Basal Insulin Update
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Introduction
The focus of this newsletter is using basal insulin in patients with type 2 diabetes mellitus (T2DM) in light of dramatic cost increases within the long-acting insulin market and the introduction of the first follow-on insulin product. With the incidence of diabetes doubling in Oregon over the past 20 years, the healthcare system has been substantially impacted. In Oregon alone, it is estimated that approximately 287,000 adults have diabetes, costing the state $2.2 billion dollars annually on medical expenditures. Effectiveness, safety and cost considerations of using basal insulin therapy will be discussed below.

The Cost of Basal Insulins
The long-acting insulin analogs have experienced a trend of escalating costs with increases in wholesale prices of more than 160% in the past five years. A 2016 analysis found that the cost of insulin tripled between 2002 to 2013, with the cost of analog insulin consistently double that of human insulin. This translates to an average cost to patients of approximately $400-$500 a month (Figure 1). There is evidence of underuse of insulin due to high costs, which subsequently has resulted in poor glycemic control. Additionally, utilization of lower cost neutral protamine Hagedorn (NPH) insulin continues to decline.

Table 1. Clinical Trial Data

<table>
<thead>
<tr>
<th>Source</th>
<th>Outcome</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane³</td>
<td>Nocturnal hypoglycemia†</td>
<td>LA insulin analogs vs. NPH</td>
<td>LA insulin: 24% NPH: 39% P&lt;0.05*</td>
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<tr>
<td>Observational, Retrospective Trial¹</td>
<td>ER visits or hospitalizations</td>
<td>LA insulin analogs vs. NPH</td>
<td>LA insulin: 39 (2%) NPH: 354 (1.5%) P&gt;0.05</td>
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</tbody>
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Key: * Data not pooled but individual comparisons were statistically significant, † Most commonly defined as an event taking place while sleeping, between bedtime and getting up

Abbreviations: LA- long-acting; NPH - neutral protamine Hagedorn

Figure 1. Comparative Costs for Basal Insulin⁶

Basal Insulins: NPH vs. Long-Acting Insulin Analogs
With the approval of insulin glargine (Lantus) in 2000 there has been the perception of superiority of long-acting insulin analogs over intermediate acting, NPH insulin. Clinical trial data suggests a modest benefit in reduced risk of nocturnal hypoglycemia with long-acting insulin analogs (glargine, detemir and degludec) compared to NPH insulin, without clinically significant differences in hemoglobin A1c (HbA1c) lowering. This is supported by evidence from a Cochrane Systematic Review (Table 1). However, the incidence of severe hypoglycemia with long-acting insulin analogs and NPH in patients with T2DM is similar. This was substantiated by a recent observational, retrospective review which analyzed the comparative hypoglycemia rates of long-acting insulin analogs (glargine or detemir) to NPH insulin and found no statistically significant difference in the incidence of emergency department (ED) visits/hospitalizations between the two groups (Table 1). There is a lack of evidence to support clinically relevant differences for most outcomes when comparing long-acting insulin analogs to NPH and additional comparative evidence between NPH and concentrated insulins (insulin glargine U-300) and ultra-long acting insulin (insulin degludec) is needed.

Follow-on Insulin vs. Biosimilars
Follow-on insulins and biosimilars may offer a cost advantage of approximately 20% to 30% less than their reference insulin for some patients; however, many reference insulin manufacturers offer incentives that provide a price advantage over follow-on insulin products. Therefore, the most cost-effective option will be dependent upon patient-specific health care coverage.

Clinically, follow-on products are similar to their reference biologic (insulin); however, biologics are complex molecules derived from a living source with small changes in manufacturing influencing efficacy and safety. Exact duplication is not possible, and therefore, follow-ons and biosimilars are not considered to be generically equivalent to their reference product. Additionally, regulations for follow-on and biosimilars differ as outlined below:

- **Follow-on biologics:**
  - Copy of reference biologic approved via the Food, Drug and Cosmetic (FD&C) Act as a new drug application and biologics submitted under the Public Health Service (PHS) Act as a biologic license application (BLA)

- **Biosimilars:**
  - Biological product licensed by the Food and Drug Administration (FDA) which are highly similar to an already FDA-approved biological product which have been shown to have no clinically meaningful difference from the reference product (e.g., safety, purity, and potency)
  - Therapies submitted under the PHS Act as a BLA

Follow-on insulins are now available in the United States. Follow-on insulins are not interchangeable without the intervention of a healthcare provider. Currently there are no interchangeable biosimilars approved in the United States.
Oregon Health Plan (OHP) Fee-For-Service (FFS) Policy

OHP FFS preferred intermediate and long-acting products are NPH vials, insulin detemir pens (Levemir FlexTouch), insulin glargine pens (Lantus Solostar), and insulin glargine vials (Lantus)

- Lantus (vials and pens) represent the most cost-effective basal insulin option for OHP FFS patients
- NPH is the most cost-effective option for most patients with other types of insurance coverage

Switching Basal Insulins

It may be appropriate to switch patients from one insulin to another based on a variety of factors such as: efficacy concerns, tolerability or cost. Many insulins can be switched on a unit-per-unit basis and some conversions require a dose reduction. Switching from a long-acting insulin to NPH may also necessitate the need to divide the total units between AM and PM doses or 2/3 in the morning and 1/3 before dinner or bedtime.16

Unit-per-unit conversions:
- insulin glargine (Lantus or Basaglar) to once-daily NPH
- NPH to insulin detemir
- Insulin glargine U-100 to U-300
- Insulin glargine (U-100 or U-300) to insulin detemir
- Any long- or intermediate-acting insulin to insulin degludec

A dose reduction of 20% conversions:
- Insulin glargine U-300 to NPH, insulin detemir or insulin glargine U-100
- Changes from twice daily to a once daily insulin dosing schedule

Key Take Home Points

- Incidence of severe hypoglycemia has been shown to be similar for NPH and long-acting insulin analogs in patients with T2DM, without clinically significant differences in hemoglobin A1c (HbA1c) lowering.
- The most cost-effective long-acting insulin is dependent upon the patient’s specific healthcare coverage, and may or may not be a follow-on insulin.

Basaglar

Basaglar (insulin glargine U-100) was the first follow-on insulin to be approved by the FDA.13 Two non-inferiority trials compared it to the reference insulin, Lantus (insulin glargine U-100), to provide evidence for the approval.13,14 Efficacy and harms data found Basaglar to be similar to Lantus in patients with type 1 diabetes mellitus (T1DM) and T2DM. The Drug Effectiveness Review Project (DERP) also found Basaglar to be equivalent to Lantus.15 Due to the equivalency findings between Basaglar and Lantus, switching between the two products can be done on a unit-per-unit conversion but must be authorized by a provider. When switching to non-glargine insulin formulations, conversion data for Lantus is applied to Basaglar.16

References

12. Basaglar Prescribing Information. Lilly USA, LLC and Boehringer Ingelheim Pharmaceuticals, Inc. Indianapolis, IN and Ridgefield, CT. 2015.