Liver Forum 6:
Summary of Proceedings

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Amsterdam, The Netherlands

Facilitating Collaborative Research in Drug Development and Health Policy
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SESSION #1: INTRODUCTION

Moderators: Veronica Miller, Forum for Collaborative Research
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Introduction and Liver Forum Updates

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/00_Intro.pdf
Presenter: Katherine Greene, Forum for Collaborative Research

- Welcome and introduction
  - The Forum for Collaborative HIV research is celebrating its 20th anniversary this year, and in recognition of the expansion in scope and focus of the Forum's work, has been rebranded as "The Forum for Collaborative Research".
    - As a result, a new logo, email server, and URL (www.forumresearch.org) have been created.
  - Thank you to the steering committee members for their involvement in all the Liver Forum's activities, and helping to identify priorities.
    - Special thanks to co-chairs David Shapiro and Arun Sanyal.
- Review of Liver Forum 5
  - LF5 was held in Boston MA on November 10, 2016, with 230 attendees:
    - 165 in-person, 65 remote
    - Nearly 75% of attendees were industry members
    - Largest number of attendees
    - Growth in in-person attendees between events:
      - **US**: LF3: 122 → LF5: 165 (increase of 43)
      - **Europe**: LF4: 97 → LF6: 137 (increase of 40)
  - The results of the LF5 evaluation found that a 75% of respondents reported the regulatory updates as the "most important" (57%) or an "important" (18%) consideration when deciding whether or not to attend.
    - Networking opportunities were the next highest rated, at 50% (29% "most important", 21% "important").
    - Working group updates were rated as the least important, at 42% (11% "most important", and 31% "important").
    - Liver Forum agendas are heavily developed based on feedback from the previous meeting. As a result of the LF5 evaluation, the time allotment for discussing working group updates was shortened.
      - Those interested in joining any of the working groups should email Katherine Greene: kgreene@forumresearch.org
  - The evaluation from LF5 also found that 100% of respondents "Agree" or "Somewhat Agree" that they would recommend joining the Liver Forum to a peer or colleague.
- Between Liver Forum 5 and 6
  - **Pediatric Working Group**: the working group held an in-person meeting on March 20th in Washington DC to discuss the development of a pediatric natural history cohort.
  - **Placebo Arm Data Working Group**: the newest working group was launched in March 2017, and the first conference call was held in April.
  - **Workshops**:
    - NASH Biomarker Workshop: the Liver Forum has partnered with Expert Medical Events/ Virology Education to co-host the 2nd International NASH Biomarker Workshop on May 5-6 in Washington, DC.

        - Causal Inference and Adaptive Design Workshop: this workshop is being hosted in Washington, DC on May 10, and is specifically for statisticians. The content of the workshop will focus on non-disease specific statistical methodologies that can be applied to the design and analysis of data from clinical trials. A portion of the workshop will also include a presentation on adaptive design specifically related to NASH.
- Manuscript updates
    - **Case Definitions**:
        - Manuscript 1, "Case definitions for inclusion and analysis of endpoints in clinical trials for NASH" has been submitted.
            - Forum "Fellow": Mohammad Shadab Siddiqui, working with Arun Sanyal
        - Manuscript 2, "Defining improvement in NAFLD for treatment trial endpoints" is under development.
            - Forum "Fellow": Amanda Cheung, working with Brent Tetri
    - **Data Standardization**:
        - Manuscript 1, "Baseline parameters in clinical trials for nonalcoholic steatohepatitis" is being prepared for submission.
            - Forum "Fellow": Yuval Patel, working with Andrew Muir
    - **Pediatric Issues**:
        - Manuscript 1, "Regulatory considerations for clinical trials in pediatric nonalcoholic fatty liver disease" is under internal review.
- Sponsorship and membership updates
    - The Liver Forum currently has members representing 110 companies, of which, 48 are sponsors.
    - Since LF5, there have been 4 new industry organizations that have become sponsors (MEDIAN Technologies, Cirius Therapeutics, CTI Clinical Trial and Consulting Services, and Humedics GmbH), and 14 new industry organizations have become members.

FDA Regulatory Project Managers

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/01_Davis-Williams.pdf
Presenter: Anissa Davis-Williams, U.S. Food and Drug Administration

- The Division of Gastroenterology and Inborn Errors Products (DGIEP) is housed under the Center for Drug Evaluations and Research (CDER) within the Office of New Drugs (OND).
    - Within DGIEP, there are 19 clinical reviewers, 7 clinical team leaders, 9 non-clinical reviewers, 2 non-clinical team leaders, 14 regulatory project managers, 1 chief project management staff officer, and 2 administrative staff members.
        - There are 2 regulatory project managers for liver applications, whose roles include:
            - Identifying, coordinating and scheduling all activities necessary to complete the review of submissions.
            - Preparing, documenting, and coordinating all reviews and access needed to reach goals.
            - Clarifying regulatory issues to present them to the team and sponsor when applicable.
            - Preparing timelines to meet target goals and ensure that all outgoing communications are consistent with laws and regulation.
- Prescription Drug User Fee Act (PDUFA) reauthorization for fiscal year 2018-2022

- In 1992, Congress enacted PDUFA to provide the necessary supplemental resources through user fees to ensure a timely and efficient review process for new drug and biologic products. Within this act, Congress stated that the PDUFA needs to be reauthorized every five years.
  - PDUFA V was reauthorized in 2012 under the Food and Drug Administration Safety and Innovation Act (FDASIA).
  - The Commitment or Goals Letters detail the specifics of the reauthorization, and are developed with the input of drug industry representatives, patients, health care professionals, and consumer advocates.
- The proposed changes for PDUFA VI have not passed legislation as of April 18, 2017; therefore, the proposed changes are not yet final.
  - No changes proposed for the timeline for NDA Class 1 & 2 resubmissions, or efficacy and manufacturing supplements submissions.
  - "The Program" review model from PDUFA V was created to promote transparency and improve communication with industry and the FDA review team doing a review of new molecular entity applications.
    - The goal of "The Program" model to improve the efficacy and effectiveness of the first cycle of reviews processed and decrease the number of review cycles necessary for approval.
    - In the assessment of "The Program" from November 18, 2016, first cycle approval rate for all applications was significantly higher since the review model was implemented; therefore, it is proposed for PDUFA VI.
- **Meeting sequence overview**:
  - Sponsors send an invitation or letter, which is granted or denied.
  - FDA schedules meeting, and sets backgrounder due date
  - Sponsor sends backgrounder, meeting is held
  - FDA sends meeting minutes or written response
- **Meeting types**:
  - Type A: sponsors want to discuss stalled development program, any pertinent safety issues, or want to talk to FDA after receiving a complete response
  - Type B: meetings that include pre-IND or pre-NDA
  - Type C: everything outside of Type A or Type B
- **Proposed changes to meetings**:
  - Currently, sponsors can request a WRO meeting request for pre-IND or Type C meetings. What's being proposed under PDUFA VI is that now sponsors can request a WRO request for any meeting type.
  - Type B (end of phase) is a new meeting type proposed: end of phase 1 meetings, where sponsors want to submit marketing application to FDA under subpart E or subpart H. Also end of phase 2 and pre phase 3.
  - Type C meeting changes: If sponsors are seeking a new surrogate endpoint for the basis of approval, they will have to submit a background at the time of the request for a Type C meeting.
  - Preliminary response from FDA will be sent to sponsor no later than 5 days prior to Type B (end of phase) and Type C meetings.
    - Sponsors have 3 days to respond, and minutes are sent out within 30 days.
    - Sponsors can submit their own meeting minutes, which will then be documented in application.

- NDAs, ANDAs, BLAs, and Master Files need to be submitted in electronic format starting 5/5/17.
    - Commercial INDs need to be submitted in electronic format starting 5/5/18.
    - Investigator-sponsored INDs can still be submitted in paper, though a PDF version is helpful during review and is requested.
- When submitting changes to protocols, FDA requests submission of both a clean and a tracked-change version, which assists with reviewing process.
    - Sponsors can begin their protocol change once it has been submitted; however, if a safety issue or concern is identified during review, the FDA will reach out to put the protocol on hold.
- FDA requests that sponsors get secure email, so that information can be sent to sponsors in a timely manner. The secure email at FDA is secureemail@fda.hhs.gov. If sponsors do not have secure email, information can be faxed or sent by post.

