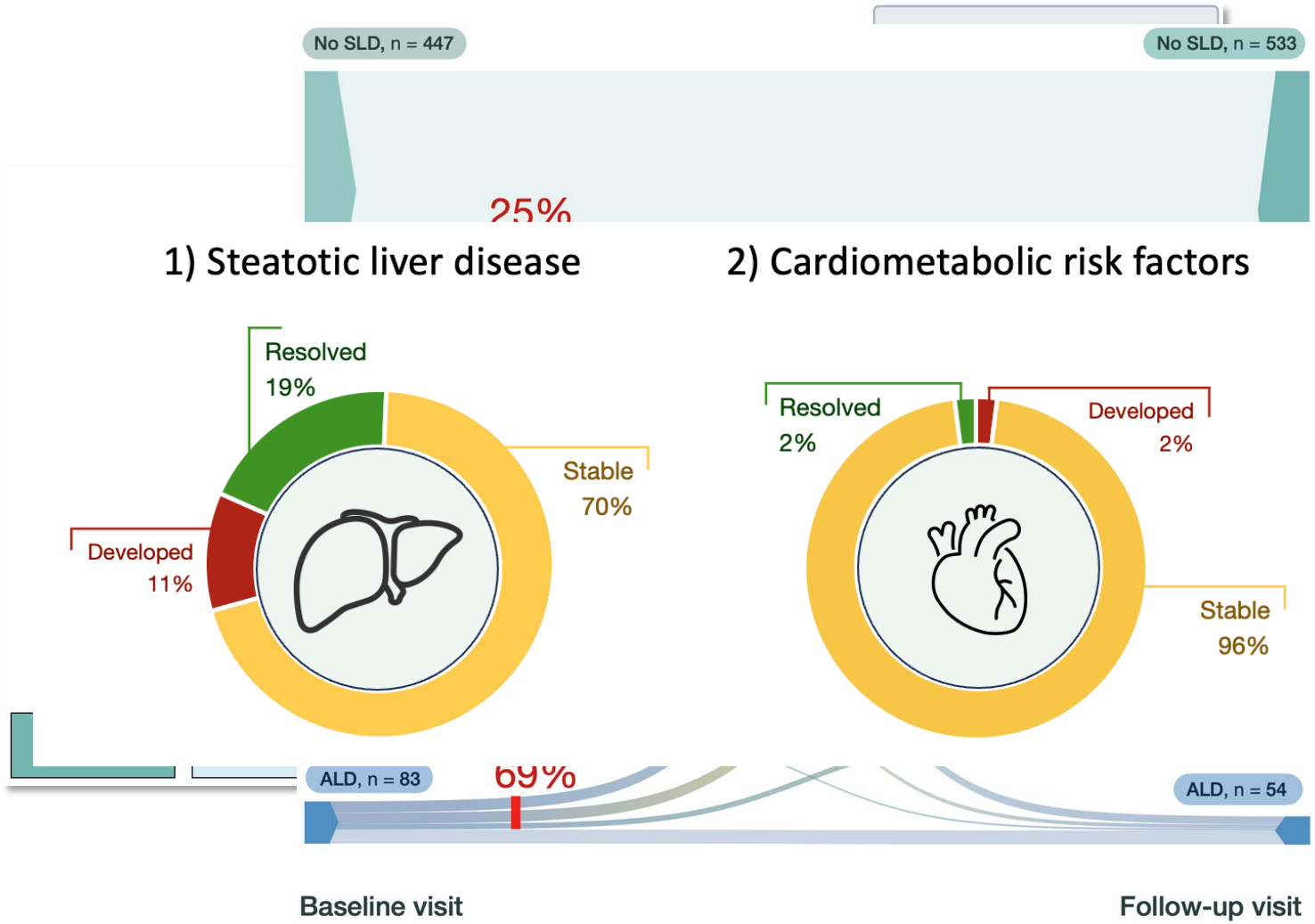

EASL presentation LB-296, Israelsen

Change from MetALD to MetALD-ALD working group

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- Emerging trials may recruit either group
- MetALD and ALD are highly dynamic categories
- Event rates not too different btw. MetALD and ALD
- Patients in the ALD category are also highly burdened by metabolic dysfunction
- No consensus on alcohol biomarker cutoffs to determine the MetALD upper and lower limits
- We are still awaiting consensus on how to deal with historical alcohol use

Position papers

Diagnosis and screening; Clinical trial design

A. Inclusion of patients with MetALD/ALD in clinical trials
B. Special considerations for a clinical trial involving MetALD/ALD
C. Primary and Secondary endpoints for Ph1, 2, 3
D. Benefit-risk evaluation across disease severity
E. Mitigation of risk including DILI
F. Inclusion of psychiatric comorbidities including dependence

