Newer Drugs in the Management of Type 2 Diabetes Mellitus

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Presentation Outline

• Introduction
• Pathogenesis of type 2 DM
• Currently used anti-diabetic agents
• Incretin Mimetics
• DPP-4 Inhibitors
• SGLT-2 Inhibitors
• Amylin Mimetics
• Dual PPAR Agonists
• Summary
Introduction

American Diabetes Association (1997)
•“A group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both”

Complications

Microvascular
• Retinopathy
• Nephropathy
• Neuropathy

Macrovascular
• IHD
• Stroke
• PVD
Diabetes – Top Five Countries in 2013.

<table>
<thead>
<tr>
<th>Countries</th>
<th>No. of Diabetic subjects (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>98.4</td>
</tr>
<tr>
<td>India</td>
<td>65.1</td>
</tr>
<tr>
<td>United States</td>
<td>24.4</td>
</tr>
<tr>
<td>Brazil</td>
<td>11.9</td>
</tr>
<tr>
<td>Russia</td>
<td>10.9</td>
</tr>
</tbody>
</table>

• IDF – 387 million cases world-wide (2014).
## Glycemic Treatment Targets

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-meal blood glucose (mg/dl)</td>
<td>80 – 130</td>
</tr>
<tr>
<td>2 hour postprandial blood glucose (mg/dl)</td>
<td>&lt; 180</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt; 7</td>
</tr>
</tbody>
</table>
Pathogenesis of Type 2 Diabetes

- ▼ insulin secretion
- ▼ Incretin effect
- ▲ lipolysis
- ▲ glucagon secretion
- ▲ glucose production
- ▼ glucose uptake
- ▲ glucose reabsorption

Neurotransmitter dysfunction
Currently used Anti-Diabetic Agents

Sulfonylureas
- Glibenclamide
- Glipizide
- Gliclazide
- Glimepiride

Meglinides
- Repaglitinide
- Nateglinide

Biguanide
- Metformin

Thiazolidinediones
- Pioglitazone

α-Glucosidase Inhibitors
- Acarbose
- Miglitol
- Voglibose
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Stimulation of Insulin release by β-cells</td>
<td>Hypoglycemia, Weight gain</td>
</tr>
<tr>
<td>Glinides</td>
<td>Stimulation of Insulin release by β-cells</td>
<td>Hypoglycemia, Weight gain</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Inhibition of hepatic gluconeogenesis</td>
<td>Diarrhoea, Lactic acidosis, Vit. B12 deficiency</td>
</tr>
<tr>
<td>α-glucosidase inhibitor</td>
<td>Inhibition of intestinal carbohydrate absorption</td>
<td>Bloating, Gas</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Reduces peripheral insulin resistance.</td>
<td>Weight gain, Edema, possible bone loss in women</td>
</tr>
</tbody>
</table>
Novel Categories

• Incretin Mimetics
• DPP-4 Inhibitors
• SGLT-2 Inhibitors
• Amylin Mimetics
• Dual PPAR agonists
INCRETIN MIMETICS

- ↓ Glucagon secretion
- ↓ Gastric emptying
- ↓ Appetite

GLP-1 
GIP 

DPP-4 

Inactive forms

- Include - Exenatide and Liraglutide
EXENATIDE

• Derivative of exedine-4, a peptide isolated from Gila monster saliva.
• Functional analogue of GLP-1.

Clinical efficacy:

• ↓ HbA1c of 1% Vs placebo.
• ↓ postprandial glucose.
• Produces weight loss.
• Proliferative effect on β-cells (animal data).
Glucose-dependent mode of action.
- ↓ iatrogenic hypoglycemia
- ↑ risk of hypoglycemia – Exenatide + SU

Adverse effects:
- Nausea, vomiting, diarrhea, dizziness, headache, dyspepsia.
- Acute pancreatitis.

USFDA approval in April 2004
- As adjunctive therapy in T2DM.

Dose – 5 to 10 μg BD by S.C. inj.
LIRAGLUTIDE

• 97% identical to human GLP-1.

