Clinical perspective

Unmet needs in fatty liver disease (NASH)

Jacob George

STORR LIVER CENTRE

Westmead Millennium Institute for Medical Research

The University of Sydney

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Why do we treat liver diseases

Progression of fibrosis

Normal → Inflamed → Fibrotic → Cirrhotic

May be reversible process with treatment of underlying disease

Extensive fibrosis and formation of repetitive nodules

Healing

Repetitive injury
Cirrhosis is not good
What is NAFLD?
NAFLD

- A spectrum of disorders characterized by predominantly steatosis (liver fat)
- In practice
  - Can worsen any liver disease (including alcohol)
The spectrum of NAFLD

- Simple steatosis
- NASH
- Fibrosis
- Cirrhosis
- HCC

5-10%
30-38%
5-20% over 20 years
3-5%/year

↑ CVD
↑ CKD
↑ T2DM

Adams, LA J Hepatol 2005
Ekstedt M, Hepatology 2006
Fassio, E Hepatology 2004
Harrison, SA Gastroenterol 2003
Why does NASH occur?

Global prevalence of Overweight/obesity

- 3.4 m deaths; 3.9% of years of life lost, 3.8% of DALYs; 1769 reports
- Global prevalence 1980-2013: 29% in men to 37%; Women 30% to 38%; 47% increase in children
- >50% in women from Kuwait, Kiribati, Micronesia, Libya, Qatar, Tonga, Samoa

Lancet 2014; 384: 766–81
The problem of obesity: US Data from CDC
Rate of obese adults by US State (BMI ≥30)
GLOBAL EPIDEMIOLOGY OF NAFLD/NASH

46 % NAFLD
12 % NASH
3 % severe fibrosis/cirrhosis
Texas
Williams Gastroenterology 2011

France:
NAFLD: 60 %  NASH: 33 %
De Ledinghen, J Hepatol 2006

Spain: NAFLD: 44%
Caballeria, Eur J Gastro 2012

Brazil:
NAFLD: 42%
NASH: 27%
27% severe fibrosis/cirrhosis
Cotrim HP, Ann Hepatol 2012

Japan:
NAFLD 29 %
Jimba S Diabet Med 2005

India
NAFLD 32 %
Survival: Study of Health in Pomerania (N= 4160)
Life expectancy in NAFLD

Overall survival of subjects in the study with NASH or bland steatosis. 

n=256; median follow up 24 years

Soderberg et al. Hepatology 2010
NASH Cirrhosis: Poor outcomes

N=247; F3/4
F/U: 85 months (7 years)
19.4% liver related complications (2.8% pa)
13.4% deaths/OLT
A Clinically Silent Disease

• **Symptoms:**
  – None 20 - 77%
  – Right upper quadrant pain 25 - 48%
  – Fatigue 50 - 75% (Obstructive sleep apnea in 40%)

• **Signs:**
  – Overweight/Obese 85 - 95%
  – Acanthosis nigricans 10 -15%
  – Hepatomegaly 25 - 50%

• **Laboratory:**
  – ALT, AST - modest elevation
  – “Normal enzymes” (up to 80% of NAFLD)

• **Radiological:**
  - **Ultrasound:** echogenic parenchyma; beam attenuation
Diagnosis

Liver ultrasound
Liver tests
Fibroscan
Liver biopsy
Principals of treatment

• Reduce liver fat aka IR aka obesity
  – Lifestyle intervention
  – Bariatric surgery

• Reduce liver inflammation

• Reduce liver fibrosis
**Current treatment**

<table>
<thead>
<tr>
<th>Steatohepatitis resolution</th>
<th>Two points improvement in NAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss &lt;5%</td>
<td>Weight loss 5-7%</td>
</tr>
<tr>
<td>21/205</td>
<td>9/34</td>
</tr>
<tr>
<td>66/205</td>
<td>21/34</td>
</tr>
</tbody>
</table>

- Steatohepatitis resolution: 10% improvement in NAS
- Two points improvement in NAS: P<0.001*

*Mantel-Haenszel $\chi^2$ test for trend

So the problem is:

• **Big!!!!!!**
  • Obesity associated NCD exceeds infectious disease as commonest global cause of death
  • Can only be managed (not prevented), unless we can change
    – Behaviour –Diet, exercise, PA
Potential treatments

- PPARγ agonists (anti-diabetic agents)
- Incretins, Glut2-I
- Vitamin E
- FXR agonists
  - Intercept, Gilead
- PPAR alpha-delta antagonists
  - Genefit
## Treatment trials for NASH

