Best of EASL 2017: Non-Viral Liver Diseases

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Chief of Hepatology
Director of Advanced Liver Therapies
Baylor College of Medicine
Baylor-St Luke’s Medical Center
Interaction between alcohol use and metabolic components in predicting severe liver disease in the general population – a decade follow-up of a nationally representative cohort

Fredrik Åberg¹, Jaana Helenius-Hietala², Pauli Puukka³, Martti Färkkilä⁴, Antti Jula³
Helsinki, Finland

Aim: To study metabolic factors which best predict severe liver complications, stratified by alcohol consumption.  

Methods: 6732 subjects without baseline liver disease who participated in the Finnish population-based Health 2000 Study (2000–2001), a nationally representative cohort. Follow-up data until 2013 for liver-related admissions, mortality, and liver cancer came from national registers. Mean follow-up: 11.4 years (SD 3.3).

Conclusions:

- Central obesity, insulin resistance, diabetes, higher serum total cholesterol, and a high average alcohol use emerged as the strongest predictors of severe liver disease in the general population.

- These factors should be considered in future population risk models to stratify risk for the development of liver disease, and in population health counseling.

<table>
<thead>
<tr>
<th>All subjects</th>
<th>HR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.99-1.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Average alcohol use (g/wk)</td>
<td>1.002</td>
<td>1.001-1.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol mmol/L</td>
<td>1.50</td>
<td>1.13-1.97</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL cholesterol mmol/L</td>
<td>0.51</td>
<td>0.37-0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.37</td>
<td>1.33-4.22</td>
<td>0.004</td>
</tr>
<tr>
<td>HOMA-index</td>
<td>1.01</td>
<td>1.00-1.02</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI</td>
<td>0.84</td>
<td>0.75-0.93</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.07</td>
<td>1.04-1.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohol use &gt;140g/wk for women and ≥210g/wk for men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohol use ≤140 g/wk for women and ≤210 g/wk for men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
</tr>
<tr>
<td>HOMA-index</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Waist circumference</td>
</tr>
</tbody>
</table>
NGM282, a Novel Variant of FGF19, Significantly Reduces Hepatic Steatosis and Key Biomarkers of NASH: Results of a Phase 2, Multicenter, Randomized, Double-Blinded, Placebo Controlled Trial in Biopsy-Confirmed NASH Patients

Stephen A. Harrison, Manal F. Abdelmalek, James F. Trotter, Angelo H. Paredes, Hays L. Arnold, Marcelo Kugelmas, Mustafa R. Bashir, Lei Ling, Stephen J. Rossi, Alex M. DePaoli, Mary E. Rinella, Rohit Loomba

The International Liver Congress™
Amsterdam, Netherlands
22 April 2017
FGF19 Has Multiple Biological Activities Relevant to the Pathogenesis of NASH

- **Insulin Sensitivity**
- **De Novo Lipogenesis**
- **Fatty Acid Oxidation**

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**Liver**

- Reduces Steatosis
- Reduces Lipotoxicity

- Reverses Steatohepatitis
- Reduces Hepatocellular Injury
- Decreases Fibrogenesis

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**FGF19** interacts with **β-klotho FGFR4** in the liver, leading to:

- **Reduction in Steatosis**
- **Lipotoxicity Reduction**

**Liver**

- **β-klotho FGFR1c** interacts with **FGF19** in the CNS, leading to:

- **Reduction in Lipotoxicity**
- **Decreases Fibrogenesis**

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**Toxic Fatty Acids**

- **Free Cholesterol**
- **Bile Acids**
- **DAG/Ceramides**
Phase 2 Study of NGM282 in NASH: Overview of Study Design

- Randomized, double-blinded, placebo controlled trial
- Eighty-two subjects enrolled across 18 sites in Australia and the United States
- Biopsy confirmed NASH with a minimum NAS ≥ 4 (1 point in each component)
- Stage 1, 2 or 3 fibrosis
- Minimum 8% absolute liver fat content by MRI-PDFF
- Abnormal ALT (≥ 19 IU/L in females; ≥ 30 IU/L in males)
- Primary endpoint is a decrease in absolute liver fat content ≥ 5%
Primary Endpoint at Both Doses with Clinically Meaningful Changes in Liver Fat Content