FDA Introductory Remarks

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/02_Omokaro.pdf
Presenter: Stephanie Omokaro, U.S. Food and Drug Administration

- Overview of FDA activities
    - In 2016, the majority of the FDA's regulatory and review activities in NASH were:
        - Pre-submission meetings (31%)
        - INDS (28%)
        - Expedited program requests (17%)
- Regulatory considerations for endpoints in NASH
    - **Early Phase Trials** (proof of concept, dose-ranging)
        - Need to consider the mechanism and anticipated time course for changes when selecting endpoints and design.
        - While liver transaminases have been used, changes have not been found to be predictive of histological changes in short-term duration trials.
        - Non-invasive biomarkers, such as elastography as measured by MRI, or serum biomarkers of disease activity based on the drug's mechanism have also been used.
            - These may reflect the activity of the drug and its effect on the underlying disease process; however, it is unclear if they are predictive or correlative with histology.
    - **Phase 2 Trials**:
        - Histological evaluation:
            - NAFLD Activity Score (NAS)
                - Decrease of greater than or equal to 2 points
                - At least a one-point reduction in lobular inflammation or hepatocellular ballooning
                - No concurrent worsening of fibrosis stage
    - **Phase 3 Trials**:
        - Biopsy-based surrogate endpoints:
            - Complete resolution of NASH on overall histopathologic interpretation by an experienced pathologist with a NAS of ballooning of zero, an

inflammation score of 0-1, and no worsening of fibrosis by the NASH/CRN Brunt-Kleiner scale.
- At least one point improvement in fibrosis score, and no worsening of NASH by NAS.
  - The choice of either of these as a primary endpoint and the other as a key secondary endpoint, or assessment of both changes as a co-primary endpoint is acceptable.

- Subpart H or E generally requires that a phase 4 trial to verify and describe clinical benefit be ongoing at the time of marketing approval.

- **Phase 4 Trials**:
  - The following clinical benefit endpoints are acceptable and reflect a meaningful change in clinical status associated with morbidity and mortality:
    - All-cause mortality
    - Liver transplant
    - Hepatic decompensation events
    - Histological progression to cirrhosis
    - Increase of MELD score from below 12 to ≤ 15
  - Hepatocellular carcinoma (HCC) has been proposed as a phase 4 endpoint; however, there are issues with HCC as a component of clinical benefit composite:
    - Multifactorial etiology and complex pathophysiology.
    - Majority of events in the endpoint analyses will be primarily cirrhosis events.
    - Few HCC events relative to the other components such as death and liver transplant.
    - HCC is not expected to have a significant impact on endpoint analysis.
    - There are issues with implying that the drug reduces HCC when not assessed and shown independently to do so from the other components.
    - Need for appropriate screening at enrollment to ensure that cases are not missed at the start of the trial and adequate assessments during the trial.

- Unsolved clinical development issues in NASH
  - **Investigational agents**:
    - Pathophysiologic concept of whether a drug is purely anti-fibrotic or purely anti-inflammatory.
      - Is it possible to affect one without impacting the other?
    - Impact of early hepatotoxic signals on drug development in a population already with underlying liver disease
  - **Population**:
    - Appropriately defining high risk F1 subjects for trial inclusion
  - **Placebo & standard of care**:
    - Precisely defining the placebo effect and exploring its mechanism and impact
    - Placebo arm sharing across multiple programs and sponsors, given the increasing drug development in NASH
    - Incorporating standardized diet and exercise programs modeled from obesity clinical trials
  - **Histology-based endpoints**:
    - Necessity for additional liver-trained pathologists

        - Standardization of the overall histologic interpretation for use across the spectrum of pathologists
        - Understanding of the intra- and inter-rater validity to better design clinical trials
    - **Role of non-invasive biomarkers**:
        - Standardization of methods and protocols for diagnostic imaging
        - Establishment of clinically meaningful thresholds
        - Increasing measurement frequency of endpoints in non-invasive biomarkers to assure validity with additional data
        - Validation via concurrent biopsies
- Pediatric development issues
    - When enrolling minors, under 21 CFR 50 subpart D, investigators are required to demonstrate the prospect of direct benefit to the subject as a result of the drug intervention.
        - Treatment of fatty liver alone is inadequate to support direct benefit in minors.
    - Need to identify subpopulations that may benefit from potential treatment, such as has been done in adult patients with F2 and F3 fibrosis who are at risk for liver-related adverse events.
    - Need for pediatric natural history data, and to incorporate natural history studies in the initial pediatric study plan.
- FDA upcoming events and updates
    - Workshops on alcoholic liver disease; pediatric chronic idiopathic constipation, and irritable bowel syndrome
    - Recruiting candidates with relevant experience for positions with DGIEP

Regulatory Update from Europe: Interim Endpoints in Phase 3 NASH Trials

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/03_Schabel.pdf
Presenter: Elmer Schabel, European Medicines Agency

- Interim evaluation of phase 3-4 trials in NASH
    - Would like to see co-primary endpoints:
        - Composite of complete resolution of steatohepatitis (0 for ballooning, 0-1 for inflammation) and no worsening of fibrosis stage
        - Composite of one point improvement in fibrosis stage (at least 1 stage) and no worsening of steatohepatitis (ballooning and inflammation score)
            - These two composite endpoints should be evaluated at the individual level, and written co-primarily. Or, one composite can be a key secondary, and that could also be acceptable.
    - The intended scenario with conditional licensing/ accelerated approval will be more difficult in later development programs with regard to the fulfillment of the condition/ phase IV.
        - This is of importance, as the relationship of inflammatory changes and fibrotic changes is not clearly known, and the endpoints at interim have to be sufficiently strong to conclude on a positive risk benefit.
        - For final analysis, things might get worse because it will be more difficult for later substances going into development to keep full trial integrity. Therefore, importance of a strong interim evaluation will increase.
- Different mechanisms of action
    - How to deal with a primary inflammatory that might not be able to show improvement of fibrosis at the interim?
        - At least should co-primarily evaluate the non-deterioration of fibrosis.

        - Effects should be shown on the individual level (the composite) and at the population level (co-primary)
    - How to deal with substance that shows effects on fibrosis but not on inflammation?
        - Investigator could not plan for a study in phase 3 that fulfills both co-primaries that have been proposed.
        - What would a "sufficiently strong" interim endpoint be?
            - Composite at the individual/patient level of 2-stage improvement of fibrosis, and at the same time, no worsening of NASH.
            - This is a strong endpoint, but takes into account uncertainties about inflammation.
    - Substance that demonstrates no relevant anti-inflammatory activity, but has relevant effects expected for fibrosis.
        - Proposed slightly different patient population, Phase 3 and 4, including cirrhotic patients.
            - Proposed to and agreed to by BfArM only (not harmonized European position).
                - Reversing cirrhosis by one stage to stage 3 fibrosis could also be part of the primary evaluation.
                - For patients with stage 3, would still need at least 2-stage improvement, with no worsening of inflammation (if inflammatory part of improvement cannot be addressed).
    - Can these endpoints be met within a realistic timeframe?
        1. Good phase 2 data can help to estimate the effect sizes that can be achieved in a certain time frame, and enables planning properly for the phase 3
        2. Prolong the time until interim analysis (increase the effect size)
        3. Increase the number of patients to be included in the interim (strengthen the statistical basis
            - 2 and 3 are interdependent, along with effect size and statistical strength.

Discussion

- To inform phase 3 and see a reduction in two points in fibrosis, phase 2 studies must be large or enroll patients at very late stage. What are recommendations for phase 2 in these cases?
    - It's always difficult to do recommendations based on data that are already available from phase 2 and where you have done the recommendation for phase 3. The recommendation shown on the slides is that phase 2 should be long enough to evaluate both the rates within one year (standard duration for a phase 2 trial) both for the resolution of the NASH, and the fibrosis development.
    - Then see what the rate of reduction of fibrosis can be, and what the rate of resolution of NASH can be, and then extrapolate for longer time periods. This is the uncertainty we cannot get rid of- we don't know whether development will be linear over time.
- If a drug company in phase 3 is able to conduct a trial to the end and prove that improvement in the soft surrogate resolution of NASH does indeed translate in the same population several years later into an improvement in clinical outcomes, is that enough proof—one trial, 2000 patients—is that enough proof so that the next drug candidate does not have to go through this whole process? Or do we need to have 10 companies conducting phase 3 trials all the way to the end, each one proving that the soft surrogate is predictable?

