Forum
Pediatric Cholestatic Liver Diseases Working Group

PFIC

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May 14, 2024

THE FIRST TWO GOALS FOR THE DISEASE SPECIFIC WORKING GROUPS

1. Explore agreed-upon outcome measures for clinical trials.

2. Identify knowledge gaps regarding the needs and natural progression

1. Outcome measures for clinical trials.

BSEP deficiency

- sBA < 102 uM (surrogate from NAPPED for SNL upon surgical bile diversion)
- survival native liver

For discussion:

- sBA below certain level or decrease with certain %; to be analyzed in NAPPED data) (used in MARCH and in PEDFIC1)
- Patient- or observer reported outcome on pruritus (placebo effect)

(Likely) invalid outcome measure:

- surgical bile diversion

1. Outcome measures for clinical trials.

BSEP deficiency

Need for development:

- postponing liver failure (development of ESLD): LFTs (low albumin, vit K independent PT/INR increase, factor V, bilirubin; decompensation; portal hypertension with / without complications)
- prevention / postponing HCC incidence
- prevention of alloimmunization (= outcome after transplantation)
- decrease of pruritus
- Responsiveness (sBA, pruritus, both)

1. Outcome measures for clinical trials.

MDR3 deficiency

- survival native liver

For discussion:

- *normalization of ALT + GGT + bilirubin*
- *decrease of pruritus*

1. Outcome measures for clinical trials.

MDR3 deficiency

To be developed:

- postponing liver failure (development of End-stage liver disease/ESLD): LFTs (low albumin, vit K independent PT/INR increase, factor V, bilirubin)
- postponing development portal hypertension (platelets, spleen size, spleen elastography)
- postpone development of complications of portal hypertension (ascites upper GI bleeding, varices, spontaneous bacterial peritonitis)
- relationship fibroscan – fibrosis

1. Outcome measures for clinical trials.

FIC1 deficiency

- survival native liver

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BSEP deficiency

- relationship between change in sBA (after SBD or IBATi) and change in pruritus
- Prevention or “just postponement” of liver transplantation by interruption of the enterohepatic circulation
- pretreatment genotype-phenotype relationships of the multitude of variants, particularly of missense variations (majority of patients is genetically unique!)
- responsiveness of different genotypes towards different types of treatments (including SBD, IBATi, UDCA, chaperones, potentiators etc.)
- definition of alloimmunization: antibodies +/- phenotypes; prevalence and incidence of posttransplant of anti-BSEP AB + corresponding phenotype of BSEP deficiency (high sBA + pruritus + pathology/BSEPstaining
- reliable functional measurement of BSEP transpoprt activity *in vivo* in patients (spontaneous and in response to treatments)
- validity and regulatory possibility of n=1 trials

2. Identify knowledge gaps regarding the needs and natural progression

FIC1 deficiency

- relationship between change in sBA (after SBD or IBATi) and change in pruritus
- responsiveness of different genotypes(?)/patients towards specific types of treatments (including SBD, IBATi, UDCA, chaperones, potentiators etc.)
- predictability of post-transplant graft complications (and efficacy of strategies to prevent / treat these)
- relationship between (variants in) FIC1 gene product and clinical/phenotypical consequences
- pre- and post-transplant extrahepatic manifestations
- validity and regulatory possibility of n=1 trials

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1. Explore agreed-upon outcome measures for clinical trials.

2. Identify knowledge gaps regarding the needs and natural progression

Thank you for your attention

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PFIC Network Activities & Priorities

Highlighting Patient and Community Perspectives in PFIC

Emily Ventura, RN, BSN
PFIC Network Executive Director

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The Forum: PCLD Workshop
May 14, 2024

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Disclosures

- PFIC Network has received grants and sponsorship from:
  - Patient Centered Outcomes Research Institute (PCORI)
  - Chan Zuckerberg Initiative (CZI)
  - Mirum Pharmaceuticals
  - Ipsen Pharmaceuticals
  - Rectify Pharma
  - Horizon Therapeutics

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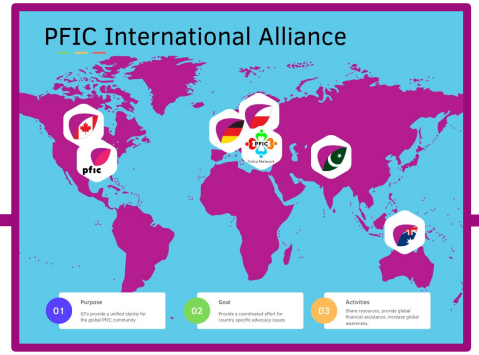
Educate, Support, Advocate, Research

- Provide Education & Support Resources
- Advocacy, Awareness, Outreach
- **Support & Accelerate Research**

INTERNATIONAL ALLIANCE
PFIC



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Aims & Activities

- **PFIC Network aims to identify & convey patient unmet needs in support of research by:**
  - Building trusting partnerships between patients and researchers
  - Crafting opportunities for meaningful scientific questions to emerge from patient unmet needs

PCORI-funded project
IMPACT

Family & Scientific Conference
Roundtables

Patient Registry

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Project IMPACT

- Goal: Prepare PFIC community to participate as equal partners in research studies.
- Activities: Modules, web app, and focus groups to identify and prioritize:
  - patient unmet needs
  - outcomes/endpoints most meaningful to patients
- Patient-identified research priorities (so far):
  - Understanding itch and other PFIC symptoms
  - Comparison of procedures and outcomes by subtype
  - Mental health & financial burdens of the disease & treatments
  - Incorporating patient-reported itch measures into care & trial recruitment

Conference Roundtables

- Goals:
  - Understand patients' and families' risk tolerance for potential future therapies
  - Explore how incorporating patient perspective is important to therapeutic development
- Key Learnings:
  1. Stability in condition increases risk aversion for some patients
  2. Reversibility of treatment is major factor in risk assessment for PFIC families
  3. Improving informed consent process is vital to prevent uninformed consent
     - Separately highlight irreversibility in treatment/trial consent forms

Patient Registry

- 135 enrolled, 4 languages (English, Spanish, Italian, Polish)
- Longitudinal data collection every 6 months (x3 waves to date)
  - 46% average completion rate
- Data collection includes
  - Demographics
  - Diagnosis
  - Symptoms
  - Medications & surgeries
  - PRO data via PROMIS scales: itch, sleep, global health, impact on family QoL, and financial burden

Immediate Next Steps

Project IMPACT

Family & Scientific Conference Roundtables

Disseminate findings to PFIC research community by roadmap/guidance

Patient Registry

Grow and enhance the registry, publish a descriptive summary

Mobilize findings & collaborations to advance research that addresses patient unmet needs…

IMPACT Activities & Conference Roundtables

Patients identify and prioritize:

- Unmet needs in clinical management & therapeutic dev
- Clinical outcomes/endpoints

Clinical management needs

Identify feasible PCOR/CER study questions, patients prioritize

Pursue PCOR/CER study funding through PCORI

Novel therapeutic needs

Quantify need using registry data (ex. patients on IBATs that itch)

Approach FDA:
PFDD or Critical Path Innovation Meeting

Thank You

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