- **Absolute Change**
  - Placebo: -0.9
  - 3 mg: -9.7
  - 6 mg: -11.9

- **Relative Change**
  - Placebo: -1
  - 3 mg: -47
  - 6 mg: -61

- **Statistical Significance**
  - Absolute Change: p < 0.012
  - Relative Change: p < 0.001

- **Clinical Significance**
  - 89% of subjects achieved a clinically meaningful >30% relative change
  - Decreases in liver fat strongly correlate with reductions in ALT, AST and C4
Greatest Magnitude of Effect in Subjects with Most Active Disease: Baseline MRI-PDFF >20%
Decreases in ALT at Week 12 Support Reductions in Inflammation

36% of subjects normalized ALT, the majority of these by Week 2
Rapid and Sustained Reductions in ALT in Patients with High Baseline Levels

Patients with a Baseline ALT > 60 U/L

Study Week

Placebo (n=11) 3 mg (n=11) 6 mg (n=12)
Decreases in Mean C4 Levels are Reflective of Potent CYP7A1 Inhibition

65% were below the LLQ (<0.9 ng/ml) 24 hours post-dose at Week 12

C4 = 7α-hydroxy-4-cholesten-3-one
Decreased Triglyceride Levels are Consistent with NGM282 Mechanism of Action

![Graph showing triglyceride levels across different treatments and time points.](image-url)
Increased LDL Levels Reflect the Potent FGFR4-Mediated CYP7A1 Inhibition

Preclinical and clinical data demonstrate a rapid mitigation of increased LDL levels within 2 weeks with administration of a statin
– Luo et al. EASL ILC 2017 Abstract FRI-353
Significant Decreases in PIIINP and TIMP-1 Supportive of Potential Anti-fibrotic Activity

- Significant absolute and percentage change in total ELF score for 3 mg NGM282 cohort with numeric decreases observed with 6 mg cohort
- No significant changes observed in hyaluronic acid
Summary of the Most Common (> 10%) Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=27) Participants (%)</th>
<th>NGM282 3 mg (N=27) Participants (%)</th>
<th>NGM282 6 mg (N=28) Participants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>2 (7.4%) 3</td>
<td>11 (40.7%) 17</td>
<td>15 (53.6%) 27</td>
</tr>
<tr>
<td>Diarrhea/Loose stools</td>
<td>6 (22.2%) 6</td>
<td>11 (40.7%) 14</td>
<td>10 (35.7%) 13</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (7.4%) 2</td>
<td>8 (29.6%) 9</td>
<td>5 (17.9%) 8</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (3.7%) 2</td>
<td>9 (33.3%) 11</td>
<td>4 (14.3%) 6</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (18.5%) 6</td>
<td>3 (11.1%) 5</td>
<td>5 (17.9%) 5</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1 (3.7%) 1</td>
<td>3 (11.1%) 3</td>
<td>4 (14.3%) 4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0%) 0</td>
<td>2 (7.4%) 2</td>
<td>5 (17.9%) 6</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>2 (7.4%) 2</td>
<td>3 (11.1%) 3</td>
<td>1 (3.6%) 1</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>0 (0.0%) 0</td>
<td>2 (7.4%) 2</td>
<td>4 (14.3%) 4</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (3.7%) 1</td>
<td>3 (11.1%) 3</td>
<td>1 (3.6%) 1</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>3 (11.1%) 3</td>
<td>2 (7.4%) 2</td>
<td>0 (0.0%) 0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0 (0.0%) 0</td>
<td>0 (0.0%) 0</td>
<td>3 (10.7%) 3</td>
</tr>
</tbody>
</table>

- The vast majority of TEAEs were Grade 1
- One SAE during study period (acute pancreatitis, possibly related)
- Adverse event profile is predictable and consistent other NGM282-treated study populations
Phase 2 Study of NGM282 in NASH Patients: Summary and Next Steps

