GLP-1 analogs and DPP-4 inhibitors

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Presenter Disclosure

- Research grants: Amylin, GSK, Lilly, sanofi-aventis
- Honoraria for consulting: Amylin, Lilly, NovoNordisk, Roche, sanofi-aventis
- Honoraria for speaking: Lilly, sanofi-aventis
Patterns of hormones which regulate plasma glucose and food intake

It's not just insulin!

Cummings DE et al. Diabetes 2001;50: 1714-1719
Ways to enhance GLP-1 receptor stimulation

**GLP-1 – chronic infusion**

**Oral DPP-4 inhibitors**
- Vildagliptin (Galvus)
- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)

**Short-acting GLP-1 agonist**
- Exenatide (Byetta)

**Long-acting GLP-1 agonists**
- Liraglutide (Victoza)
- Exenatide Q weekly (Bydureon)

**Intermediate-acting agonist**
- Lixisenatide (Lyxumia)
Effects of GLP-1 infusion
Glucose profiles in 40 patients with T2DM

Larsen J et al. Diabetes Care 2001; 24: 1416-21
6-week GLP-1 sc infusion by pump
Glucose profiles in 20 patients with T2DM

Week 0 -- off OAD 3 wks
Week 6 -- on sc infusions

Saline
GLP-1

mg/dL

Hours

4-weeks vildagliptin orally
Responses to breakfast

- **Glucose mmol/L**
  - Placebo (yellow)
  - Vilda 100mg (red)

- **Insulin pmol/L**

- **GLP-1 pmol/L**

- **Glucagon pg/mL**

Ahrén B et al. J Clin Endocrinol Metab 2004;89:2078-84
Effects of DP-4 Inhibitors

Sitagliptin is as effective as $\frac{1}{2}$ dose metformin
1091 patients randomized to PLBO, sitagliptin, or both

## Effects of GLP-1 agents

<table>
<thead>
<tr>
<th>Effect</th>
<th>Agonists</th>
<th>DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentiate insulin secretion</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Suppress glucagon</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Reduce calorie intake</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Slow gastric emptying</td>
<td>+ or ++</td>
<td>-</td>
</tr>
</tbody>
</table>
Tachphylaxis to GLP-1 effects

Reduced effect with ongoing Rx

Potentiate insulin secretion  No
Suppress glucagon  No
Reduce calorie intake  No
Slow gastric emptying  Yes
Tachyphylaxis to GLP-1 effects

9 healthy subjects
8.5 hour GLP-1 or placebo infusions
Meal tests as 0 and 4 hours

<table>
<thead>
<tr>
<th></th>
<th>0 hours</th>
<th>4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>No increase</td>
<td>Blunted</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Markedly slowed</td>
<td>Less slowed</td>
</tr>
<tr>
<td>Insulin</td>
<td>Much reduced</td>
<td>Less reduced</td>
</tr>
</tbody>
</table>

Nauck MA et al. Diabetes 2011;60: (on-line 24 March)
Liraglutide vs placebo

Vildagliptin vs placebo

Ahrén B et al. J Clin Endocrinol Metab 2004;89:2078-84
Ways to enhance GLP-1 receptor stimulation

GLP-1 – chronic infusion

Oral  DPP-4 inhibitors
- Vildagliptin (Galvus)
- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)

<table>
<thead>
<tr>
<th>Type</th>
<th>GLP-1 agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td>Exenatide (Byetta)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>Liraglutide (Victoza)</td>
</tr>
<tr>
<td></td>
<td>Exenatide Q weekly (Bydureon)</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>Lixisenatide (Lyxumia)</td>
</tr>
</tbody>
</table>
Single-dose lixisenatide: Effect on postprandial glucose
Drug naïve T2DM patients, standard meal 1 hour after injection

Not approved by FDA

Christensen M et al, IDrugs 2009 12(8):503-513
28-day treatment with lixisenatide: Effect on fasting and postprandial glucose

T2DM patients on metformin and/or SU, subgroup treated with up to 20 mcg taken in AM

Baseline

28 days of treatment

Strong effect on postprandial increment after breakfast, less after lunch and none after dinner

Distiller LA, Ruus R. Diabetologia 2008; 51 (Suppl1): A155
Lixisenatide dose-ranging study
Reduction of A1c and weight


*p < 0.0001, **p < 0.005, †p < 0.05 vs. placebo
A family of GLP-1 agonists with different durations of action?

