Case 3

Patient Medical History

- Diabetic Patient
- Male
- Age: 62
- Duration of Disease: 8 Years
- HbA1c: 7.8
- FBS: 220
- BS 2hPP: 350

- History of medication therapy
- Metformin 1000 mg (2 years)

- Medication therapy
- Humalog Mix 50/50
- 26 IU Morning / 20 IU before dinner

Current Patient situation:

Covid_19

Medication therapy
- Dexamethasone
- Remdesivir
- Insulin Crystal (In hospital)
- Prednisolone 20 mg
- Insulin Glargine 2 IU
- Metformin 2000 mg

New Insulin Therapy Consideration

- Humalog Mix 50/50
- 26 IU Morning / 20 IU before dinner

- SMBG result (in 28 H)
- FBS: 136
- BS 2hPP: 184
- BS 4qm: 213
Lilly Diabetes: 90 Years of Milestones

1923
Lilly* is the first company to make insulin commercially available.

1982
Humulin is the first human drug produced through recombinant DNA technology.

1996
Humalog is the first rapid-acting human insulin analogue.

1999
Actos®, Lilly’s first OAD, is approved (jointly marketed by Lilly and Takeda†).

2005
Byetta® (exenatide BID injection) is the first GLP-1 RA (developed by Lilly and Amylin‡).

2011
Bydureon® (exenatide 2 mg powder and solvent for prolong release suspension for injection) is the first weekly GLP-1 RA, developed by Lilly, Alkermes, and Amylin.

2014
Trulicity (dulaglutide once-weekly injection) is in a ready-to-use pen with no reconstitution and a hidden, pre-attached needle.

Basaglar®, BI/Lilly's new insulin glargine product, is the first biosimilar product approved by the EMA.

Jardiance, BI/Lilly’s once-daily empagliflozin tablet, is approved.

*Eli Lilly and Company; †Takeda Pharmaceutical Company Ltd.; ‡Amylin Pharmaceuticals, Inc.; §Alkermes, Inc.

EMA = European Medicines Agency; OAD = oral antidiabetic drug.

http://www.lilly.com/about/heritage/Pages/heritage.aspx.
♦ Progression of T2DM
♦ Insulin Initiation in T2DM
♦ Introduction to Premix Insulins
♦ Premix vs. Basal Insulin Regimens
♦ Premix vs. Basal-Bolus Regimens
♦ Comparison of Premix, Basal-Bolus, and Basal Insulin Regimens
♦ Guidelines and Treatment Algorithms
♦ Conclusions
What are Premix Insulins?

♦ Premix human insulins¹
  • Composed of human insulin and NPH (intermediate-acting human insulin)
  • Dosing in T2DM: 2-3 injections per day, approximately 30-45 minutes before a meal

♦ Premix insulin analogs¹
  • Composed of a rapid acting analog and the same insulin attached to protamine, which prolongs its absorption
  • Dosing in T2DM: 2-3 injections per day, up to 15 minutes before or right after meals

♦ Target both FPG and PPG²

Benefits of Premix Insulins

<table>
<thead>
<tr>
<th>Desirable Features</th>
<th>Resulting Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Premix”</td>
<td>• No mixing errors</td>
</tr>
<tr>
<td>Rapid and Basal Components</td>
<td>• Both FPG and PPG control</td>
</tr>
</tbody>
</table>
| “Single Pen”       | • Convenient dosing schedule  
|                    | • Less number of injections and glucose testing\(^a\) than basal-bolus therapy |

\(^a\)Less number of glucose testing for premix insulin (QD or BID) vs. basal-bolus insulin with prandial insulin (TID)  
Garber AJ. *Drugs* 2006;66:31-49
“Ideal” Patient Characteristics for a Premix Insulin$^{1,2}$

♦ Organized lifestyle

♦ Regular intake of meals

♦ Less motivated for frequent blood glucose monitoring and insulin dose adaptation

♦ Prefers fewer injections
  • Older age, poor cognitive ability, limited manual dexterity, need for caretaker

1. Mosenzon O and Raz I. *Diabetes Care* 2013;36(Suppl 2)S212-8
Time-Action Profile of Premix Insulins

N=30. Nondiabetic subjects. 0.3 U/kg dose.

