Lessons From Peglispro: IMAGINE How to Improve Drug Development and Affordability

Matthew C. Riddle

Diabetes Care 2016;39:499–501 | DOI: 10.2337/dc15-2754

> Imagination is more important than knowledge.
>
> —Albert Einstein, 1931

On 4 December 2015, Eli Lilly announced it was ceasing development of its basal insulin peglispro, a new long-acting insulin analog (1). This was not entirely unexpected, given that in February 2015 Lilly announced a delay in submitting this product for regulatory review due to signs of liver injury apparently related to fat accumulation (2). The company presumably made this difficult decision because peglispro's prospects for regulatory approval and commercial success were dimmed by potential hepatic toxicity in the context of a market already including several other basal insulins, among them Lilly's biosimilar version of insulin glargine. Still, the story behind this costly, late-stage failure of a new product offers several messages for the diabetes community.

Part of this story concerns an unusual property of peglispro. The active component is insulin lispro, an analog of human insulin, which is linked to a large hydrophilic polyethylene glycol polymer (3). Due to its structure, peglispro is slowly absorbed after injection and also slowly cleared from circulation. Early studies—including a clinical development program named IMAGINE—showed that peglispro has a long and stable profile of action (4) and causes less hypoglycemia than insulin glargine (5). Moreover—and herein lies its novelty—peglispro was as effective as regular human insulin (6) or glargine (7) in suppressing hepatic glucose production but had less effect on peripheral tissues. A possible explanation for its hepatic specificity is better access of the large peglispro molecule to liver tissue through windows (fenestrae) in portal vessels than to peripheral tissues. Thus, peglispro might control glucose through the reduction of hepatic glucose release with less risk of hypoglycemia caused by variable peripheral uptake by muscle and might favor weight loss rather than gain (8). Surely, the investigators working on peglispro were intrigued by these possibilities.

However, this assessment focused on the peripheral actions of basal insulin on muscle and did not fully consider the effects on fat metabolism (Fig. 1). Peripheral glucose uptake in muscle is less insulin sensitive than hepatic glucose production (9), but free fatty acid (FFA) release by adipose tissue is quite responsive to insulin, and FFA levels rise when peripheral insulin action declines. High FFA levels are associated with insulin resistance and are routinely seen in obesity and type 2 diabetes (10). Much of the effect of injected insulin on hepatic glucose production results from suppression of FFA (11,12). High FFA may promote fat deposition in the liver, which is strongly associated with insulin resistance and can lead to hepatic injury that is reflected even in early stages by elevation of serum alanine aminotransferase levels (13–15). Finally, high FFA levels are associated with cardiovascular risk markers (16) and cardiac arrhythmias (17), although causal relationships are not firmly established.

Given these pathophysiologic associations, it is (in retrospect) not surprising that treatment with peglispro led to findings that were of concern to regulatory reviewers. In the IMAGINE 5 study (5), 26 weeks of peglispro treatment for type 2 diabetes already requiring basal insulin caused relative increases of hepatic fat content (45%), alanine aminotransferase (36%), and plasma triglycerides (13%), while HDL decreased (5%). Glycemic control was better with peglispro (final HbA_{1c} 6.6 vs. 7.1%) and some measures of hypoglycemia were lower than with glargine. Other studies are generally consistent with these observations. Thus, peglispro nicely improves glycemic control while limiting the risk of hypoglycemia but causes worrisome alterations of lipid metabolism. Unfortunately, and despite an appealing rationale, this example of tissue specificity of insulin did not work out as expected.

The commercial dilemma posed by these findings is easy to understand. The glycemic benefits of peglispro are at least equal to those of the other new basal insulins, insulin degludec (Tresiba) and the 300 unit/mL formulation of insulin glargine (Toujeo). But for peglispro, degludec, and 300 unit/mL insulin glargine alike, the average reduction of hypoglycemia compared with 100 unit/mL insulin glargine is modest in

Division of Endocrinology, Diabetes & Clinical Nutrition, Oregon Health & Science University, Portland, OR

Corresponding author: Matthew C. Riddle, riddle@ohsu.edu.

