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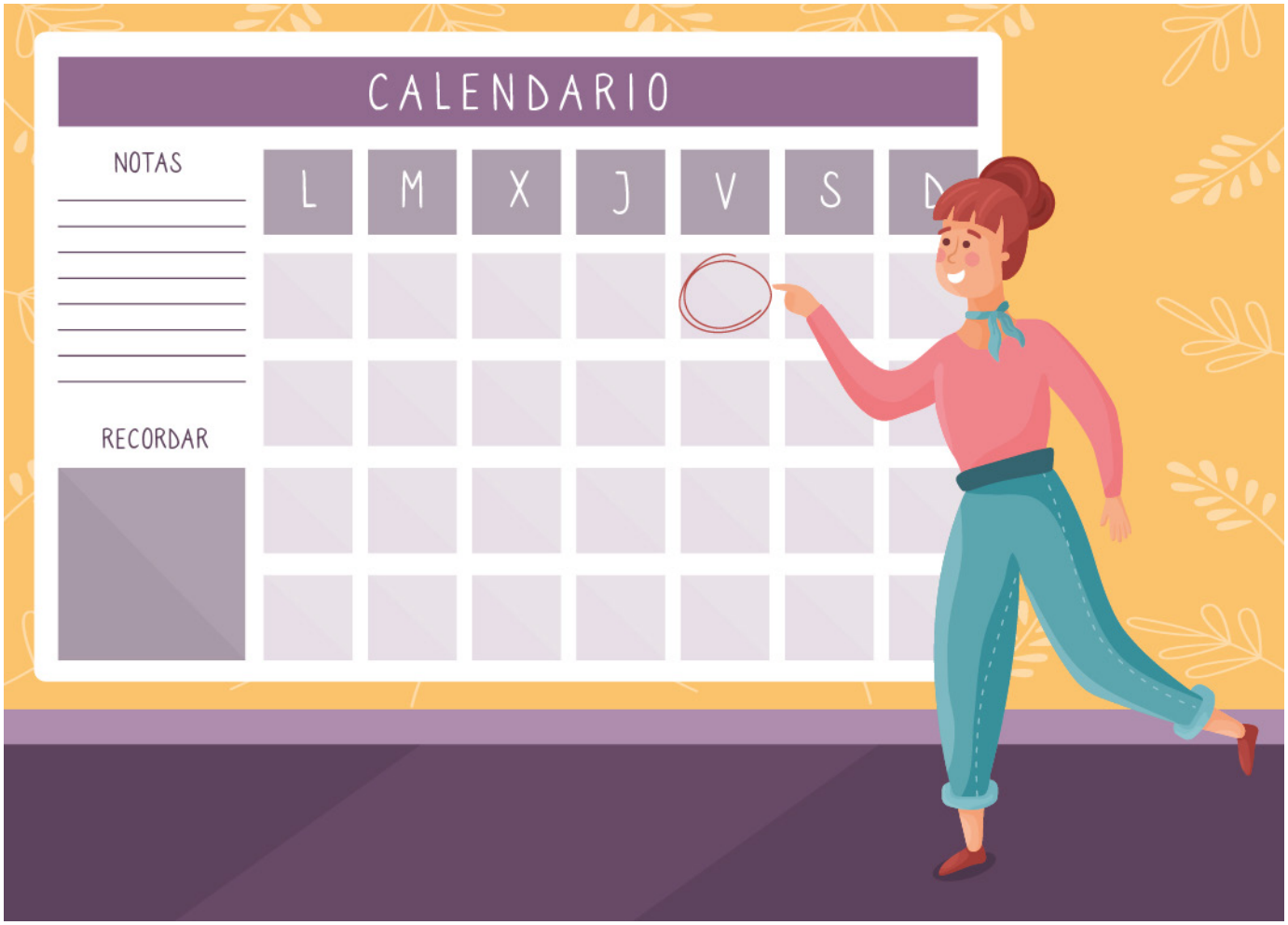

Seminal Insulin for People with Type 2 Diabetes:

A Major Breakthrough

Recently, in 2021, we celebrated the first century of insulin's history. In 1921, researchers in Toronto, Frederick Banting and Charles Best, successfully extracted insulin from a dog pancreas and analyzed its effects, bringing hope for the first time in history to people with diabetes (1).