- Primary endpoint met in 79% of NGM282-treated subjects, with over one third of subjects normalizing liver fat content
- Significant and rapid reductions in multiple markers that are relevant to the resolution of NASH and improvement in fibrosis
- No significant difference between 3 mg and 6 mg doses in the overall efficacy parameters; some differences in tolerability
- Adverse event profile is consistent with other NGM282-treated study populations
- Further clinical studies are ongoing to evaluate lower doses of NGM282 and the use of statins for mitigation of LDL
- Data strongly supports continued development in NASH
BMS-986036 (pegylated FGF21) in patients with non-alcoholic steatohepatitis: A phase 2 study

Arun Sanyal,1 Edgar D. Charles,2 Brent Neuschwander-Tetri,3 Rohit Loomba,4 Stephen Harrison,5 Manal F. Abdelmalek,6 Eric Lawitz,7 Dina Haleigha-DeMarzio,8 Yuping Dong,2 Stephanie Noviello,2 Saravanan Krishnamoorthy,2 Yi Luo,2

Rose Christian2

1Virginia Commonwealth University, Richmond, Virginia, USA; 2Bristol-Myers Squibb, Lawrenceville, New Jersey, USA; 3Saint Louis University, Saint Louis, Missouri, USA; 4University of California – San Diego, San Diego, California, USA; 5Pinnacle Clinical Research, San Antonio, Texas, USA; 6Duke University, Durham, North Carolina, USA; 7Texas Liver Institute, University of Texas Health, San Antonio, Texas, USA; 8Thomas Jefferson University, Philadelphia, Pennsylvania, USA

The International Liver Conference, European Association for the Study of the Liver (EASL 2017)
Amsterdam, The Netherlands, April 19-23, 2017
Publication number: LBO-01

Presenting author: Arun Sanyal
FGF21 may have direct and indirect beneficial effects on non-alcoholic steatohepatitis (NASH) and NASH-related fibrosis.

FGF, fibroblast growth factor; HDL, high density lipoprotein; LDL, low density lipoprotein.

Kharitonkov A and Larsen P, Trends Endocrinol Metab. 2011;22(3):81-86;
**Study Design**

**Phase 2 Double-Blind, Placebo-Controlled Study**

- **Key Eligibility Criteria:** biopsy-proven NASH with fibrosis stage 1-3 (within 1 year of screening), BMI $>25$ kg/m$^2$, hepatic fat fraction $\geq 10\%$ (MRI-PDFF)

- **Primary Efficacy Endpoint:** change in hepatic fat fraction ($\%$) from baseline to Week 16

- **Key Exploratory Endpoints:** adiponectin, lipids, ALT, AST, MRE, and serum Pro-C3

- **Safety Assessments** included AEs, laboratory parameters, and vital signs

*Planned sample size was 30 per group; enrollment ended early due to the significant effect of BMS-986036 on the primary endpoint seen during preplanned interim analysis at treatment Week 8.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, non-alcoholic steatohepatitis; QD, once daily; QW, once weekly; SC, subcutaneous; T2DM, type-2 diabetes mellitus.
**Absolute Improvement in Hepatic Fat Fraction (MRI-PDFF) at Week 16**

BMS-986036 QD and QW treatment compared with placebo significantly reduced hepatic fat fraction.

*Inferential statistical analyses were conducted using a MMRM and not adjusted for multiple comparisons; †1 patient in each group completed treatment but did not have adequate MRI-PDFF scans at baseline and Week 16.

CI, confidence interval; MRI-PDFF, magnetic resonance imaging-proton density fat-fraction; MMRM, mixed effects model for repeated measures; QD, once daily; QW, once weekly.
Categorical Improvement in Hepatic Fat Fraction (MRI-PDFF) at Week 16

- Relative reduction of ≥ 29% in MRI-PDFF is associated with histologic response in NASH patients\(^1\)
- Significantly more BMS-986036 QD patients compared with placebo patients had ≥30% reduction in MRI-PDFF
  - More QW patients versus placebo patients had ≥30% reduction in MRI-PDFF

\(^*\) Inferential statistical analyses were conducted post hoc using Fisher’s Exact test and not adjusted for multiple comparisons;
\(^†\) 1 patient in each group completed treatment but did not have adequate MRI-PDFF scans at baseline and Week 16.

