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Basal Insulin Update

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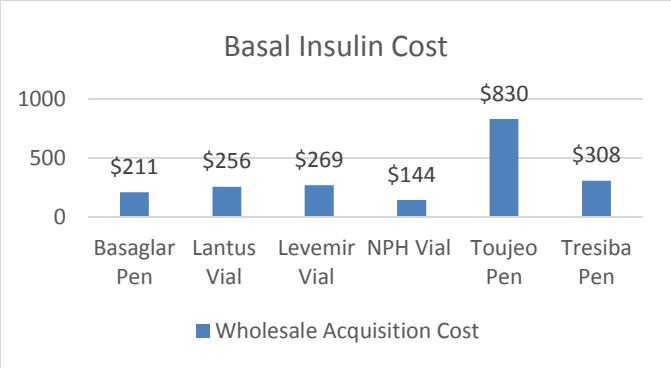
Introduction

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.[1] In Oregon alone, it is estimated that approximately 287,000 adults have diabetes, costing the state $2.2 billion dollars annually on medical expenditures.[1] 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.[2] 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.[3,4] This translates to an average cost to patients of approximately $400-$500 a month (Figure 1).[3,5,6] There is evidence of underuse of insulin due to high costs, which subsequently has resulted in poor glycemic control.[7] Additionally, utilization of lower cost neutral protamine Hagedorn (NPH) insulin continues to decline.

Figure 1. Comparative Costs for Basal Insulin[6]



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).[8] However, the incidence of severe hypoglycemia with long-acting insulin analogs and NPH in patients with T2DM is similar.[9] 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).[9] 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.[8]

Table 1. Clinical Trial Data

Source	Outcome	Comparator	Results
Cochrane[8]	Nocturnal hypoglycemia†	LA insulin analogs vs. NPH	LA insulin: 24% NPH: 39% P<0.05*
Observational, Retrospective Trial[9]	ER visits or hospitalizations	LA insulin analogs vs. NPH	LA insulin: 39 (2%) NPH: 354 (1.5%) P>0.05

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

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.[10] Exact duplication is not possible, and therefore, follow-ons and biosimilars are not considered to be generically equivalent to their reference product.[11] 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)[10]
- 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.[11]

Basaglar

Basaglar (insulin glargine U-100) was the first follow-on insulin to be approved by the FDA.[12] 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]

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-acing 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.

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