Since then, changes to the insulin molecule have been made to improve its pharmacokinetics, resulting in the synthesis of insulin analogs that better replicate the physiological action of human insulin. These changes aim for longer action duration, reduced variability, greater predictability, and fewer nocturnal hypoglycemic events (2) *(Figure 1)*.

In pursuit of simplifying and improving treatment efficacy, new weekly or ultra-long-acting insulins are being developed. Currently, their indication is limited to patients with type 2 diabetes mellitus, with the expectation that they may later be used for type 1 diabetes mellitus, depending on the results of future studies.

In 2020, pivotal studies on a weekly insulin called Icodec were presented through the ONWARDS program. This is the first ultra-long-acting basal insulin analog, achieving greater molecular stability, reduced enzymatic degradation, and lower receptor-mediated clearance. These characteristics result in Icodec having a half-life of approximately 196 hours, allowing for once-weekly administration.

Another weekly insulin, albeit in earlier research phases, is Efsitora Alfa, a basal insulin with a half-life of about 17 days and hypoglycemic effects lasting up to 10 days. It has demonstrated reductions in glycated hemoglobin (HbA1c) and a safety profile comparable to that of daily insulin. Positive phase 3 clinical trial results (QWINT-2 and QWINT-4) have been announced, evaluating weekly Efsitora in adults with type 2 diabetes, including those starting insulin for the first time or requiring multiple daily insulin injections. In "treat-to-target" clinical trials (a strategy involving specific therapeutic goals and adjusting treatment based on results), Efsitora demonstrated non-inferiority in HbA1c reduction compared to the most commonly used daily basal insulins globally.

As we know, insulin treatment is not straightforward, with barriers faced by both patients and healthcare providers. Below, we discuss these barriers and consider whether weekly insulins might help overcome some of them, thereby improving treatment outcomes.

Barriers from the patient's perspective include:

1. Feelings of stigma.
2. Perception of insulin as the final stage of the disease.
3. Sense of failure.
4. Loss of independence.
5. Difficulty managing the disease.
6. Fear of hypoglycemia and weight gain.
7. Complexity of the treatment.
8. Increased responsibility for decision-making by patients and caregivers.

Barriers from the health care provider's perspective include: »