  - Unable to answer whether one program is going to be able to change the paradigm for all programs and how the disease is thought about. It likely will not be one program, though not sure that 10 would be needed.
  - This will require a lot of discussion and inter-agency collaboration with FDA, EMA and other regulatory agencies to be able to determine whether once you've shown it, have you shown it for all potential drugs? Have you shown it for all potential pathophysiology?
- What is the process to become a generally accepted surrogate? Is there an example from bone density or from hemoglobin A1c, lessons learned that could be applied here?
  - Example of sustained viral titer response in HCV, which started out as a surrogate reasonably likely to predict and required clinical benefit. After several different trials, and several different drugs with different mechanisms, they were able to show that it did predict clinical output, and it was accepted as a validated surrogate. So generally, for a surrogate to show reasonably likely causality requires several clinical trials to be done with different mechanisms or the surrogate is only validated for a particular mechanism.
  - A drop in blood pressure by 10 points is accepted as a valid surrogate only after multiple trials showed consistently clinical benefit. When approximately 500,000 patients across multiple trials showed this benefit, that's when FDA accepted lowering of blood pressure as a surrogate.
- Up to a quarter of NASH patients who develop HCC do so before developing cirrhosis. There are companies with pre-clinical data suggesting that their drug may inhibit the development of HCC. It may be different to include HCC in the power of the endpoint. On the other hand, there may be effects, but those are very hard to discern out of a phase 2 study. Is this a one-size-fits-all, or should this be something discussed and considered on a drug-by-drug basis?
  - Up to now this has been discussed on a case-by-case basis. There was some discrepancy between the position of the FDA and CHMP with regard to the inclusion of HCC into the final endpoint. This is up for discussion. There are reasons to believe that this could have an effect, but there are also reasons to believe it might not be possible. The worst thing to do is add noise to the evaluation of the final endpoint.
  - It is really hard to know once treatment starts whether there's a prevention occurring, or there's a cure occurring. Always open to case-by-case discussions.

SESSION #2: FIBROSIS IN THE CONTEXT OF NASH

Moderators: Detlef Schuppan, Mainz University Medical Center
Vlad Ratziu, Hôpital Pitié Salpêtrière

- Liver disease in patients with NASH is both a destructive and inflammatory process, with a fibrosis component that determines progression to cirrhosis. The interdependencies between these two pathways are still unclear:
  - Can we act on one without having any impact on the other?
  - Can we have long-term benefit with a purely anti-fibrotic drug that does not have any anti-inflammatory effect?
- The drugs that had a clinical benefit in terms of reduction of fibrosis stage also have anti-inflammatory property.
  - Does a purely anti-fibrotic drug exist?
  - Do these drug candidates impact both fibrosis and the inflammatory and lipotoxicity pathways to different degrees?
- The first talk by Detlef will cover the biological basics of fibrosis and will try to answer the following questions:
  - Which mechanisms of hepatic fibrogenesis are amenable to drug intervention?

  - What are the most promising molecular targets for an anti-fibrotic drug?
  - Is this dichotomy between anti-fibrotic drugs vs anti-inflammatory drugs justified?
    - Does an anti-fibrotic action require an anti-inflammatory mechanism, or is a purely anti-fibrotic drug sufficient for clinical benefit?
- The second talk by Arun will look into the clinical aspects of fibrosis, and try to answer:
  - How to best measure the anti-fibrotic effect in a human trial?
    - Still hesitating between one-stage fibrosis reduction and two stages or no fibroids at all. What is really achievable/ realistic? How can we measure that beyond histology?
  - What are the benefits for disease progression from an anti-fibrotic drug candidate?
    - Is it enough to have more patients that have a one-stage reduction of fibrosis in one arm than in placebo?
    - Can you have more people improving fibrosis but the same number of people progressing to cirrhosis?
  - What are optimal endpoints for anti-fibrotics, and what are trial development issues?
  - What would combination therapy with an anti-NASH and anti-fibrosis drug look like?

Liver Fibrosis in NASH: A Roadmap for Drug Discovery and Pharmacotherapy

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/04_Schuppan.pdf
Presenter: Detlef Schuppan, Mainz University Medical Center

- Relevance of advanced liver fibrosis/cirrhosis as endpoint
  - Cirrhosis (including compensated) greatly increases risk of decompensation, HCC, and liver-related death and is therefore considered a hard endpoint.
  - Non-cirrhotic fibrosis is not a hard endpoint; however, demonstrating that treatment interferes with or reverses the progression of fibrosis to cirrhosis, is considered acceptable.
- Underlying mechanisms
  - Normally resting myofibroblast hepatic stellate cells contribute to both cirrhosis and fibrosis
  - Many signaling pathways and cells involved that are equally important in cirrhosis and HCC, including macrophage, oxidative stress, insulin resistance, progenitor cells, cholangiocytes, activated myofibroblast HSC.
  - Effective anti-fibrotic treatment would revert the fibrogenic phenotype of the activated myofibroblast, decrease excess synthesis of matrix, decrease synthesis of proteinase inhibitors, and the synthesis of certain proteinases in a regulated way would increase to induce degradation of excess matrix.
    - If combined with a stimulation of hepatocyte regeneration, theoretically that could reverse a decompensated cirrhosis
- Reversibility of advanced fibrosis
  - In chronic hepatitis B, hepatitis C, and also autoimmune hepatitis, reversal of at least compensated cirrhosis can be induced when the causal trigger is hit very effectively.
  - In the 5 year follow-up of Tenofovir treatment of chronic hepatitis B, 28% of enrolled patients had compensated cirrhosis, and within 5 years, reduced to 7%.
    - Overall, all groups improved, and there was a decrease in HCC development.
    - Patients with a BMI ≥ 25 had a 7 times higher increased risk of progression to cirrhosis.
- Anti-fibrotic approaches

    - Fibrosis is an interplay between the epithelial cells, the sinusoidal cells, and also an interplay between the portal cells and the inflammatory cells that finally determines the final development of fibrosis or fibrolysis.
        - Very complex interactions between cells, cytokines, chemokines and other factors and the matrix.
        - Anti- or pro-fibrotic effect of certain factors is context-dependent, and dependent on the stage of the fibrogenesis or fibrolysis or inflammation.
        - Unambiguous targets are rare, and most targets can have a pro-fibrotic or antifibrotic effect depending on the context.
        - Future should be biomarker guided therapies for the individual patient, but also in phase 2 clinical studies.
- Role of activated cholangiocytes
    - "First hit": inflammation and proliferation stimulus to hepatocytes to regenerate
    - "Second hit": oxidative stress (in NASH)
    - Combined, cause hepatocyte apoptosis and growth arrest, resulting in progenitor cells.
        - Progenitor cells: fibrogenic
            - Substrate/ substance of ductular proliferations seen beyond stage 2 fibrosis, and have unique surface equipment, for example, the alpha (v) beta (6) integrin.
            - Produce a host of pro fibrogenic cytokines and factors that induce a matrix and the myofibroblasts.
            - The myofibroblasts and development of ductular reaction produce factors that maintain these ductular proliferations.
- Inflammatory cells and macrophages
    - M1: classically activated macrophage, pro-inflammatory, seem to promote fibrolysis in an acute inflammation.
    - M2: alternatively activated macrophage, immunosuppressive and pro-fibrogenic in chronic inflammatory conditions. A subgroup also belong to tumor-associated macrophages.
    - Regenerative macrophages: appear to be anti-fibrotic and anti-inflammatory, though still ill-defined.
- Mechanism-based anti-fibrotic therapies
    - There are many drugs in phase I-II trials to address fibrosis, including: Ask1 has promising data but a small study in terms of fibrosis; αVβ6 integrin inhibitors have been proven safe to certain degree; Anti-Tweak antibody prevents emergence of fibrogenic progenitor cells; TGFβ antibody decreases fibrosis; GLP-1 agonists beneficially modulate macrophages.
    - Anti-inflammatory agents are not necessarily also anti-fibrotic agents. It can be the opposite in fact.
        - anti-TGFβ1: inhibit fibrosis, but enhance inflammation. TGFβ1 is a major pro-fibrotic and immunosuppressive cytokine.
        - anti-CCR2, CCR5: reduces fibrosis, though no impact on inflammation.
- Assessment of fibrosis
    - Several studies have demonstrated that biopsies taken from two parts of the liver at one time in a single patient have high sampling variability for one out of four stage difference in fibrosis.
        - Hepatitis C: ~30-35%
        - NASH: ~40%
        - Biliary diseases: ~60%