Improvement in Triglycerides, LDL, and HDL Cholesterol at Week 16

- BMS-986036 QD and QW groups showed improved triglycerides and HDL levels from baseline
- BMS-986036 10 mg QD reduced LDL levels relative to baseline
- No meaningful changes in triglycerides, LDL or HDL levels were observed with placebo

HDL, high density lipoprotein; LDL, low density lipoprotein; QD, once-daily; QW, once weekly.
Improvements in ALT and AST Over Time

- BMS-986036 QD and QW treatment were associated with improvements from baseline in biomarkers of liver injury.
- Changes from baseline were minimal in the placebo group.

* indicates number of patients with ALT/AST data at EOT.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; QD, once daily; QW once weekly.
Categorical Improvement in Liver Stiffness (MRE) at Week 16

BMS-986036 QD and QW groups relative to placebo had a numerically greater percentage of patients with ≥ 15% reduction in liver stiffness*

*MRE, magnetic resonance elastography; CI, confidence interval; QD, once daily; QW, once weekly.

*Sample size for the liver stiffness (MRE) analysis was smaller than other endpoints because MRE was only conducted at a subset of imaging facilities with the appropriate hardware and software.
Reduction in Serum Pro-C3 at Week 16

- Elevated serum Pro-C3 levels are associated with fibrosis, progression of fibrosis, and may identify patients who are likely to benefit from antifibrotic therapy.\(^1\)\(^-\)\(^3\)
- All patients had comparable serum Pro-C3 levels at baseline
- BMS-986036 QD and QW compared with placebo significantly reduced serum Pro-C3 levels


*Inferential statistical analyses were conducted post hoc using a longitudinal repeated measurements model analysis.
†Sample size for serum Pro-C3 was smaller than MRI-PDFF due to some non-evaluable samples at baseline.
Categorical Improvement in Serum Pro-C3 at Week 16

- BMS-986036 QD and QW groups compared with placebo had a significantly greater percentage of patients with a ≥ 15% reduction in serum Pro-C3 levels

*Inferential statistical analyses were conducted post hoc using a longitudinal repeated measurements model analysis.
†Sample size for serum Pro-C3 was smaller than MRI-PDFF due to some non-evaluable samples at baseline.

CI, confidence interval; MRI-PDFF, magnetic resonance imaging-proton density fat-fraction; QD, once daily; QW, once weekly.
# Safety Summary

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>BMS-986036</th>
<th>Placebo (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg QD (n=25)</td>
<td>20 mg QW (n=23)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs*</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related SAEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs in &gt; 10% of participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (13)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (16)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>5 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-emergent grade 3 &amp; 4 laboratory abnormalities</td>
<td>1 (4)†</td>
<td>2 (9)‡</td>
</tr>
</tbody>
</table>

- BMS-986036 was generally well tolerated
  - Most AEs were considered mild
  - No AEs were considered severe

- There were no deaths, treatment-related SAEs, or discontinuations due to AEs

* 2 SAEs were depression/suicide attempt (10 mg QD) and cellulitis (placebo), neither was considered related to treatment; †Grade 3 ALT elevations; ‡High fasting glucose (1 patient) and grade 3 ALT elevation (1 patient).
BMS-986036 10 mg QD and 20 mg QW for 16 weeks, compared with placebo, significantly decreased hepatic fat fraction in patients with NASH (F1-F3)

BMS-986036 QD and QW relative to placebo was associated with improvements in biomarkers of fibrosis (MRE and Pro-C3), metabolic parameters (adiponectin and lipids), and markers of hepatic injury (ALT and AST)

BMS-986036 QD and QW were generally well tolerated with no deaths, SAEs related to treatment, or discontinuations due to AEs

These results suggest that BMS-986036 has beneficial effects on steatosis, liver injury, and fibrosis in NASH

