“GLP 1 Analogues: Role in the Management of Type 2 Diabetes Mellitus (T2DM)

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By the end of this session...

1. Understand newer insight into pathophysiology of T2DM
2. Mechanisms of newer agents-GLP-1 analogues
3. Indications for use
4. New ADA/EASD guidelines
Natural History of Type 2 Diabetes (T2DM)

Glucose (mg/dL)

Insulin Resistance

Post-meal Glucose

Fasting Glucose

PREVENT BETA CELL LOSS

Obesity - Inactivity
Genetics

Early β cell defect

Onset

Pre-diabetes (IFG, IGT)
Metabolic Syndrome

Diabetes diagnosis

Progressive β-cell dysfunction

Insulin Response
The Triumvirate

Impaired Insulin Secretion

Hyperglycemia

Increased HGP

Decreased Glucose Uptake

DeFronzo RA, Diabetes 2009; 58:773-95
OMINOUS OCTET

Increased HGP

Hyperglycemia

ETIOLOGY OF T2DM

DEFN75-3/99

Decreased Glucose Uptake

Impaired Insulin Secretion

Increased Lipolysis

HYPERGLYCEMIA

DeFronzo RA, Diabetes 2009; 58:773-95
Diabetes is 2 diseases

Microvascular
- retinopathy, neuropathy and nephropathy

Macrovascular
- Stroke and CAD

1% reduction in A1c reduces microvascular complications by 25-30%
A NEW PARADIGM FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

DeFronzo RA, Diabetes 2009; 58:773-95
IDEAL HYPOGLYCEMIC AGENT

- Corrects pathophysiologic disturbances responsible for T2DM. i.e. preserves beta-cell function.
- Corrects hyperglycemia and prevents microvascular complications
- Improves known CVRFs and prevents macrovascular complications
• Without causing undesirable effects such as hypoglycemia and weight gain.
## Oral meds for Type 2 DM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight</th>
<th>Risk for Hypo</th>
<th>A1c Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU’s/Meglitinides</td>
<td>Increase</td>
<td>Yes</td>
<td>1-2%</td>
</tr>
<tr>
<td>Metformin</td>
<td>Decrease</td>
<td>No</td>
<td>1-2%</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Neutral</td>
<td>No</td>
<td>0.5-0.8%</td>
</tr>
<tr>
<td>TZD’s</td>
<td>Increase</td>
<td>No</td>
<td>0.5-1.4%</td>
</tr>
</tbody>
</table>

Nathan et al, Diabetes Care, vol 32, Number 1, Jan 2009: 193-203
TREATMENT OF TYPE 2 DIABETES: A NOVEL APPROACH BASED UPON ITS PATHOPHYSIOLOGY

Impaired Insulin Secretion

Hyperglycemia

Increased Lipolysis

TZDs

GLP-1 analogues

DPP-IV Inhibitors

Metformin

Sulfonylureas

TZDs

GLP-1 Analogues

Increased HGP

Bromocriptine

Decreased Glucose Uptake

DeFronzo RA, Diabetes 2009; 58:773-95
INCRETINS
In response to an oral glucose load

1. Insulin
   - Increases
   - Lower blood glucose

2. Glucagon
   - Decreases
   - Lower blood glucose

3. Gastric emptying
   - Decreases
   - Weight loss

4. Satiety Fullness
   - Increases

K-cells

L-cells

GIP

GLP-1

INCRETIN HORMONE PHYSIOLOGY
GLP-1 effect is diminished in Type 2 Diabetes
Natural GLP-1 has a short half-life (1-2 minutes)

**INJECTABLE**
Add GLP-1 agonist with longer half-life
- Exenatide
- Liraglutide
- Exenatide once weekly

**ORAL**
Block DPP-4, the enzyme that degrades GLP-1
- Sitagliptin
- Saxagliptin
- Linagliptin

**GLP-1 levels**
- Pharmacologic (supraphysiologic)
- Physiologic
DPP-4 Inhibitors

1. **Saxagliptin (Onglyza):** 2.5 mg or 5mg, once daily
   Available in combination with metformin (Kombiglyze XR)

2. **Linagliptin (Tradjenta):** 5 mg once daily
   Available in combination with metformin (Jentadueto)

3. **Sitagliptin (Januvia):** 50 mg or 100 mg once daily. Available in combination with metformin (Janumet)
DPP-4 inhibitors

1. Effectively reduce \( \text{HbA}_{1c} \)
2. May preserve beta cell function
3. Weight neutral
4. Do not cause hypoglycemia
EFFECT OF SITAGLIPTIN ON HbA$_{1c}$:
CHANGE FROM BASELINE (HbA$_{1c}$ ~ 8.0%)

Diabetes Care 29:2638, 2006; Clin Ther 28:1556, 2006; Diabetologia 49:2564, 2006

Drug Naive: -0.60
Metformin: -0.67
Pioglitazone: -0.85

ADDICTION OF SITAGLIPTIN TO
GLP-1 ANALOGUES

- Exenatide and Exenatide LAR
- Liraglutide
GLP-1 Analogues

1. Effectively reduce HbA$_{1c}$
2. Preserve beta cell function
3. Promote weight loss
4. Correct known pathophysiologic defects in T2DM
5. Do not cause hypoglycemia
Heloderma suspectum (Gila Monster)

EXENDIN 4
How to Use??

