



Weekly Insulin Becoming a Reality

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Insulin was first isolated in 1921 and developed as a therapeutic agent in the 1920s. The initial crude preparations were injected multiple times daily because of their short duration of action. Consequently, there were many attempts to develop insulin preparations with prolonged biological availability in the hope that less frequent once-daily administration would be feasible (1). A host of such preparations were introduced, including protamine insulin, protamine zinc insulin, surfen insulin, globin insulin, iso-insulin, isophane insulin (NPH), and insulin zinc suspensions (lente insulins) (1) (Fig. 1). The goal was mainly to reduce the number of injections and thus the patient burden. Yet, with the development of a radioimmunoassay for insulin (2), it became apparent that physiologic insulin secretion involved two components: meal-related insulin secretion with postprandial spikes and basal insulin secretion that remains relatively constant with some minor pulsatility (3). Subsequently, as modern insulin therapy evolved, facilitated by patient self-monitoring of blood glucose (4,5), it became apparent that the inherent peaks in basal insulin preparations, such as with the nonsoluble NPH or lente insulins, created risk of hypoglycemia, especially if the insulin vials were not correctly rolled to create a proper suspension. Moreover, these insulins did not have sufficiently long duration of action to be used once daily. Consequently, in addition to making

them soluble, two of the goals in development of basal insulin analogs, such as insulin glargine and insulin detemir, were to eliminate insulin peaks and to prolong the action to approach 24 h (6,7). Second-generation basal insulin analogs, such as insulin degludec and insulin glargine U300, came with further improvements by having flatter insulin profiles and sustained action beyond 24 h (8,9).

Buoyed by the successful use of once-weekly glucagon-like peptide 1 receptor agonists (GLP-1 RA) for the treatment of type 2 diabetes, manufacturers have begun to develop once-weekly insulin preparations (10,11). A report on the initial clinical trial of one such preparation, insulin icodec, appeared last year (12). In that study of patients with type 2 diabetes naive to insulin therapy, insulin icodec once weekly was compared with insulin glargine once daily in a double-dummy placebo-controlled treat-to-target study. Despite the use of a rigorous titration algorithm (weekly dose increments of 28 units/week) and aggressive fasting glucose target of 70–108 mg/dL (3.9–6.0 mmol/L), the insulins did not differ in robust reduction of A1C or in frequency of significant or severe hypoglycemia (12).

Two reports in this issue of *Diabetes Care* (13,14) further expand on the clinical potential of insulin icodec. In one, patients with type 2 diabetes inadequately controlled on basal insulin are switched to either insulin icodec or to

insulin glargine (13). In this study, two approaches to initiation of insulin icodec were evaluated, one of which involved a loading dose in which double the initial dose was used, given the consideration that it would otherwise take longer to achieve steady-state insulin levels. It turned out that the primary outcome measure, time in range (TIR) of 70–180 mg/dL (3.9–10.0 mmol/L) during weeks 15 and 16 as assessed by continuous glucose monitoring, was statistically significantly better with the loading dose versus insulin glargine and numerically better than when a loading dose was not used. Hypoglycemia rates were comparable versus the insulin glargine U100 and were not affected by the initial loading dose.

In the second report, also involving insulin-naive patients with type 2 diabetes, three different titration strategies for insulin icodec were compared, along with an insulin glargine group (14). The insulin glargine group and two of the insulin icodec groups had a fasting glucose target of 80–130 mg/dL (4.4–7.2 mmol/L), one using weekly dose increments of 28 units/week (equivalent to the 4 units/day in the glargine group), while the other used a smaller dose increment of 21 units/week. The third insulin icodec group used both the aggressive fasting glucose target of 70–108 mg/dL (3.9–6.0 mmol/L) and the larger dose increment of 28 units/week. Again, the primary outcome measure was TIR 70–180 mg/dL (3.9–10.0

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See accompanying articles, pp. 1586 and 1595.

