THE FORUM
For Collaborative Research℠

Liver Forum Histology Working Group Update

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Liver Forum 14

Disclosures

- I have nothing to disclose

Liver Forum Histology Series Webinars

Sept 2020-Jan 2022

- **Session 1**: Increasing the Reliability of Histology in NASH Clinical Trials
- **Session 2**:Innovations: Utilizing Digital Methods and New Technology
- **Session 3**:The Role of Liver Biopsy as part of Causality Assessment for Suspected DILI in NASH Clinical Trials
    - **Part 1**: Best Practices to Implement When Abnormal Histologic Findings are Discovered on Liver Biopsy- Lessons Learned from *Seladelpar*
    - **Part 2**: Improving The Reliability of NASH Clinical Trial Outcomes: What Is the Optimal Number of Hepatopathologists and Digital Slides, Pros and Cons?
    - **Part 3**: Causality Assessment and the Role of Liver Biopsy as Part of the Evaluation of Suspected DILI in NASH Clinical Trials

White papers

- 3-4 papers
- Working and writing group

Working Group
Melissa Palmer Chair
Raj Vuppalanchi Co-Chair
Arun Sanyal
Mark Avigan
David Kleiner
Beth Brunt
Zach Goodman
Paul Hayashi
Stephen Harrison
Charles McWherter
Ruby Mehta
Arie Regev
Naga Chalasani
Massimo Siciliano
Cynthia Behling
Jim Lewis
Veronica Miller

Paper 1. Submitted to **Journal of Hepatology** -Feb 3rd

Liver Biopsy for Assessment of Drug Induced Liver Injury in Clinical Trials of NAFLD/NASH: Consensus Recommendations from the Liver Forum

Melissa Palmer [1], David E. Kleiner [2], Zachary Goodman[3], Elizabeth Brunt [4], Mark I.Avigan [5], Arie Regev [6], Paul H. Hayashi [7], James H. Lewis [8], Stephen A. Harrison [9], Massimo Siciliano [10], Charles A. McWherter [11], Raj Vuppalanchi [12], Cynthia Behling [13], Veronica Miller [14], Naga Chalasani [15], Arun J. Sanyal [16]

Paper 2: Best Practices to Implement When Abnormal Histologic Findings are Discovered on EOT Liver Biopsy

- Atypical histologic findings in NASH
- What is done with atypical findings
- How is the information handled?
- There is a dearth of literature available
- This paper will address that gap and encourage more publications regarding these types of findings

Paper 3: Best Practices for Increasing the Reliability of Histologic Outcomes

- Digital vs glass slides
  - The field is moving towards digital slides but there are currently no best practices yet
  - Digital slides need to be validated.
  - Operational factors and validation
- Required number of hepatopathologists needed for successful assessment of NASHPanel versus 1 versus 2 etc uch as the, there may not be enough evidence to make a determination at this time. As more data is available from clinical trials, the ability to make these types of determinations will increase.
- Liver pathology manual – toward best practice

Paper 4: Revisiting the NAS scoring system?

- Is 0 ballooning too high a bar for resolution of NASH?
- The NAS scoring system was designed to be used as an aggregate measure of multiple features that generally improve or worsen simultaneously and magnify changes in histology.
- If individual parameters are extracted, then the dynamic scale of measurement is reduced.
- Resolution of NASH is often interpreted through the resolution of ballooning.
- However, it is unclear why this criterion is being used solely to evaluate NASH. No other measure demands complete resolution of any feature to be successful.
- As an example, fibrosis is evaluated based on improvement, not elimination. Similarly, enzymes are evaluated by percentage of improvement, not normalization.
- NASH cannot be cured; it is suppressed.
- What does the resolution of NASH mean?
    - What does the resolution of NASH mean as an endpoint?
- What happens to balloons. Their form may change with treatment but persist. A recent paper indicates that certain genotypes of patients with NASH have persistent balloons. These patients have a tremendous number of balloons to start, so they don't resolve their NASH ballooning with treatment.
- A paper is being considered focused on ballooning as seen by a pathologist.