TITLE: IQ DILI CONSENSUS OPINION: BEST PRACTICES FOR RECHALLENGE FOLLOWING SUSPECTED DRUG-INDUCED LIVER INJURY IN CLINICAL TRIALS

JOURNAL: Drug Safety

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Electronic Supplementary Materials # 2

IQ DILI - Drug Development Rechallenge Questionnaire – Defining gaps and clarifying the role of Liver Biopsy in Rechallenge

IQ Consortium Survey Notice

Page description:
This survey aims to understand current practices surrounding rechallenge,define gaps, and clarify the role of liver biopsy in rechallenge among varied stakeholders hose decisions impact drug development. This survey is sponsored by Causality Assessment, a working group under the IQ DILI Affiliate. The anonymized results will be published in a peer review journal.

This survey is being conducted according to IQ's Bylaws and Antitrust Guidelines. Please do NOT disclose names of any compounds, partners (e.g., companies, contractors, vendors, universities, or other collaborators), or other proprietary information. Please do not disclose any information that could identify a study subject, patient, investigator, healthcare provider, or consumer.

Please ensure that you have all necessary permissions and approvals from your company to respond to this survey and do NOT disclose any information your company would not want disclosed, even if in a form not attributable to your company.

Although the survey asks for your name and your organization affiliation, the IQ Secretariat will remove this information before sharing the anonymized aggregated results. Your responses will not be identified as coming from your organization. The IQ Secretariat is the only party who can link individual survey responses to responding companies and individuals, and can follow-up with companies to clarify responses if needed. The IQ Secretariat may also redact, anonymize, or aggregate responses to help protect the confidentiality of survey respondent's identities.

Questions about the administration of or content within this survey may be directed to Fatou Sarr (Fatou.Sarr@faegredrinker.com).

Your response is requested by Friday September 23, 2022.

BACKGROUND:

Thank you for agreeing to complete the Drug Development Rechallenge Questionnaire from the IQ DILI Causality Assessment Working Group. The group is currently writing a manuscript with the goal of providing a consensus opinion, recommendations and best practices surrounding issues in drug rechallenge and clarifying whether histologic assessment would alter the decision to rechallenge after occurrence of DILI a patient participating in a clinical trial. During the preparation of this manuscript, several knowledge gaps have been identified. In fact, limited or no information have been published on the topics included in this questionnaire. This questionnaire has been developed following recommendations by our external experts during most recent face-to-face virtual IQ DILI Consortium meeting. This questionnaire is circulated to academic and regulatory experts and IQ DILI collaborators, as well as representative members from the 17 IQ DILI Industry partners, to determine what the current practices are and how they may differ among regulators, clinical development and clinical safety individuals in industry, and academic experts in the field of DILI. Collected data will be deidentified and summary published as part of the Rechallenge manuscript. Our objectives are to understand current practices among varied stakeholders whose decisions impact drug development, highlight the gaps in this field and generate interest in studying these issues in a systematic manner.

INSTRUCTIONS:

When answering these questions please assume the following 9 factors have already been taken into consideration and should not be included in the answers:

1. All questions refer to rechallenge during clinical drug development.
2. There are either no or limited studies/literature that exist on which to base the answer.
3. The benefits versus risks are being weighed in each scenario.
4. One size does not fit all – there are numerous variables which factor into decisions.
5. The decision to recommend/not recommend a liver biopsy, is made in conjunction with weighing other test results and the clinical scenario.
6. Liver biopsy is not the initial Investigation performed.
7. Histology results are used in conjunction with other test results and the clinical scenario to assess causality.
8. There are no right or wrong answers- please provide your best practice.
9. If you would like to comment on a question, the survey, or to provide any other additional information there is an open free text space provided

VALIDATION Open text with **Title Case**

Please enter your information below. *

First Name

Last Name

VALIDATION %s format expected

Email Address *

LOGIC Show/hide trigger exists.

