Amsterdam UMC
University Medical Centers

Tytgat Institute for Intestinal and Liver Research

Patient participation in rare liver disease research

Stan van de Graaf | Sept 5th 2022

Patient participation in my research

- Example of 2 events I co-organized; rationale and lessons
- Joint publication (opinion)
- Influence on current research focus
- Remarkable difference between pediatric/adult primary endpoints in trials with cholestatic liver diseases

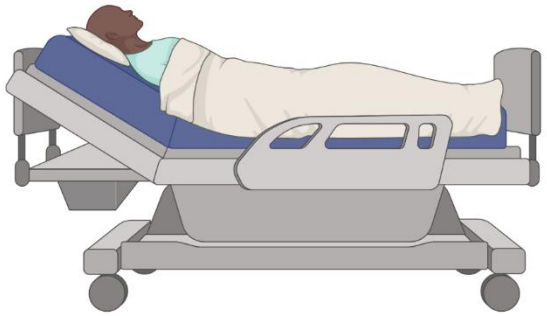
Tytgat Institute for Liver and Intestinal Research

~70 researchers. Pre-clinical/translational research:

Liver: common metabolic diseases + genetic/auto-immune

- What underlies (rare) liver diseases where bile flow is disturbed?
- How is bile flow regulated in health?
- Which molecular targets for therapy?
- Mechanisms underlying drug-side effects?

Patient participation in pre-clinical research



- *2016: Marleen Katee (PSCPE), Anneke Mels (MLDS), Jose Willemsen (NLV), and me sat together AND…*
- *The MLDS (Dutch Digestive Disease Foundation) planned to celebrate their 35th anniversary*
- **> Let's organize an event where patients with a rare liver disease and researchers (lab/clinic) meet.**

Joint effort

Nederlandse Vereniging voor Hepatologie

PSC Patients Europe

NLV 30 jaar

MAAG LEVER DARM STICHTING

Aims

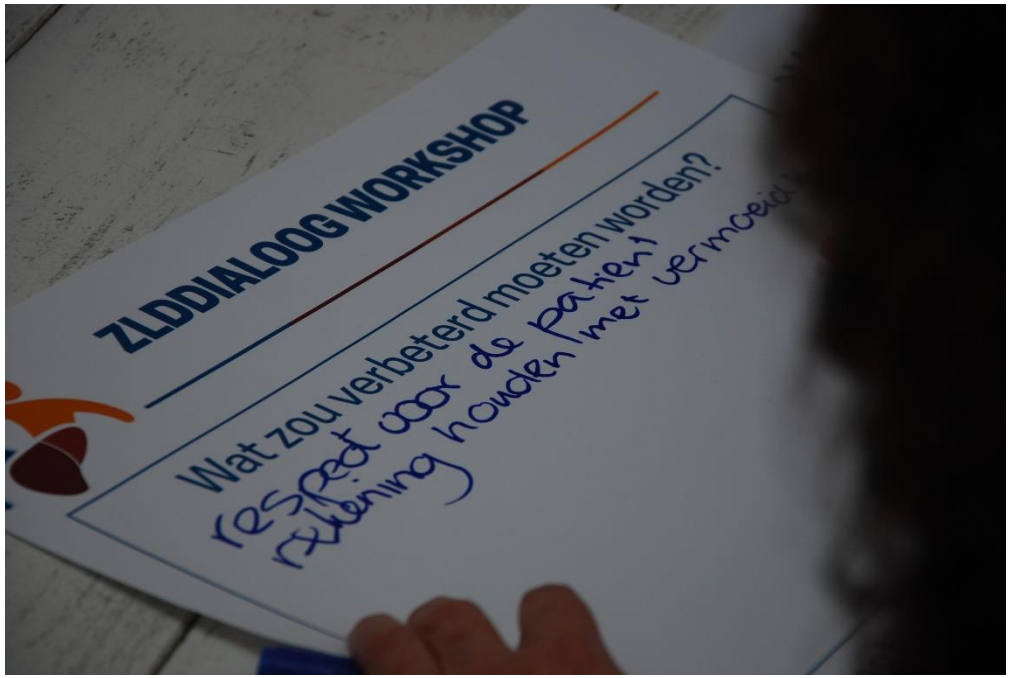
1. To introduce researchers to patients and to develop a greater understanding of the patient's needs
2. Introduce patients to researchers in order to understand more about what research entails and what role the patient can play in the design, conduct and implementation of research
3. Creating a group feeling: the patient is not alone, all kinds of parties are involved in the patient's well-being