    - Smaller patient cohorts do not yield very reliable data on fibrosis progression or reversal even if results are statistically significant.
    - Small HCV study, compared 6 biomarkers scores, F0-1 vs. F2-4
        - All had AUROCs 0.80-0.85, which indicates only modest tests are needed to distinguish no/mild vs. significant fibrosis.
- Biological plausibility for direct markers of fibrosis
    - Looking at myofibroblasts that produce matrix proteinases like pro-collagens (ProC1 and ProC3 are major fibrillar collagens in scar tissue and liver), normally these peptides have to be cleaved off before fibrils in the extra-cellular space can form, and are released into the circulation, where can be measured as markers of fibrogenesis.
    - When certain degradation fragments produced by matrix metalloproteinase are detected, this could be related to fibrolysis.
    - Panel used in many clinical studies is a composite of P3NP, TIMP-1, and hyaluronic acid
- Example of large chronic hepatitis C fibrosis study, nonresponsive to antiviral therapy, they received PPAR-gamma agonist with high potency (farglitazar) at two doses versus placebo.
    - Clinical study with biopsy data as well as the serological data to predict retrospectively the outcome of the clinical study.
    - Biopsies large, centrally read, and there was no difference in fibrosis between all groups.
        - Retrospectively looking with a pro-C3 marker, the patients who initially had a low pro-C3 level did not respond in follow up. Where those with a high initial pro-C3 level had a significant decrease with treatment.
        - Replicated histologically – those with high initial value who had an increase in fibrosis (measured by morphometry), had a significant decrease in their pro-C3 levels.
        - Anti-fibrotic treatment response was indicated in the subgroup that had not been detected before.
- Markers of fibrogenesis and fibrolysis
    - Comparing healthy patients and patients with a rapid progression towards cirrhosis after transplant:
        - A2 is high in healthy patients, and low in highly fibrogenic patients
            - A2 increases in highly fibrogenic patients after highly effective antiviral therapy.
        - A9 is low in healthy patients, and high in highly fibrogenic patients
            - A9 decreases in highly fibrogenic patients after highly effective antiviral therapy.
- Summary:
    - Early cirrhosis is reversible when the major fibrogenic (inflammatory) trigger is eliminated.
        - Might be possible for even decompensated cirrhosis.
    - Most NASH drugs target the hepatocyte and its metabolic derangement, which may have secondary anti-fibrotic effects due to cholangiocytes or progenitor cells.
        - Some drugs target inflammation, but this does not necessarily go hand-in-hand with anti-fibrotic activity.
        - Other drugs address multiple cells, and effects are difficult to predict.
    - The major antifibrotic targets are related to the activated progenitors or cholangiocytes, the macrophages, and hepatic stellate cells.
    - Several pharmacological therapies that may inhibit progression and speed up reversal have already entered the clinic.

- Starting to have biologically plausible markers of fibrosis and especially fibrogenesis and fibrolysis to be able to stratify patients before treatment and to noninvasively monitor their treatment response and hopefully predict their long-term treatment response.
  - Should permit short proof-of-concept studies, and also the testing of combinations and personalized, individualized therapy for the patient

Challenges and Opportunities in Clinical Trials Focusing on Fibrosis

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/05_Sanyal.pdf
Presenter: Arun Sanyal, Virginia Commonwealth University

- Current paradigms for drug development in NASH
  - NAFLD → NASH → NASH w/ NAS ≥ 4, F2-3 → Cirrhosis → Outcomes
    - Goal: reduce outcomes
    - Target: Cirrhosis, or NASH w/ NAS ≥ 4, F2-3 (high risk) to prevent progression
  - Issues:
    - Anchoring drug development on histology
    - Debate about activity scores versus fibrosis
    - Assessment of changes in activity
    - Assessment of fibrosis
- Current fibrosis staging system
  - Stage 1 and 2, measure the distribution of collagen more than the amount of collagen.
  - Stage 1 could potentially have more fibrosis, which is primarily sinusoidal fibrosis.
  - Stage 2 is excess fibrosis in the portal area and in the sinusoidal area.
  - Stage 3 there is a big jump in amount of collagen present.
  - Stage 4 further increases in collagen.
    - Progression through stages is a continuous process; however an ordinal scale is used, resulting in errors introduced at the boundaries of the scale.
    - Progress from stage 2 (some scar in sinusoid and portal area) to bridging fibrosis (sinusoid to sinusoid, or sinusoid to portal tract) – are those processes the same? Not captured well by current system of histologic classification.
  - New tools being developed such as multi-photon microscopy that allow a large amount of collagen fibrillary properties to be observed- which requires different ways to visualize the data, such as a heat map.
    - Using this type of technique, can observe progression from no fibrosis to advanced fibrosis across the different regions, and start to see where the changes are occurring, and using this to create mathematical models.
    - Possibility that there is room for improvement and understanding the evolution of fibrotic changes using histology- particularly from F2-F4 which is being missed by the current staging system.
- Activity vs. Fibrosis Debate:
  - Scientific questions need to be framed accurately. Bad question = bad answer unless by coincidence. Disease activity and disease stage are not the same.
    - Disease activity: all of the processes trying to make the liver turn into cirrhosis
      - what's going to happen to the scarring or the disease stage over time
      - helps to understand progression towards cirrhosis
    - Disease stage: how far along on the journey towards cirrhosis
      - how likely it is that you're going to have outcomes (linked to development of cirrhosis)
  - Disease activity is assessed by presence of steatohepatitis, or with activity scores.

        - "Steatohepatitis": having some fat, inflammation, and ballooning, no information on distribution.
            - "Definite Steatohepatitis"- clearly centri-zonal distribution (Beth Brunt and David Kleiner)
            - "Borderline"- don't fit into clear-cut pattern
        - Example NASH CRN cohort- definite, borderline, and NAFL
            - "Definite" patients tend to progress more over time than borderline and NAFL. If lumped together, would introduce noise.
            - Important to pay attention to the definition used, and account for it in study design.
    - Evaluating Activity
        - Scores: combine steatosis, ballooning, and inflammation in various combinations
            - All linked- to varying degree- with biological plausibility, all are measurable and reproducible. More confusion with association with progression.
            - Limited dynamic range- 0-2, not much ability to change in either direction (i.e., score of 1)
        - Confounding problems: Progression to cirrhosis → burn out of disease activity, and lose de novo lipogenesis though continue to have hyperinsulinemia
        - Underlying physiology and biology of metabolic disturbances, cell stress, and inflammation → reflected in circulation in form of altered cytokines, lipids, metabolites, and proteins. Possibility to link to histologic progression and develop new paradigms.
        - Hypothesize that there is an internal "biological clock" that is not well understood influencing the waxing and waning of both disease activity and fibrosis.
    - Activity Summary:
        - Disease activity waxes and wanes
        - Conventional histological findings and scores do not entirely account for the risk of progression to cirrhosis
        - Changes in NAS likely more important than baseline NAS
        - Need to validate new histological systems- think about including portal inflammation. There is room for improvement.
        - Endpoints must align with mechanism of action
    - Evaluating Fibrosis
        - In addition to biopsy, three other tools: sheer wave elastography, MRE, and transient elastography. All measure different things, and each has pros and cons.
        - A sound wave traveling through the liver generates both a compression (quick) and shear (slow) wave. They can be separated temporarily.
            - With 2 axes, need to remove compression wave, requires additional mathematical manipulation. The z-axis is not available, so the result is a simplified version of the formula- may not be fully accurate.
                - Highlights need to move to 3D MRE
            - Still need to draw a region of interest- raises issue of translating data from one site/machine to another. Need to automate and validate.
                - No issue using MRE for early POC, but need to be aware of limitations.
        - Both placebo and active drug response rates appear to go up, showing how difficult it is to interpret as the disease waxes and wanes.
        - Subset of patients who completely resolve fibrosis.

- Argue that complete resolution is a clinically meaningful benefit.

- Subset of patients progress to cirrhosis.
  - Placebo: risk of progression is curvilinear → increase in fibrosis increases the risk for progression to cirrhosis.
- Fibrosis Benefit: $\frac{\text{\% fibrosis resolution (benefit)}}{\text{\% progression to cirrhosis (harm)}}$
  - Great drug: 100% resolution/ 0% progression
  - Bad drug: 0% resolution/ 100% progression
  - Fibrosis benefit index: $\text{benefit}^{\text{active}}$ Rx/ $\text{benefit}^{\text{placebo}}$
    - Both dynamic ranges, clinically meaningful, measurable, reproducible, analyzable.