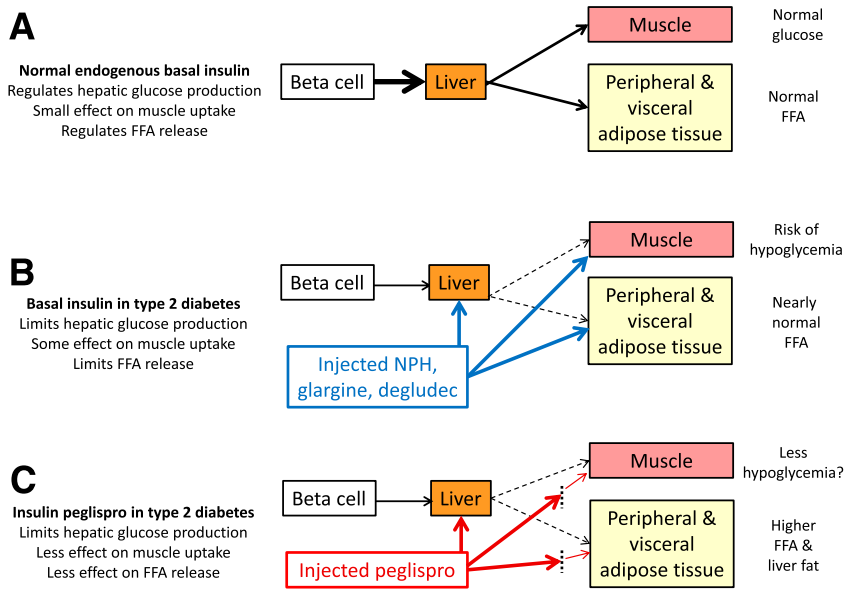

Figure 1—The figure summarizes the actions on liver and peripheral tissues resulting from basal insulin during normal endogenous insulin secretion (*A*); after subcutaneous injection of human NPH insulin, insulin glargine, or insulin degludec (*B*); or after subcutaneous injection of insulin peglispro (*C*). Insulin secreted by β-cells is partially cleared by the liver, resulting in lower concentrations in peripheral compared with portal circulation. Injection of most long-acting insulins for type 2 diabetes suppresses endogenous insulin secretion and leads to higher peripheral levels due to its lack of initial passage through the liver. Injection of insulin peglispro is fully effective in limiting hepatic glucose production at the liver but is hypothesized to have reduced transcapillary access and thus reduced action at both muscle and adipose tissues. Insulin peglispro appears to have adverse effects at the liver, possibly directly but more likely through failure to suppress lipolysis.

large populations of patients, and enthusiasm for clinical use will likely depend on finding subgroups of patients who derive the most benefit from the new products. In the context of competition from alternative new basal insulins, the safety signal with peglispro is significant and would require expensive further studies. Lilly probably made the right decision in canceling further development.

However, the experience with peglispro raises additional issues. One is the possibility of harnessing the tissue specificity of insulin action in other ways. For example, the actions of insulin in the central nervous system might be enhanced by an agent preferentially affecting this target. Weight loss observed during treatment with detemir might be related to such an effect, and other evidence suggests specific neurologic effects of this insulin (18). Other ways of modulating insulin's various effects might be possible, and we can hope for future research in this direction.

