Adjunctive Therapies for T1D

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University of Miami Miller School of Medicine
Dualities of Interest:

Jay Skyler has acted as an advisor to Adocia, Boehringer-Ingelheim, Dance Biopharm, Elcelyx, Eli Lilly, Ideal Life, Immunomolecular Therapeutics, Intarcia, Intrexon, Merck, Orgenesis, Sanofi, Valeritas, and Viacyte.

He has research funding from NIH, JDRF, and DRIF.

He chairs the Strategic Advisory Board of the EU INNODIA consortium.

He is a member of the board of directors of Dexcom, Intarcia, and Moerae Matrix.
Unmet Needs & Challenges
Mean HbA1c

Age (years)

- <6
- 6-<13
- 13-<18
- 18-<26
- 26-<50
- ≥50

Enrollment

Current
Meeting ADA HbA1c Targets

Enrollment Current

A1c Goal = <7.0%
A1c Goal = <7.5%
A1c Goal = <8.0%
A1c Goal = <8.5%

Mean HbA1c (%)

Mean HbA1c (%)

Age (years)

<6 6-<13 13-<18 18-<26 26-<50 ≥50

62% 62% 42% 41% 23% 18% 29% 31% 28% 30%

A1c Goal = <8.0%
A1c Goal = <8.5%

6-<13 13-<18 18-<26 26-<50 ≥50

23% 18% 29% 31% 28%

Mean HbA1c (%)

0% 20% 40% 60% 80% 100%
Frequency of Overweight /Obese (T1D)

- <6: 46%
- 6-<13: 31%
- 13-<18: 41%
- 18-<26: 46%
- 26-<50: 68%
- ≥50: 66%

Age (years)
Frequency of Severe Hypoglycemia by Age

Seizure or loss of consciousness > 1 event in 12 months

- Age <6: 5% (N=169)
- Age 6-<13: 1% (N=2072)
- Age 13-<18: 1% (N=2768)
- Age 18-<26: 2% (N=1436)
- Age 26-<50: 1% (N=1114)
- Age ≥50: 1% (N=942)
Severe Hypoglycemia
In Adults by A1C

Seizure or loss of consciousness > 1 event in 12 months

<table>
<thead>
<tr>
<th>Mean A1c</th>
<th>Percent with ≥1 SH Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.0</td>
<td>13.2%</td>
</tr>
<tr>
<td>7.0-&lt;7.5</td>
<td>8.3%</td>
</tr>
<tr>
<td>7.5-&lt;8.0</td>
<td>12.4%</td>
</tr>
<tr>
<td>8.0-&lt;9.0</td>
<td>13.7%</td>
</tr>
<tr>
<td>9.0-&lt;10.0</td>
<td>9.4%</td>
</tr>
<tr>
<td>≥10.0</td>
<td>12.1%</td>
</tr>
</tbody>
</table>
Severe Hypoglycemia
In Children and Young Adults by A1C

Seizure or loss of consciousness > 1 event in 12 months

<table>
<thead>
<tr>
<th>Mean A1c</th>
<th>Percent with ≥1 SH Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.0</td>
<td>5.6%</td>
</tr>
<tr>
<td>7.0-&lt;7.5</td>
<td>5.7%</td>
</tr>
<tr>
<td>7.5-&lt;8.0</td>
<td>4.2%</td>
</tr>
<tr>
<td>8.0-&lt;9.0</td>
<td>6.3%</td>
</tr>
<tr>
<td>9.0-&lt;10.0</td>
<td>7.8%</td>
</tr>
<tr>
<td>≥10.0</td>
<td>7.4%</td>
</tr>
</tbody>
</table>
Frequency of Diabetic Ketoacidosis According to A1c

| A1c Range | Frequency (%)
|-----------|--------------
| <6.0%     | 0%           
| 6.0% - <6.5% | 1%          
| 6.5% - <7.0% | 1%          
| 7.0% - <8.0% | 1%          
| 8.0% - <9.0% | 3%          
| 9.0% - <10.0% | 5%         
| 10.0% - <11.0% | 7%        
| ≥11.0%     | 14%          

Frequency of Diabetic Ketoacidosis According to Age

- Overall: 4%
- <6: 6%
- 6-<13: 4%
- 13-<18: 5%
- 18-<26: 5%
- 26-<50: 2%
- 50-<65: 1%
- ≥ 65: 2%

Age (years)
Unmet Needs and Challenges in Type 1 Diabetes

- **Limitations of Insulin Therapy**
  - Near-normoglycemia only in few at the expense of great efforts
  - Chronic hyperglycemic control in most
  - Wide glucose fluctuations and variability of insulin responses to stress and nutrients
  - Unpredictable mild hypoglycemic episodes and often severe hypoglycemia
  - Progressive weight gain over the years
  - Increasing frequency of late CVD
  - DKA remains a problem
  - Adjunct therapies are needed to aid and improve MDI or CSII options
Purpose of Adjunct-Therapies in Type 1 Diabetes

• More stable glucose profiles
• Less hypoglycemia
• Less weight gain

NOT

• Replacing insulin
• Decreasing insulin doses per se
Pramlintide
Amylin Is Co-Secreted With Insulin

Healthy male adults (n=6).

