ADJUNCTIVE THERAPIES FOR TYPE 1 DIABETES

Dr. Mohammad Alhadj Ali, MD, PgDip, MSc, PhD (UK)
with Prof. David Owens (UK)

Outline

- Type 1 Diabetes
- Immunology of Type 1 Diabetes
- Treatment of Type 1 Diabetes
- Adjunct non-insulin therapies in Type 1 Diabetes
- Future directions
Type 1 Diabetes

- 5-10% of cases of diabetes
- Affecting 18 to 20/100 000 children/year in UK
- ~50% diagnosed > 18 years
- Particular HLA molecules are associated with susceptibility to T1DM (HLA-DR4 and HLA-DQ8)

Outline

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Type 1 diabetes is an autoimmune disease

Auto-reactive T-cells are involved in destruction of β-cells

Abs to insulin, GAD and IA2 precede T1DM 10 y or more

20% High risk children have Abs by age 2
On January 23, 1922, at the University of Toronto, Dr. Frederick Banting and his student C. H. Best made one of the greatest discoveries of the 20th century.
Insulin in Type 1 Diabetes

- It has been used for diabetes treatment for more than 90 years
- It is effective in lowering blood glucose
- Side effects are not common
- It is still a cornerstone in the treatment of T1DM
## Barriers to Treatment with Insulin

<table>
<thead>
<tr>
<th>Patients</th>
<th>Suppliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fear of injections and insulin</td>
<td>• Cost and expenses</td>
</tr>
<tr>
<td>• Fear of hypoglycaemia</td>
<td>• Time constraints</td>
</tr>
<tr>
<td>• Weight gain</td>
<td>• Patient’s compliance</td>
</tr>
<tr>
<td>• Inconvenience</td>
<td>• Physicians inertia</td>
</tr>
<tr>
<td>• Physical (hearing and visual problems)</td>
<td>• Support and service</td>
</tr>
<tr>
<td>• Mental (learning difficulties)</td>
<td>• Follow up</td>
</tr>
</tbody>
</table>

## Advances in Insulin Therapy

- Newer insulin
- Other forms of insulin (oral, nasal..)
- New delivery systems
- Advanced glucose monitoring systems
- The closed-loop pumps and the artificial pancreas
The Challenge in treating T1DM

Outline

- Type 1 Diabetes
- Immunology of Type 1 Diabetes
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- Future directions
Goals of Adjunct Non-insulin Therapies in T1DM

- Improve glycaemic control
- Improve patient’s safety and reduces hypoglycaemia
- Preserve endogenous β-cell function
- To compliment rather than necessarily replace insulin therapy
- Reduce insulin resistance and weight gain

George et al. 2012, Diabetic Medicine, 179-188.
Adjunctive therapy in T1DM

The focus of these therapies is to improve the glycaemic control by using treatments to address some of the metabolic and physiological abnormalities which are less responsive to insulin replacement therapy.
Goals of Adjunct Non-insulin Therapies in T1DM

- Improve glycaemic control
- Preserve endogenous β-cell function
- To compliment rather than necessarily replace insulin therapy
- Reduce insulin dependence

Adjunctive-non insulin therapy in T1DM

- Metformin
- GLP-1 analogues
- Pioglitazone
- α-glucosidase inhibitors
- DDP-4 inhibitors
- Amylin analogues
- SGLT-2 inhibitors
Adjunctive therapy in C-peptide negative T1DM

- **Insulin sensitizing**
  - Metformin
  - Poglitazone
  - α-glucosidase Inhibitors

- **Targeting Hyperglucagonaemia**
  - DPP-4 Inhibitors
  - GLP-1 Analogues
  - Amylin Analogues

**Metformin**

**Actions**
- Inhibits hepatic gluconeogenesis
- Improves insulin-mediated glucose utilization
- Reduces intestinal glucose absorption
- Reduces fatty acid oxidation
- Reduces LDL and VLDL
Metformin