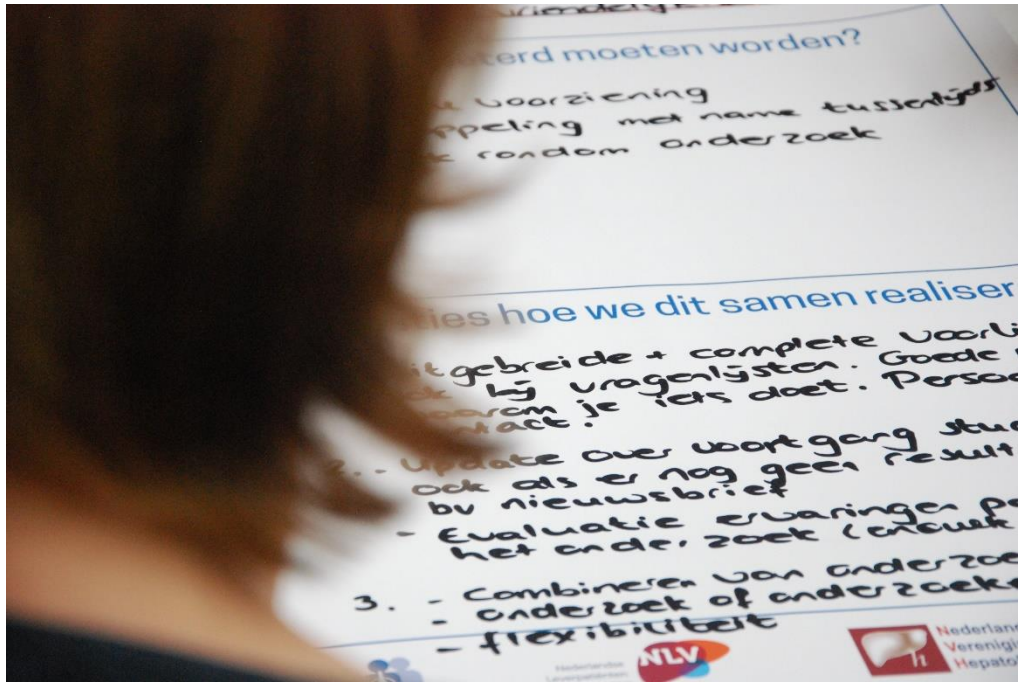
Program ZLD

1. Patient in the driver's seat:
   - how patients can engage in research
   - (participate in trials; advocate specific research focus; role in trial-design; grant proposal jury)
   - Tools/training for this
   - Best decision making in trial participation
2. Researcher of the 21st century: patient involvement
3. Workshops
4. Posters from young scientists


ZLDDIALOOG WORKSHOP 2
Wat zou verbeterd moeten worden?
Suggesties hoe we dit samen realiseren
ZLDDIALOOG WORKSHOP 2
Wat zou verbeterd moeten worden?
Suggesties hoe we dit samen realiseren
ZLDDIALOOG WORKSHOP 2


ZLDDIALOOG WORKSHOP 2
ZLDDIALOOG WORKSHOP 2
Wat zou verbeterd moeten worden?
Suggesties hoe we dit samen realiseren


ZLDDIALOOG WORKSHOP
Wat zou verbeterd moeten worden?
respect voor de patient
rekening houden met vermoeid


erd moeten worden?
ies hoe we dit samen realiser
NLV

The next year

Short movies of patient/researcher/clinician

Challenges in organizing patient-research events

1. Funding
2. Reaching the right audience
3. Transport/parking/walking distance
4. Planning/fatigue
5. Receiving/Sending information
6. False hope *vs* Inspiring future possibilities
7. Privacy (foto's/badges)
8. Follow-up