Clinical efficacy:
• Reduces body weight.
• Decreases visceral fat.
• Lowers systolic BP
• Improves lipid profile
• Reduces insulin resistance.
Kinetics:
• Reaches Cmax after 9-12 hours
• Half-life 13 hours (11-15 hours)
• Binds to albumin.
• Provides 24-hrs glycemic control.
• Predominantly excreted by glomerular filtration.
Liraglutide

Adverse effects:
• Nausea, gastric upset and headache.
• Acute pancreatitis.

Contraindications:
• Renal and hepatic insufficiency.
• Pregnancy and lactation and Type 1 DM.
• Risk of acute pancreatitis.

USFDA approval in January 2010.
• Dose – 0.6 to 1.8 mg once daily by S.C. inj.
NEWER INCRETIN MIMETICS IN THE PIPELINE

- Exenatide LAR (long acting)
- Albiglutide (long acting)
- Dulaglutide (long acting)
- Semaglutide (long acting)

- Can be administered once a **WEEK**.
DIPEPTIDYL-PEPTIDASE IV (DPP-4) INHIBITORS

- Sitagliptin, Vildagliptin and Saxagliptin

GLP-1 GIP → DPP-4

- ↑ Insulin secretion
- ↓ Glucagon secretion
- ↓ Gastric emptying
- ↓ Appetite

Inactive forms
DPP-4 inhibitors

• Orally active agents
• Can be administered with or without food.

Clinical efficacy:
• Primarily ↓ post-prandial glucose.
• HbA1c by around 0.5 to 1%.
• ↓ fasting plasma glucose by 20 - 40 mg/dl.
SITAGLIPTIN

• Selective DPP-4 inhibitor
  – ↑ glucose dependent insulin secretion

Kinetics:
• Bioavailability 87%
• Plasma half life 8 – 12 hours.
• 38% bound to plasma proteins
• Undergoes CYP3A4 and CYP2C8 mediated metabolism.
• Excreted mainly in urine.
Sitagliptin

Adverse effects:

• Upper Respiratory tract infections, U.T.Is.
• Headache, arthralgias, fatigue, dizziness and diarrhea.
• Hypoglycemia with SU.
• Rarely hypersensitivity reactions.
Contraindications:
• In children,
• In diabetic ketoacidosis
• In pregnancy (lack of adequate data)
• Cautious use in nursing mother

USFDA approval:
• Sitagliptin in October 2006
  — as monotherapy
  — as add-on therapy to metformin / glitazones.
USFDA approval:

• Sitagliptin + Metformin in April 2007.
  – Not adequately controlled on either Metformin or Sitagliptin monotherapy.

Dose:

• 100 mg OD
VILDAGLIPTIN

• High affinity for DPP-4 enzyme.
• ↓ fasting and postprandial plasma glucose.
• Enhances the sensitivity of α–cells to glucose.

Kinetics:
• Oral bioavailability 85%
• Low plasma protein binding (9.3%)
• NOT metabolized by CYP-450 enzymes.
• 85% excreted in urine, 15% in faeces.
Adverse effects:
• Dizziness, headache, constipation and peripheral edema.

Contraindications:
• Renal and hepatic impairment
• Hypersensitivity to vildagliptin/any excipients.
USFDA approval:

• Vildagliptin not approved in US, but approved by European Union.

Dose:

• 50 mg BD
SAXAGLIPTIN

Kinetics:

• Extensively absorbed.
• Metabolized by hepatic CYP3A4/5.
• Renal excretion (12-29%)

USFDA approval:

• In July 2009
  – As adjunct to diet and exercise
  – Dose 5 mg OD.
SGLT-2 INHIBITORS

• Family of transmembrane proteins
• Co-transport of Sodium and Glucose.

SGLT-2 isoform:

• Preferentially expressed in the brush-border membrane of proximal renal tubular cells.
• ↑ Renal glucose reabsorption.

