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EDITORIAL

Once-Weekly Insulin: A Breakthrough in Diabetes Management or an Unresolved Challenge?

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Abstract

The advent of once-weekly insulin icodec is a promising development in the care of individuals with diabetes. These once-weekly formulations aimed to improve patient adherence and quality of life for patients who find daily injection administration challenging. Insulin icodec has demonstrated comparable glycemic control to conventionally used daily basal insulins, such as insulin glargine and degludec, in the ONWARDS clinical trials. This approach is aligned with patient-centred guidelines, offers better convenience, and can potentially improve adherence, particularly among older adults with type 2 diabetes and those experiencing distress related to frequent injection administration. However, several challenges persist before widespread adoption is feasible. One main concern is ensuring consistent insulin levels over a full week as fluctuations can lead to an increased risk of hypo- or hyperglycemia. Education, precise dosing, and further research are required to ensure long-term efficacy and safety. Moreover, logistical hurdles, including production costs and supply chain complexities need to be addressed especially in low-resource settings. Future studies should evaluate the broader health impacts of weekly insulin, including cardiovascular outcomes, quality of life, and personalized dosing strategies. Making weekly insulin safe, affordable, and widely available is important to fully realize its potential in diabetes management.

Key words: insulin; diabetes

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Introduction

The treatment of diabetes has undergone substantial changes in recent decades, with major advancements in pharmacotherapy, technology, and individualized care strategies. Yet one challenge has persisted: providing the best possible adherence to insulin therapy among patients (Doggrell and Chan, 2015). Multiple types of insulin are available with daily insulin injections being most widely used among diabetes patients. However, daily injections can be a significant deterrent to long-term adherence leading frequently to suboptimal glycemic control (Schaper et al, 2017). The introduction of weekly insulin formulations represents a potential breakthrough in diabetes care, which could deliver better compliance and patient satisfaction leading to better associated quality-of-life aspects.

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Once-weekly insulin development is oriented toward a strategy of decreasing injection frequency with strong glycemic control (Rosenstock et al, 2024). Basal insulin, such as insulin glargine and more recently insulin degludec, has revolutionized the management of diabetes by offering a long-lasting action over 24 to 48 hours. A once-weekly insulin regimen has been a long-standing goal, and recent developments suggest that we are closer than ever to achieving this. Once-weekly insulin injections are currently being considered primarily for patients with type 2 diabetes (T2D). This approach addresses the challenges of basal insulin therapy, which can be more cumbersome for these patients compared to those with type 1 diabetes, who typically rely on either insulin pumps or multiple daily injections. It is worth mentioning that the extended duration of once-weekly insulin is achieved by formulating an insulin analogue with a C20-fatty di-acid side chain that allows binding to albumin, along with specific amino acid substitutions that modify insulin receptor binding and reduce clearance. This structural modification enables subcutaneously injected insulin to remain effective for an extended period.

Insulin Icodec and Clinical Evidence

Insulin icodec, a once-weekly basal insulin that provides stable insulin release over seven days, was one such developmental highlight. In recent clinical trials, insulin icodec-based therapy showed similar efficacy relative to daily basal insulin in terms of glycemic control (Mathieu et al, 2023). The pivotal Phase 3 ONWARDS clinical trials have been instrumental in establishing the efficacy and safety of insulin icodec (Shetty and Suvarna, 2024). In ONWARDS 2 and 3, the researchers directly compared insulin icodec with insulin glargine U100 in adults with T2D. At the end of 26 weeks, the study established non-inferiority of insulin icodec to insulin glargine U100 regarding haemoglobin A1c (HbA1c) level reductions (Lingvay et al, 2023; Philis-Tsimikas et al, 2023).

Additional studies are investigating the potential of combination therapies that combine insulin with glucagon-like peptide-1 receptor agonists (GLP-1RAs) to provide prolonged glucose control and induce weight reduction (Cariou, 2015). These combination therapies are especially important for patients living with T2D, who often struggle with both hyperglycemia and weight management. In early clinical studies, once-weekly basal insulin/GLP-1RA combinations have led to significant reductions in blood glucose levels while favourably impacting body weight and reducing cardiovascular risk factors (Anderson and Trujillo, 2016; Gourdy et al, 2023). This dual-action approach is seen as a significant innovation in diabetes management, reflecting the move toward personalized, multifaceted treatments.

Current American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines recommend daily basal insulins, like glargine and degludec, for patients with T2D (Davies et al, 2022). However, with once-weekly insulin therapies like insulin icodec showing efficacy comparable to daily insulin in clinical trials, guidelines may soon evolve. Both the ADA and EASD advocate a patient-centred approach to care, weighing in on factors such as patient preference, comorbidities, and risk of hypoglycemia by advocating indi-

vidualized therapy. Once-weekly insulin is perfectly aligned with these principles making the regimen easier to follow and potentially improving adherence, particularly for older adults and the ones burdened by diabetes-related distress.