Future clinical studies of weekly administration of BMS-986036 for NASH are warranted
Fecal Microbiota Transplant Using a Precision Medicine Approach is Safe, Associated with Lower Hospitalization Risk and Improved Cognitive Function in Recurrent Hepatic Encephalopathy

Jasmohan S. Bajaj* 1, Zain Kassam2, Andrew Fagan1, Edith A. Gavis1, Eric Liu3, Jane Cox4, Raffi Kheradman3, Douglas Heuman1, Jessica Wang3, Thomas Gurry5, Roger Williams4, Masoumeh Sikaroodi3, Michael Fuchs1, Eric Alm5, Binu John1, Ben Arrowsmith6, Antonio Riva4, Mark Smith2, Simon D. Taylor-Robinson6, Patrick Gillevet3

1Virginia Commonwealth University, Richmond, United States, 2OpenBiome, Somerville, 3George Mason University, Manassas, United States, 4Institute of Hepatology, London, United Kingdom, 5Massachusetts Institute of Technology, Cambridge, United States, 6Imperial College, London, United Kingdom
Background

• Hepatic encephalopathy (HE) is a leading cause of readmission due to recurrence.
• These readmissions often occur despite standard of care (SOC), lactulose and rifaximin.
• These pts also receive multiple antibiotic courses and can develop lasting cognitive injury.
• Fecal microbiota transplantation (FMT) is a promising approach for non-cirrhotic patients but there is a paucity of data in a systematic fashion

Aim

To define the safety profile, impact on liver and cognition of FMT for recurrent HE using a rationally-derived stool donor in a randomized, clinical trial
Methods-I  
Rational Donor selection

- Using cross-sectional HE microbiome data, the ideal OpenBiome donor for HE pts (with highest autochthonous taxa) was identified using Random Forrest analysis.
- Samples collected from one bowel movement of this donor were the basis for all FMT donor material.
- An IND was obtained under FDA supervision for this Phase 1 study.
FMT group had lower negative outcomes compared to SOC

- All admit: SOC 11, FMT 2
- HE-related: SOC 6, FMT 0
- No of pts admit: SOC 8, FMT 2
- No of pts with HE: SOC 5, FMT 0
- Infections: SOC 2, FMT 0
- Variceal bleeding: SOC 2, FMT 0
**EncephalApp Stroop Seconds**

- High = worse

**PHES score**

- Low = worse

**Stroop 0 minus Day 20 (Positive indicates improvement)**

- SOC: 50th Percentile = 0
- FMT: 50th Percentile = 0

**PHES Day 0 minus Day 20 (Negative indicates improvement)**

- SOC: 50th Percentile = 0
- FMT: 50th Percentile = 0

**SOC**

- P = 0.26

**FMT**

- P = 0.009

**SOC**

- P = 0.98

**FMT**

- P = 0.001

**Stroop Seconds**

- 50th Percentile = 0

**PHES score**

- 50th Percentile = 0
• SOC arm remained similar over time.
• Within the FMT group, reduced phenylacetylglutamine (PAG), hippurate and formate after antibiotics were seen, which returned to baseline post-FMT
Conclusions

• We conclude that in this randomized trial, FMT from a rationally selected donor was safe, associated with lower hospitalizations, especially related to recurrent HE and improved cognitive tests among cirrhotic patients with recurrent HE.

• FMT restores antibiotic associated loss of gut microbial diversity and is not associated with infections

• Further studies are needed in women, those without pre-treatment antibiotics and in those with higher MELD scores
Multicenter randomized trial comparing short-term stenting versus balloon dilatation for dominant strictures in primary sclerosing cholangitis”

Cyriel Ponsioen, on behalf of the DILSTENT group
Academic Medical Center
Amsterdam
background

• 50% of PSC patients will have dominant strictures
• annual incidence ≈ 9%
• patients with increasing cholestatic complaints and a rise in ALP or bilirubin of ≥ 50% will have a dominant stricture in 60%

Ponsioen et al. Am J Gas 1999; 94: 2403
Gotthardt et al. GIE 2010; 71: 527
background