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>MoA</th>
<th>RoA</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raptor</td>
<td>RP103</td>
<td>Antioxidant - cysteine depleting agent</td>
<td>Oral</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Zydus-Cadila</td>
<td>Saroglitazar</td>
<td>PPAR agonist ((\alpha, \gamma))</td>
<td>Oral</td>
<td>Phase 3</td>
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<tr>
<td>Novo Nordisk</td>
<td>Liraglutide</td>
<td>GLP-1</td>
<td>SubQ</td>
<td>Phase 2</td>
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<tr>
<td>Takeda</td>
<td>Pioglitazone</td>
<td>PPAR agonist</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Islet Sciences</td>
<td>Remogliflozin etabonate</td>
<td>SGLT-2 inhibitor</td>
<td>Oral</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Aptalis Pharma</td>
<td>Ursodeoxycholic acid</td>
<td>Bile acid</td>
<td>Undefined</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Gilead</td>
<td>Simtuzumab</td>
<td>LOXL2 antibody</td>
<td>IV and SubQ</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Conatus</td>
<td>Emricasan</td>
<td>Caspase protease inhibitor</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Galmed</td>
<td>Aramchol</td>
<td>Synthetic fatty acid/bile acid conj</td>
<td>Oral</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Tobira</td>
<td>Cenicriviroc</td>
<td>Dual CCR2/CC5 antagonist</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Genfit</td>
<td>GFT 505</td>
<td>PPAR alpha/delta agonist</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Intercept</td>
<td>OCA</td>
<td>FXR agonist</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Phenex</td>
<td>PX 104</td>
<td>FXR agonist (non bile acid)</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Mochida</td>
<td>Icosapent ethyl ester</td>
<td>Caspase protease inhibitor</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Immunon</td>
<td>IMM 124E</td>
<td>Immunomodulators</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>KT&amp;G Life Sciences</td>
<td>MB 12066</td>
<td>Sirtuin stimulants</td>
<td>Oral</td>
<td>Phase 2</td>
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Adis R&D Insight, Thomson Reuters Cortellis
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<tr>
<td>PharmaKing</td>
<td>Oltipraz</td>
<td>Fatty acid inhibitor</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Novartis</td>
<td>Pradigastat</td>
<td>DGAT1 inhibitor</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Therapix</td>
<td>TRX 318</td>
<td>CD3 antigen</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Takeda</td>
<td>Roflimilast</td>
<td>PDE-4</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
<td>Antipodean</td>
<td>Mitoquinone</td>
<td>Antioxidant</td>
<td>Oral</td>
<td>Phase 2</td>
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<td>KT&amp;G Life Sciences</td>
<td>MB 11055</td>
<td>AMPK stimulant</td>
<td>Undefined</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Naia</td>
<td>NC 101</td>
<td>Undefined mechanism</td>
<td>Undefined</td>
<td>Phase 2</td>
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<tr>
<td>Galectin</td>
<td>GR MD 02</td>
<td>Galectin-3</td>
<td>IV and SubQ</td>
<td>Phase 1</td>
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<tr>
<td>Kadmon</td>
<td>KD 025</td>
<td>ROCK2 inhibitor</td>
<td>Oral</td>
<td>Phase 1</td>
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<tr>
<td>Phenex</td>
<td>PX 102</td>
<td>FXR agonist</td>
<td>Oral</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Shire</td>
<td>SHP 626</td>
<td>ASBT inhibitor</td>
<td>Oral</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Durect</td>
<td>DUR-928</td>
<td>Undefined small molecule</td>
<td>Oral</td>
<td>Phase 1</td>
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<tr>
<td>Daewoong</td>
<td>DWP-10292</td>
<td>Undefined small molecule</td>
<td>Oral</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Gilead</td>
<td>GS-4997</td>
<td>ASK1 inhibitor</td>
<td>Oral</td>
<td>Phase 1</td>
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<tr>
<td>TaiwanJ</td>
<td>JKB-121</td>
<td>TLR-4 antagonist</td>
<td>Oral</td>
<td>Phase 1</td>
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<tr>
<td>Madrigal</td>
<td>MGL-3196</td>
<td>THR beta agonist</td>
<td>Oral</td>
<td>Phase 1</td>
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<tr>
<td>Virobay</td>
<td>VBY-376</td>
<td>Cathepsin B inhibitor</td>
<td>Oral</td>
<td>Phase 1</td>
</tr>
<tr>
<td>La Jolla</td>
<td>LGPC-1010</td>
<td>Galectin-3 inhibitor</td>
<td>Oral</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
Incretin-based therapies (Liraglutide)

The LEAN Study:

- Multicentre, 26 Liraglutide, 26 placebo
- Double-blinded, randomised, placebo-controlled phase II trial.
- Primary endpoint: Resolution of definite NASH and no worsening F

Overweight patients with NASH with or without diabetes

SC injections of 1.8mg liraglutide

Liraglutide-placebo

48 Weeks

Armstrong MJ, EASL 2015
Liraglutide and NASH

As expected with liraglutide, improvements were also seen in BMI and fasting glucose levels.

