TZD SHOULD BE USED TO TREAT ADVANCED NASH
Role of insulin resistance in NASH

Safety of TZD

Effectiveness of Pioglitazone in treating NASH
Decreased survival in patients with NAFLD

10y follow-up
Observed - 77%
Expected - 87%
p<0.005

Ischemic heart disease – 25%
Malignancy – 18%
Liver disease – 13%

Adams et al, Gastroenterology, 2005, 129:113-121
"Simple" steatosis

Steatohepatitis/NASH

Insulin Resistance
CV mortality
Cirrhosis
Obesity correlates with presence of biopsy proven NASH

Adapted from Chitturi S. et al. Hepatol 2002;35:373-9
In biopsy proven NASH, insulin resistance correlated better than obesity.

Adapted from Chitturi S. et al. Hepatol 2002;35:373-9
Insulin resistance is an independent predictor of persistence of NASH after bariatric surgery.

Mathurin et al. Gastro 2006; 130:1617-1624

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression coefficient (95% CI)</th>
<th>Standard error</th>
<th>Significant $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative severe steatosis</td>
<td>2.87 (0.44–5.3)</td>
<td>1.24</td>
<td>.006</td>
</tr>
<tr>
<td>Weight loss (difference of BMI)</td>
<td>0.23 (0.09–6.93)</td>
<td>0.8</td>
<td>.8 (NS)</td>
</tr>
<tr>
<td>Preoperative IR index</td>
<td>5.45 (0.49–10.4)</td>
<td>2.54</td>
<td>.01</td>
</tr>
<tr>
<td>Preoperative ALT level</td>
<td>−0.06 (−0.15 to 0.04)</td>
<td>0.05</td>
<td>.1 (NS)</td>
</tr>
</tbody>
</table>

NS, not significant.
Need to improve insulin resistance to effectively treat NASH
Outline

- Role of insulin resistance in NASH
- Safety of TZDs
- Effectiveness of Pioglitazone in treating NASH
**Rosiglitazone is associated with higher CV related mortality**

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,285 (0.43)</td>
<td>22/6,106 (0.36)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td>9/2,634 (0.34)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td>41/2,895 (1.42)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Death from cardiovascular causes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,845 (0.36)</td>
<td>7/3,980 (0.18)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,635 (0.46)</td>
<td>10/2,634 (0.38)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td>5/2,895 (0.17)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Lipid metabolism and the TZDs

<table>
<thead>
<tr>
<th></th>
<th>Pioglitazone</th>
<th>Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (small dense)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>TG</td>
<td>↓</td>
<td>...</td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
<td>...</td>
</tr>
<tr>
<td>DNL</td>
<td>↓</td>
<td>...</td>
</tr>
</tbody>
</table>

Goldberg et al., *Diabetes Care* 2005; Beysen et al., *JLR* 2008
Pioglitazone reduced MI and CV mortality in patients with CAD

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Pioglit (n = 1,230)</th>
<th>Placebo (n = 1,215)</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (fat/non-fat)</td>
<td>65 (5.3%)</td>
<td>88 (7.2%)</td>
<td>0.72</td>
<td>0.52-0.99</td>
<td>0.045</td>
</tr>
<tr>
<td>ACS</td>
<td>35 (2.8%)</td>
<td>54 (4.4%)</td>
<td>0.63</td>
<td>0.41-0.97</td>
<td>0.035</td>
</tr>
<tr>
<td>Comp end pt of all cardiac events</td>
<td>180 (14.6%)</td>
<td>217 (17.9%)</td>
<td>0.81</td>
<td>0.66-0.98</td>
<td>0.034</td>
</tr>
</tbody>
</table>
Rosiglitazone, but not pioglitazone, is associated with increased CV mortality.
Outline

- Role of insulin resistance in NASH
- Safety of TZD
- Effectiveness of Pioglitazone in treating NASH
A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

Renata Belfort, M.D., Stephen A. Harrison, M.D., Kenneth Brown, M.D., Celia Darland, R.D., Joan Finch, R.N., Jean Hardies, Ph.D., Bogdan Balas, M.D., Amalia Gastaldelli, Ph.D., Fermin Tio, M.D., Joseph Pulcini, M.D., Rachele Berria, M.D., Jennie Z. Ma, Ph.D., Sunil Dwivedi, M.D., Russell Havranek, M.D., Chris Fincke, M.D., Ralph DeFronzo, M.D., George A. Bannayan, M.D., Steven Schenker, M.D., and Kenneth Cusi, M.D.
Piaglitazone normalized amiotransferases

Belfort et al. NEJM. 2006;355:2297-307
Adiponectin is inversely related to severity of Insulin Resistance and NASH.

Pioglitazone doubles adiponectin levels.

Belfort et al. NEJM. 2006;355:2297-307
Hepatic fat content improved with Pioglitazone

54% reduction in hepatic fat content

Belfort et al. NEJM. 2006;355:2297-307
Pioglitazone improves histology

**Inflammation**
- 65% improvement
- P = 0.008

**Ballooning**
- 54% improvement
- P = 0.019

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D.,
Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D.,
Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D.,
James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S.,
Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D.,
David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D.,
and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

PIVENS – (Non- Diabetic patients)
PIVENS Study Design

Randomization
Eligibility assessed by local pathologist
(1:1:1)
Wk 0

Vitamin E (rrr α-tocopherol) 800 IU/day

Placebo

Pioglitazone (30 mg/day)

Liver biopsy

Month -6

End of treatment
Liver Biopsy
Wk 96

Week 120 end of study

Sanyal et al., NEJM 2010
Primary Endpoint

• Improved histology
  • > 1 drop in ballooning
  • No increase in fibrosis

AND

• Reduction in NAS ≤ 3 or
• NAS decrease of ≥ 2
Vit E met the primary endpoint

P = 0.04

P = 0.001

Porportion of patients (%)

P = 0.04

P = 0.001

19

43

34

Placebo

Vitamin E

Pioglitazone
Pioglitazone group was disadvantaged

- Percent of patients without ballooning at enrollment:
  - Placebo: 17%
  - Vitamin E: 18%
  - Pioglitazone: 28%

You can’t improve better than none
Pioglitazone met the primary endpoint (when patients with no ballooning on initial biopsy are excluded from analysis)

When patients with no ballooning at the start of the study excluded, the proportion of patients (%) met the primary endpoint was as follows:

- Placebo: 19, 25
- Vitamin E: 43, 51
- Pioglitazone: 34, 48

The p value is ≤ 0.002.
Pioglitazone improved steatosis, lobular inflammation and resolution of NASH

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>31</td>
<td>54</td>
<td>69</td>
</tr>
<tr>
<td>Inflammation</td>
<td>35</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Resolution of NASH</td>
<td>21</td>
<td>36</td>
<td>47</td>
</tr>
</tbody>
</table>

$\textit{p} < 0.001$  
$\textit{p} = 0.004$  
$\textit{p} = 0.001$
Pioglitazone improves aminotransferases
Pioglitazone improved Insulin Resistance
PIVENS shows that Pioglitazone

- Improved aminotransferases
- Improved steatosis
- Improved inflammation
- Increases resolution of NASH
- Improved insulin resistance
- Pioglitazone was well tolerated without any side-effects
Piaglitazone Improves Insulin Resistance despite weight gain
Conclusion

- NASH is a complicated and chronic liver disease strongly associated with insulin resistance.
- CV related deaths are the most common cause of death among NASH patients.
- Pioglitazone reduces the risk of MI and cardiovascular mortality.
- Pioglitazone effectively treats NASH by:
  - Improving insulin resistance
  - Improving histology