• narrowing to ≤ 1.5 mm in CHD or CBD
• narrowing of ≤ 1.0 mm in LHD/RHD

Stiehl et al. J Hepatol 2002; 36: 151
treatment of DS leads to amelioration of symptoms and cholestasis

Ponsioen et al. Am J Gas 1999; 94: 2403
7. ESGE/EASL suggest performing endoscopic treatment with concomitant ductal sampling (brush cytology, endobiliary biopsies) of suspected significant strictures identified at MRC in PSC patients who present with symptoms likely to improve following endoscopic treatment.

*Strong recommendation, low quality evidence.*
Dilatation or Stenting?

2-yr recurrence-free rate 30% (?)

2-yr recurrence free rate 70%

Gotthardt et al. GIE 2010; 71: 527
Ponsioen et al. Am J Gas 1999; 94: 2403
Aim

to compare single-session balloon dilatation versus short-term stenting with regard to efficacy and safety
Methods

- non-endstage large duct PSC patients (CPT <8, Mayo RS<2)
- either of the following:
  - bilirubin >3xULN
  - increase in cholestatic complaints + >50% increase in ALP or bilirubin
  - >20% increase in ALP/bilirubin + documented stricture <4 mth
  - increase in cholestatic complaints + documented stricture <4 mth +

Table 1. Semiquantitative Scoring of Cholestatic Complaints

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>None</td>
<td>Sometimes</td>
<td>Daily</td>
<td>Wakes me up/need medication</td>
<td>Intolerable</td>
</tr>
<tr>
<td>Fatigue</td>
<td>None</td>
<td>Cannot do everything</td>
<td>Have to rest</td>
<td>&lt;50% daytime in bed</td>
<td>Intolerable</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>No fever</td>
<td>Fever</td>
<td>RUQ pain</td>
<td>None</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUQ = right upper quadrant.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ponsioen et al. Am J Gas 1999; 94: 2403
Methods

- co-primary endpoint: cumulative recurrence free rate of DS in patients without initial failure
- secondary endpoints: safety
Results

Enrollment

Assessed for eligibility n=80

Excluded during ERCP n=15
- no dominant stricture (n=6)
- stricture deemed not amenable to both treatment modalities (n=9)

Randomized n=65

Allocation

Balloon dilatation n=31
- received allocated intervention (n=30) and included in safety analysis

Stent(s) n=34
- received allocated intervention (n=33) and included in safety analysis

Analysis

included in intention-to-treat analysis n=31

included in intention-to-treat analysis n=34
Results

- Randomization:
  - Balloon
  - Stent
  - Balloon-censored
  - Stent-censored

- Cumulative Survival

- Weeks 0-120

- Initial failure:
  - Balloon: 48%
  - Stent: 41%

- No initial failure:
  - Balloon: 52%
  - Stent: 59%

- p = 0.55
Results

Procedure-related serious adverse events

<table>
<thead>
<tr>
<th></th>
<th>balloon dilatation n=30</th>
<th>short-term stenting n=33</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>all cause n (%)</td>
<td>2 (6.7)</td>
<td>15 (45)</td>
<td>11.7 (2.4-57.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>cholangitis/cholecystitis n (%)</td>
<td>1 (3.3)</td>
<td>4 (12)</td>
<td>4.0 (0.42-38.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>PEP n (%)</td>
<td>1 (3.3)</td>
<td>8 (24)</td>
<td>9.3 (1.1-79.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>post-procedural pain (other) n (%)</td>
<td>0</td>
<td>2 (4.5)</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>ascites</td>
<td>0</td>
<td>1(3)</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