Clinical Challenges and Considerations

Although a once-weekly insulin concept is appealing, there are still many hurdles that need to be addressed before it can be widely adopted in clinical practice. One of the main considerations is that these new formulations maintain a consistent pharmacokinetic and pharmacodynamic profile over the entire seven-day period (Pieber et al, 2024). Any fluctuation in insulin levels could lead to hyperglycemia or hypoglycemia, both of which are dangerous for patients with diabetes. While clinical trials have shown promising results, larger studies with longer follow-up periods are required to verify the permanence of these formulations over time and in a broader patient population.

Furthermore, there is a significant risk of hypoglycemia due to the slow onset and long half-life. While basal insulin allows for a relatively rapid adjustment if someone experiences hypoglycemia, once someone is on a weekly formulation this can become difficult. If a patient is overdosed, or if their insulin administration needs modification due to illness or changes in diet, the prolonged insulin effect may increase the risk of sustained hypoglycemia. This risk can be mitigated by observing strict titration criteria and optimizing patient education.

Furthermore, patient compliance and psychological determinants have to be taken into account. Indeed, reducing the frequency of injections should facilitate adherence; however, some patients might be uncomfortable switching to a once-weekly administration schedule due to concerns about the potency of the drug and the fear that missing a dose could result in prolonged periods of hyperglycemia. Hence, it will also be necessary to educate patients and healthcare providers about the newer formulations to ensure their successful uptake.

It also poses logistical challenges, namely on the manufacturing and supply chain side. The longer duration of action achieved with the combination will require changes in production that could affect cost and availability, as producing insulin that works for a solid seven days is more challenging than shorter-acting formulations. Moreover, further studies and innovations are needed to guarantee the stability of once-weekly insulin during transportation and storage, especially in regions with suboptimal cold chain systems.

Future Directions and Global Implications

The current studies on once-weekly insulin showed promising potential (Ahmed et al, 2024), but many areas still require further investigation to ensure long-term effectiveness, safety, and tolerability. Firstly, long-term clinical trials centred on patient-oriented outcomes, such as cardiovascular health, mortality, and quality of life are crucial. Although glycemic control is the primary endpoint in most current studies, diabetes is a systemic disease that involves multiple organ systems (Teck, 2022). Hence, it is important to understand how weekly insulin treatment might moderate these broader health outcomes.

Further research investigating the performance of once-weekly insulin in other patient populations and those with co-morbidities such as chronic kidney disease or heart failure is needed. These are populations with more complicated insulin needs and they might need different dosing strategies. Further investigations into the best combination therapy for once-weekly insulin are also required, particularly with other commonly used diabetes drugs such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Future research should explore the potential for personalized dosing algorithms for a patient's unique insulin sensitivity, lifestyle, and glycemic patterns. Advances in artificial intelligence and machine learning could enable real-time monitoring and insulin adjustments based on continuous glucose monitoring (CGM) data, making weekly insulin not only a convenient but also a precise option. Future work should ultimately be centred on the worldwide availability of once-weekly insulin. Diabetes therapy is expensive already and the introduction of new, perhaps more costly insulin formulations may further burden healthcare systems globally. Policymakers, the pharmaceutical industry, and healthcare providers should consider making affordable once-weekly insulin more available, especially in low- and middle-income countries where diabetes rates are rising most rapidly.

Conclusion

The development of once-weekly insulin represents a major advancement in diabetes care, offering improved glycemic control, adherence, and quality of life, especially for patients with type 2 diabetes. Clinical trials like ONWARDS have demonstrated its efficacy and safety, comparable to daily basal insulin regimens. However, challenges such as maintaining pharmacokinetic stability, managing hypoglycemia risks, ensuring patient education, and addressing logistical and cost-related barriers remain. Long-term studies, personalized dosing strategies, and global affordability efforts are crucial for its successful adoption.

Key Points

- Once-weekly insulin, such as insulin icodec, aims to improve patient adherence by reducing the frequency of injections, which is often a barrier to consistent diabetes management.
- Clinical trials, including the ONWARDS studies, have shown that insulin icodec achieves glycemic control comparable to daily basal insulins like insulin glargine.
- Maintaining stable insulin levels over a week is essential to avoid hypo- or hyperglycemia, necessitating further research and careful patient education.
- Manufacturing complexities, cost, and supply chain issues may limit accessibility, particularly in low- and middle-income countries.
- Long-term studies are needed to assess cardiovascular outcomes, quality of life, and personalized dosing algorithms to maximize the benefits of once-weekly insulin.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Author Contributions

RA designed the research study. MA and AS performed the research. AS and MA worked on writing the manuscript. RA and MA provided help and advice on the manuscript writing. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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