INTRODUCTION

Even with the emergence of numerous pharmacological therapies, insulin therapy has a pivotal role in diabetes treatment and many manipulations of the insulin molecule achieved over the recent years have resulted in newer advanced types, thus allowing for a more individualized therapy. Newer ones such as insulin analogs, including long-acting and rapid-acting insulins serve as promising alternative treatment options to human insulin. Such advancements in insulin formulations and innovations in insulin delivery methods have been able to reduce insulin-associated hypoglycemia, lower intraindividual pharmacokinetic (PK) and pharmacodynamic (PD) variability, and improve imitation of physiological insulin release.\(^1\) The current article outlines some of the newer insulins that are on the horizon.

NEWER INSULINS ON THE HORIZON (TABLE 1)

Longer-acting Version of Insulin Glargine (Glargine U300, Toujeo\(^*\))

Glargine U300 (Toujeo\(^*\), Sanofi), an ultralong-acting basal insulin analog, is a higher-strength formulation (300 units/mL) of the original insulin glargine U100 and has differential PK/PD profile than the latter. Upon subcutaneous injection, U300 forms subcutaneous depot with smaller surface area, creating a prolonged release that results in a flatter PK/PD profile than glargine U100.\(^2\) It offers PK/PD advantages compared with the glargine U100 and bestows effective glycemic control with less risk of hypoglycemia.\(^3\) Glargine U300 is intended especially for these patients and its concentrated formula helps to significantly lower the injection volume. The formulation is also highly useful for those type 1 diabetes (T1D) and type 2 diabetes (T2D) patients who are at high risk of hypoglycemia. Due to its prolonged action that allows once-daily dosing, the formulation will be useful for those who otherwise require twice-daily dosing.\(^6\)

Faster-acting Insulin Aspart (Fiasp\(^*\))

An ultrafast-acting insulin with a faster onset and faster offset of action was postulated to reduce postprandial hyperglycemia and frequency of hypoglycemia and ease the severe hypoglycemia anxiety, with more time spent in range. Faster aspart, "Fiasp" is a modified formulation of insulin aspart (1Asp). It is a mealtime insulin with a flexible dosing regimen. It can be administered soon before a meal or within 20 minutes from the start of the meal.\(^7\) Faster absorption of Fiasp compared to 1Asp is even more pronounced in those using continuous subcutaneous insulin infusion (CSII).
<table>
<thead>
<tr>
<th>Type of insulin</th>
<th>Name of Insulin formulation</th>
<th>Manufacturer</th>
<th>Product details/characteristics</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer-acting version of insulin glargine</td>
<td>Glargine U300, Toujeo*</td>
<td>Sanofi</td>
<td>Higher-strength formulation (300 units/mL) of insulin glargine U100; flatter pharmacokinetic/pharmacodynamic (PK/PD) profiles; prolonged duration of action (&gt; 24 h)</td>
<td>Received European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approval (<a href="https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206538Orig1s000TOC.cfm">https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206538Orig1s000TOC.cfm</a>)</td>
</tr>
<tr>
<td>Faster-acting insulin aspart</td>
<td>Fiasp*</td>
<td>Novo Nordisk</td>
<td>Newer and stable formulation of insulin aspart with faster initial absorption; flexible dosing regimen</td>
<td>Received EMA and the US FDA approval (<a href="https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208751Orig1s000TOC.cfm">https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208751Orig1s000TOC.cfm</a>)</td>
</tr>
<tr>
<td>Insulins or insulin combos with BioChaperone* (BC) technology</td>
<td>BC Lispro U100—ultra-rapid formulation of insulin lispro</td>
<td>Adocia</td>
<td>Accelerated insulin action profile</td>
<td>Now ready to enter Phase 3</td>
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<td></td>
<td>BC Lispro U200—the first concentrated ultra-rapid prandial insulin (under development)</td>
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<td>HinsBet U100—rapid insulin</td>
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<td></td>
<td>BC Combo—combination of the basal insulin glargine and the rapid insulin lispro</td>
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<tr>
<td>Once-weekly basal insulins</td>
<td>AB101</td>
<td>Rezolute</td>
<td>Sustained and near peakless insulin level</td>
<td>Under first-in-human Phase 1 study (<a href="https://www.rezolutebio.com/pipeline/overview">https://www.rezolutebio.com/pipeline/overview</a>)</td>
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</thead>
<tbody>
<tr>
<td>Liver-preferrerual mealtime insulin analog</td>
<td>LAI287 (NN1436)</td>
<td>Novo Nordisk</td>
<td>Once-weekly ultralong-acting basal insulin analog</td>
<td>Undergoing Phase 2 clinical trials in type 1 diabetes and type 2 diabetes (T2D) (<a href="https://clinicaltrials.gov/ct2/show/NCT03922750">https://clinicaltrials.gov/ct2/show/NCT03922750</a>)</td>
</tr>
</tbody>
</table>
Moreover, in CSII using T1D subjects, Fiasp was found to be noninferior when compared to IAasp in terms of pump compatibility. In both T1D and T2D subjects, clinical trials have shown superior reduction in postprandial hyperglycemia within 1 hour with Fiasp compared to IAasp, with comparable efficacy at 2 hours.\(^7\)