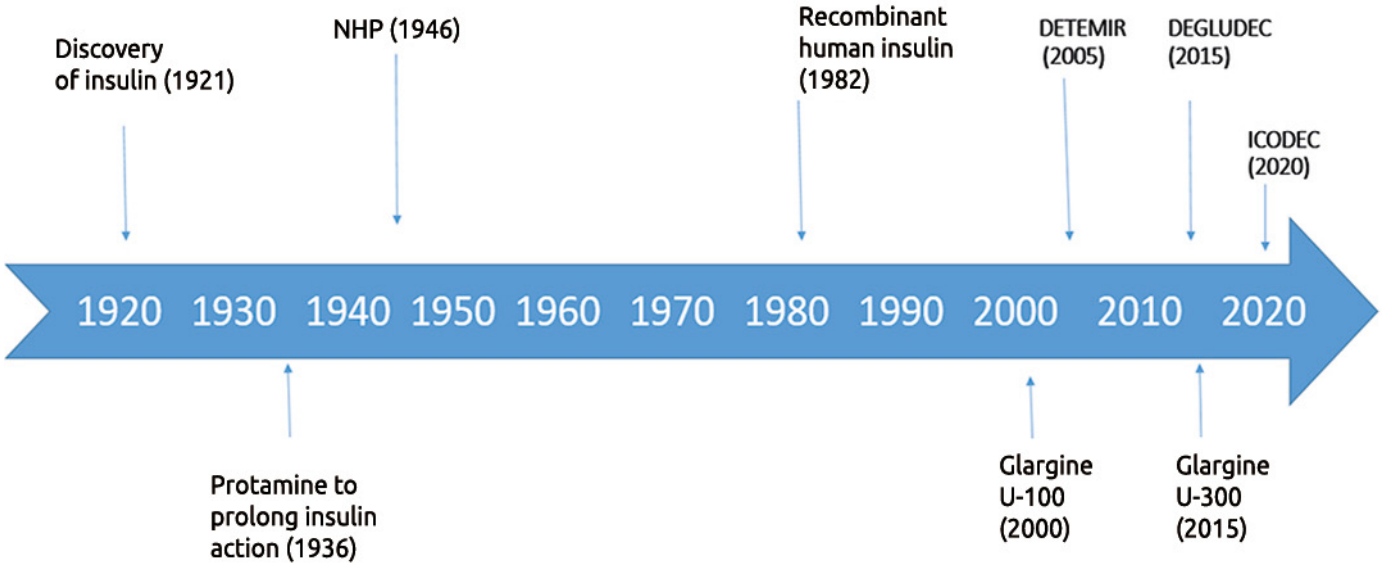

FIGURE 1

1. Lack of experience, knowledge, training, skills, or confidence.
2. Insufficient patient education and support.
3. Complexity of therapeutic regimens and titration.
4. Limited time in daily practice.
5. Pressure from patients or caregivers to delay insulin initiation.

These challenges contribute **to a reported one-third (33.2%) of patients omitting or failing to adhere to insulin treatment for at least one day in the past month, with a mean 3.3 days**. Additionally, three-quarters (72.5%) of physicians reported that their patients did not use insulin as prescribed (3).

Weekly treatment administration is not new, as we already have experience in other therapeutic areas. Weekly medications are associated with positive attributes compared to daily administration, such as:

1. Greater treatment satisfaction.
2. Improved adherence. Studies across medical disciplines show that simplifying therapeutic regimens enhances compliance, goal achievement, and quality of life.
3. Improved perception of quality of life.
4. Significant reduction in the feeling of being "under treatment."
5. Easier care and monitoring of treatment.

Despite these anticipated benefits, these

» new weekly insulins will need to address key questions:

1. Does it reduce blood glucose levels as expected for basal insulin?
2. Does it increase the risk of hypoglycemia? What is the duration of hypoglycemia induced?
3. What happens with time in range? Or time below range?
4. What if an extra dose is administered?
5. How should it be initiated and titrated?

Let's begin.

Does it reduce blood glucose levels as expected for basal insulin?

Pivotal studies of the molecules mentioned at the beginning of this review show that in terms of effectiveness in diabetes control, icodec is not inferior to insulin glargine (4), and efsitora is not inferior to insulin degludec (5). The results uniformly favor weekly insulins.

In both the ONWARDS and QWINT programs, these insulins were compared with daily insulins in patients without prior insulin treatment and those already using insulin. These studies demonstrated a slightly greater reduction in HbA1c compared to daily basal insulin analogs (glargine U100 and degludec), except in patients on basal-bolus regimens, where no differences were observed.

Does it increase the risk of hypoglycemia? And its duration?

Studies show that icodec achieved excellent glycemic control similar to degludec, without significant concerns about hypoglycemia or other safety findings.

In the ONWARDS 2 and 4 studies, the duration of hypoglycemia was analyzed using the Dexcom G continuous glucose monitoring (CGM) device during weeks 0–4, 22–26, and 27–31. These studies revealed that the duration of hypoglycemia was similar to that induced by daily basal insulins (6). »