Pramlintide in T1D - Postprandial Glucose Concentrations after a Meal Test with Pre-meal Regular Insulin or Insulin Lispro

Weyer et al. Diabetes Care 2003; 26:3074–3079
Pramlintide in T1D – Changes in A1c, Insulin Use, and Body Weight

Pramlintide as an adjunct to insulin therapy in T1D

All subjects

Subjects on Stable Insulin Dose

Meta-Analysis of A1c with Pramlintide in T1D

Qiao YC et al. Oncotarget 2017; 8:66504-66515
49yo woman with T1D x 33 years, A1C 9%
Avg Glucose 176.9 / S.D. 66.3
After 3 months on Pramlintide, A1C 7.4%, lost 12 lbs.
Avg Glucose 122.4 / S.D. 30.4
Metformin
REMOVAL Study – Metformin in T1D

A1c

Insulin Dose (U/kg)

Body Weight (kg)

Effect of Metformin on Glycemic Control in T1D: Meta-Analysis of Randomized Controlled Trials

A1c

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Metformin Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Codner 2013</td>
<td>10.4</td>
<td>2.6</td>
<td>13</td>
<td>9.6</td>
<td>1.4</td>
<td>11</td>
<td>0.5%</td>
<td>0.80 [-0.84, 2.44]</td>
</tr>
<tr>
<td>Hamilton 2003</td>
<td>9</td>
<td>1.4</td>
<td>14</td>
<td>8.9</td>
<td>0.8</td>
<td>13</td>
<td>1.9%</td>
<td>0.10 [-0.75, 0.95]</td>
</tr>
<tr>
<td>Jacobsen 2009</td>
<td>8.85</td>
<td>0.1</td>
<td>12</td>
<td>9.34</td>
<td>0.94</td>
<td>12</td>
<td>4.8%</td>
<td>-0.49 [-1.02, 0.04]</td>
</tr>
<tr>
<td>Khan 2006</td>
<td>7.8</td>
<td>1.1</td>
<td>15</td>
<td>8.5</td>
<td>1.4</td>
<td>15</td>
<td>1.7%</td>
<td>-0.70 [-1.60, 0.20]</td>
</tr>
<tr>
<td>Libman 2015</td>
<td>9</td>
<td>0.86</td>
<td>71</td>
<td>8.9</td>
<td>1.06</td>
<td>69</td>
<td>13.3%</td>
<td>0.10 [-0.22, 0.42]</td>
</tr>
<tr>
<td>Lund 2008</td>
<td>9.25</td>
<td>0.94</td>
<td>48</td>
<td>9.12</td>
<td>0.86</td>
<td>50</td>
<td>10.7%</td>
<td>0.13 [-0.23, 0.49]</td>
</tr>
<tr>
<td>Meyer 2002</td>
<td>7.45</td>
<td>0.78</td>
<td>31</td>
<td>7.46</td>
<td>0.6</td>
<td>31</td>
<td>11.4%</td>
<td>-0.01 [-0.36, 0.34]</td>
</tr>
<tr>
<td>Nadeau 2015</td>
<td>9.2</td>
<td>1.2</td>
<td>40</td>
<td>9.6</td>
<td>1.2</td>
<td>40</td>
<td>4.9%</td>
<td>-0.40 [-0.93, 0.13]</td>
</tr>
<tr>
<td>Nwosu 2015</td>
<td>8.58</td>
<td>1.5</td>
<td>15</td>
<td>8.25</td>
<td>0.4</td>
<td>13</td>
<td>2.2%</td>
<td>0.33 [-0.46, 1.12]</td>
</tr>
<tr>
<td>Petrie 2017</td>
<td>8.1</td>
<td>0.9</td>
<td>193</td>
<td>8.1</td>
<td>0.8</td>
<td>194</td>
<td>47.4%</td>
<td>0.00 [-0.17, 0.17]</td>
</tr>
<tr>
<td>Sarnblad 2003</td>
<td>8.7</td>
<td>1.5</td>
<td>13</td>
<td>9.2</td>
<td>1.3</td>
<td>13</td>
<td>1.2%</td>
<td>-0.50 [-1.58, 0.58]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>465</td>
<td></td>
<td></td>
<td>461</td>
<td></td>
<td>100.0%</td>
<td>-0.02</td>
<td>[-0.14, 0.10]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 10.99, df = 10 (P = 0.36); I² = 9%
Test for overall effect: Z = 0.36 (P = 0.72)

Effect of Metformin on Glycemic Control in T1D: Meta-Analysis of Randomized Controlled Trials

BMI

Insulin Dose (U/kg)

Effect of Metformin on Glycemic Control in T1D: Meta-Analysis of Randomized Controlled Trials

GLP-1 Receptor Agonists
Exenatide in T1D - Glucose and Glucagon Responses with exenatide (♦) or vehicle (○) in 8 volunteers with T1D and no β-cell function (paired studies) compared with responses in 6 healthy volunteers (dotted line).