Data from Heise T et al. Diabetes Care 1998;21:800-3
### Premix Insulins Currently Available (US)\(^a\)

<table>
<thead>
<tr>
<th>Insulin Analogs</th>
<th>Human Insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Insulin lispro mix 75/25(^1)</td>
<td>♦ Human insulin 70/30(^4,5)</td>
</tr>
<tr>
<td>♦ Insulin lispro mix 50/50(^2)</td>
<td></td>
</tr>
<tr>
<td>♦ Insulin aspart 70/30(^3)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Insulin components are stated as basal/prandial

---

1. Humalog\(^®\) Mix75/25™ [Prescribing Information]. 2015
2. Humalog\(^®\) Mix50/50™ [Prescribing Information]. 2015
4. Humulin\(^®\) 70/30 [Prescribing Information]. 2015
5. Novolin\(^®\) 70/30 [Patient information]. 2010

US=available within the United States of America
# Premix Insulins Currently Available (OUS)\(^a\)

<table>
<thead>
<tr>
<th>Insulin Analogs</th>
<th>Human Insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Insulin lispro mix 25/75(^1)</td>
<td>♦ Human insulin 15/85(^4)</td>
</tr>
<tr>
<td>♦ Insulin lispro mix 50/50(^2)</td>
<td>♦ Human insulin 25/75(^5)</td>
</tr>
<tr>
<td>♦ Insulin aspart 30/70(^3)</td>
<td>♦ Human insulin 30/70(^6)</td>
</tr>
<tr>
<td></td>
<td>♦ Human insulin 40/60(^7)</td>
</tr>
<tr>
<td></td>
<td>♦ Human insulin 50/50(^8)</td>
</tr>
</tbody>
</table>

\(^a\)Insulin components are stated as prandial/basal

2. Humalog Mix 50, SPC 2016
3. Novo Mix 30, SPC 2014
4. Insuman Comb 15, SPC 2013
5. Insuman Comb 25, SPC 2013
6. Humulin, SPC 2015
7. Novolin\(^\circledast\)ge Penfill\(^\circledR\) Premixed insulin preparations, 2011
8. Insuman Comb 50, SPC 2013

OUS=available outside of the United States of America
Premix Analogs vs. Human Premixes\textsuperscript{1,2}

- Compared to human premix insulins, premix analogs showed
  - An improved PK/PD profile
  - Improved postprandial glycemic control
  - Similar rates of hypoglycemia
  - Similar mean doses of insulin, changes in body weight, and incidence of adverse events

## Clinical Trials: Premix Insulin BID vs. Basal-Bolus Insulin

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Trial Design and Duration</th>
<th>Treatment Arms</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowering et al, 2012¹</td>
<td>48-week, multinational, randomized, prospective, open-label study</td>
<td>Glargine + Lispro vs. LM25 QD-TID</td>
<td>N=426; insulin-naïve on OAMs</td>
</tr>
<tr>
<td>Liebl et al, 2009²</td>
<td>26-week, multicenter, randomized, treat-to-target study</td>
<td>Detemir + Aspart vs. BiAsp30 BID</td>
<td>N=719; with or without concomitant basal insulin</td>
</tr>
<tr>
<td>Rosenstock et al, 2008³</td>
<td>24-week, multicenter, randomized, open-label, active-controlled study</td>
<td>Glargine + Lispro vs. LM50 TID</td>
<td>N=374; On ≥30 IU of insulin glargine</td>
</tr>
<tr>
<td>Aschner et al, 2015⁴</td>
<td>24-week, multinational, randomized, parallel-arm, open-label study</td>
<td>Glargine QD ± Glulisine vs. Premix insulin QD or BID</td>
<td>N=934; on concomitant metformin ± insulin secretagogues</td>
</tr>
<tr>
<td>Jain et al, 2010⁵</td>
<td>36-week, open-label, randomized trial</td>
<td>Glargine + Lispro vs. LM50 TID</td>
<td>N=484; insulin-naïve</td>
</tr>
<tr>
<td>Guigliano et al, 2011⁶</td>
<td>Meta-analysis of 3 RCTs</td>
<td>Basal-bolus vs. Premix BID regimens</td>
<td>N=559; insulin-experienced</td>
</tr>
</tbody>
</table>

2. Liebl A et al. *Diabetes Obes Metab* 2009;11:45-52
Evidence for Intensification with Premixes in ADA 2017 Guideline

Premix Thrice Daily

Figure 8.2 outlines these options, as well as recommendations for further intensification, if needed, to achieve glycemic goals. If a patient is still above the A1C target on premixed insulin twice daily, consider switching to premixed analog insulin three times daily (70/30 aspart mix, 75/25 or 50/50 lispro mix). In general, three times daily premixed analog insulins have been found to be non-inferior to basal-bolus regimens with similar rates of hypoglycemia (41). If a patient is still above the A1C target on basal insulin + single injection of rapid-acting insulin before the largest meal, advance to a basal-bolus regimen with ≥2 injections of rapid-acting insulin before meals. Consider switching patients from one regimen to another (i.e., premixed analog insulin three times daily to basal-bolus regimen or vice-versa) if A1C targets are not being met and/or depending on other patient considerations (39, 40).
A Practical Approach to Insulin Intensification: Humalog Mix50
Case 3

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♦ HbA1c: 7.8
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New Insulin regimen Consideration

♦ Medication therapy
  ♦ Humalog Mix 50/50
  ♦ 26 IU Morning / 20 IU before dinner

♦ SMBG result
  ♦ After 28 Hours
  ♦ FBS: 136  BS 2 hpp:184  BS 4Qm: 213
Why mix 50 could be an appropriate option for intensification from twice daily low mix insulins?