- Native GLP-1 <1 hr?
- Exenatide 4-8 hr?
- Lixisenatide 8–16 h?
- Liraglutide >24 h
- Exenatide QW > 1 wk

**Hours:**

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
A family of GLP-1 agonists with different durations of action?

Exenatide 4-8 hr?
Lixisenatide 8–16 h?
Liraglutide >24 h

Hours
Action profiles of insulin formulations

- Aspart, glulisine, lispro 4–5 h
- Regular 6–8 h
- NPH 12–16 h
- Detemir 6–18 h
- Glargine ~24 h

Hours

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Effects of Exenatide BID vs Exenatide QW
252 T2DM patients on one or more OAD
24 weeks randomized open-label treatment

Δ A1c %
-0.7% A1c
P<0.0001

Δ FPG mg/dL
-23 mg/dL
p<0.001

Δ weight kg
-0.9 kg
(NS)
Effects of Exenatide BID vs Exenatide QW
295 T2DM patients on diet ± OAD
30 weeks randomized open-label treatment

Δ FPG mmol/L

Δ glucagon ng/L

SMBG profile

QW vs BID
- 0.33% A1c
P=0.0023

Mainly basal vs PP effect

Same wt reduction (3.7 vs 3.6 kg)

Effects of Liraglutide vs Exenatide BID

464 T2DM patients on 1-2 OAD
26 weeks randomized open-label treatment

- 0.33% A1c
  P=0.001

More basal vs PP effect

Same wt reduction (3.2 vs 2.9 kg)

Effects of Exenatide BID vs Glargine
551 T2DM patients on metformin + sulfonylurea
26 weeks Rx with titrated glargine or exenatide 10 mcg BID

A1c and weight: changes from baseline

Effects of Exenatide vs Glargine

551 T2DM patients on metformin + sulfonylurea
26 weeks Rx with titrated glargine or exenatide 10 mcgBID

SMBG and BG after test meal: changes from baseline

Exenatide BID added to titrated glargine ± OAD

7-point glucose profiles
LS Means ± SE

Not approved by FDA

A1c ~6.7%, weight difference 2.7 kg

* p<0.05, ** p<0.01

Titrated glargine added to exenatide+metformin

Distribution of A1c after 24 weeks

Not approved by FDA

Riddle MC et al. ADA Annual Scientific Sessions 2010, Late-breaking abstract, Poster 18-LB
# A1c lowering power of GLP-1 agents

Placebo-adjusted reductions (A1c%)  

<table>
<thead>
<tr>
<th></th>
<th>Added to Met</th>
<th>Added to Met+SU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>0.7 vs baseline</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide 1.8 mg</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>1.5 vs baseline</td>
<td></td>
</tr>
</tbody>
</table>
Preliminary safety concerns with GLP-1 agents

“Pancreatitis, pancreatic and thyroid cancer with glucagon-like peptide-1 based therapies”

Review of FDA adverse event reporting system database 2004-2009
Odds Rations from case-control analysis of pancreatitis and cancers.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Exenatide</th>
<th>Sitagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>10.68</td>
<td>6.74</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>2.95</td>
<td>2.72</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>4.73</td>
<td>1.48</td>
</tr>
<tr>
<td>Other cancers</td>
<td>1.08</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Elashoff M et al. Gastroenterology 2011;141: 150-6
Springer J & Stammschulte U. Gastroenterology 2011;141:20-3
Preliminary CV findings with a DPP-4 inhibitor

“Linagliptin has similar efficacy to glimepiride but improved cardiovascular safety over 2 years in patients with type 2 diabetes inadequately controlled by metformin”

1519 patients with T2DM treated with metformin
Randomized double-masked to linagliptin 5 mg or glimepiride up to 5 mg
Baseline A1c 7.7%

<table>
<thead>
<tr>
<th></th>
<th>Glimepiride</th>
<th>Linagliptin</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c reduction %</td>
<td>-0.5</td>
<td>-0.4</td>
<td>Noninferior</td>
</tr>
<tr>
<td>Change of weight kg</td>
<td>+1.3</td>
<td>-1.4</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>CV death, MI, stroke, angina</td>
<td>1.7 %</td>
<td>3.4 %</td>
<td>RR 0.50, p=0.04</td>
</tr>
</tbody>
</table>