The peglispro experience is also relevant to the financing of drug development. Development of a new product may cost between $800 million and $2.6 billion, depending on how this expense is calculated (19,20). An obvious question arises: Might the same investment have been safer if devoted to developing a new member of a class of drugs already well tested? Imagining a breakthrough product with fine and unique properties may be better for science and medical care, but the knowledge that a "me-too drug" is unlikely to fail to attain regulatory approval is reassuring for business. There is visible evidence that such thinking affects the allocation of resources for product development. In the U.S., three sodium–glucose cotransporter 2 inhibitors, four dipeptidyl peptidase 4 inhibitors, and five glucagon-like peptide 1 receptor agonists are now approved for use, and additional drugs in each class are in development. Also, there is a steady stream of new fixed-dose combinations of established products, each aiming to extend commercial value without the cost of further research. Aside from combinations with other generic agents, metformin has been combined with canagliflozin, dapagliflozin, empagliflozin, alogliptin, linagliptin, saxagliptin, and sitagliptin. Fixed-dose combinations of on-patent injectable agents are also appearing. Do we really need all these similar and redundant products? Investment in new classes of agents might be better for the diabetes community but, with unknowable risks and a high cost of failure, commitment to novel therapies must be an alarming prospect for those who make such decisions.

There is also a dilemma faced by medical providers and patients. For years, by all appearances, drug development for the whole world has been disproportionately supported by high prices for branded pharmaceuticals in the U.S. We are now witnessing a tipping point at which expensive new drugs are no longer affordable, no matter what their incremental benefits may be. Insurers are erecting barriers to their dispensation, and consumers (that is, all of us) are bearing an increasing part of the cost through higher insurance premiums and co-pays. The gap in pricing between generic oral therapies for diabetes and new products has widened remarkably, and price competition does not seem to be limiting costs of the branded agents. At some large U.S. pharmacies, a month's supply of metformin, glipizide, or glimepiride costs $4 (price at Walmart, according to its website as of 24 November 2015). Information on prices of branded agents is difficult to obtain—another big problem. In many cases, discounted contracts with large health or pharmacy systems exist and the cost to consumers varies widely. But according to the website GoodRx.com, as of 24 November 2015, monthly direct retail costs to consumers for all the dipeptidyl peptidase 4 inhibitors are more than $330, and those for the sodium–glucose cotransporter 2 inhibitors are more than $370. A new drug would have to be very much better to justify, for routine use, an 80-fold or 90-fold pricing premium over a sulfonylurea as a second agent after metformin. The price differential between older and newer insulins is smaller but still substantial. From the same sources as above, quoted prices are $25 for 1,000 units of NPH human insulin versus more than $250 for the currently available longer-acting insulin analogs. At 10% of the cost of insulin analogs, human insulin is cost-effective and some people

are going back to it despite its inferior pharmacokinetics.

To summarize, the conception, development, and ultimate demise of insulin peglispro offer important lessons for the diabetes community. In this case, a drug development program based on a novel concept did not yield the desired result. In its failure, we find links to financial dilemmas for pharmaceutical companies, insurers, medical providers, and people with diabetes. How to resolve these issues is not clear, but it is obvious that we have a crisis in funding new research and also in delivering the best possible health care to people with diabetes and that these problems are not unrelated. The financial risk of drug development must be matched by suitable reward, but the cost of new agents now surpasses the means of many consumers. Discovery of novel therapies should be encouraged, but the resources to support it should not come only from those struggling with management of their diabetes and not in just one country. A conversation between all the stakeholders in the diabetes community is needed to address the problem. Let us imagine the possibilities.

Funding. This work was supported in part by the Russell Standley and Rose Hastings Memorial Trusts for diabetes research.

Duality of Interest. M.C.R. has received research grant support through his institution from AstraZeneca, Eli Lilly, Novo Nordisk, and Sanofi; has received honoraria for consulting from AstraZeneca, Biodel, Elcelyx, Eli Lilly, GlaxoSmithKline, Sanofi, Theracos, and Valeritas; and has received honoraria for speaking at professional meetings from Sanofi. These dualities of interest have been reviewed and managed by Oregon Health & Science University. No other potential conflicts of interest relevant to this article were reported.