Discussion

- Cirrhosis is looked at as a histologically defined threshold, but patients' continue to progress following identification of that threshold, with increasing fibrosis, vascular changes in the liver, bile duct changes and progressing anatomical differences. Patients don't die at the threshold of cirrhosis, but rather 5-10 years later from complications. What are the current thoughts on the evaluation of patients with NASH cirrhosis, particularly integrated functional tests, HVPG and portal disease, and the relationship of those integrated functional tests with progressing fibrosis?
  - This is the ceiling effect of the classical staging system we have. One of the problems is that we are looking at a small part of the liver. To look at fibrosis as a continuous variable, we must change the sampling effect, and remove the ceiling effect where stage four is end of cirrhosis. Researchers should double up on methodology which looks at all of the liver as a continuous variable for which likely need cross-sectional imaging, such as MRI. MRI can also measure some of the functions such as hemodynamic function. Then you can really look at wedged pressures or portal changes, portal flow changes, and actually turn this test into a continuous variable. Currently we don't have this, but it is what is needed.
  - Historically looking at the cirrhosis literature, it's almost etiology agnostic. The assumption has been that cirrhosis from alcohol, hepatitis C, etc. is the same. But that's not true and the rates at which clinical endpoints develop are based on different etiology. This was published for NASH vs. hepatitis C 10+ years ago, and others who have looked at it also see the same patterns. Our experience has been a lot of NASH patients decline much more rapidly and surprisingly after having looked great in clinic. This is where some of these quantitative liver function tests may be very valuable. There's already published literature on some of these quantitative tests with breath test, cholate clearance, etc., in being able to identify these people, and these may be very valuable but need more validation in the context of large clinical trials.
  - Many cirrhotics can stay compensated for a very long period of time. And then it doesn't look like most of the complications of cirrhosis are directly related and exclusively related to the amount of fibrosis. A lot of complications that are fatal have to do with infections, with the intestinal permeability being altered, with portal hypertension which is not all about the amount of fibrosis. At that late stage, we have to think about the mechanisms that are needed to rescue the patient, and those mechanisms shouldn't be exclusively focused on inhibiting progression of fibrosis at the cirrhotic stage. The suggestion that one of the endpoints in treating cirrhotics would be a regression of one stage in fibrosis

is surprising. So going from F4 to F3 or from Ishak 5 or 6 to Ishak 4. That would not capture most of the reasons for decompensation in cirrhotics.
    - There will be some data shown at AASLD that regression from stage 4 to stage 3 is associated with decreased clinical outcomes.
    - Cirrhosis sets the stage for more decompensation or propensity to decompensate and to get infections and so on. There are short-term benefits with anti-inflammatory or antibiotic therapies in cirrhotics, and there are long-term benefits when reversed to a non-cirrhotic/ functionally non-cirrhotic, which is not linked tightly to the amount of connective tissue you have in cirrhosis.
- From the studies with antiviral treatment in hepatitis B and hepatitis C, we know that after 5-6 years of treatment, a proportion of patients with cirrhosis will regress and cirrhosis will disappear. Are there any predictors for patients with NASH cirrhosis that will be able to identify which patients will resolve cirrhosis and which will persevere? If the treatment starts too late, the collagen is too solid; maybe it is beyond the point of no return. Are there likely to be any markers to predict the reversibility of NASH cirrhosis?
    - There are novel histological technologies which provide some idea about fiber structure that could be predictors. There's a big initiative in China now looking at cirrhotic hepatitis B patients who do not reverse - about 25% of patients with highly effective antiviral therapies. There are histological efforts and now discussions about using novel fibrogenesis, fibrolysis markers as a predictive tool for these subpopulations.
    - It might be that those that reverse are the ones with very early cirrhosis and were years away from decompensation.
    - There's bridging fibrosis with thick, well-formed septa and then there's fine, wispy, very early bridging. And it is the same with cirrhosis. Sometimes there is early nodule formation, and the more cross-linked your collagen gets the harder it is to move it. Historically, we've looked at portal pressures. In the bariatric or HCC fields, the paradigm has been that a resection is not done if there's clinically significant portal hypertension.
    - The cross-linking plays a role, but it doesn't play the ultimate role. So even highly cross-linked collagen can be degraded completely by collagenases. The drug may only have a little more difficulty getting there. These upcoming studies from China have shown that it's not just the thickness of the septa and not tightly linked to the amount of collagen deposited. There are other factors, for example, the density of inflammatory cells that potentially can reverse fibrosis by producing proteolytic enzymes.
    - The concept of F3 and F4, are too broad and there is work going on redefining and dividing out some of those fibrosis stages that might be productive in that setting.
    - Histologically we have defined 4, A4, B4, C which are very well correlated with the clinical and the HVPG. And this is exactly the same for stage 3. One of the issues is that the scoring system for fibrosis is probably the worst we have. In stage 3, you can have one fibrosis bridge, or a pre-cirrhotic liver and both be in stage 3. So each stage should be looked at a little better and developing some scoring system which is more accurate. The one we have is not linear at all: 1 and 2 is very little fibrosis, and it gets up to 3 and even 4. And in clinical trials regression of one stage is completely different if we consider regression from stage 4 to stage 3, or from stage 2 or stage 1. It is not linear and does not cover all the clinical features.
        - How good is collagen quantification by Picrosirius red?
            - There is a rough correlation with the collagen quantification, but we have to think that stages are not only the amount of collagen; it's also associated with architecture and distortion, with vascular modification.

And you cannot quantify that when you just measure the amount of collagen.
    - A combined score of collagen and stage would probably be a good way to go. But we have to think about a more accurate scoring system that we can do on the biopsy, even if it is a very small part of the liver.
- An important point is that to move from stage 4 to stage 3, a patient must move a ton of collagen. Whereas, moving from stage 2 to stage 1 or stage 1 to zero is much less movement of collagen.
    - This provides support for treating early, and feeds into the use of noninvasive biomarkers because the opportunity to detect is much easier at the higher ends of fibrosis than it is at the more modest ends.

- A slide showed that people with high pro-C3 levels respond to farglitazar in terms of antifibrotic response, and those with low pro-C3 do not. And that probably is because pro-C3 is a marker of active fibrogenesis though this may or may not be confirmed in larger validation trials. Do we have to fully validate pro-C3 as a fibrosis or fibrogenesis marker in order to use it as a way to select or stratify patients for antifibrotic therapy? Or is it enough to find some biological surrogate that predicts response even if that biological surrogate is not fully validated as a fully fibrosis biomarker?
    - The marker should be fully validated for the full outcome. Research on the noninvasive assessment of fibrosis has been going on for the last 20 years, but most of the focus has been on validating the clinical way, to use in daily clinical practice. The issue with histology is variability- is it enough to have an area under the ROC somewhere between 0.85 and 0.89? The problem is that we do not know whether anything can be better than histology. If we want an assessment to be better, or at least as good as histology, we need a validation study that uses the hard endpoint, the outcome.
    - You can't beat the gold standard unless you change the gold standard. The only way to leapfrog is when the gold standard becomes clinical outcomes. When the NASH CRN was set up 17 years ago, all analyses were anchored to histology because that seemed to be the expedient thing to do. But of course we are still having the same discussion.
    - We do have better tools which are better defined now. Pro-C3 is much better defined than the other markers that we have in terms of biosynthesis. To support this claim we can do pre-clinical studies and use the same parameters and do this in NASH and fibrosis studies and co-validate. We still have to stick with histology for a while, but quite a few developers are trying this, and that's the reason for the LITMUS IMI proposal. We have to co-validate with ongoing studies, and also think about POC studies with low numbers of patients to allow early decision-making for drug development.
        - From a drug development standpoint, since there is so much heterogeneity in the disease, are we at a point where we can have a set of markers that will be used in a 'standardized' sort of way? With standardization of cut-offs for these parameters? Otherwise, everybody is doing everything under the sun, and that's one of the key challenges.
        - We are the farthest advanced with pro-C3 because there's some semi-approval already, it has been cited in a lot of clinical trials retrospectively, and is being studied in ongoing POC studies. There are a few others like pro-C6 on the way, and there are a few others less developed. With the LITMUS proposal we are trying to develop these as far as the pro-C3, if they make sense.
    - Are we saying that every marker we don't really use as a marker of efficacy of intervention should be demonstrated as a marker of efficacy rather than cross-sectional marker of individual pathological process? With ELF, it changed in a positive way in the