**Potential benefits in T1DM**

- Improves fasting and postprandial glycaemic profile
- Improves the overall glycaemic profile
- Reduces weight
- Insulin-sparing effect
- Improves the cardiovascular outcomes
**Standardised mean differences in insulin dose between Metformin-treated and Metformin-free Type 1 Diabetes patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyo et al. [85]</td>
<td>-0.68 (-1.16, -0.17)</td>
<td>26.48</td>
</tr>
<tr>
<td>Hascif et al. [95]</td>
<td>-0.941 (-1.17, -0.70)</td>
<td>10.87</td>
</tr>
<tr>
<td>Santoli et al. [115]</td>
<td>-0.890 (-1.17, 0.79)</td>
<td>11.74</td>
</tr>
<tr>
<td>Land et al. [118]</td>
<td>-0.89 (-1.12, -0.66)</td>
<td>40.80</td>
</tr>
<tr>
<td>Joshipra et al. [118]</td>
<td>-0.841 (-1.27, 0.03)</td>
<td>10.89</td>
</tr>
<tr>
<td>Overall [17-0.00, p=0.00]</td>
<td>10.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Pioglitazone**

**Actions**
- Improves glucose delivery to the periphery
- Decreases gluconeogenesis

**Potential benefits in T1DM**
- Reduces insulin resistance
- Improves the overall glycaemic effect
Effect of Pioglitazone on the Course of New-Onset Type 1 Diabetes Mellitus

Kimberly Sue Tofani1, Mustaq Ahmed Godil1, Andrew Harry Lane1, Thomas Allen Wilson1

1Division of Pediatric Endocrinology, Steck-Hocking Children’s Hospital, Stonebrook, United States

Table 1:

<table>
<thead>
<tr>
<th>Week</th>
<th>Pioglitazone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.8 ± 0.2</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>12</td>
<td>8.0 ± 1.4</td>
<td>5.9 ± 0.9</td>
</tr>
<tr>
<td>24</td>
<td>9.2 ± 0.7</td>
<td>7.6 ± 1.1</td>
</tr>
</tbody>
</table>

Graph 1:

- Pioglitazone
- Placebo

Graph 2:

<table>
<thead>
<tr>
<th>C-peptide Peak</th>
<th>Pioglitazone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.0 ± 0.3</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>24 weeks</td>
<td>1.8 ± 0.2</td>
<td>2.5 ± 0.7</td>
</tr>
</tbody>
</table>
Pioglitazone may accelerate disease course of slowly progressive type 1 diabetes

Actions
- Inhibit digestion of disaccharide to monosaccharide

Potential benefits in T1DM
- Improve the postprandial glycaemic profile
- Improve the overall glycaemic profile
- Insulin-sparing effect
DPP-4 inhibitors

**Actions**
- Inhibit the endogenous GLP-1 breakdown

**Potential benefits in T1DM**
- Improve the postprandial glycaemic profile
- Improve the overall glycaemic effect
- Insulin-sparing effect
The New insights from DPP-4 inhibitors: their potential immune modulatory function in autoimmune diabetes

Conclusion
In conclusion, DPP-4 inhibitors orchestrate a T-cell-specific modulation of autoimmunity by inhibiting pathogenic Th1 and Th17 cells and promoting valuable Th2 and Treg cells, which plays a critical role in ameliorating autoimmune diabetes. Thus, DPP-4 inhibition may be a novel therapeutic target for autoimmune diabetes. Large-scale randomized and placebo controlled clinical trials are required to confirm this.

Article: Treatment
Effect of sitagliptin on glucose control in adult patients with Type 1 diabetes: a pilot, double-blind, randomized, crossover trial
GLP-1 Analogues

**Actions**

- Increase the insulin secretion
- Regulate the postprandial glucagon release
- Delay the gastric emptying
- They have central effect on satiety
GLP-1 Analogues

Potential benefits in T1DM

- Inhibit β-cell apoptosis
- Halt disease progression and reversal of disease
- Improve the postprandial and overall glycaemic profiles
- Reduce the glycaemic variability
- Reduces weight
Effects of Incretin Hormones on β-Cell Mass and Function, Body Weight, and Hepatic and Myocardial Function

Sunder Mudaliar, MD, Robert R. Henry, MD
Section of Diabetes/Metabolism, VA San Diego Healthcare System, San Diego, California, USA; and Department of Medicine, University of California at San Diego, San Diego, California, USA

![Graphs showing islet mass, β-cell proliferation, and β-cell apoptosis.]

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Antidiabetic Actions of Endogenous and Exogenous GLP-1 in Type 1 Diabetic Patients With and Without Residual β-Cell Function

Ulf Kleigasi1,2, Jens J. Hoist,3 and Stein Madsbad1

![Graphs showing glucose levels over time in different conditions.]