No treatment related side effects
FXR effects on lipid metabolism

- FXR activates hPPAR$_{ii}$, which in turn increases FA $\beta$-oxidation.
- FXR activates VLDLR and hSyndecan-1, which increases HDL clearance.
- FXR activates ANGTPL3, which increases LPL activity and TG clearance.
- FXR decreases SREBP-1c, which decreases TG/FA synthesis.
- FXR decreases SHP, which decreases TG/FA synthesis.
- FXR decreases Plasma TG/FFA.
- FXR decreases Plasma HDL-C.
Changes in histological features of the liver after 72 weeks of Obeticholic acid treatment

P=0.004  P=0.03  P=0.001  P=0.006

Obeticholic acid  Placebo

Fibrosis: 35  19  
Hepatocellular ballooning: 46  31  
Steatosis: 61  38  
Lobular inflammation: 53  35

Systemic FXR agonists have issues!

- FLINT Study:
  - Increased LDL, decreased HDL
  - Increased hepatic insulin resistance
  - Pruritus
- The first two problems are likely due to FXR activation in liver
- Pruritus due to Obeticholic Acid being a bile acid
GFT505, New dual PPARα/δ–non PPARγ compound

• GFT 1007 main active circulating metabolite
• **PPAR α activity** (15 nmol vs 30µmol fenofibrate); **PPAR δ activity** (75 nmol vs 1 nmol GW501516)
• Extensive enterohepatic cycling and liver targeted
• No induction of PPAR α or δ genes in muscle
• No PPAR γ activity (no adiponectin induction)
### GFT505, Metabolic effects in abdominally obese and prediabetic patients

#### Insulin induced effect on HGP (%)

<table>
<thead>
<tr>
<th></th>
<th>GFT505</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>effect</td>
<td>49.2</td>
<td>-34.3</td>
</tr>
</tbody>
</table>

#### Glucose infusion rate (mg/kg/min)

<table>
<thead>
<tr>
<th></th>
<th>TG</th>
<th>CHOL</th>
<th>HDL-C</th>
<th>NON HDL-C</th>
<th>LDL-C</th>
<th>ApoA2</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9</td>
<td>18</td>
<td>***</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

#### Median % change vs Baseline

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen</th>
<th>Haptoglobin</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFT505</td>
<td>-13.5%</td>
<td>-20.8%</td>
<td>-27.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>-6.8%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Liver enzymes

<table>
<thead>
<tr>
<th></th>
<th>ASAT</th>
<th>ALAT</th>
<th>GGT</th>
<th>ALP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect size vs placebo (% change)</td>
<td>-6.7%</td>
<td>-20.5%</td>
<td>-30.5%</td>
<td>-19.3%</td>
</tr>
</tbody>
</table>

*Cariou, Diabetes Care 2011*
*Cariou, Diabetes Care 2013*
Targeting inflammation

• Vascular adhesion protein-1 (VAP-1)
  – Semicarbazide-sensitive amine oxidase (SSAO)
  – Promotes white cells entering injured tissues
  – Promotes inflammation
  – Promotes oxidative stress
Targeting inflammation

Weston et al JCI 2014
Targeting fibrosis
Lysyl Oxidase-Like 2: LOXL2

SIMTUZUMAB

- Humanized monoclonal antibody that binds LOXL2
- Half life of ~10-20 days when dosed iv
- SC dose is well tolerated
- Safe and well tolerated in >300 subjects some for >1 year of exposure
- To date has been dosed safely in 57 patients with liver fibrosis

Courtesy J Bornstein, Gilead
Reduction of Fibrosis and Myofibroblasts

♦ AB0023 administered concurrently with CCL4, Balb/C mice
♦ Significant reduction of bridging fibrosis with AB0023 (F1 rather than F3)
♦ Reduction of myofibroblasts, LOXL2 in porto-portal bridges

Courtesy J Bornstein, Gilead

Summary

- NAFLD/NASH are common
- Major cause of liver disease burden
- Significant cause of liver cancer
- Currently an unmet therapeutic need
- **Target:** fat, inflammation, fibrosis
- Major area for therapeutic drug discovery
Thank you!