Editorial

# Weekly Insulin Therapy : Where Do We Stand ?

Basal insulins are an essential part of diabetes therapy. In the last 20-25 years, significant advances have been made in this area resulting in the development of long-acting basal insulin analogues. These have prolonged and less variable action profiles, better efficacy, safety and reduced incidence of nocturnal hypoglycaemia. Despite these improvements, adherence to therapy remains much lower than desired, mainly due to concerns related to glycaemic variability, hypoglycaemia and the burden of daily injectable therapy.

**An ideal basal insulin** should simulate endogenous insulin profile as closely as possible. It should effectively and continuously control basal glucose production by mimicking the hepatic/peripheral insulin gradient seen with endogenous insulin. Thus, overin sulinization at periphery will be prevented, lowering the risk of hypoglycaemia. Moreover, it should be predictable with minimum day-to-day variability and should have a simple dosing schedule which will improve adherence to therapy. Unfortunately, the presently available daily basal insulins have their share of limitations. As they are injected into the subcutaneous spaces, the hepatic/peripheral insulin gradient seen with endogenous insulin is absent. This leads to under insulinization in the liver and Hepatic Glucose Production (HGP) is not effectively controlled. The other shortcoming is that once-daily basal insulins are affected by absorption differences between different subcutaneous sites, the physical state of insulin and the frequency of dosing. This leads to significant glycaemic variability.

**The once-weekly insulins** in the late stages of clinical development are expected to offer several advantages over and above the daily basal insulins currently in use. The stable and predictable Pharmaco-kinetic (PK) profile of a once-weekly basal insulin is expected to reduce treatment burden of daily injections and the other hassles of current insulin therapy. These ultra-long-acting insulins would provide more flexibility in the timing of the dosing and would overlook dosing errors or skipped doses once the insulins reach a steady state. Additionally, the flat PK profile of once-weekly insulins will lead to a steady basal insulin coverage over days, particularly during the night and will control HGP more efficiently. The need for bolus therapy is also likely to reduce. The flatter PK profile of once-weekly insulins is expected to result in a decrease in day-to-day glycaemic variability, thereby reducing the burden of unpredictability with insulin therapy, particularly the fear of hypoglycaemia.

**Insulin Icodec (Novo Nordisk) and Insulin Efsitora Alfa (Eli Lily and Company)** are two such insulins designed for once weekly administration and have the potential to further basal insulin replacement. Icodec is an acylated insulin analogue with three amino acid changes to enhance stability and reduce Insulin Receptor (IR) binding. A C20 icosane diacid is added with a spacer which leads to strong and reversible Human Serum Albumin (HSA) binding to prolong plasma half-life. Icodec absorption from subcutaneous tissue is delayed by hexameric dissociation and binding of monomers to HSA. Efsitora is an IR agonist which is composed of a novel single chain variant of insulin fused to a human IgG2Fc domain. The absorption shifts from subcutaneous site to the lymphatic system. There are amino acid changes to reduce IR affinity and reduce post receptor clearance. Once injected, circulating Efsitora binds to FcRn within the endothelial cells. There it is protected from degradation and recycled back to the cell surface creating a reservoir of insulin. The recycling system is controlled by pH switching.

**The mode of action** of these two once-weekly basal insulins is almost alike, using similar strategies to extend basal activity. They create a circulating reservoir of insulin from which active insulin is released in a sustained manner which then acts on IR. Both molecules have large hydro-dynamicsizes and have reduced IR affinity compared to native insulin. Thus, internalization and IR-mediated clearance is limited. These properties decrease transport across capillary endothelium, activity is limited and time-action profile is prolonged making once-weekly administration feasible. Apart from the difference in binding property of the two insulins the other differences lie in their half-lives, which are approximately 8 days for Icodec and approximately 17 days for Efsitora.

**Icodec and Efsitora phase 2 clinical trials,** as well as data from the phase 3 Icodec programme indicate thatonce-weekly insulins provide glycaemic control which is comparable to once-daily analogues, with a similar risk of hypoglycaemia. Studies were carried out in T2D patients, both insulin naïve and insulin treated. T2D patients with renal and hepatic impairment were included in the studies. T1D patients were also included in the studies.