Patient participation in my research

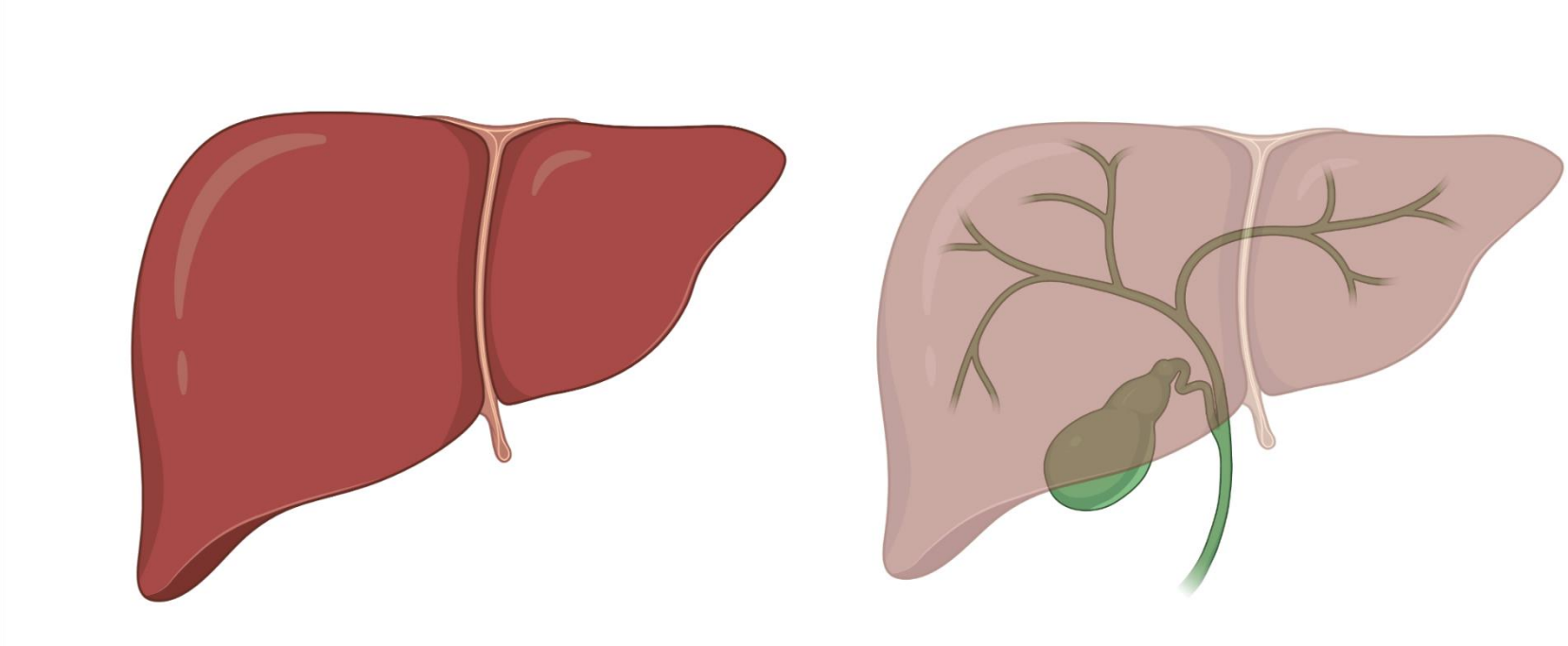
- Example of 2 events I co-organized; rationale and lessons
- Joint publication (opinion)
- Influence on current research focus
- Remarkable difference between pediatric/adult primary endpoints in trials with cholestatic liver diseases

Towards joint publication

Lancet Gastroenterology & Hepatology 2018
The case for combining treatments for primary sclerosing cholangitis

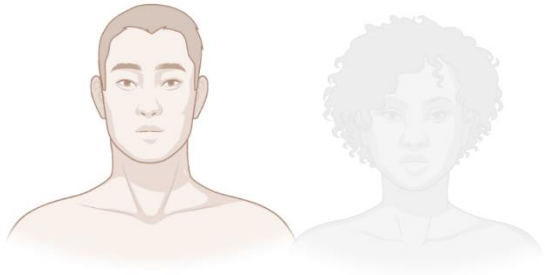
Reinout L P Roscam Abbing, Larissa M de Lannoy, Stan F J van de Graaf