- Start with 5 mcg twice daily for the first month and then advance to 10 mcg bid.
- Take 60 mins before the 2 largest meals of the day.
- When they feel full ➔ they must stop eating.
- Do not take it after they are done eating.
- Approved as monotherapy for T2DM.
INJECT 2 MG SUBCUTANEOUSLY
ONCE WEEKLY
LIRAGLUTIDE IS A ONCE-DAILY HUMAN GLP-1 ANALOGUE

Native human GLP-1

Liraglutide

Degraded by DPP-4

$T_{1/2} = 1–2$ min after iv dosing$^{1,2}$

$1.5$ h after sc dosing$^2$

97% sequence homology to human GLP-1$^3$

Enzymatic stability to DPP-4$^3$

Suitable for once-daily dosing$^3$

$T_{1/2} \sim 13$ h$^3$


Victoza® Summary of Product Characteristics
INDICATIONS AND USAGE: Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.
**DOSING**

- Initiate at 0.6 mg per day for one week.
- After one week, increase the dose to 1.2 mg.
- If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg.
TIME COURSE OF EFFECT OF EXENATIDE ON HbA$_{1c}$

Baseline HbA$_{1c}$ = 8.3%

**DeFronzo et al, Diabetes Care 28:1092-1100, 2005**

*Data on file, Amylin Pharm*

**Placebo**

Exenatide - 10 μg bid

**Placebo-Controlled Trials**

**Open-Label Extension**
EFFECT OF EXENATIDE ON BODY WEIGHT

Time (wk)

Baseline Weight
215 lbs
220 lbs

Placebo BID (N = 128)
BYETTA 10 mcg BID (N = 137)

Δ Weight (lbs)

Placebo-Controlled Trials
Open-Label Extension
Changes in Glycemia and Weight in 3 Head-to-Head Studies: Exenatide vs Insulin

Heine et al\textsuperscript{1}  
Barnett et al\textsuperscript{2}  
Nauck et al\textsuperscript{3}

Glargine, Once Daily

-1.1%  -1.4%  -0.9%

Insulin Aspart, 70/30

Heine et al\textsuperscript{1}  
Barnett et al\textsuperscript{2}  
Nauck et al\textsuperscript{3}

BYETTA

-1.1%  -1.4%  -1.0%

Δ A1C (%)  
Δ Weight (lb)


See accompanying Prescribing Information and safety information included in this presentation
LIRAGLUTIDE PHASE 3 PROGRAM: CHANGE IN HbA₁C

ONCE-WEEKLY (LAR) EXENATIDE VERSUS DAILY (BYETTA)

SUBJECTS: 295 T2DM on SU/Metformin; HbA$_1$c > 7.0%

STUDY DESIGN: Once-weekly exenatide (2 mg) vs twice daily Byetta (10 ug) for 30 weeks

RESULTS: Decrement in HbA$_1$c = 2.0% (LAR) versus 1.6% (Byetta)

- 75% achieved HbA$_1$c < 7.0%
- 8 lb weight loss with both
- Nausea occurred in only 20% of LAR
DAILY EXENATIDE VERSUS ONCE WEEKLY LAR
DECREMENT IN HbA$_{1c}$

LIRAGLUTIDE (n=233) VERSUS EXENATIDE (n=231) ADDED TO METFORMIN AND/OR SULFONYLUREA IN T2DM

Nausea = 26% LIRA vs 28% EXEN

## COMPARISON OF GLP-1 ANALOGUES VS DPP-4 INHIBITORS

<table>
<thead>
<tr>
<th>Variable</th>
<th>GLP-1 analogue</th>
<th>DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency (% reduction in A1c)</td>
<td>-0.9% to 1.6%</td>
<td>≈ -0.8%</td>
</tr>
<tr>
<td>Effect on FPG</td>
<td>Liraglutide and Exenatide LAR reduce both fpg and ppg</td>
<td>No effect observed</td>
</tr>
<tr>
<td>Weight</td>
<td>Average -10lbs</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Minimal to none</td>
<td>None to minimal</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Nausea, GI MTC with Liraglutide Pancreatitis with all Pancreatic cancer</td>
<td>Nausea (less), pancreatitis and pancreatic cancer.</td>
</tr>
</tbody>
</table>
Dose–response relationships for the effects of GLP-1.
SYNTHESIS