RR stent vs balloon=6.8
**Results**

Univariate and multivariate analysis for confounders

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Univariate 95% CI</th>
<th>p-value</th>
<th></th>
<th>OR</th>
<th>Multivariate 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomization</td>
<td>11.2</td>
<td>2.4-57.2</td>
<td>0.002</td>
<td>randomization</td>
<td>11.3</td>
<td>2.3-56.2</td>
<td>0.003</td>
</tr>
<tr>
<td>centre</td>
<td>0.8</td>
<td>0.6-1.1</td>
<td>0.16</td>
<td>centre</td>
<td>0.8</td>
<td>0.6-1.2</td>
<td>0.24</td>
</tr>
<tr>
<td>previous EPT</td>
<td>0.6</td>
<td>0.2-2.0</td>
<td>0.39</td>
<td>previous EPT</td>
<td>0.6</td>
<td>0.2-2.0</td>
<td>0.4</td>
</tr>
<tr>
<td>sphincterotomy</td>
<td>0.7</td>
<td>0.2-2.15</td>
<td>0.48</td>
<td>sphincterotomy</td>
<td>0.7</td>
<td>0.2-2.15</td>
<td>0.48</td>
</tr>
</tbody>
</table>
conclusions

- recurrence-free survival of balloon dilatation and stenting is equal.
- stenting associated with much higher occurrence of procedure-related SAEs.
- in patients with intact papilla balloon dilatation is first treatment of choice.
A 2-YEAR MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF BEZAFIBRATE FOR THE TREATMENT OF PRIMARY BILIARY CHOLANGITIS IN PATIENTS WITH INADEQUATE BIOCHEMICAL RESPONSE TO URSDOXYCHOLIC ACID THERAPY (BEZURSO, NCT01654731)


BEZURSO study group, French network for inflammatory biliary diseases, France
Study rationale

• PBC: progressive cholestatic liver disease
• UDCA: universal first-line treatment
• Inadequate biochemical response to UDCA: 30%-40%
• Increased risk of death or liver transplantation
• Obeticholic acid: second-line therapy recently approved
• Fibrates: encouraging reports but still limited to small-sized, non-blinded controlled studies
Study objectives

• Primary objective:
  • Efficacy of bezafibrate as an adjunctive therapy for PBC in patients who did not respond adequately to UDCA

• Secondary objectives:
  • Effect on disease symptoms
  • Effect on prognostic markers
  • Safety and tolerance
Study design / Patient criteria

• Study design:
  • 2-year multicenter, double-blind, randomized, placebo-controlled trial of bezafibrate (400 mg/d) in combination with UDCA (13-15 mg/kg/d)

• Participants:
  • Inadequate biochemical response to UDCA as defined by the Paris-2 criteria (alkaline phosphatase > 1.5 x ULN, or AST > 1.5 x ULN, or total bilirubin > 17 µmole/L)
  • Exclusion criteria: decompensated cirrhosis, total bilirubin > 50 µmole/L, typical features of autoimmune hepatitis, hepatocarcinoma or any other severe life-threatening comorbidities
Study endpoint / Hypothesis

• Primary endpoint:
  • Complete biochemical response as defined by normal levels of total bilirubin, alkaline phosphatase, aminotransferases, albumin and prothrombin time at month 24

• Statistical analysis:
  • Hypothesis: 40% of the patients in the bezafibrate group versus 10% in the placebo group will fulfill the primary endpoint
  • Number of patients needed (α=5%, β=10%, two-sided test): 92
  • Analyses were performed on the intent-to-treat population
Flowchart

Recruiting centers: 21
Recruiting period: 2012/10/22 - 2014/12/22

Inadequate biochemical response to UDCA (Paris-2 criteria)

Randomization on N=100

Placebo N=50

Premature termination N=4

Bezafibrate 400 mg/d N=50

M0 M3 M6 M9 M12 M15 M18 M21 M24

Placebo N=46

Placebo N=44

UDCA 13-15 mg/kg/d

Premature termination N=2

Premature termination N=2

Premature termination N=4

Premature termination N=2

UDCA 13-15 mg/kg/d
M24 complete biochemical response

*Primary endpoint*

$p < .0001$

<table>
<thead>
<tr>
<th>M24 complete biochemical response</th>
<th>Placebo</th>
<th>Bezafibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>35%</td>
<td>0%</td>
<td>30%</td>
</tr>
<tr>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
M24 normal alkaline phosphatase level