- Trial evidence and adoption into major guidelines
- Risk of hypoglycaemia limiting further low mix insulin dose escalation
- Suboptimal glucose control with low mix insulins despite dose optimization
- Need for coverage of additional post-prandial peaks (e.g., lunch)

Humalog Mix50 as a suitable option
**Recommended Starting dose:**
- Divide current total daily insulin (TDI) dose by 3 and give subcutaneously at premeal 1/3 the total dose for each main meal\(^1\) [e.g., A patient on 12 units of NPH twice daily has TDI dose of 24 units (12x2), could be switched to 8 units (24÷3) before each of 3 main meals]
- Increase dose gradually and adjust accordingly\(^1\)\(^-\)\(^4\)

**Oral antihyperglycemic medication recommendation (OAM):**
- Maintain at least metformin 850-1700 mg/day in divided doses
- Other OAMs can also be maintained\(^1\),\(^2\)

**BG measurements during early initiation:**
- Frequently monitor and adjust pre-breakfast, pre-lunch, and pre-supper BG and assess every 3-4 days**

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**Notes:**
- Additional measurements are often needed (for example, once per day or more frequently).
- This decision is the responsibility of the practicing physician.

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\(^3\)Kazda C. et al., *J Diabetes Complications* 2006; 20:145-152
Humalog® Mix50™TID
Recommended Dose Adjustment

Adjust dose every 3-4 days (twice weekly) to achieve and stabilize BG targets

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmol/L</td>
<td>mg/dL</td>
</tr>
<tr>
<td>2.7</td>
<td>50</td>
</tr>
<tr>
<td>2.8-4.3</td>
<td>51-79</td>
</tr>
<tr>
<td>4.4-6.0</td>
<td>80-109</td>
</tr>
<tr>
<td>6.1-7.7</td>
<td>110-139</td>
</tr>
<tr>
<td>≥ 7.8</td>
<td>≥ 140</td>
</tr>
</tbody>
</table>
Advancing Insulin Therapy With Insulin Lispro Mix 50 vs. Insulin Glargine + Insulin Lispro in Patients With T2D Previously Treated With Insulin Glargine Plus OADs

Insulin Lispro Mix 50 vs. Glargine + Lispro: Study Overview

♦ Study objective
  • Demonstrate noninferiority of insulin lispro mix 50 compared to insulin glargine + insulin lispro, both arms TID

♦ Primary efficacy measure
  • Change in HbA1c at endpoint

♦ Secondary measures
  • % of patients achieving HbA1c targets at endpoint (post hoc analysis)
  • 8-point plasma glucose profiles
  • Total daily dose of insulin
  • Body weight
  • Hypoglycemic event rate

Insulin Lispro Mix 50 vs. Glargine + Lispro: Study Design

- 24-week, multicenter, randomized, open-label, active-controlled study
- Doses adjusted to reach a preprandial plasma glucose <6.1 mmol/L (<110 mg/dL)

Inclusion criteria:
- Age 30-75 years with T2D
- HbA1c levels 7.5-12.0%
- On ≥30 IU of insulin glargine in combination with OADs for ≥90 days before the study

Insulin Lispro Mix 50 vs. Glargine + Lispro: Starting Daily Dose


Total daily insulin dose = pre-study insulin glargine dose

Glargine + Lispro

1/6 Dose (insulin lispro) | 1/6 Dose (insulin lispro) | 1/6 Dose (insulin lispro) | 3/6 Dose (insulin glargine)

Breakfast | Lunch | Dinner | Bedtime

Insulin Lispro Mix 50

1/3 Dose | 1/3 Dose | 1/3 Dose

[If FPG >110 mg/dL, could switch to insulin lispro mix 25]

Preprandial PG target <6.1 mmol/L (110 mg/dL)
## Insulin Lispro Mix 50 vs. Glargine + Lispro: Insulin Dosing Algorithm

<table>
<thead>
<tr>
<th>Preprandial Blood Glucose (mg/dL [mM])</th>
<th>Algorithm 1, TDD &lt;100 IU (IU Dose Increased)</th>
<th>Algorithm 1, TDD ≥100 IU (IU Dose Increased)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110-150 (6.1-8.3)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>151-200 (8.4-11.1)</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>201-250 (11.2-13.9)</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>251-300 (13.9-16.7)</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>&gt;300 (&gt;16.7)</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preprandial Blood Glucose (mg/dL [mM])</th>
<th>Algorithm 2 (IU Dose Increased)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110-200 (6.1-11.1)</td>
<td>2</td>
</tr>
<tr>
<td>201-300 (11.2-16.7)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;300 (&gt;16.7)</td>
<td>4</td>
</tr>
</tbody>
</table>