1. All GLP-1 agonists lower A1c and weight.
2. Longer acting GLP-1 analogues have a primary effect on the fasting plasma glucose.
3. Shorter acting GLP-1 agonists predominantly affect the post-prandial plasma glucose.
4. All DPP-4 inhibitors lower A1c by predominantly affecting the post-prandial blood glucose and are weight neutral.
2012 UPDATES
Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

care.diabetesjournals.org

Diabetes Care Publish Ahead of Print, published online April 19, 2012
Position Statement

Healthy eating, weight control, increased physical activity

Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low

If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination
(order not meant to denote any specific preference)

- Metformin + Sulfonylurea
  - Efficacy (↓ HbA1c)
  - Hypoglycemia
  - Weight
  - Side effects
  - Cost
  - high
  - moderate risk
  - gain
  - hypoglycemia
  - low

- Metformin + Thiazolidinedione
  - Efficacy (↓ HbA1c)
  - Hypoglycemia
  - Weight
  - Major side effect(s)
  - Cost
  - high
  - low risk
  - gain
  - edema, HF, FX's
  - rare

- Metformin + DPP-4 Inhibitor
  - Efficacy (↓ HbA1c)
  - Hypoglycemia
  - Weight
  - Major side effect(s)
  - Cost
  - intermediate
  - low risk
  - gain
  - GI
  - rare

- Metformin + GLP-1 receptor agonist
  - Efficacy (↓ HbA1c)
  - Hypoglycemia
  - Weight
  - Major side effect(s)
  - Cost
  - high
  - low risk
  - gain
  - hypoglycemia
  - variable

If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination
(order not meant to denote any specific preference)

- Metformin + Sulfonylurea + TZD
- Metformin + Thiazolidinedione + SU
- Metformin + DPP-4 Inhibitor + GLP-1-RA
- Metformin + GLP-1 receptor agonist + Insulin
- Metformin + Insulin (usually basal) + DPP-4

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:

- Insulin (multiple daily doses)
CUSTOMIZE THERAPY
1. In the short-term (1 year), the potency of most agents is similar and thus other advantages/disadvantages of these agents (e.g., hypoglycemia risk and weight gain) should be afforded importance. Metformin as first line therapy if tolerated.

2. More consideration should be given to durable glycemic-control.

3. Newer agents should be considered early in the course of the disease.

4. Combination therapies used early.
What do I do with all this information?

DIET

HYPOGLYCEMIC AGENTS

EXERCISE
CASE STUDIES
Case 1: JA

- JA is a 41 year old female.
- Mexican American.
- No other medical problems
- goes to a health fair at Western U and is told she has DM as her blood sugar was “high”
- FH: mother and 2 sisters with Type 2 DM.
- Mother is on dialysis
- **BMI 33 kg/m², BP 144/92.**
- No neuropathy, retinopathy
- Labs: HbA1c 9%, FPG 183 mg/dl,
  - TC 220 mg/dl, HDL-24 mg/dl, LDL-135 mg/dl, Triglycerides 164 mg/dl.
- UACR is 30, eGFR is 88
Case # 1

- What will you start?
  A- Glipizide 10mg qd
  B- Metformin 500mg bid with meals and then titrate
  C- Pioglitazone 30mg qd
  D- Pioglitazone+ Met start once per day and then titrate
  E- Start Exenatide 5 mcg sq bid
1 year later

• You put JA on Metformin 500 mg bid and titrate up to 1000 mg bid, and her A1c is 7.4% initially, but gradually you note an increase and today it is 8.5%.

• After ensuring compliance

• BMI: 38 kg/m2
What will you start next?

A- Add Glipizide 10mg qd
B- Add Pioglitazone 30mg qd
C- Start Exenatide 5 mcg sq bid
D- Start Januvia 100 mg once daily
E- Start Acarbose once daily
Selection of Glycemic Goals and Glucose-lowering treatments

Patient-specific factors
1. Age
2. Stage of diabetes
3. CVRF
4. Weight
5. Risk of hypoglycemia

Glycemic Durability i.e the pathophysiologica basis of diabetes
MR is a 50 year old Hispanic male with T2DM. A1c: 11.1 % (1 year ago), Weight: 328 lbs. Intractable diarrhea on Metformin

On Basal-bolus regimen with Lantus and Humalog
Requiring total daily dose (TDD): 280 units of insulin.

Medications added: ( 2 months ago)
Victoza 0.6 mg sq daily and now at 1.2 mg sq daily
Actos 30 mg once daily

Over 2 months:
Weight stable, Insulin TDD: 185 units and A1c is 6.7%
Retinopathy progression arrested.
Improved lipid panel.
Expect to see more weight loss over next 3 months
On the horizon
1. GLP-1 Agonists under clinical development

- Dulaglutide
- Lixisenatide
- Albiglutide
2. Targeting L cells of the gut

- L-cells of the gut produce and release GLP-1
- Understanding L-cell physiology will produce newer drugs and target molecules.
My take-home message

Screen all patients by calculating “BMI”
PREVENTION