**Insulins or Insulin Combos with BioChaperone® Technology**

BioChaperone® (BC) technological platform from Adocia is designed to improve the effectiveness and/or safety of therapeutic proteins while making them easier for patients to use. Many novel insulin formulations are in its clinical pipeline such as two ultrarapid formulations of insulin analogs (BC Lispro U100 and U200), a rapid-acting formulation of human insulin (HinsBet U100), and a combination of basal insulin glargine and rapid-acting insulin lispro (BC Combo). Two combinations of insulin glargine with glucagon-like peptide-1 (GLP-1) (BC Glargine Dulaglutide and BC Glargine Liraglutide), two combinations of insulin lispro with synergistic prandial hormones (BC Lispro Pramlintide and BC Lispro Exenatide), and a concentrated rapid-acting formulation of human insulin (HinsBet U500) are also under preclinical development.\(^8\)

**Once-weekly Basal Insulins (AB101, LAPS-Insulin 115, and LAI287)**

AB101 (from Rezolute), is a once-weekly injectable basal insulin for T1D and T2D and releases human insulin slowly and uniformly over a period of 1 week. It has comparable activity to regular human insulin in vitro and a weekly insulin time-action profile in vivo, with no acute or delayed sudden insulin increase. It is postulated to stabilize endogenous insulin-glucose homeostasis and reduce glycemic variability.\(^9\)

LAPS-Insulin 115 (HM12470, from Hanmi Pharmaceutical) is a once-weekly insulin analog which has substantially prolonged PK/PD profiles and activates insulin receptor (IR) signalling in all major target tissues. When compared to insulin, LAPS-Insulin 115 has a very slow onset of action, a similar off-rate and a less and reversible IR downregulation under in vitro conditions.\(^10\)

Novo Nordisk is developing a once-weekly ultralong-acting basal insulin analog LAI287 (NN1436), intended for use in T1D and T2D patients.\(^12\)

**Liver-preferential Mealtime Insulin Analog (NN1406)**

This liver-preferential mealtime insulin from Novo Nordisk intended for T1D and T2D, mimics physiological insulin distribution and is associated with lesser hypoglycemia and weight gain.\(^13\)

**Oral Insulins (Tregopil and ORMD 0801)**

Oral insulins are a more viable alternative to conventional insulins and can enhance patient compliance to insulin therapy.

Tregopil (formerly IN-105) from Biocon is an oral version of insulin intended for postprandial glycemic control. A clear linear relationship has been noted between the administered dose and the decrease in postprandial glucose excursion rates. No drug interaction has been noted and diet seems to have no influence on the efficacy of tregopil.\(^14\)

ORMD 0801 oral insulin capsule from Oramed, intended as a monotherapy for T2D, is based on Protein Oral Delivery (POD™) technology. The omega-3 fatty acid component protects the insulin from small intestinal proteases and enables direct absorption across the intestinal lumen with the help of an absorption enhancer. This physiological insulin delivery system inhibits hepatic glucose production and reduces night-time glucose levels.\(^15\)

**Glucose-responsive Insulin (Smart Insulin)**

Glucose-responsive insulin (GRI)/“smart” insulin, can automatically respond to changing blood glucose levels. Smart insulin project by SmartCells, Inc., later on acquired by Merck & Co., Inc., initially involved an injectable gel that consisted of lectin and an insulin analog with a sugar moiety attached. During hypoglycemia the lectin binds to insulin inhibiting its action, and during hyperglycemia lectin binds to glucose thereby releasing insulin to stimulate glucose uptake. The technology evolved gradually thus eliminating the need of injecting a
lectin that is toxic and instead the insulin analog binds reversibly to a ubiquitous cell receptor. “Smart” insulin from Merck, MK-2640, is the first smart insulin to be tested on humans.16

Inhaled Insulin (Dance-501)

Inhaled insulin was launched for the first time by Pfizer (Exubera®). Only one inhaled insulin, MannKind Corporation’s rapid-acting inhaled insulin, Afrezza®, has survived in the market.17 Inhaled insulin Dance-501 is a recombinant human insulin administered with a small handheld electronic inhaler. It produces a soft mist of consistently sized insulin particles, allowing an efficient and consistent delivery of insulin into the lungs in a few breaths. Intra- and inter-subject variability is similar to injections, has a faster onset and longer duration than Humalog, and shows dose linearity and absence of any adverse events like cough.18

CONCLUSION

Even with much advancement in diabetes care, treatment of diabetes is still highly unsuccessful across the world and in India, this rate is much lower (only around 4% success rate). The average blood glucose in India, irrespective of the geographical location, remains above 9.4%. The most prominent reason behind this is the clinical inertia to initiate and intensify insulin treatment due to the underlying fear of hypoglycemia and the impending death. With more effective and safer insulin formulations being available, they would be able to extend the promise of a more scientific, safer, and individualized mode of insulin therapy, increase patient compliance and make diabetes management a highly successful one.

REFERENCES

2. Becker RH, Dahmen R, Bergmann K, et al. New insulin glargine 300 units·mL-1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units·mL-1. Diabetes Care. 2015;38(4):637-43.
5. Zhou FL. Lower Risk of Hypoglycemia after Switch to Insulin Glargine 300 U/Ml (Gla-300) vs Other Basal Insulins in Patients with Type 2 Diabetes (TZD) on Basal Insulin in Real-World Clinical Settings (DELiVER 2 study). Orlando, FL, US; Endocrine Society 2017 Annual Meeting [ENDO 2017]; 2017.