## Insulin Lispro Mix 50 vs. Glargine + Lispro: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Glargine + Lispro (N=187)</th>
<th>Insulin Lispro Mix 50 (N=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>54.0 ± 9.2</td>
<td>55.4 ± 9.8</td>
</tr>
<tr>
<td><strong>Sex (male:female), %</strong></td>
<td>52:48</td>
<td>53:47</td>
</tr>
<tr>
<td><strong>Race, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>54.6</td>
<td>55.1</td>
</tr>
<tr>
<td>Black or African descent</td>
<td>9.6</td>
<td>13.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>28.3</td>
<td>26.2</td>
</tr>
<tr>
<td>Other</td>
<td>7.5</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>99.8 ± 21.3</td>
<td>99.1 ± 19.8</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>34.8 ± 5.5</td>
<td>34.1 ± 5.3</td>
</tr>
<tr>
<td><strong>Duration of diabetes, years</strong></td>
<td>11.2 ± 6.2</td>
<td>10.9 ± 6.3</td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>8.89 ± 1.09</td>
<td>8.83 ± 1.04</td>
</tr>
<tr>
<td><strong>Total daily glargine dose at study entry, IU (IU/kg)</strong></td>
<td>54.9 ± 27.8 (0.56 ± 0.27)</td>
<td>52.5 ± 24.1 (0.53 ± 0.21)</td>
</tr>
</tbody>
</table>

Data are mean ± SD or %; No statistically significant differences between groups
Insulin Lispro Mix 50 vs. Glargine + Lispro: HbA1c Change From Baseline (Completer Population)

Δ*=-0.22% (90% CI: -0.38% to -0.07%)

Limit for noninferiority: -0.3%

* p=.021 for comparison of endpoint HbA1c values
Insulin Lispro Mix 50 vs. Glargine + Lispro: Percentage of Patients at HbA1c Targets at 24 Weeks (Completer Population)

Cumulative Percent of Patients

HbA1c Target Value

- ≤6.0%
- ≤6.5%
- <7.0%
- <7.5%

Glargine + Lispro (n=158)
Insulin Lispro Mix 50 (n=158)

*p<.05

**Insulin Lispro Mix 50 vs. Glargine + Lispro: SMBG Profile (Completer Population)**

- **Glargine + Lispro (n=158)**
- **Insulin Lispro Mix 50 (n=158)**

*Mean Plasma Glucose (mM)*

*Mean Plasma Glucose (mg/dL)*

*Baseline*

*Endpoint*

*P<.05 (between treatments at endpoint)*

Insulin Lispro Mix 50 vs. Glargine + Lispro: Total Daily Insulin Dose and Body Weight

Data were presented as mean ± SD
Insulin Lispro Mix 50 vs. Glargine + Lispro: Symptomatic Hypoglycemia† (Randomized Population)

Incidence (% Patients)

<table>
<thead>
<tr>
<th></th>
<th>Glargine + Lispro (n=187)</th>
<th>Insulin Lispro Mix 50 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>88.8%</td>
<td>90.4%</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>58.8%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Severe</td>
<td>2.1%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Rate (Events/Year/Patient)

<table>
<thead>
<tr>
<th></th>
<th>Glargine + Lispro (n=187)</th>
<th>Insulin Lispro Mix 50 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>48.7</td>
<td>51.2</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>6.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

†Irrespective of plasma glucose confirmation
Insulin Lispro Mix 50 vs. Glargine + Lispro: Hypoglycemia Confirmed by Plasma Glucose Values (Randomized Population)

Insulin Lispro Mix 50 vs. Glargine + Lispro: Key Findings

♦ Noninferiority of insulin lispro mix 50 to glargine + lispro was not demonstrated based on the prespecified margin of 0.3%
  • Difference ([glargine + lispro] − [insulin lispro mix 50]) in HbA1c change from baseline to endpoint was -0.22% (90% CI -0.38 to -0.07)

♦ Both regimens reduced mean endpoint HbA1c to <7.0%
  • Glargine + lispro group had a larger proportion of patients achieving HbA1c targets of ≤6.5% and <7.0%

♦ 55% of patients on insulin lispro mix 50 TID switched to insulin lispro mix 25 at the evening meal

♦ Significantly higher total daily dose of insulin seen in the glargine + lispro group

♦ Weight gain and hypoglycemia were similar in both groups

Conclusions

Intensifying therapy with Humalog mixtures may benefit some of your patients.

Patient characteristics:

- Not achieving HbA$_1^c$ targets with basal or low mix insulin alone
- Experiencing high postprandial BG excursions particularly at lunch
- Willing to inject insulin 3 times a day
- Have concerns about hypoglycaemia, particularly later in the day