**Several concerns** have naturally arisen related to the use of once-weekly insulins. Several major differences in dosing regimens between once-daily andonce-weekly insulins are anticipated. Firstly, since an entireweek's basal insulin dose will be administered at onetime, there will be the fear that the dose is too large and will be stressful both for the patient and health careprovider. Secondly, to shorten the time toreach a steady-state concentration, a one-time loading (or starting) dose may be indicated which is likely to be unique for each once-weekly basal insulin. The concept of a loading dose will be a cause of greater concern. Fortunately, data from 2 Icodecphase 3 studies on switch from once-daily basal insulin to Icodec showed that such switches did not worsen glycaemic control or lead to more hypoglycaemic episodes when a loading dose was administered.

**Risk of hypoglycaemia** remains one of the main concerns with once-weekly insulins. The duration of a hypoglycaemic episode and the chance of recurrence are the two vital areas we need to be clear about. Studies were conducted with double or triple doses of Icodec *versus* IGlarU100 in a crossover study on T2D patients. Since both the hypoglycaemia scores and counter regulatory responses were similar with Icodec and IGlarU100, it is likely that hypoglycaemia recognition and acute treatment would be similar. However, the risk of hypoglycaemia recurrence may be increased with once-weekly insulin and calls for intensive monitoring after a single episode of hypoglycaemia.

**Glycaemic monitoring** with once-weekly insulins is emerging as a grey area. Keeping in mind the long duration of action of once weekly insulins and with the increasin gavailability of Continuous Glucose Monitoring (CGM) technology, Time in Range (TIR) may be the appropriate parameter for monitoring the responseto therapy. A lack of concordance between reduction of Fasting Blood Glucose (FBG)and reduction of HbA1c has been shown in Icodec trials. These findings raise some important issues as to whether FBG is the ideal way to monitor response to therapy with weekly insulins and whether the FBG targets that are applicable for once-daily basal insulins would also be appropriate for weekly insulins. Perhaps,

the actual response to therapy will be better assessed with CGM since it would provide more details on glycaemic trends. Another approach that may be considered is the widening of the FBG targets beyond the treat-to-target goals of 80 to130 mg/dL and these could be used with once-weekly insulins, even in the absence of CGM.

**Use of once-weekly may be challenging** in specific scenarios. In long standing T1D there is not only the lack of endogenous insulin production, the counter regulatory responses are also inadequate. Then again, because of the slow onset of action, once-weekly insulins may not always be the best initial basal insulin in recently diagnosed TIDM. These insulins are not appropriate either, to initiate in patients hospitalized with acute illness, since they can take weeks to achieve glycaemic control. Basal insulin with amore rapid onset of action is preferred in these situations.

**Combination of once-weekly insulins with GLP1-RA** may simplify the treatment of T2D further and improve adherence. Guidelines recommend GLP1-RA as first- line agents because of their marked CV benefits beyond glycaemic control. Guidelines also recommend that if insulin is to be used, it combination with GLP-RAs is preferred for better efficacy and durability. Once-weekly basal insulins may be integrated with once weekly incretin therapies either as separate injections or as one combined fixed-dose preparation. One such fixed-dose combination of Icodec and Semaglutide (IcoSema), is currently in phase 3 studies.

**Looking forwards,** Icodec has completed an extensive phase 3 program (ONWARDS trials) and has applied for regulatory review. The first decisions are expected in 2024. Efsitora has commenced phase 3 trials (QWINT trials). Both the trials are designed for once-weekly use with an initial one-time loading dose. However, education about the new dosing regimens for once weekly insulins, will be needed for their safe and effective use.These would include the need for an initial one-time loading dose, the need for transition from once-daily to once weekly insulins, management for missed doses or dosing errors and management during hospitalizations, surgery and exercise.

**To conclude,** data available so far indicate that both the insulins are as efficacious as once-daily insulins. Overall frequency of hypoglycaemia is low and major hypoglycaemic events are not significantly different from once-daily basalinsulins in people with T2D. In people with T1D, however, thereis reason for caution until additional data is available. We are still in the learning curve and further data along with longer evaluation in clinical practice will be informative. However, these insulins do offer endless possibilities and have the potential to become “game changers” in the management of diabetes. We eagerly look forward to improved acceptance, adherence and persistence on insulin therapy because of several advantages including the significant reduction in injection burden. Overall, these molecules are empowered to bring about a sea change in basal insulin therapy.

## Further Readings


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