Secondary endpoint

Comparison of M24 normal ALP levels between Placebo and Bezafibrate groups, showing a significant difference (p < .0001).
Course of alkaline phosphatase level

Secondary endpoint
Course of total bilirubin level

Secondary endpoint
## M24 changes in biochemical tests

### Secondary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Bezafibrate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total bilirubin</strong></td>
<td>+18% (0%; +40%)</td>
<td>-14% (-33%; +6%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase</strong></td>
<td>+0% (-14%; +20%)</td>
<td>-60% (-66%; -46%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>GGT</strong></td>
<td>+7% (-14%; +51%)</td>
<td>-38% (-59%; -24%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>AST</strong></td>
<td>+8% (-17%; +26%)</td>
<td>-8% (-30%; +3%)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>+0% (-24%; +31%)</td>
<td>-36% (-53%; -14%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>-3% (-7%; +3%)</td>
<td>+0% (-4%; +7%)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>+0% (-9%; +7%)</td>
<td>-16% (-24%; -9%)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

*medians (interquartile range)*
M24 preestablished response criteria

*Secondary endpoint*

**Paris-2 criteria**

- Placebo: 10%
- Bezafibrate: 70%

**Barcelona criteria**

- Placebo: 10%
- Bezafibrate: 68%

*p < .0001*
M24 changes in itch score

*Secondary endpoint*

Median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Bezafibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100%</td>
<td>0%</td>
<td>-75%</td>
</tr>
</tbody>
</table>

P < .01
M24 changes in fibrosis markers

Secondary endpoint

Liver stiffness

Placebo: +14%  p < .01
Bezafibrate: -10%

ELF score

Placebo: +3%  P < .05
Bezafibrate: -1%
End-stage liver complications

Secondary endpoint

- Ascites x 1
- Doubling bilirubin > 50 µmole/L x 1
- Liver transplantation x 1
- Waiting list x 1

- Placebo: 4%
- Bezafibrate: 4%
Serious adverse events (SAE)

Secondary endpoint

- No SAE: 80% Placebo, 74% Bezafibrate
- 1 SAE: 16% Placebo, 16% Bezafibrate
- 2 SAE: 2% Placebo, 8% Bezafibrate
- ≥ 3 SAE: 2% Placebo, 2% Bezafibrate

p = NS
Summary

• A complete biochemical response was achieved significantly more frequently in the bezafibrate than in the placebo group
• Significant decrease in alkaline phosphatase activity was detectable from the third month of treatment
• Improvement in pruritus was achieved more frequently in the bezafibrate than in the placebo group
• Non-invasive markers of fibrosis significantly increased in the placebo group as compared to the bezafibrate group
• Frequency of serious adverse events did not differ between the two groups
Conclusion

• In PBC patients with inadequate biochemical response to UDCA, adjunctive therapy with bezafibrate is safe, improves pruritus, normalizes biochemical prognostic markers, and prevents liver stiffness progression

• This supports the use of bezafibrate in combination with UDCA as an effective second-line therapy for PBC
Predicted prevalence and stratification of NAFLD in a large population using non-invasive multiparametric MRI.

Henry Wilm1,2, Matt Kelly1, Andrea Dennis1, Cat Kelly1, E. Louise Thomas2, Stefan Neubauer1,3, Jimmy D. Bell2, Rajeshri Banerjee1.

1Perceptum Diagnostics, Oxford, UK 2Department of Life Sciences, University of Westminster, UK 3OCMR, Division of Cardiovascular Medicine, University of Oxford, UK

Aims

- To determine the suitability of multiparametric MRI of the liver for the assessment and stratification of NAFLD in large populations.
- To show cT1 can augment PDFF as a screening measure for NAFLD and NASH.

Conclusions

- Multiparametric MRI with LiverMultiScan™ can identify individuals with steatosis and high risk NASH.
- LiverMultiScan™ acquisition takes < 3 minutes, requires no contrast, and can be used for high throughput analysis of a general population.
- cT1 can be used in addition to PDFF to further enrich a population for NASH with significant fibrosis.