EDITORIAL

Insulin Analogues for Type 2 Diabetes

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Clinical trials have shown that insulin analogues, such as glargine, detemir, aspart, and lispro, do not offer major advantages over human insulin products, such as neutral protamine Hagedorn (NPH) and regular human insulin, for patients with type 2 diabetes.[1,2] In these studies, neither the rate of severe hypoglycemia nor the achieved glycemic control improved with insulin analogues. Results from observational studies largely confirmed these findings in clinical settings. One such study, conducted at Kaiser Permanente, showed no significant differences in health care use related to hypoglycemia or in levels of glycemic control among patients with type 2 diabetes who started a basal insulin analogue vs patients who started NPH insulin.[3] However, in clinical trials, insulin analogues modestly reduced the rate of nocturnal hypoglycemia, an important outcome for patients with diabetes. Notably, the clinical trials were open label, so they do not have the advantage of blinding, and the nocturnal hypoglycemia outcome was self-reported. Therefore, these trials are subject to risk of bias.

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The choice to use an insulin analogue over a human insulin may have little clinical consequence for most patients with type 2 diabetes, but it comes at a substantial cost. In the United States, compared with NPH or regular human insulin, insulin analogues cost up to 10 times more.[4] For example, a vial containing 1000 U of NPH or regular human insulin can be purchased for $25, whereas the retail price for a vial of analogue insulin ranges between $178 and $320.[5] It is difficult to imagine that consumers in almost any other setting would be willing to pay such a significant price difference without evidence of concomitant benefit. Yet, when it comes to insulin, patients, physicians, and insurers have been willing to spend increasing amounts on these products.

For US patients with type 2 diabetes, insulin analogues have largely replaced human insulin.[6,7] As a result, spending on insulin accounts for an increasing proportion of expenditures for diabetes medications.[7] For example, in 2013, expenditures for insulin (estimated at $736 per patient) were higher than expenditures for all other glucose-lowering drugs combined (estimated at $503 per patient).[8] This trend is unlikely to change. A 2019 modeling study suggested that the amount of insulin required to treat patients with type 2 diabetes, globally, is expected to increase by more than 20% from 2018 to 2030.[9] If both the price of insulin and the number of patients who need it continue to increase, insulin may become increasingly unaffordable for many patients. Based on a single-center study that included 199 participants, 1 in 4 patients in the United States already ration insulin because of the cost.[10]

Why then have insulin analogues been so readily adopted in clinical practice? Analogues are newer versions of insulin and may have the appeal of novelty. In addition, the manufacturers of insulin orchestrated a series of postmarketing studies of insulin analogues; some believe that the goal of these studies was simply to encourage physicians to prescribe the newer drug.[11,12] Many of these postmarketing "seeding" trials were conducted in low- and middle-income countries. Many of the studies did not ask a clear scientific question and did not have a comparator group. The marketing efforts were clearly successful; the substantial increase in the use of insulin analogues in high-income countries has been mirrored, although delayed, in middle-income countries.[13]

There have been some efforts to reverse these trends. One strategy to reduce expenditures for insulin is to switch patients from insulin analogues to human insulin. This is precisely what Luo and colleagues examined in their study published in this issue of *JAMA*.[14] Starting in February 2015, a health plan initiated an intervention in 4 states to incentivize a shift from insulin analogue to human insulin use among patients with diabetes (93.1% had type 2 diabetes). The program was led by pharmacists, supported by clinicians, and based on a protocol that involved switching patients from basal and/or prandial insulin analogues to premixed human 70/30 or NPH insulin. The financial incentives accompanying this program included moving insulin analogues to a tier with a $37.50 co-pay while leaving human insulin in a tier with no co-pay. Over the 3-year study period, 14 635 health plan members filled 221 886 insulin prescriptions. Following implementation of the program, human insulin use increased from 11% at baseline to 70% by the end of 2016, whereas the use of insulin analogues declined from 89% to 30%.

The investigators used an interrupted time series design to examine changes in glycemic control and rates of serious hypoglycemia and hyperglycemia before, during, and after the intervention. Hemoglobin A_{1c} levels did increase slightly (0.14%), but this level of change is not typically considered clinically meaningful. Rates of serious hypoglycemic and hyperglycemic events were low and did not change significantly over time. However, overall expenditures for insulin decreased by more than 50%, from approximately $3.4 million per month in December 2014 to $1.4 million per month in December 2016. Even though expenditures for human insulin increased during the same period (from more than $200 000 to approximately $900 000 monthly), this was offset by a large decrease in expenditures for insulin analogues (from approximately $3.2 million monthly to $500 000 monthly). The proportion of patients who reached the Medicare Part D coverage gap also decreased, from 109 of 526 patients (20.6%) in 2014 to 143 of

1289 patients (11.1%) in 2016. If this program was widely implemented, the potential financial savings for patients and insurers could be quite substantial.

The ecologic nature of the study by Luo et al comes with some limitations. First, the interventions were not randomized. Patients who switched to human insulin differed from those who continued to use insulin analogues, and these differences could be related to the outcomes of glycemic control or acute complications. The authors conducted a post hoc propensity matched analysis to address this issue and found no differences in either glycemic control or acute complication outcomes, although the CIs were wide because of low numbers of events. Second, similar to other observational studies using administrative claims data, the authors could not account for severe hypoglycemia that was managed outside of the health care system. Third, the intervention occurred at a time when health systems were switching from the *International Classification of Diseases, Ninth Revision, Clinical Modification* to the *International Classification of Diseases, Tenth Revision, Clinical Modification* coding. Changes in diagnostic codes for the hypoglycemia or hyperglycemia outcomes could contribute to apparent shifts in documentation of acute complication rates over time. Fourth, the levels of hemoglobin A_{1c} in the population were quite high at baseline (mean, 8.5%). Simplification of the treatment regimen (from multiple injections a day to a maximum of 2) and improved adherence, rather than the switch from analogue to human insulin, could have affected both glycemic control and acute complication rates.[15]

Some patients may not do as well with a switch to human insulin products. Patients with type 1 diabetes or risk factors for severe hypoglycemia may benefit from insulin that minimizes hypoglycemia risk,[16] including hypoglycemia occurring at night. The study by Luo et al included a small number of patients with type 1 diabetes, precluding subgroup analyses. For patients who require consistent prandial coverage, such as all patients with type 1 diabetes or with absolute insulin deficiency, insulin analogues afford the convenience and flexibility of administration directly before meals. In addition, the least expensive human insulin products do not come packaged as pens and may be more difficult to administer, especially for patients with compromised vision or dexterity. This study was not designed to investigate these potential advantages of insulin analogues. Any program designed to promote switching to human insulin should take individual patient needs into account and allow for flexibility with respect to the choice of insulin.

In the study by Luo et al, patients with diabetes used less expensive insulin with minimum compromise in glycemic control over the short term and without a significant increase in health care use due to hypoglycemic or hyperglycemic events. These findings should prompt physicians and patients to reconsider which type of insulin is best. Human insulin may not be the optimal choice for everyone, but it could be a solution for many patients with diabetes. On the individual patient level, use of human insulin may minimize out-of-pocket spending, and, on the health care system level, it may allow insurers to maximize the value of diabetes care.

ARTICLE INFORMATION

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