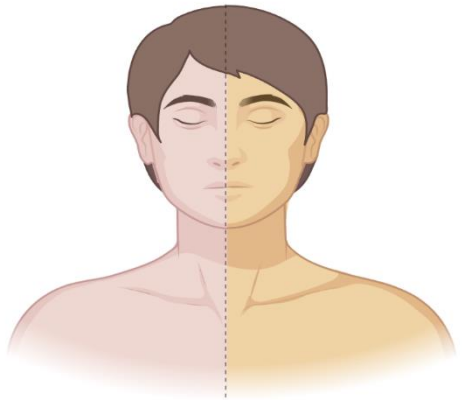
Primary Sclerosing Cholangitis

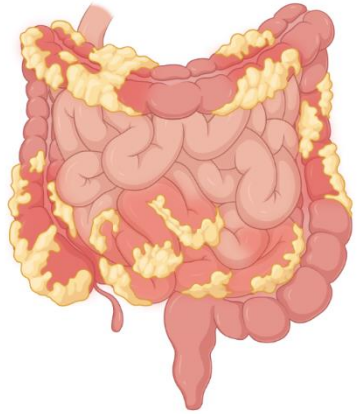


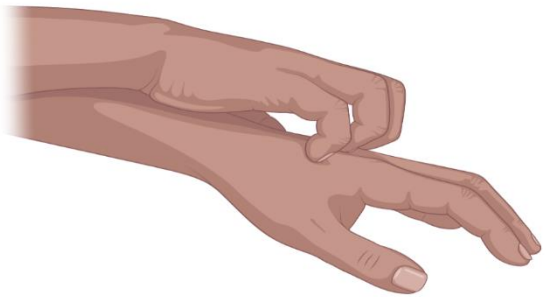
Blockade > accumulation of toxic bile salts > more damage/fibrosis > blockade

Disease characteristics



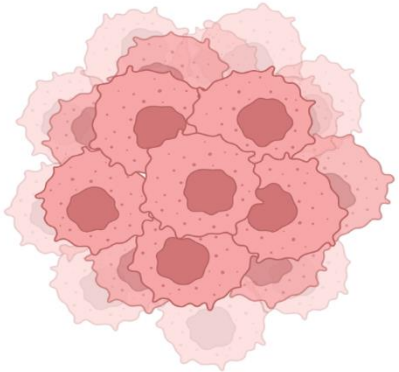






Itch

fatigue



Fear: high cancer risk

Two drug classes approved for other cholastatic disorders

A: Drugs that lower bile salt synthesis
B: Drugs that increase excretion of bile salts via feces.
(body responds by increased bile salt synthesis)

Both give improvement in “liver enzymes”

A: increase itch (mechanism unknown)
B: induce diarrhea (bile salts in colon) (but reduced itch)