PATIENTS GO FROM INJECTING THEMSELVES 365 TIMES A YEAR TO ONLY 54 TIMES

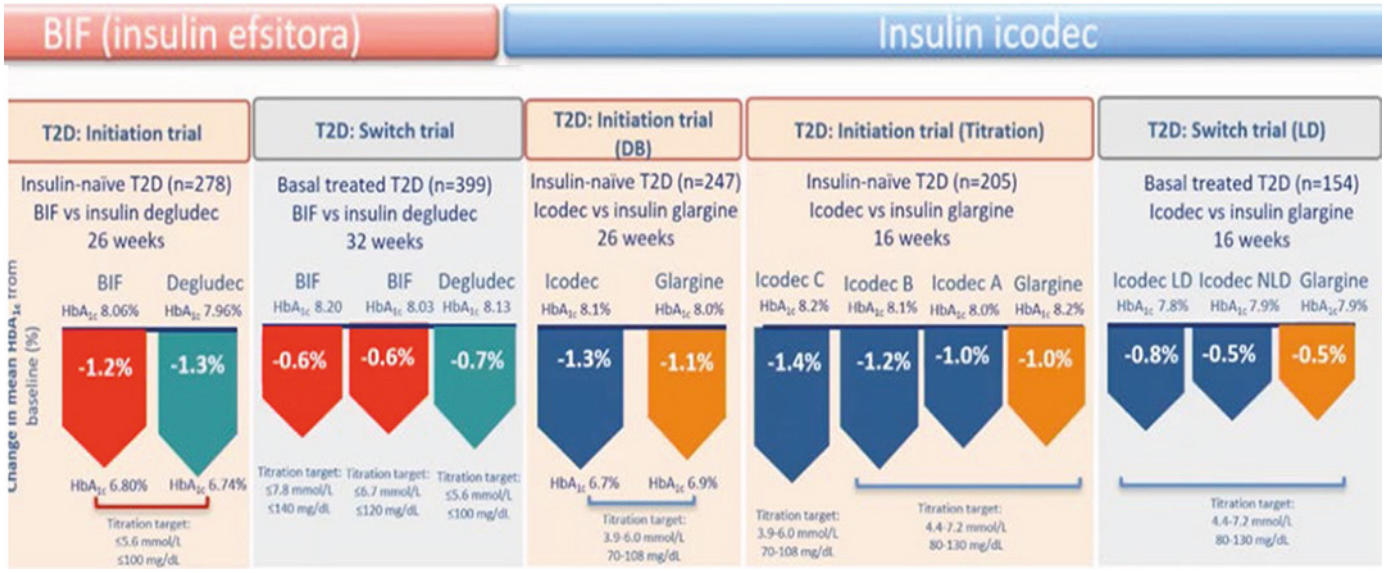

FIGURE 2. Comparison of weekly vs daily insulins. Adapted from (4) and (5).

FOR PATIENTS TRANSITIONING FROM DAILY BASAL INSULIN TO WEEKLY INSULIN, THE DOSAGE WILL BE CALCULATED BY INCREASING THE DAILY BASAL INSULIN DOSE THEY WERE PREVIOUSLY USING BY A FACTOR OF SEVEN