phase 2 trial when obeticholic acid was used, but it did not change when the phase 3 trial came up in a way the histology changed.
    - The phase 3 trial is ongoing, but in the FLINT trial, ELF was not run. This was only done in the first Gastroenterology paper. The context of use is very important for biomarkers. Looking at something as a general diagnostic is a different study versus doing a study to validate it as a marker of therapeutic efficacy.
- Prior data in pro-C3 could be used to leverage information to be able to validate it. That would aid the process of validation and potentially expedite it. There's probably a lot of research and prior data on other diseases other than NASH and pro-C3 that could help that process. Is time incorporated into considerations for patient outcomes? For example, if a patient moved from F4 to F3 and was there for a year or two.
    - A move from a good, solid F4 to an F3 is a positive change. Where it becomes more subtle is at the earlier end of the spectrum, the F1s, F2s, where changes of one point possibly depend on the histologist's mood that day. But at the more advanced end of the spectrum, that is a meaningful change. However it's a work in progress to get the long-term data to back that up.
    - There would be more confidence if we would describe one stage reduction with something else than the Kleiner or METAVIR score because F4 to F3, in the Kleiner and NASH CRN classification can mean either almost total disappearance of bridging fibrosis if it's very early stage 3 or it can be just pre-cirrhotic if it's very advanced stage 3. In that case, favor using a more detailed and granular scale of fibrosis, demonstrating a move from Ishak 6 to Ishak 3 or Ishak 4; that would be a more meaningful antifibrotic effect.
        - If there was a smaller change but it was for a long period of time, would that be meaningful?
        - We don't have an evidence-based answer to that question. But to come back to this whole issue of changing from stage 4 to a stage 3, new results being presented show that with a change from stage 4 to stage 3, clinical outcome risk is substantially lowered. Hopefully, as more and more studies start reading out, if we can show in study after study that going from a stage 4 to stage 3 does reduce clinical outcomes, then that's very relevant.
        - Graphically, if you look at these kaplan-meier curves at the different Ishak fibrosis stages and correlation with survival free of hepatic complications, they don't overlap. So you clearly go from one step to another. You clearly gain in terms of survival free from hepatic complications. So it might be that histology somehow underestimates the real clinical benefit because there is benefit in terms of survival, even with one stage reduction.
        - We are looking for refinement of histology, not to throw histology out because otherwise that really stops development.
    - Does the antifibrotic effect of a drug wane with time? Is it maximal in the very beginning of the disease process and, then after a while, it's like with diabetes where the progression of the disease takes over even in responders? That is something that could reduce the long-term benefit of a one-stage fibrosis reduction, coming to the point of how long patients stay with an inferior stage on a drug.
    - That may be influenced by the nature of the drug and where is being targeted. If going higher up into the biological drivers of injury, it's more likely that the fibrosis benefit will be maintained. Whereas, if just targeting sort of a plastic fibrosis stage later on, the effect may wear off quite quickly.

- The points about having continuous measures of fibrosis are good ones. There is nice data showing that collagen content predicts outcomes. Changing collagen content over time predicts outcomes in advanced fibrosis. ELF test does the same, so I think we have many pieces of data that line up, and we should be looking more closely at these in further trials.

SESSION #3: CLINICAL TRIAL MANAGEMENT

Moderators: Laurent Fischer, Allergan
Rebecca Taub, Madrigal Pharmaceuticals

Common Issues in Clinical Trials: Patient Recruitment, Retention, Eligibility, Screening Failure

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/06_Francque.pdf
Presenter: Sven Francque, University Hospital Antwerp

Recruitment and Referral

- Previously, recruiting patients was relatively easy (few trials, in phase II, with patients waiting to be recruited); however, now that there are two phase 3 trials ongoing and two more start up shortly- needing 2000 patients per trial- there is a challenge to find patients and recruit them into trials.
    - The expert centers have a pool of NASH patients, but with all these trials, that pool is rapidly exhausted.
    - Referrals from colleagues are now very important.
- Increasing awareness: patients themselves know little about the disease, and the general population knows even less.
- Need to provide general information about the disease and also trial-specific information.
    - Can run into issues on country- specific regulations (for example, approval by ethics committee).
- Use media to provide information, for example the NASH Education Program aims to increase general awareness and also awareness in the medical community.
    - Developed flyer with general information which is hopefully easily understandable, and is meant to be general information which is available to everybody with some details on the natural history, on the prevalence of the disease, the consequences of the disease, and what we can do or try to do about it.
    - Also videos with easily accessible information.
        - It is important not to just look at it from a specialized hepatological perspective but also from other fields because, in this population, obesity, diabetes, and so on are very important players within this multi-systemic disease.
- Increasing awareness of general practitioners is an important step
    - Students currently in medical school learning about NASH, but those previously graduated will have less knowledge.
    - Need to be involved in post-graduate courses, conferences, and meetings
    - Developing posters, leaflets for the waiting room
- Working together with other specialists
    - Developing common guidelines: EASL has written guidelines with European Association for the Study of Diabetes and the European Association for the Study of Obesity
        - This is the first step, need to make sure people are aware of the guidelines and that they are implemented in clinical practice.
        - Little in published diabetes care guidelines about the liver.
        - Conferences/ meetings that involve other specialists (cardiologists, diabetologists, etc.)

- Prepare referral letters to make it easier for them to refer patients to the centers that run the clinical trials or are more specialized in this disease.
- Send newsletter with an update on the clinical trials you are running to referral network
- Once patients come in and you talk about the clinical trial, it's important to send that information back to the referring physician, whether it's a general practitioner or specialized colleague.

Discussion

- In hepatitis C, there are models of how patients fall off at different stages. It seems like NASH patients fall off even after they're diagnosed, and they're less engaged in the treatment options. Is there data on the elements where patients fall out? In hepatitis C, there's a cure and we still have trouble getting people into treatment, but a lot is related to access. How much is related to access to health care, how much is related to understanding of disease, how much is related to the procedures they have to go through, and how much is related to the deciding to get treated?
  - Not aware of any good data on that, but that is definitely a problem. We are still very early in our understanding of the disease but also in taking care of these patients in a systematic way. For example, even though there's still a long way to go for diabetics, we have diabetic clinics. But that's not the case for the NAFLD or the NASH patients yet.
  - Often when explaining to patients about the disease and fat accumulation in liver cells, they aren't surprised because they are overweight in general. With NASH, the discussion addresses part of their lifestyle and their basic decision-making over a long period of time. It's a big hurdle, which is reflected in the trouble recruiting for these trials, even though there are 30 million people in the US or 5 million with significant NASH.
  - The level of unawareness in NASH is higher than in other diseases. A recent paper highlighted that in patients with liver cirrhosis, almost 70% got diagnosed with an incidental diagnosis, so even patients with liver cirrhosis are referred very late. There is a need for education- we all know that education and awareness in general is low. We need more meetings like the Seville meeting to create awareness among endocrinologists and obesity experts. We need to work in education not only on the consequences of NASH but also of the risk/benefit of liver biopsies and the small number of potential consequences relative to the advantages of preventing progression to liver cirrhosis.
- What are the groups' thoughts about a web-based registry of the trials with a little blurb in simple patients' language, about what the trial is about and the list of sites for each of the trials. A URL that patients could click on to learn more, and some educational material. A lot of patients get told they have fatty liver and don't worry about it, but they're curious and want to go to the internet to find more information. With a website like this, you are able to advertise the trials directly to patients. Is this something that would work or has been done in other diseases?
  - Yes that type of website exists; there is one called "Patients Like Me", though it is mostly for cancer patients so far. We don't know why patients enroll in trials, why they drop out. We've never conducted any randomized controlled trials of patient recruitment and retention, so it's hard to say what works and what doesn't work. This data should be collected from patients to help understand why. It's going to be more difficult to recruit patients into NASH trials than it was into hepatitis C trials. Things like "Patients Like Me" are a direct response from patients to the inadequacy of the current recruitment retention systems.
  - Part of the issue for fatty liver and NASH is that patients and primary care doctors are in denial. If the primary care doctors say to patients that they don't need to worry about it, then they are less inclined to listen to a hepatologist who says they need a liver biopsy.