Accepted joint publication

Lancet Gastroenterology & Hepatology 2018

The case for **combining treatments** for primary sclerosing cholangitis

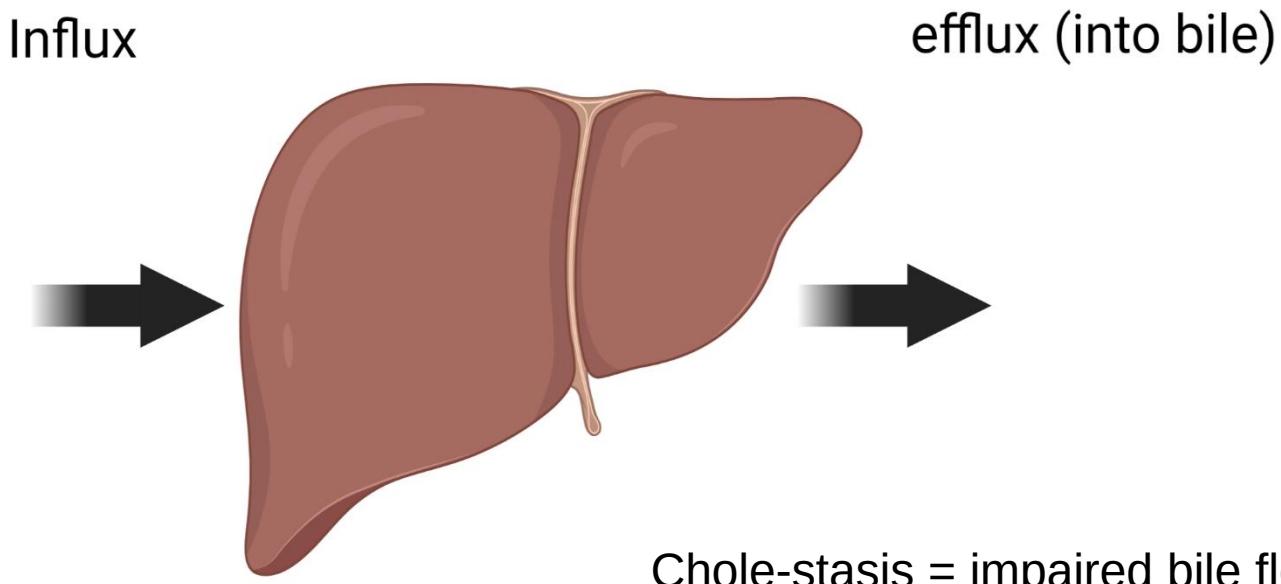
Reinout L P Roscam Abbing, Larissa M de Lannoy, Stan F J van de Graaf

We now have have experimental evidence supporting this hypothesis

Patient participation in my research

- Example of 2 events I co-organized; rationale and lessons
- Joint publication (opinion)
- Influence on current research focus
- Remarkable difference between pediatric/adult primary endpoints in trials with cholestatic liver diseases

