Role of incretins in the treatment of type 2 diabetes

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Incretin function in type 2 diabetes

- Secretion of GLP-1 impaired
- Beta-cell sensitivity to GLP-1 decreased
- Secretion of GIP slightly impaired
- Effect of GIP abolished or grossly impaired
• If the impaired incretin response contributes significantly to the defective insulin secretion in type 2 diabetes, will restoration of incretin action improve metabolism?
Proof of hypothesis: Glucose tolerance can be restored by iv GLP-1 in T2DM

Rachman et al., Diabetologia 1997
Actions of GLP-1

- Insulin secretion:
  - Potentiates glucose-induced insulin secretion
  - Enhances all steps of insulin biosynthesis
  - Upregulates insulin gene expression
  - Upregulates expression of genes essential for beta-cell function (glucokinase, Glut 2, etc.)
  - Mitotic for beta-cells
  - Promotes differentiation of duct progenitor cells
  - Inhibits apoptosis
- Inhibits glucagon secretion
- Inhibits gastrointestinal secretion and motility
- Inhibits appetite and food intake
- Expedient cardiovascular effects
Native GLP-1 is rapidly degraded by DPP-IV

$T_{1/2} = 1–2 \text{ min (i.v.)}$

MCR = 5–10 l/min

Vilsboll et al. J Clin Endocrinol Metab 2003
How can we exploit the therapeutical potential of GLP-1?

- Continuous administration of GLP-1
Effects of six weeks’ continuous subcutaneous infusion of GLP-1 in patients with type 2 diabetes

Zander et al, Lancet 2002
Main findings: Zander et al. Lancet 2002

• Continuous subcutaneous infusion of GLP-1 for 6 weeks in type 2 diabetes patients:
  – Reduced fasting and mean plasma glucose by 4.3 and 5.5 mmol/l, respectively
  – Reduced HbA1c by 1.3% and normalised fructosamine
  – Resulted in a weight loss of 2 kg, presumably because of significantly reduced appetite
  – Improved insulin sensitivity and enhanced beta-cell secretion
  – Had no significant side effects
Results

Beta-cell function (C-peptide levels)

Saline   NS

Incremental AUC:
(0–90 min):
\( p = 0.001 \)

\( \Delta \) values:
\( p = 0.0002 \)
How can we exploit the therapeutical potential of GLP-1?

• Continuous administration of GLP-1
• Resistant analogues of GLP-1
  (receptor activators, incretin mimetics)
GLP-1 receptor agonists

- Exendin 4, from saliva of the Gila Monster, 53% homologous with GLP-1 and full agonist on the GLP-1 receptor
- Insensitive to DPP-IV
Kinetics of s.c. AC2993 in type 2 diabetes patients

Kolterman et al 2005
Exenatide reduces HbA1c after 2 years

Add-on to existing OHA

Exenatide 10µg bid

Placebo-Controlled Trials

Open-Label Uncontrolled Extension studies

Baseline A1c
8.2%

Δ A1C (%) -1.2 ± 0.1%

Duration of treatment (years)

2 yr data for 82-wk cohort  N = 146

Mean ± SE

Ratner et al, ADA 2005
Exenatide reduces body weight after 2 years
Add-on to existing OHA

Exenatide 10µg bid

<table>
<thead>
<tr>
<th>Time (wk)</th>
<th>Mean change in body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>-4.7 ± 0.3 kg</td>
</tr>
<tr>
<td>110</td>
<td>-4.7 ± 0.3 kg</td>
</tr>
</tbody>
</table>

Baseline Weight: 100 kg

N = 283; Mean (SE).

Henry et al. ADA 2006: 485-P
Survival during 2-year carcinogenicity study

Male mice
- Last dose: week 98
- Control 1
- 18 µg/kg/day
- 70 µg/kg/day
- 250 µg/kg/day
- Control 2

Female mice
- Last dose: week 96
- Control 1
- 18 µg/kg/day
- 70 µg/kg/day
- 250 µg/kg/day
- Control 2

Male rats

Female rats

Hiles et al. ADA 2004
Exenatide has been on the market in the US since June 1 2005 under the name ”Byetta” and launch in Europe is expected in May 2007
Liraglutide is a long-acting GLP-1 derivative

Improved pharmacokinetics by:
• Self association
• Albumin binding

• Slow absorption from subcutis
• Metabolic stability
• Long plasma half-life
• Stability against DPP-IV
Multiple-dose pharmacokinetics: a fast and flat plateau

Single subject profile

- Multiple dose kinetics mirrors single dose
- Steady-state reached after 3 doses

Liraglutide, Phase 2b-studies (June 2006):

- 165 patients with type 2 diabetes previously treated with OAA, HbA1c 8.5 %
- Double-blind, placebo-controlled, randomised trial
- Liraglutide was given for 14 weeks in monotherapy

- HbA1c decreased 1.5-2 %, 45 % had < 7% (vs < 8 % in Placebo)
- Fasting BG reduced by > 3 mmol/L
- Body weight decreased by 3 kg from 90 kg.