Something that sites that are recruiting well do is have nurses specifically doing chart review at the end of every clinic to find patients, and then going and talking to them. In addition, certain companies have done advisory boards with just patients and nurse coordinators to look at feasibility of their trial design and will a patient really enroll in this study if there's a liver biopsy every six months. There's a lot going on, not only in the denial aspect but also in the kinds of procedures that a patient has to go through, that makes it very difficult to recruit.
    - We talk about patients in denial, but we just showed that the American Diabetes Society hasn't mentioned the liver in their guidelines. Is it possible that we are so focused on liver outcomes that other societies haven't taken notice? Why don't we make an outcome of onset of new diabetes or a cardiovascular event as endpoints for NAFLD studies? It's not the liver mortality alone that matters, and we should think of how we can make it relevant to others.
    - Regarding a web-based registry, some hepatologists have done this with PSC. The Toronto group has a list of PSC trials and it's very possible to do that for NASH, and a great idea. Secondly, we can never blame patients. If they don't understand, it's because we've not communicated correctly. And if that means we need to invest research efforts into how to communicate with patients, more emphasis on qualitative studies, then we should probably prioritize that over some of the quantitative studies because it will accelerate them if you design the right study. It is possible to do this fast and effectively, but the elephant in the room here is we will struggle to do that if patients need to commit to a study with two to three to sometimes even six biopsies on the consent form.
- How much more willing are patients to undergo a variety of noninvasive tests, particularly imaging which gives them a picture of their disease as compared with a liver biopsy? And how can that be used to help increase the awareness of the disease?
    - The recruitment issue is hard to address, but the retention issue is available as the causes for discontinuation are always recorded in a trial. Do agencies have complete records across trials? These data across many companies could be compiled and shared to understand what the retention issues are.
    - The FDA actually does not have that data, and doesn't receive data sets from sponsors until phase 3 trials are submitted for a marketing application. The FDA will have this data, but does not have it yet. The FDA may get study reports, but don't actually have the data sets to be able to interrogate these issues. Secondly, related to the topic about recruitment, the Liver Forum could maybe write some articles or papers to submit to the medical journals and the nursing journals and the nurse practitioner journals and those kinds of journals that will raise awareness. The Liver Forum could potentially have a site for patients like the one discussed and maybe we could have some way to funnel a search engine into that site.
    - While it's important to include as many biomarkers and all the right diagnostics but it gets very complicated. We calculate the patient burden time from screening all the way through the course of the study as well as the site burden time. In some of these NASH trials, it's 48 hours just on screening. So it's a huge patient and resource burden. As protocols are being designed, really look at it in respect to patient burden and site burden. Because otherwise, they're just not going to do it. They're not going to sign up. They're not going to follow through, and the sites aren't going to have the resources.
    - The issue is patient motivation and understanding that there's something that's likely to treat their disease and physician referral motivation for the same reason. In hepatitis C early on, it was easy because there were only 2-3 companies that were recruiting patients. And when it became many companies in the DAA era, it was widely recognized

and there was an easy biomarker. It took quite a long time in hepatitis C for the big patient flow to come, but it wasn't a problem because there were so few companies. There was actually quite a bit of backlash in the early days when companies went out aggressively. So it has to be done carefully and probably is a group effort. Some of it is just going to be maturation of time and some kind of phenotype or biomarker that's going to help the referring physician.

Patient Recruitment and Retention

- Need to increase both general awareness and also awareness of general practitioners and referring physicians.
    - Have good contact with practitioners and make it as easy as possible for them to inform and refer patients.
    - Getting information back to referring physician facilitates the process. If the patient returns to physician for advice, you are on the same page and it is easier to get the patient on board.
- Once referred, difficult to motivate them to participate
    - Difficult understanding long-term risk (i.e., risk of progression to cirrhosis in 10-20 years)
    - Time consuming to provide good, easily understandable information
    - Repeated biopsies are a deterrent to participation
        - The first biopsy will be very memorable so it is important that it be performed by an experienced physician, to make sure everything goes as smoothly as possible.
    - Difficulty explaining to patients that their condition requires treatment, but there is a possibility that they will be in the placebo group, especially with long-term studies.
        - Need to set realistic expectations for the trial.
    - The possibility of side effects can be difficult for a patient who wasn't feeling anything from their liver disease.
    - Need different types of tools for different types of patients
        - Mobile apps, websites, booklets.
    - Make it easy as possible to participate by offering: Travel reimbursement, parking passes, reminders, appreciation

Discussion

- The critical factor is the interaction with the patient. We have to think of information at two levels. One is the kind of general information that one can find on the web or be provided, the idea of patient manuals, clinical trial booklets, all relates to patient navigation and helping a patient navigate through recruitment and retention in the clinical trial. From experience participating in a clinical trial, there was no way to report symptoms and problems and it did not seem that people really cared about patient experience. A dedicated patient manager is the number one factor to improve patient recruitment and probably retention as well. Having somebody who actually knows how to do this is a really good idea, both from the patient perspective and probably for the hospital trial itself. In some places, there is dedicated clinical trial infrastructure, people who do this for a living. In the US, CCTS grants have a community engagement component and they have portals for patients to come from the community into clinical trials, and that's an established, running machine that can perhaps be utilized. Patients always have to come to the hospital or go someplace far away to be tested that is far away, pay for parking and meals, so thinking of community-based or even, home-based testing for clinical trial participation would be an excellent way to keep people engaged in clinical trials.

- Thank you for a really thoughtful discussion about some of the barriers because some of those things as simple as parking can interfere with a patient participating, and something as simple as the thank you really can make a big difference. In response to the question about the placebo, if we are designing a trial having comparator groups that perhaps might not be as effective, we know that patients take dietary supplements and the evidence for some of these supplements is minimal. If they could be taking a vitamin C or some sort of supplement, so their concern about being on placebo is minimized, instead they are on a vitamin supplement. Doing that obviously in an ethical way may be a mechanism to try to get the long-term data because if we don't get that pure placebo-controlled trial data, at least under the current paradigm, we're not going to ultimately get the approvals and the reimbursement.
- For larger, multi-national trials, there's also the factor that every country and every site is going to do things differently. There's not one general way of educating, so we have to adapt these tools and be ready to do a lot of work to adapt, be flexible, and listen country by country and often site by site. What will be useful at one site in the same country might not be useful for another.
- This is very much like when HIV physicians were trying to get into treating coinfection. Not sure that primary care doctors or endocrinologists aren't engaged, they just don't feel that there's anything that can be done. Two things that we have to keep in mind: 1.) put services that they feel they can actually provide their patients with something that actually can help them through to the next step, for example, several companies and the most successful recruiters are putting FibroScans in their endocrinologist's office. 2.) it's great to have an experienced physician who can do a biopsy, but the realities are very similar to the HIV days. That's a stop-gap right now, and there just isn't the ability to do that. And most biopsies right now are being done by interventional radiology. We have to think about how to connect the patient and the physician and actually help them through that process. With how trials and care is developing around this, it's not as easy as just doing education. There's got to be something tangible that goes with it.
- One of the root causes that we need to bridge is we have a very heterogeneous disease and we sit in our own silos. Especially at FDA, you have a section of metabolism and you have a section of liver disease, and it takes an enormous effort to get the two sections together. As hepatologists, we work independent of endocrinologists and cardiologists and only this year was it recommended that endocrinologists check liver enzymes. Cardiologists and obesity experts don't check liver enzymes. While reaching out to our patients is a good step, we have to reach out to our own colleagues- regulatory, academic, clinical, professional society. We need to have partnered meetings, and maybe we need a presence as hepatologists at the ADA or at the American Heart Association. And we need to extend this Liver Forum to those that aren't yet at level of understanding. These silos need to be unified in the care of a metabolic disease, unlike the paradigm that we saw with HIV or that we saw with hepatitis C where care of a patient can sit in one silo and do just fine. That will not happen with fatty liver.
    - Agree and we really need to get a broader picture of the metabolic and liver together. The FDA divisions do work together and consult as divisions all the time. IDGIEP reviews multiple I&Ds from endocrinologists because they're related to fatty liver disease. The FDA at this time does not recognize metabolic syndrome, and can understand that thought process from endocrinology because it's similar to recognizing portal hypertension as a disease in itself. Recognize the complications of it or the result of it in a particular disease, but this needs further discussion and further work.
    - There are two different problems: 1.) patient recruitment for trials so that we can have therapies for NASH, and 2.) education of all the relevant stakeholders which includes patients and all of the providers. At CDC, they can issue something in MMWR, and if you're an infectious disease or public health doctor, you read MMWR religiously. But in

general, most practitioners do not read that or it's not as relevant to them. Most in primary care listen to their professional organization or to someone from that specialty within their hospital. Something the Liver Forum could consider is creating a slide deck on fatty liver disease/NASH including the fact that there are no treatments and there are clinical trials. Then work with relevant primary care groups and specialists within relevant professional organizations like AASLD to get the information out into the community.

- Have any sponsors or investigators considered community-based tests in a NAFLD trial to reduce the number of visits needed? Are there examples?
    - One of the reasons this hasn't been done is because of using centralized labs, due to multi-site and multi-country trials. Also talking about the metabolic part of NASH and not just the biopsy, so that was one of the reasons for not doing it. For patient retention, we found that we needed patients to actually have frequent visits with the physicians. We do have intermediate phone visits. Having study nurses coming to patients to do the labs, that sort of thing could probably be added. It's the reasoning around a large phase 3 trial where it makes it very difficult.
    - The difficulty too is that you cannot involve the physician who is not a part of the investigators. So anybody who takes part in a clinical trial has to be part of the investigators. If you manage to associate detached working physicians at the local level and include them in the list of the investigators, maybe the problem can be solved. But you can't just send somebody from a tertiary center to a community physician who is not part of the investigator team.
- There is a paucity of data relating to what patient experience is and how they have done and whether they liked it. There's not a lot of data that then looks at adverse experiences versus attitudes, data across different diseases. As a community, and certainly in hepatology, there's a lot more we could do that would help a positive enforcement and educate ourselves.