Source information

A. How should MetALD/ALD be diagnosed in terms of eligibility for trial inclusion?

1. What is the relevance of MetALD alcohol consumption thresholds in clinical trials?
    a. How does a patient's history of alcohol use (duration and amount) and current alcohol use factor into clinical trial inclusion?
    b. Is a definitive diagnosis of MetALD important before clinical trial enrollment?
2. How to quantify present and prior duration and magnitude of alcohol intake for trial eligibility?
3. Is metabolic dysfunction as requirement for trial inclusion?
    a. How many features, which features, of what severity, for how long, independent of alcohol consumption?
4. What is the relevance of the presence and severity of steatosis and fibrosis for trial inclusion eligibility, and what should be the reference non-invasive/invasive tests to diagnose those aspects?
    a. Can compensated advanced chronic liver disease (cACLD), as defined non-invasively according to the Baveno VI consensus, be used as a diagnostic inclusion criterium in phase 2 and 3 trials?
5. What is the epidemiology and socioeconomic characteristics of SLD patients who drink alcohol, especially in terms of prevalence and disease severity, differences according to age groups, sex, and geography, presence and distribution of metabolic dysfunction?

B. Special considerations for clinical trials in MetALD/ALD

1. What should be the concomittant behavioral interventions for a clinical trial in MetALD/ALD?
    a. For metabolic dysfunction?
    b. For alcohol use disorder
2. What is the preferred method for of quantification of alcohol consumption in:
    a. The screening period?
    b. The treatment period?
3. What methods ensure the highest rates of participant retention?

A. Which primary and secondary endpoints are relevant to consider for phase 2 and 3 trials?

1. Can changes in non-invasive biomarkers of steatosis, inflammation, and/or liver fibrosis be used as primary endpoints in phase 2 and 3 trials? If so, at which disease stages are non-invasive liver fibrosis tests relevant as primary endpoints?

    a. pre-cirrhosis: significant fibrosis (≥F2) and advanced fibrosis (≥F3/F4)

    b. compensated cirrhosis

    c. decompensated cirrhosis

2. Is liver histology mandatory for MetALD/ALD participants of phase 2 and/or phase 3 trials?

    a. If liver biopsy is performed in MetALD/ALD clinical trials, are these histological lesions similarly prognostic and predictive of treatment response to MASLD lesions?

    b. If liver biopsy is performed, which histological score should be used: Kleiner & NAS-CRN, SALVE, SAF?

A. Which primary and secondary endpoints are relevant to consider for phase 2 and 3 trials?

3. Which non-invasive biomarkers of liver function (e.g. MELD score, Child-Pugh class, etc) be used as primary endpoints in phase 2 and 3 trials of decompensated cirrhosis?

4. What defines a relevant change in non-invasive steatosis, inflammation and fibrosis tests, and liver function scores in small and large trials, respectively? How might this differ for the following categories:

   a. pre-cirrhosis

   b. compensated cirrhosis

   c. decompensated cirrhosis

   d. abstinent patients

   e. patients with continued alcohol drinking

A. Which primary and secondary endpoints are relevant to consider for phase 2 and 3 trials?

5. What are the required secondary endpoints in phase 2 and 3 trials, and how should they be measured?

    a. Alcohol intake

    b. Metabolic dysfunction

    c. Liver dysfunction

    d. Liver-related clinical events

    e. Patient-reported outcome measures including HRQoL and others

    f. Adverse events

B. Benefit-risk evaluation across disease severity in Ph1, 2, 3

1. At what disease severity and clinical trial phase should clinical benefit be the primary outcome in SLD patients who drink alcohol? If so, how should clinical benefit be defined?
    a. pre-cirrhosis;
    b. compensated cirrhosis;
    c. decompensated cirrhosis
2. How does the benefit/risk evaluation of a therapy differ across disease stages and levels of alcohol drinking?
3. What are the benefits of therapy, as described by harm-reduction, vs acceptable risks that are sought by prescribers, payers and patients for an effective drug in MetALD/ALD?
4. What routes of administration would be preferred by patients with MetALD/ALD?
5. What should the comparator arm be for patients with MetALD/ALD?
6. Which MASH drugs might be especially suitable for re-purposing? Is there a need for de novo (non-repurposed) drugs for MetALD/ALD

C. Mitigation of risk including DILI

1. What safety safeguards should be in place within MetALD/ALD trial protocols?

Linked to IQ DILI paper

D. Inclusion of psychiatric comorbidities including dependence

1. Can patients with psychiatric comorbidities be included in these studies?

   - AUD, depression, psychosis, anxiety.

2. Can patients with severe psychiatric disorders be managed in a clinical trial?

3. Should patients with alcohol dependence be excluded from such trials?

   - If they should be excluded, at what severity of dependence syndrome and how should dependence syndromes be evaluated?

Discussion

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Thank You

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