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Amylin Analogues

**Actions**

- Inhibit hepatic gluconeogenesis
- Regulate the postprandial glucagon release
- Reduce gastric emptying
- They have central effect on satiety

**Potential benefits in T1DM**

- Improve the postprandial and overall glycaemic profiles
- Reduce weight
Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial

R. E. Ratner*, R. Dickey†, M. Fineman†, D. G. Maggs†, L. Shen*t, S. A. Stoebelt, C. Weyert, O. G. Koltermant
**A Double-Blind, Placebo-Controlled Trial Assessing Pramlintide Treatment in the Setting of Intensive Insulin Therapy in Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo</th>
<th>30 µg</th>
<th>50 µg</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td>1.48</td>
<td>1.4</td>
<td>1.0</td>
<td>1.81</td>
</tr>
<tr>
<td>Reduced appetite (%)</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
<td>1.81</td>
</tr>
<tr>
<td>Meticulousness</td>
<td>0.7</td>
<td>2.0</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>0.8</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Brief Report**

Addition of exenatide or sitagliptin to insulin in new onset type 1 diabetes: A randomized, open label study

K.V.S. Hari Kumar, A†, Altamash Shaikh, Pitarbar Prusty

1. Department of Endocrinology, Center Hospital, Lucknow 226001 Uttar Pradesh, India
2. Department of Endocrinology, PD Hinduja Hospital & Medical Research Centre, Mumbai 400016, India

**Graphs and Charts**

- Group 1
- Group 2
- Group 3

- Body Weight (kg)
- Daily Insulin Dose (units)
- Meticulousness (Toddler)
SGLT-2 Inhibitors

Actions
- Reduce renal glucose absorption in proximal renal tubules

Potential benefits in T1DM
- Improve the overall glycaemic profiles
- Reduce weight
Adjunct Non-insulin-based Therapies in C-peptide Positive T1DM

- The focus of these therapies is to restore self-tolerance to pancreatic β-cells by controlling the autoimmune responses to these cells.
Adjunct Non-insulin-based Therapies in C-peptide Positive T1DM

- The purpose of these therapies is to halt the ongoing autoimmune process, preventing β-cells from further destruction and allowing them for a potential regeneration.
Immunosuppression or Immunomodulation?

De Filippo et al, 1988

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Immunomodulatory therapy to preserve pancreatic β-cell function in type 1 diabetes

Frank Waldron-Lynch and Kevan C. Herold

**Primary prevention**
The aim is to prevent the development of type 1 diabetes in susceptible individuals before the development of autoimmunity to pancreatic islet β-cells. This requires the identification of individuals at high risk of developing autoimmune type 1 diabetes.

**Secondary prevention**
The aim is prevent the development of type 1 diabetes in individuals who have developed autoimmunity, before they present with symptomatic hyperglycaemia. This strategy aims to diagnose and treat autoimmunity at the earliest stages of the disease, before significant pancreatic β-cell damage has occurred.

**Tertiary prevention**
The aim is prevent the progression of type 1 diabetes in individuals at clinical onset of the disease, when a reduction in pancreatic β-cell mass results in symptomatic hyperglycaemia. This strategy aims to treat established autoimmunity, prevent further β-cell damage and preserve endogenous insulin production.
Immunotherapy Treatment Strategies

Antigen–specific Immunomodulation

- Oral and parental insulin
- Intranasal insulin
- GAD-65
- DiaPep 277
- Proinsulin peptide

Non-antigen–specific Immunomodulation

- Systemic (Cyclosporine A)
- Stem cell transplant
- T cell-targeted therapy
- B cell-targeted therapy
- Cytokines-targeted therapy

Antigen Specific Immunotherapy for Autoimmune Disease:

Fighting Fire with Fire?

Colin M Dayan and Mark Peakman

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Monday, 13 December, 2004, 10:44 GMT

Diabetes vaccine trials to begin

A vaccine that could cure Type 1 diabetes is to be tested on people for the first time.

""" It will be of help for people who have just been diagnosed

Dr Colin Dayan from the University of Bristol
Outline

- Type 1 Diabetes
- Immunology of Type 1 Diabetes
- Treatment of Type 1 Diabetes
- Adjunct non-insulin therapies in Type 1 Diabetes
- Future directions

Future Directions

- Combined treatments that act on insulin sensitizing with agents that target hyperglucagonaemia
- Combined immunotherapies in new-onset T1DM
- Emerging immunotherapies and pancreatic islet transplantation
- Dual-hormone artificial pancreas
- Stem cells and β cells regeneration
Thank You