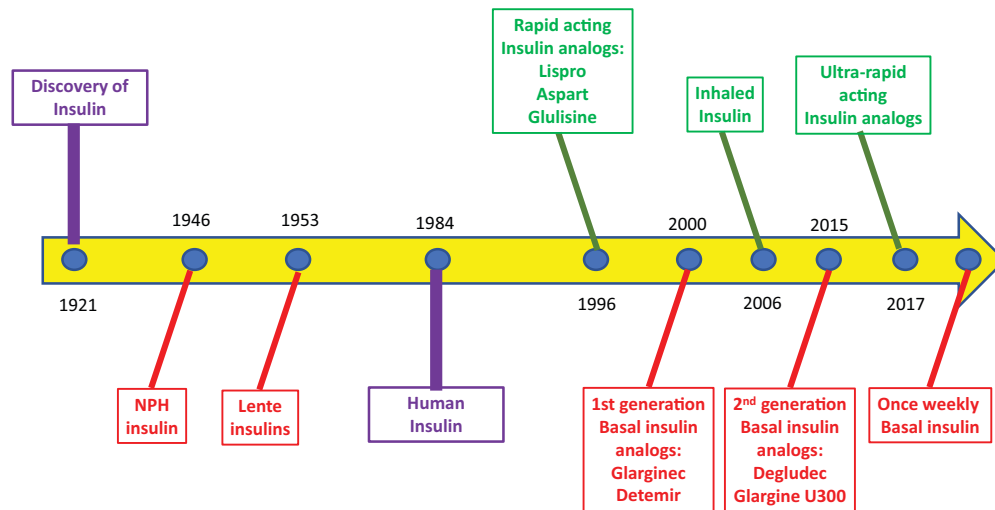


Figure 1—Timeline of major clinical developments in insulin’s evolution. Green highlights meal-related insulin developments; red highlights basal insulin developments; and purple highlights discovery of insulin and development of human insulins.

mmol/L) during weeks 15 and 16 as assessed by continuous glucose monitoring. There was marked improvement in TIR, with more hypoglycemia in the group with the aggressive glucose target. Although the authors concluded that the regimen with the smaller weekly increments displayed the “best balance” between glycemic control and risk of hypoglycemia, this commentator feels that the main difference was more hypoglycemia with the more aggressive glucose target (70–108 mg/dL) and that either titration approach was reasonable with the 80–130 mg/dL target. There was no severe hypoglycemia in the study at all, and time below range during weeks 15 and 16 was minimal.

These studies extend our understanding of how a once-weekly insulin can be used safely. The major concerns expressed by earlier commentators about the initial icodex study were the aggressive targets and the rigorous titration strategy (15,16). Lingvay et al. (14) have resolved the target concern in their study by relaxing the fasting glucose target higher than the glucose target used for the development of insulins degludec and glargine U300. One should appreciate that healthy individuals have basal insulin constantly circulating and that a once-weekly insulin with a flat action profile theoretically should not result in significant hypoglycemia by itself. Hypoglycemia might occur with sporadic exercise or with skipped meals

but in general should not be a major issue. Nonetheless, further studies are needed where these issues (e.g., exercise) are evaluated.

Weekly insulin has the potential to be transformational in our management of diabetes. This is most likely to be the case in type 2 diabetes, as it would dramatically reduce the burden of daily insulin injections and likely increase adherence and persistence with therapy, just as weekly GLP-1 RA therapy has done (17). Moreover, it has been shown that combination therapy of basal insulin with a GLP-1 RA—both iDegLira and iGlarLixi—improves glycemic control while limiting side effects of each of the components (18,19). Consequently, one can imagine that weekly insulin could be combined with a weekly GLP-1 RA to create a product that would be simpler to use and have the patient benefit of only a single once-weekly injection.

Weekly insulin is likely also to be attractive to patients with type 1 diabetes, although this requires further studies. Conceivably, once-weekly basal insulin would allow patients with type 1 diabetes to only concern themselves with prandial insulin whenever they eat, thus giving complete flexibility in meal timing, number of meals per day, and meal content.

The authors should be commended for choosing TIR for their primary outcome, which is quite novel. Indeed, another learning from the current studies is that TIR is a useful and desirable

outcome measure that should be used for clinical trials. TIR has been championed as an important assessment for management of patients (20) and is included in current Standards of Care (21). It also has been an important measure for regulatory agencies in the evaluation and approval of automated insulin delivery systems (22,23), yet it has not been used by regulators for the evaluation of drugs. It is time for that view to change, as these studies indicate.

Weekly insulin likely will change the landscape of diabetes management and is an important therapeutic advance. Indeed, as Jacques Mirouze wrote, insulin is “a non-stop revolution” (24).

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