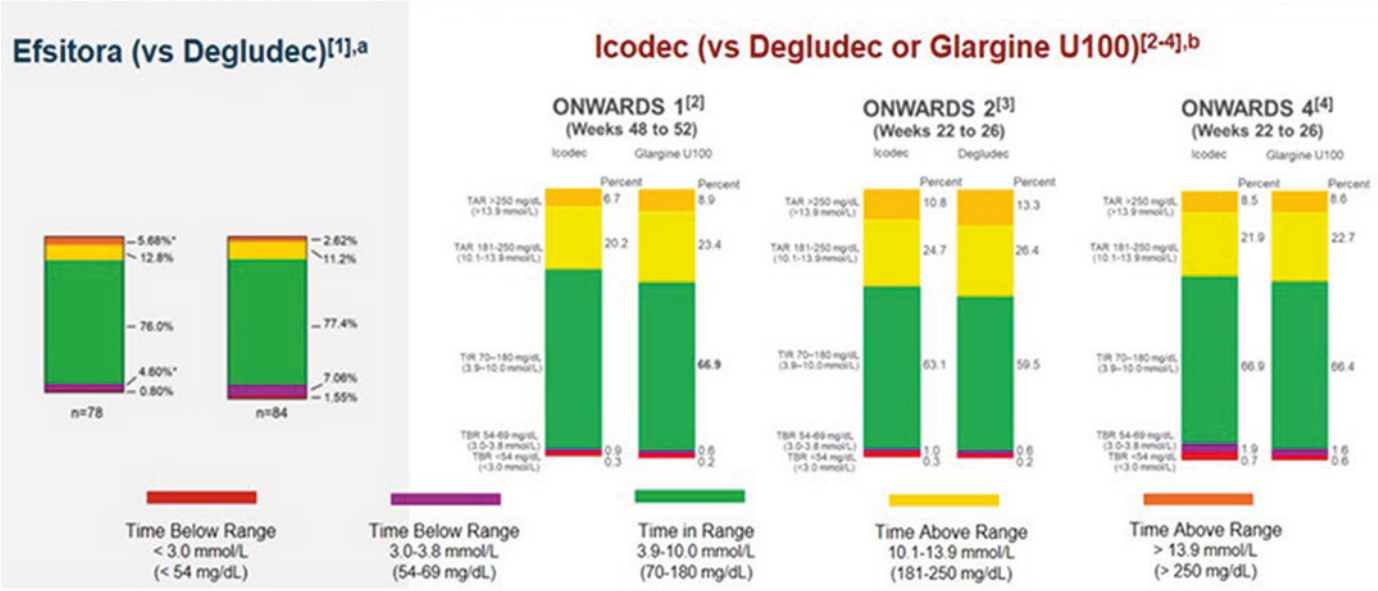

FIGURE 3

» Overall, a slight increase in hypoglycemia incidence was reported, but these episodes were mild and clinically insignificant. The duration of hypoglycemia was comparable (7).

Most hypoglycemic episodes were <70 mg/dL, with episodes < 54 mg/dL lasting < 15 minutes.

There were no substantial differences in the number of hypoglycemia episodes <54 mg/dL lasting more than 15 minutes (8, 9).

A meta-analysis[9] found a significantly higher incidence of level 1 hypoglycemia (mild) with icodec, but no significant differences in the incidence of level 2 (clinically significant) or level 3 (severe) hypoglycemia, or in combined levels 2/3. Despite this, it was concluded that there were no significant safety concerns regarding hypoglycemia or adverse events.

Similar results are being reported for efsitora.

What happens with time in range (TIR)? Or time below range (TBR)?

Studies evaluating TIR, TBR, and time above range (TAR) using CGM in individuals transitioning from daily basal insulin to weekly insulin show comparable values between the transition period (weeks 0–4) and weeks 22–26, with a slight improvement in TIR favoring weekly insulin[8] (Figure 3).

Patients spent less time out of range and experienced fewer nocturnal hypoglycemia episodes.

What happens if an extra dose is administered?

A double or triple dose of icodec administered once weekly does not lead to a higher risk of hypoglycemia compared to daily glargine. During hypoglycemia, a comparable symptomatic response and a moderately greater endocrine res- »

FOR THE FIRST INJECTION ONLY, THE DOSE WILL BE UP TITRATED BY 50% (DAILY BASAL DOSE MULTIPLIED BY 7, PLUS AN ADDITIONAL 50%). STARTING WEEK 2, THE DOSAGE WILL RETURN TO THE CALCULATED AMOUNT (DAILY BASAL DOSE MULTIPLIED BY SEVEN)

» ponse were observed with icodec vs glargine (10).

How to initiate and titrate?

Weekly insulin is administered subcutaneously on the same day each week at any time of the day. If needed, administration can be shifted by up to three days, provided there are at least four days between injections.

For patients naïve to insulin, treatment begins with 70 IU.

For patients transitioning from daily basal insulin to weekly insulin, the dose is calculated by multiplying the previous daily basal dose by seven.

For the first injection only, the dose is increased by 50% (daily basal dose × 7 + 50%), returning to the calculated dose (daily basal dose × 7) in the second week. This loading dose helps improve TIR by reducing transient glycemic control deterioration until steady state is achieved (4). D

CONCLUSIONS

In conclusion, these weekly basal insulins appear to be a significant innovation—a more user-friendly way to begin insulin therapy, improving the quality of life for individuals with type 2 diabetes mellitus. For health care professionals, these treatments are easy to use and train patients on, with high acceptance rates.

However, further exploration is needed into areas such as the impact of exercise, intercurrent illnesses, prolonged fasting, hospitalization, weight changes, pregnancy, switching between daily and weekly insulin, the psychological effects of administering large weekly insulin doses, and new dosing strategies distinct from those currently known. These and other aspects will be clarified in future studies and clinical practice.

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