1. Please indicate your current affiliation *

- FDA - Clinical Safety
- FDA - Clinical Development
- Industry - Clinical Safety
- Industry - Clinical Development
- Academic - please specify specialty
- Other – please describe

LOGIC Hidden unless: #1 Question "Please indicate your current affiliation" is one of the following answers ("FDA - Clinical Safety","FDA - Clinical Development","Industry - Clinical Safety","Industry - Clinical Development")

We are seeking one response from Clinical Safety and Clinical Development colleagues from each organization. If multiple individuals of the same department receive this survey, we kindly ask you to consolidate your responses into a common response. We will be providing a PDF copy of this survey to facilitate internal coordination. Please use the PDF as a reference, but kindly submit your responses via the online survey and not the PDF.

LOGIC Hidden unless: #1 Question "Please indicate your current affiliation" is one of the following answers ("Academic - please specify specialty","Other – please describe")

Please specify the name of your organization. *

LOGIC Hidden unless: #1 Question "Please indicate your current affiliation" is one of the following answers ("Industry - Clinical Safety","Industry - Clinical Development")

2. Please select your member company affiliation. *

- AbbVie
- Aligos
- Amgen
- AstraZeneca
- Bayer
- Bristol Myers Squibb
- Daiichi Sankyo
- Eli Lilly
- Genentech
- Gilead
- GSK
- Janssen
- Merck & Co.
- Mirum
- Novartis
- Otsuka
- Pfizer
- Sanofi
- Takeda

RECHALLENGE

Page description:
Please feel free to use the comment box after each question to provide additional details regarding your response.

3. How many times per year, on average, do you conduct/recommend /support a rechallenge assessment

- Never
- 1-2x /year
- 2-5x /year
- > 5x /year
- Not applicable

Comments

4. Overall, what percentage of the time do you conduct/recommend/support study drug rechallenge during a clinical trial?

- Never
- 0-25%
- 26-50%
- 51-75%
- > 75%
- Not applicable

Comments

LOGIC Show/hide trigger exists.

5. Does the type of DILI contribute into your decision making process for rechallenge?

- Yes
- No

Comments

LOGIC Hidden unless: #5 Question "Does the type of DILI contribute into your decision making process for rechallenge?" is one of the following answers ("Yes")

6. If you answered Yes to above, would you be more likely to rechallenge a subject who had:

Please provide a response for each type of DILI.
If you would like to respond regarding another type of DILI, please specify in the textbox marked with "enter another option"

	Yes	No
Cholestatic DILI	○	○
Hepatocellular DILI	○	○
Mixed DILI	○	○

Comments

7. Upon rechallenge, do you consider that patients with underlying chronic liver disease versus those with normal livers are at increased risk for:

	Yes	No
A positive rechallenge	○	○
Liver-related complications	○	○

Comments

8. You decide that you want to rechallenge a patient in a clinical trial. What is the ALT threshold value that you require to return to prior to rechallenge? Mark all that apply

- [ ] ≤ 1.5x baseline
- [ ] ≤ 1.5x ULN
- [ ] ≤ baseline
- [ ] ≤ ULN
- [ ] Other – please comment

Comments

LOGIC Show/hide trigger exists.

9. Does total bilirubin (TBIL) play a role in your decision to rechallenge?

- ○ Yes
- ○ No

LOGIC Hidden unless: #9 Question "Does total bilirubin (TBIL) play a role in your decision to rechallenge?" is one of the following answers ("Yes")

10. If you answered “Yes” to the above what level of TBIL do you consider prior to Rechallenge?

LOGIC Show/hide trigger exists.

11. Does direct bilirubin (DBIL) play a role in your decision to rechallenge?

- Yes
- No

LOGIC Hidden unless: #11 Question "Does direct bilirubin (DBIL) play a role in your decision to rechallenge?" is one of the following answers ("Yes")

12. If you answered Yes to the above what level of DBIL do you consider prior to Rechallenge

13. Which of the following factors listed below do you take into consideration when deciding to rechallenge a patient in a clinical trial? – mark all that apply

- [ ] Drug washout
- [ ] Maximum elevation of ALT prior to drug pause?
- [ ] Maximum elevation of TBIL prior to drug pause?
- [ ] Recovery time
- [ ] Demonstration of clinical benefit preceeding event
- [ ] None of the above
- [ ] Other-please specify

Comments

14. How often should a patient be at minimum monitored and for how long after rechallenge in a clinical trial?

Please use the comment box below to provide detail on the frequency of monitoring based on liver enzyme elevations.