Gallwitz B et al. ADA annual scientific sessions, June 2011, poster presentation 39-LB
Preliminary CV findings with GLP-1 agonists
CV benefit in animal model

Langendorff-perfused rat heart model (intact animal)

Infarction induced by 45 min LAD occlusion, 120 min reperfusion

Vehicle or GLP-1 agonist administered before/during reperfusion

Change of infarct size vs vehicle:

- Native GLP-1: -32%
- Liraglutide: -29%
- Lixisenatide: -36%

Interpretation: direct (or indirect?) myocardial protection

Huber J et al. ADA annual scientific sessions, June 2011, Abstract # 968-P
CV risk factors after exenatide treatment
T2DM patients treated with exenatide + SU/met
n=314 completing 30 wks randomized and 52 wks open label followup

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change from baseline to 82 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>- 1.1 %</td>
</tr>
<tr>
<td>Weight</td>
<td>- 4.4 kg</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>- 38.6 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>- 1.6 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+ 4.6 mg/dL</td>
</tr>
<tr>
<td>BP-syst</td>
<td>- 1.3 mmHg</td>
</tr>
<tr>
<td>BP-diast</td>
<td>- 2.7 mmHg</td>
</tr>
</tbody>
</table>

Blonde L et al. Diab Obesity Metab 2006;8: 436-447
Long-term placebo-controlled outcome trials of GLP-1 agents

**TECOS**
- **Sitagliptin** CV outcome study
- 2008-2014
- 14,000 patients with T2DM and known CVD

**CAROLINA**
- Cardiovascular outcome study of **linagliptin** versus glimepiride in patients with type 2 diabetes
- 2010-2018
- 6000 patients with T2DM and high CV risk

**LEADER**
- **Liraglutide** effect and action in diabetes: evaluation of CV outcome results - a long-term evaluation
- 2010-2016
- 8800 patients with T2DM and high CV risk

**EXSCEL**
- Exenatide study of CV event lowering: a trial to evaluate CV outcomes after treatment with **exenatide once-weekly** in patients with T2DM
- 2010-2017
- 9500 patients with T2DM

**ELIXA**
- Evaluation of CV outcomes in patients with T2DM after acute coronary syndrome during treatment with **Lixisenatide**
- 2010-2013
- 6000 patients with T2DM and acute coronary syndrome
# Current costs of GLP-1 agents vs others

**Drugstore.com quotations 7-8-11**

<table>
<thead>
<tr>
<th></th>
<th>Daily dose</th>
<th>90 day supply</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sitagliptin (Januvia)</strong></td>
<td>100 mg</td>
<td>$620</td>
</tr>
<tr>
<td><strong>Saxagliptin (Onglyza)</strong></td>
<td>5 mg</td>
<td>$620</td>
</tr>
<tr>
<td><strong>Glimepiride</strong></td>
<td>4 mg</td>
<td>$42 ($10 at Fred Meyer)</td>
</tr>
<tr>
<td><strong>Glipizide extended</strong></td>
<td>5 mg</td>
<td>$36</td>
</tr>
<tr>
<td><strong>Exenatide (Byetta)</strong></td>
<td>10 mcg BID</td>
<td>$825</td>
</tr>
<tr>
<td><strong>Liraglutide (Victoza)</strong></td>
<td>1.2 mg</td>
<td>$860</td>
</tr>
<tr>
<td><strong>NPH insulin (Humulin vial)</strong></td>
<td>30 units</td>
<td>$191</td>
</tr>
<tr>
<td><strong>Glargine (Lantus vial)</strong></td>
<td>30 units</td>
<td>$332</td>
</tr>
</tbody>
</table>
Thanks for your attention!
Lixisenatide dose-ranging study
Frequency of nausea

% with nausea

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>Placebo</th>
<th>Lixisenatide QD</th>
<th>Lixisenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4.6</td>
<td>11.5</td>
<td>22.2</td>
</tr>
<tr>
<td>10</td>
<td>7.3</td>
<td>25.5</td>
<td>14.3</td>
</tr>
<tr>
<td>20</td>
<td>14.3</td>
<td>35.2</td>
<td>22.2</td>
</tr>
<tr>
<td>30</td>
<td>7.5</td>
<td>35.2</td>
<td>33.0</td>
</tr>
</tbody>
</table>

A1c Patterns in UKPDS and ADOPT

UKPDS 34. Lancet 1998;352: 854-65