SESSION #4: WORKING GROUPS UPDATE

Moderators: Veronica Miller, Forum for Collaborative Research
Arun Sanyal, Virginia Commonwealth University

Case Definitions Working Group

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/07_Case_Def.pdf
Presenter: Sophie Megnien, Genfit

- First manuscript was submitted to Hepatology
- Next manuscript underway is working to define improvement of NAFLD/ NASH for clinical trial endpoints. The goal is to help everyone who is performing or involved in clinical trials, by producing recommendations from the Liver Forum.
    - Began October 2016, have had several calls, and smaller writing team, with Amanda Cheung doing much of the drafting.
    - Recommendations from the Liver Forum
    - We want to be able to give some suggestions and clear definitions on the clinical trial endpoints around NASH and fibrosis, in the context of a regulatory and scientific framework.
    - We want to come up with clear definitions when we talk about different endpoints and we would like to come up with a consensus on definitions. At least we want to describe them and give all the gaps and all the data that we have used.
- Outline:

    - Clearly define the disease, current regulatory state for assessing improvement of disease.
        - This is not for the management of patients for clinicians; it's targeted for clinical trial endpoints.
    - Presenting both pathways: drug development in NASH, and drug development in fibrosis (and combination).
    - Biopsy limitations
    - Assessing severity of NASH
        - Current measures
        - Exploratory messages
        - Endpoints: definitions, correlation with outcomes, data needed to validate
    - Assessing severity of fibrosis
        - Current measures
        - Exploratory messages
        - Endpoints: definitions, correlation with outcomes, data needed to validate
- Discussion points to consider:
    - What is the definition of the activity of NASH versus the severity of the disease as a whole. Are we talking about severity of NASH, severity of fibrosis, or are we talking of global severity of the disease?
        - We don't want to have inconsistency between an improvement of NASH or degradation or worsening of fibrosis or vice versa.
    - We need to define what is the change, what are we targeting, what would be the change in the endpoints to be used for the clinical trials?
    - To date, we're only look at NASH as steatohepatitis for clinical trials with and without fibrosis or with more severe stages of fibrosis also for the antifibrotic NASH trials.
        - Will have a separate paragraph to discuss steatofibrosis, but not going all the way to defining what will be the endpoints.
        - Have to discuss this differently for early stage trials, proof of concept or early phase 2s rather than for late stage phase 2b or phase 3 trials.
- Recommendations:
    - In the recommendations, the aim is not to come out with "this is the endpoint"; it's really to list the endpoints.
        - Different ones for different clinical trial stages.
        - Define the population that you need to study
        - Linked to the indication that you will use your drug for
    - Definitions need to be precise, quantifiable, reproducible
        - Helpful for the regulatory agencies to have data from one trial to the other where they know that the same definition for the endpoint was used
        - Easier to compile and extrapolate all these data across trials

Pediatric Issues Working Group

Presenter: Miriam Vos, Emory University

- The pediatric working group has grown a little bit, but is always looking for new people to focus on pediatrics. Reach out if you'd like to join the working group.
    - Increased number of people from Europe which has been a big benefit, and we have more academic folks involved now.
- In-person meeting:
    - The group had a lively in-person meeting on March 20th, with over 30 attendees and more people on the phone as well

- The focus of that meeting was to talk about the pediatric natural history problem, in other words the gap in knowledge that we have about what happens to children who have the disease after they become adults (10-15 year outcomes of pediatric disease)
- Included an overview of the science, and a good discussion about what the gaps are, and then we heard from the regulatory agencies about what data items they need to see answered in order to better design clinical trials for pediatrics.
- Pediatric cohorts already in existence: NASH CRN pediatric cohort, a number of individual cohorts that are a little bit smaller, and the new TARGET-NASH cohort that will soon also be a large cohort
- Conclusions of the meeting:
  - Consensus that we need another cohort and that it is a benefit to have multiple cohorts because they answer diverse questions that really then fill in the knowledge that we need.
  - Consensus around the idea of developing a new cohort to solve this pediatric natural history issue which would be specifically designed to go back and find the children who were diagnosed 10-15 years ago and evaluate their state of health currently.
  - One action plan that came out of that meeting is that TARGET PharmaSolutions is now setting up an academic steering committee to work on the design and the collaborators in a pediatric natural history study.

- Manuscripts:
  - Have one manuscript so far in the final revision stages and hope to get it back from FDA coauthors and then will submit it for final reviews.
  - Contributed to the disease definitions manuscript, but there's a whole different set of papers and evidence that go into those discussions when talking about children and it's a little hard to kind of tag it into a paper that already has a lot of complex issues.
  - Would like to proceed with a couple of short papers that really narrow in on a couple of the immediate challenges in pediatrics that have enough data now to make a statement.
    - For example, what age child should be included in drug development for pediatrics and who could be appropriately excluded from that. And I think there's enough evidence that the working group could put together a commentary on that, and I think that might be helpful.
    - Another example of a short paper could be biomarkers or noninvasive development in pediatrics.

Placebo Arm Data Working Group

Slides: http://www.forumresearch.org/storage/documents/LiverForum6/09_Placebo.pdf
Presenters: Eric Lefebvre, Allergan
Veronica Miller, Forum for Collaborative Research

- It is a critical time in drug development in NASH right now to be really looking into all the data that we generate from placebo arms in these studies.
- The goal of having a placebo arm working group is to evaluate the potential for placebo arm cohort to be used as a natural history cohort. We know that we still have a lot to learn in NASH, and certainly these studies that we're conducting do involve serial biopsies which are not necessarily doable in routine practice. But in the context of the study, we will generate a lot of information, so it's important to make the most use of it.
  - Potentially down the line, this project could lead to potentially reducing the number of patients that are required in the placebo arms in future studies. We're not there yet, but this is a long-term aspiration and something we should keep in mind.

- Pooled data approach
    - Advantages include being able to fulfill the growing expectations for data sharing earlier in the drug development process. We're all learning from each other and we understand that what we find in one cohort may not necessarily be translatable in another cohort. Working together and trying to answer some of these questions will be really important.
    - Avoids duplication/ 'one-off' efforts.
    - One of the things that we've talked about is the spontaneous resolution of placebo patients that we need to better understand.
    - Having governance from the agencies, sponsors, and the experts would be really important to make the best use of the data.
    - The benefit of the Liver Forum is that it provides a noncompetitive space and open forum for discussion, so this is a great place to do something like this.
- Objectives:
    - Review the IRB regulatory issues surrounding placebo arms
        - Barriers that we may have in terms of pooling the data from the different studies
    - Establishing the process to generate a database with placebo arm data from completed phase 2 and phase 3 studies
        - That will involve cross-company collaboration. Important to have a working group to handle some of these challenges.
    - Establish the governance structure for the database
    - Establish the analysis plan to evaluate the utility of the placebo arms to serve as a natural history cohort and potentially serve as a virtual placebo arm in future studies.
- Next Steps:
    - Develop subgroup that will also focus on standard of care issues
        - We're not so well equipped at the moment in clinical studies to really get all the information we need from how adherent or compliant are the patients with their lifestyle modification recommendations. What are they doing with their diets? Other things that we're not necessarily asking questions on that maybe we should to get a better understanding of how the placebo patients can behave in a study.
    - Learn from other initiatives: data sharing agreements, navigating HIPAA, intellectual property, and IRB requirements are all important.
    - Understand who, what, where, when of data analysis, so really making sure that we make the most of this project

SESSION #5: WRAP-UP

Moderator: Veronica Miller, Forum for Collaborative Research

Overview of the NASH Biomarker Workshop

Presenter: Veronica Miller, Forum for Collaborative Research

- NASH Biomarker Workshop, May 5-6, in Washington DC
    - This is the first year the Liver Forum is co-organizing the workshop, rather than setting up our own independent biomarker working group, we thought we would join this effort of an ongoing meeting public workshop that was started last year.
    - This is one of the ways the Liver Forum is contributing to a complement of activities around biomarkers which includes projects sponsored by the FNIH as well as the LITMUS collaboration in Europe.
    - The workshop is public and so it is open to everyone and there is no restriction as to how many people can come.