Inhibitors of SGLT-2:

• Enhance renal glucose excretion.
Tubular Lumen

PCT Cell

Interstitium

Na⁺

Glucose

SGLT-2

Na-K Exchanger

K⁺

GLUT-4

28

Na⁺-

K⁺
Tubular Lumen

PCT Cell

Interstitium

Na⁺

Glucose

K⁺

Na-K Exchanger

SGLT-2 Inhibitor

GLUT-4

SGLT-2

GLUT-4

Na⁺

K⁺
CANAGLIFLOZIN & DAPAGLIFLOZIN

• Highly selective SGLT-2 inhibitor.

Kinetics:

• Rapidly absorbed after oral administration with Cmax within 2 hours.

• Inactive metabolite by glucuronosyltransferase enzyme

• Renal clearance.
Canagliflozin & Dapagliflozin

Clinical efficacy:
• HbA1c – ↓ 0.7 -1.0% Vs. placebo
• Minimal risk of hypoglycemia

Additional benefits:
• Modest weight loss (approx. 2 kg)
• Can be used at any stage of type 2 diabetes
• Lowering of systolic and diastolic BP.
Canagliflozin & Dapagliflozin

Adverse effects:
• Genital mycotic infections

Contraindication:
• e-GFR < 60 ml/min/1.73 m²

Approved by ADA as second line agent.

Dose:
• Canagliflozin – 100-300 mg/day OD
• Dose reduction in renal insufficiency.
• Dapagliflozin – 5-10 mg/day OD.
AMYLIN MIMETICS

- β-cell polypeptide, from human pancreas.
- Reduces glucagon secretion
- Central satiety enhancing activity
- Delays gastric emptying.

- In type 1 and late stages of type 2 DM
  - Deficiency of Amylin together with insulin.
- HbA1c reduction 0.4 to 0.6% vs. placebo
PRAMLIINTIDE

• For insulin-using patients with obesity.

Actions:
• To slow gastric emptying,
• Suppress inappropriately elevated postprandial glucagon secretion,
• Reduce food intake.
• Improve overall glycemic control.
Clinical efficacy:
• 0.10 to 0.67% reduction in HbA1c.
• 2-hour PPG levels – ↓ 3.6 to 4.8 mmol/L

Adverse events:
• Transient nausea and hypoglycemia
• Loss of appetite, pain in abdomen, indigestion
• Excessive cough, sore throat
• Tiredness, dizziness, joint pain
• Injection site related side effects.
Pramlintide

**USFDA approval:**

- With mealtime insulin in type 1 & type 2 DM.

**Dose:**

- ↓ 50% when given with insulin.
DUAL PPAR AGONIST

Peroxisome Proliferator-Activated Receptors:
• Ligand-activated transcription factors
• Potential targets for obesity and diabetes

Three isoforms of PPAR:
• PPAR - α
• PPAR - β
• PPAR - γ
PPAR - α:
• Improvement in deranged lipid profile
• Decrease in atherosclerotic lesions

PPAR - γ:
• ↑ peripheral insulin sensitivity
• ↓ hepatic gluconeogenesis

• Glitazars – dual activation of PPAR-α / PPAR-γ.
MURAGLITAZAR

• Advanced stages of clinical development
  – for type 2 diabetes with dyslipidemia.

Clinical efficacy:
• Improve glycemic control
• Improve TG, HDL-C, Apo-B and non-HDL levels.
• Muraglitazar + Glyburide
  – More effective glycemic control vs. control.
• Greater improvement in HbA1c and lipid profile than pioglitazone (30 mg/day)

Adverse effects:
• Increase body weight and edema (5 mg/day)
• Above 5 mg/day, adverse CV events.
ALEGLITAZAR

• In phase III clinical trials
• Improvement in glycaemia, HDL-C, LDL-C, TG, Apo-B and blood pressure.
• PPAR-α and PPAR-γ associated side effects.
• Long term clinical studies are necessary.
SUMMARY

• Tremendous advancements in past few years.
• Newer anti-diabetic medications – promising.
• Newer agents + Present drugs.

• Treatment is always INDIVIDUALIZED.
  – Diabetic profile
  – Other associated co-morbid conditions.
thank you