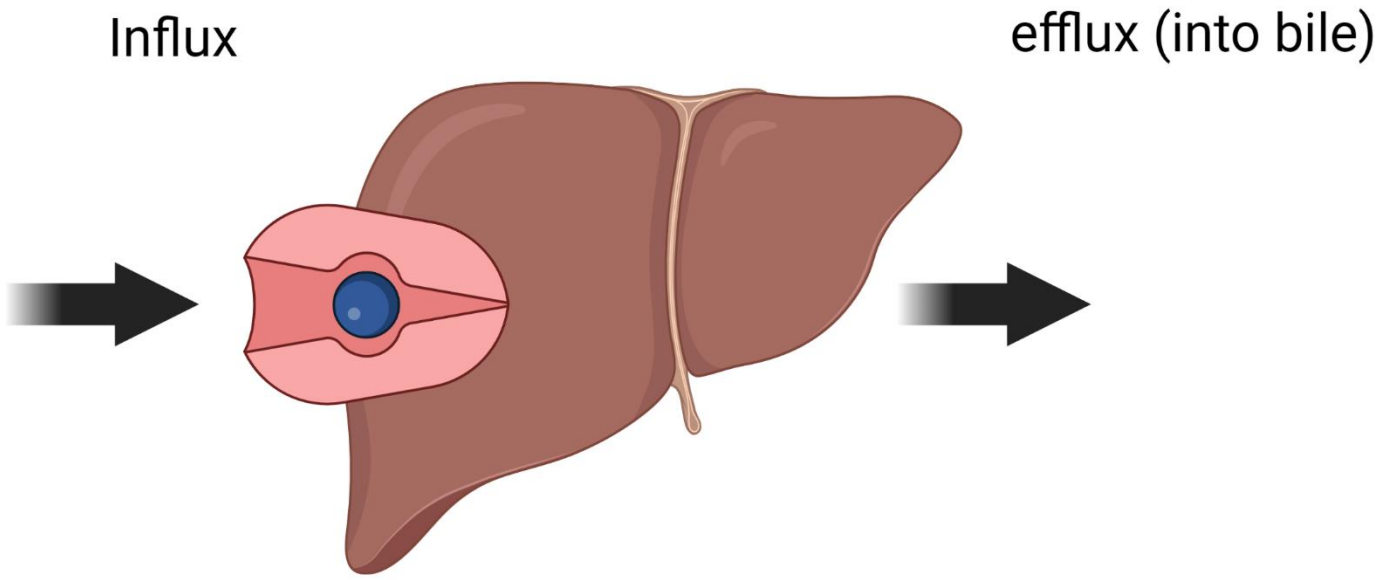
Second example



Proposed therapy:
Reduce influx of toxic bile acids

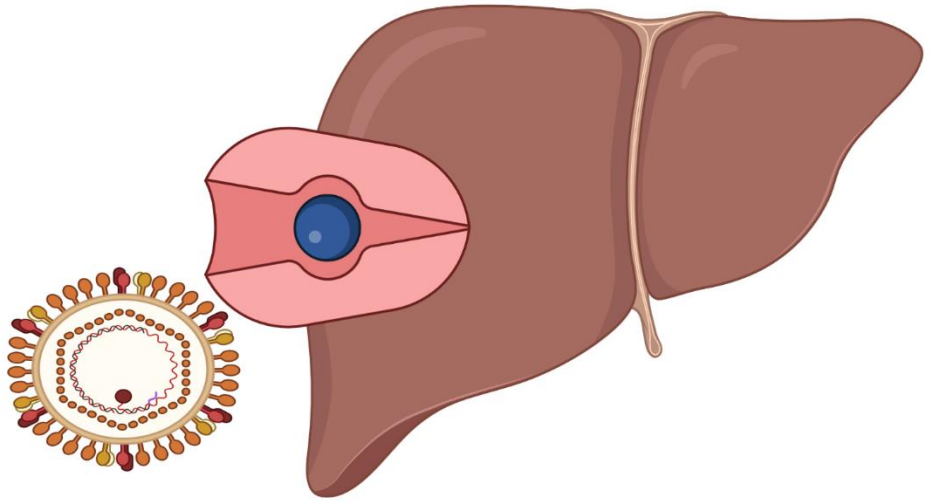
Chole-stasis = impaired bile flow = impaired efflux

Impaired secretion > try reducing influx



NTCP: Na+ Taurocholate Cotransporting polypeptide

NTCP is also the docking receptor for the hepatitis B virus



Bulevirtide: anti- HBV/HDV drug EMA conditional market approval in 2020
Inhibits also hepatic bile acid uptake via NTCP
Requires daily injection….

NTCP inhibitor for PSC?

1: Pre-clinical support for efficacy / safety in cholestatic models

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY, VOL. 68, NO. 3, 2018

Na^+-Taurocholate Cotransporting Polypeptide Inhibition Has Hepatoprotective Effects in Cholestasis in Mice

Davor Slijepcevic,[1*] Reinout L.P. Roscam Abbing,[1*] Claudia D. Fuchs,[2] Lizette C.M. Haazen,[1] Ulrich Beuers,[1] Michael Trauner,[2] Ronald P.J. Oude Elferink,[1] and Stan F.J. van de Graaf[1]

2: Orally available small molecule NTCP inhibitor (in collab)

Patient participation in my research

- Example of 2 events I co-organized; rationale and lessons
- Joint publication (opinion)
- Influence on current research focus
- Remarkable difference between pediatric/adult primary endpoints in trials with cholestatic liver diseases

Patient reported outcomes in trials

Pediatric cholestasis

Odevixibat (Bylvay; by Albireo) or Maralixibat (Livmarli by Mirium); : inhibits intestinal bile acid uptake:

Primary endpoint:
the proportion of patients with at least a 70% reduction in fasting serum bile acid levels or who achieved a level ≤ 70 µmol/L at week XX.

Secondary endpoints:
- Alanine aminotransferase (ALT) and bilirubin (total and direct) change from Baseline
- Pruritus as measured by ItchRO (Observer ItchRO/patient ItchRO) change from Baseline

Acknowledgements

Larissa de Lannoy
Marleen Katee
Jose Willemsen

Esther Vogels
Ronald Oude Elferink
Ulrich Beuers
Joanne Verheij
Rudi de Waart
Suzanne Duijst
Davor Slijepcevic
Reinout Roscam Abbing

NVH
NEDERLANDSE
VERENIGING VOOR
HEPATOLOGIE

Nederlandse
Leverpatiënten
Vereniging

Lever

maag
lever
darm
stich
ting

NWO
Netherlands Organisation
for Scientific Research

erc
European Research Council
Established by the European Commission

Disclaimers:
Pending Consultancy agreement with Albireo
Collab with CD3 aims to license our lead compound