- Twice weekly for 1 month
- Weekly for 1 month
- Weekly for 2 months
- Other – please specify

Comments

15. What dose would you rechallenge the patient with?

- Reduced dose for remainder of trial
- Reduced dose with plan to dose escalate
- Full dose

Comments

16. If the suspect drug in the clinical trial belongs to a class of drugs with proven hepatotoxicity, would rechallenge still be considered?

- Yes
- No

Comments

17. Prior to rechallenge, how often do you seek external expert opinion of this hepatic adverse event?

Please use the text box below to comment on what specialty this expert would be from.

- Never
- 0-25%
- 26-50%
- 51-75%
- 76-99%
- Always

Comments

18. What is considered a positive rechallenge?

- Any ALT elevation
- ALT elevation to same level which caused cessation of therapy
- Other – please specify

Comments

LIVER BIOPSY

Page description:
Please feel free to use the comment box after each question to provide additional details regarding your response.

19. Overall, what percentage of time do you recommend a liver biopsy as part of causality assessment of suspected DILI?

- Never
- 0-25%
- 26-50%
- 51-75%
- > 75%

Comments

20. Overall, what percentage of the time do you suggest a liver biopsy in the process of causality assessment of suspected DILI during a Phase 1 clinical trial in the following populations:

If you would like respond regarding a different indication or patient population that is not listed please specify in the "Enter another option" textbox.

	Never	0-10%	11-25%	26-50%	>50%
Healthy volunteers?	○	○	○	○	○
Oncology patients?	○	○	○	○	○
Enter another option	○	○	○	○	○

Comments

21. Overall, what percentage of the time do you suggest a liver biopsy in the process of causality assessment of suspected DILI during a Phase 2 and 3 clinical trial

	Never	0-10%	11-25%	26-50%	>50%
Phase 2	○	○	○	○	○
Phase 3	○	○	○	○	○
Phase 2 or 3 with CLD	○	○	○	○	○

Comments

22. Cumulative clinical trial data from all studies done to date indicate that there have been cases meeting severe DILI stopping criteria (Hy's law). How many cases would be necessary before a liver biopsy would be recommended on the next subject meeting stopping criteria?

	Would not recommend	One subject is enough	>1	Would discontinue (D/C) drug development
Phase 1	○	○	○	○
Phase 2	○	○	○	○
Phase 3	○	○	○	○

Comments

23. Cumulative clinical trial data from all studies done to date indicate that there have been cases meeting DILI stopping criteria (not Hy's law). How many cases would be necessary before a liver biopsy would be recommended on the next subject meeting stopping criteria?

	Would not recommend	One subject is enough	> 1-5	> 5
Phase 1	○	○	○	○
Phase 2	○	○	○	○
Phase 3	○	○	○	○

Comments

24. Other than the following 6 factors, please comment on any other reason/s to recommend a liver biopsy during clinical development (other than as part of protocol for efficacy endpoint):

- Identification of features that support or refute the diagnosis of DILI
- Identification or confirmation of previously undiagnosed chronic liver disease (e.g., cirrhosis or NASH)
- Identification of histologic features that might respond to an alternative treatment: for example- histologic autoimmune features that might respond to steroid treatment
- Assessment of the extent of liver damage which may estimate prognosis
- Characterization of the liver injury that may be attributed to the study drug
- Identification of features that support or refute the progression of the underlying liver disease (if there is an previous or baseline liver biopsy for comparison applicable)

25. When a liver biopsy was done, how often did it influence rechallenge decision?

- Never
- < 25% of the time
- 26-50% of the time
- > 51% of the time

Comments

26. When a liver biopsy was done, how often did it change causality assessment?

- Never
- < 25% of the time
- 26-50% of the time
- > 51% of the time

Comments

Thank You!

Thank you for completing this survey. Your answers are crucial to defining gaps in the field in order to advance further research.