Dupré J et al. *JCEM* 2004;89:3469-3473
59 yo woman
On insulin pump x 2 years
After adding Exenatide 5 mcg twice daily
Liraglutide in T1D


Weekly CGM Record for One Patient Prior to Liraglutide
Weekly CGM Record for One Patient Following Liraglutide
SGLT Inhibitors
Dapagliflozin in T1D

Dandona et al. Lancet DE 2017; 5:864-876

Adjusted mean change in HbA1c (%)

Dapagliflozin 5 mg (difference vs placebo): -0.42 (95% CI -0.56 to -0.28); p<0.0001
Dapagliflozin 10 mg (difference vs placebo): -0.45 (95% CI -0.58 to -0.31); p<0.0001

Adjusted mean change in TID

Dapagliflozin 5 mg (difference vs placebo): -8.80 (95% CI -12.56 to -4.88); p<0.0001
Dapagliflozin 10 mg (difference vs placebo): -13.17 (95% CI -16.75 to -9.43); p<0.0001
Sotagliflozin in T1D

A1c < 7.0% at week 24, with no episodes of severe hypoglycemia or DKA

## Positively Adjudicated Severe Hypoglycemic Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SOTA 400mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients, n</strong></td>
<td>703</td>
<td>699</td>
</tr>
<tr>
<td><strong>Number (%) of patients with SH</strong>*</td>
<td>17 (2.4)</td>
<td>21 (3.0)</td>
</tr>
<tr>
<td><strong>Number (%) discontinued study drug due to SH</strong></td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td><strong>Patients on pump, n</strong></td>
<td>280</td>
<td>275</td>
</tr>
<tr>
<td><em><em>Number (%) with SH</em> on pump</em>*</td>
<td>5 (1.8)</td>
<td>10 (3.6)</td>
</tr>
<tr>
<td><strong>Patients on MDI</strong></td>
<td>423</td>
<td>424</td>
</tr>
<tr>
<td><em><em>Number (%) with SH</em> on MDI</em>*</td>
<td>12 (2.8)</td>
<td>11 (2.6)</td>
</tr>
</tbody>
</table>

## Positively Adjudicated Diabetic Ketoacidosis Events

<table>
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<tr>
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<th>Placebo</th>
<th>SOTA 400mg</th>
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<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>703</td>
<td>699</td>
</tr>
<tr>
<td><strong>Number (%) with DKA</strong></td>
<td>4 (0.6)</td>
<td>21 (3.0)</td>
</tr>
<tr>
<td><strong>Number (%) discontinuation study drug due to DKA</strong></td>
<td>1 (0.1)</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td><strong>Patients on pump, n</strong></td>
<td>280</td>
<td>275</td>
</tr>
<tr>
<td><strong>Number (%) with DKA on pump</strong></td>
<td>2 (0.7)</td>
<td>12 (4.4)</td>
</tr>
<tr>
<td><strong>Patients on MDI, n</strong></td>
<td>423</td>
<td>424</td>
</tr>
<tr>
<td><strong>Number (%) with DKA on MDI</strong></td>
<td>2 (0.5)</td>
<td>9 (2.1)</td>
</tr>
</tbody>
</table>

CGM Time in Target, Hyperglycemic, & Hypoglycemic Ranges

Baseline CGM
Days –2 to –6

Placebo
% time in ranges

Sotagliflozin
% time in ranges

Treatment CGM
Days 3–27

Blood glucose CGM

<70 mg/dL

70–180 mg/dL

>180 mg/dL

P=0.003
vs. placebo

P=0.002
vs. placebo

Sands et al. Diabetes Care 2015;38:1181–1188
CGM Measures of Glycemic Variability

**Standard deviation**
- Placebo: 1.2%
- Sotagliflozin: -8.9%

**Mean amplitude of glycemic excursions**
- Placebo: 7.5%
- Sotagliflozin: -20%

**Low blood glucose index**
- Placebo: -0.6%
- Sotagliflozin: -0.2%

**High blood glucose index**
- Placebo: 0.5%
- Sotagliflozin: -2.9%

*P = 0.022 relative to placebo
*P = 0.041 relative to placebo
*P = 0.006 relative to placebo
**Empagliflozin Development Program in T1D: EASE-2 & EASE-3 Trials**

**Summary of Key Results**

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>2.5 mg</th>
<th>10 mg</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c Reductions</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>No Increase in Symptomatic Hypoglycemia*</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>No Increase in Severe Hypoglycemia**</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Confirmed DKA</td>
<td>↔</td>
<td>→</td>
<td>→</td>
</tr>
</tbody>
</table>

*Placebo-Subtracted
**Investigator-reported events with symptoms and BG <54 mg/dl
***Requiring third party assistance
Take Away Messages

• Despite recent advances in diabetes management, patients with T1D still do not achieve A1c goals and have wide glucose fluctuations
• Patients with T1D have progressive weight gain and CVD risk
• Adjunct therapies are needed to aid and improve treatment options
• Adjunct therapies should improve glucose control, increase time in range, without increasing hypoglycemia or promoting weight gain
• Several adjunct therapies are under development