References

1. PRNewswire. Lilly ends basal insulin peglispro development program, 4 December 2015. Available from http://www.prnewswire.com/news-releases/lilly-ends-basal-insulin-peglispro-development-program-300188076.html. Accessed 24 November 2015
2. PRNewswire. Lilly announces update on regulatory submission timing for basal insulin peglispro, 23 February 2015. Available from http://www.prnewswire.com/news-releases/lilly-announces-update-on-regulatory-submission-timing-for-basal-insulin-peglispro-30003944.html. Accessed 24 November 2015
3. Caparrotta TM, Evans M. PEGylated insulin lispro, (LY2605541)—a new basal insulin analogue. Diabetes Obes Metab 2014;16:388–395
4. Sinha VP, Howey DC, Choi SL, Mace KF, Heise T. Steady-state pharmacokinetics and glucodynamics of the novel, long-acting basal insulin LY2605541 dosed once-daily in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2014;16:344–350
5. Buse JB, Rodbard HW, Trescoli Serrano C, et al.; IMAGINE 5 Investigators. Randomized clinical trial comparing basal insulin peglispro and insulin glargine in patients with type 2 diabetes previously treated with basal insulin: IMAGINE 5. Diabetes Care 2016;39:92–100
6. Moore MC, Smith MS, Sinha VP, et al. Novel PEGylated basal insulin LY2605541 has a preferential hepatic effect on glucose metabolism. Diabetes 2014;63:494–504
7. Henry RR, Mudaliar S, Ciaraldi TP, et al. Basal insulin peglispro demonstrates preferential hepatic versus peripheral action relative to insulin glargine in healthy subjects. Diabetes Care 2014;37:2609–2615
8. Herring R, Jones RH, Russell-Jones DL. Hepatoselectivity and the evolution of insulin. Diabetes Obes Metab 2014;16:1–8
9. Rizza RA, Mandarino LJ, Gerich JE. Dose-response characteristics for effects of insulin on production and utilization of glucose in man. Am J Physiol 1981;240:E630–E639
10. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and β-cell dysfunction. Eur J Clin Invest 2002;32 (Suppl. 3):14–23
11. Rebrin K, Steil GM, Getty L, Bergman RN. Free fatty acid as a link in the regulation of hepatic glucose output by peripheral insulin. Diabetes 1995;44:1038–1045
12. Lewis GF, Zinman B, Groenewoud Y, Vranic M, Giacca A. Hepatic glucose production is regulated both by direct hepatic and extrahepatic effects of insulin in humans. Diabetes 1996;45: 454–462
13. Kotronen A, Yki-Järvinen H. Fatty liver: a novel component of the metabolic syndrome. Arterioscler Thromb Vasc Biol 2008;28:27–38
14. Cusi K. Nonalcoholic fatty liver disease in type 2 diabetes mellitus. Curr Opin Endocrinol Diabetes Obes 2009;16:141–149
15. Kotronen A, Seppälä-Lindroos A, Bergholm R, Yki-Järvinen H. Tissue specificity of insulin resistance in humans: fat in the liver rather than muscle is associated with features of the metabolic syndrome. Diabetologia 2008;51: 130–138
16. Mathew M, Tay E, Cusi K. Elevated plasma free fatty acids increase cardiovascular risk by inducing plasma biomarkers of endothelial activation, myeloperoxidase and PAI-1 in healthy humans. Cardiovasc Diabetol 2010;9:9
17. Oliver MF. Prevention of ventricular fibrillation during acute myocardial ischemia: control of free fatty acids. J Cardiovasc Pharmacol Ther 2001;6:213–217
18. Rossetti P, Porcellati F, Ricci NB, et al. Different brain responses to hypoglycemia induced by equipotent doses of the long-acting insulin analog detemir and human regular insulin in humans. Diabetes 2008;57:746–756
19. Avorn J. The $2.6 billion pill–methodologic and policy considerations. N Engl J Med 2015; 372:1877–1879
20. DiMasi JA, Grabowski HG, Hansen RW. The cost of drug development. N Engl J Med 2015; 372:1972