- Nausea in 5-10 % initially, decreasing markedly with time.
- No hypoglycaemia

- Vilsboll et al: ADA 2006
Liraglutide, japanese study (August 2006):

• 200 subjects previously treated with diet/exercise and/or single oral agent were given liraglutide once daily
• HbA1c down 2.0 % after 15 weeks
• 75 % below 7 %
• No hypoglycemia
How can we exploit the therapeutical potential of GLP-1?

- Continuous administration of GLP-1
- *Inhibition of GLP-1 degradation*
- Resistant analogues of GLP (receptor activators, incretin mimetics)
Survival of s.c. GLP-1 in type 2 diabetes

Intact GLP-1 + metabolite

Intact GLP-1

Deacon et al. 1995
DPP IV in complex with valine-pyrrolidide

Valine-Pyrrolidide inhibits plasma DPP IV activity in anaesthetised pigs.

DPP-IV inhibition prevents N-terminal degradation of GLP-1 in anaesthetised pigs

Deacon et al. Diabetes 1998;47:764–9
DPP-IV inhibition enhances GLP-1 induced insulin secretion in pigs
More than 30 companies start to develop DPP-IV inhibitors

Leading compounds:

Novartis: LAF 237 (Vildagliptin, Galvus)

Merck: MK-0431 (Sitagliptin, Januvia)
Ahrén et al. LAF 237 for 12 and 52 weeks

![Graph showing HbA1c (%)](image)

Diabetes Care 2004

MET, metformin; PBO, placebo
Meal-related beta-cell function and insulin sensitivity by LAF 237 (vildagliptin) in metformin-treated patients with type 2 diabetes

Vildagliptin (Galvus) enhances endogenous GLP-1 and suppresses glucagon levels throughout the night.

Balas et al. ADA 2006, 122-OR
Vildagliptin (Galvus) suppresses endogenous glucose production throughout the night

Balas et al. ADA 2006, 122-OR
Sitagliptin Showed Similar Glycemic Efficacy to Glipizide When Added to Metformin

Mean change from baseline (for both groups)*: -0.67%

* Per-protocol analysis; -0.51% and -0.56% for sitagliptin and glipizide in LOCF analysis.
Progressively Greater Reductions in A1C as Baseline A1C Rises

Per Protocol Population

Baseline A1C Category

- <7%
- 7 - <8%
- 8 - <9%
- ≥9%

Study inclusion criteria 6.5-10%.

Protocol 024
Sitagliptin Once Daily Showed Decreased Body Weight Compared to Glipizide (52 Weeks)

Δ between groups = −2.5 kg (p<0.001)

Hypoglycaemia: Sitagliptin 4.9 %, Glipizide 32 %
Sitagliptin + Metformin Factorial Study Design

N = 1091 Randomized
Mean baseline A1C = 8.8%

If on an OHA, D/C’ed

Eligible if A1C 7.5 to 11%

Screening Period
Duration up to 12 weeks based on prior therapy

Diet/exercise Run-in Period

Single-blind Placebo

Randomization

Double-blind Treatment Period

Placebo

Sitagliptin 100 mg qd

Metformin 500 BID

Metformin 1000 BID

Sitagliptin 50/Met 500 BID

Sitagliptin 50/Met 1000 BID

Open Label Cohort Sitagliptin 50/Met 1000 BID

Week-2 Day 1

Week 24
Initial Combination of Sitagliptin and Metformin Produced a Marked Improvement in A1C

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C (%)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>6.5</td>
</tr>
<tr>
<td>Sita 100 mg q.d.</td>
<td>7.0</td>
</tr>
<tr>
<td>Met 500 mg b.i.d.</td>
<td>7.5</td>
</tr>
<tr>
<td>Met 1000 mg b.i.d.</td>
<td>8.0</td>
</tr>
<tr>
<td>Sita 100 mg q.d. + Met 500 mg b.i.d.</td>
<td>8.5</td>
</tr>
<tr>
<td>Sita 50 mg b.i.d. + Met 1000 mg b.i.d.</td>
<td>9.0</td>
</tr>
</tbody>
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Week
Clinical experience with DPP-IV inhibitors:

- There is experience from up to 104 weeks treatment in thousands of patients.
- The inhibitors are comparable to existing OADs in monotherapy.
- They show additional efficacy when used in combination both with SU, glitazones, metformin and insulin.
- Their effect on HbA1C is maintained for 104 weeks.
- Effect on HbA1c depends on starting level (up to 3%).
DPP-IV inhibition:

• Inhibitors (Januvia) for once daily oral administration are already on the market in the US and in Mexico

• Recommended for Approval in Europe, Jan. 2007

• So far no class related adverse effects

• Effective in experimental and clinical diabetes

• Potential for diabetes prevention

• Neutral with respect to body weight
Conclusions

• GLP-1 based therapy of type 2 diabetes mellitus can be expected to:
  – reduce hyperglycaemia and HbA$_{1c}$ levels
  – Reduce appetite and lower body weight (agonists) or be weight neutral (inhibitors)
  – Improve blood lipids
  – Improve insulin sensitivity
  – Enhance beta-cell secretion
  – Be efficacious without side effects

• Will the therapy prevent progression of disease?