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Breaking the complexity of T2D management with iGlarLixi: a simplified innovation in T2DM management paradigm

Abstract

Type 2 Diabetes Mellitus (T2DM) is a multifaceted metabolic disorder characterized by chronic hyperglycemia resulting from insulin resistance, impaired insulin secretion, or both. Effective management of T2DM necessitates a comprehensive approach, integrating lifestyle modifications, oral antidiabetic drugs (OADs), and injectable therapies. iGlarLixi, a fixed-ratio combination of insulin glargine (a long-acting insulin) and lixisenatide (a GLP-1 receptor agonist), emerges as a novel therapeutic strategy aimed at simplifying T2DM management. This article examines the efficacy, safety, and clinical implications of iGlarLixi, drawing on insights from clinical studies and prescribing information.

Keywords: iGlarLixi, insulin glargine, lixisenatide, efficacy, safety, clinical implications

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Introduction

Type 2 Diabetes Mellitus (T2DM) represents a multifaceted metabolic condition marked by persistent high blood sugar levels, which arise from insulin resistance, inadequate insulin secretion, or both.[1] Effectively managing T2DM usually necessitates a comprehensive strategy that encompasses lifestyle adjustments, oral antidiabetic medications (OADs), and injectable treatments.[2] iGlarLixi, a novel fixed-ratio therapy combining insulin glargine (a long-acting insulin) and lixisenatide (a GLP-1 receptor agonist), offers a promising and simplified approach for T2DM management. This paper delves into the effectiveness, safety profile, and clinical outcomes associated with iGlarLixi, compiling detailed information from clinical trials and prescribing guidelines.

India faces one of the highest global burdens of T2DM, presenting a substantial public health challenge. Patients with diabetes in India often exhibit a range of pathophysiological issues, including insulin resistance, insufficient insulin secretion, and elevated hepatic glucose production. Additionally, obesity is a prevalent comorbidity, with an average BMI of 27.2 among diabetic individuals.[3,4] Further complicating the management of T2DM, approximately 80% of patients in India fail to achieve optimal glycemic control, and about 18% suffer from microvascular or macrovascular complications. Major barriers to achieve glycemic control include: improper diet and poor lifestyle, limited awareness, non-adherence or non-compliance to medications including insulin hesitancy, socio-economic factors and also,limited access to healthcare facilities in rural areas.[5,6] These challenges underscore the urgent need for effective and simplified treatment regimens such as iGlarLixi.

Advancing insulin therapy in clinical practice

For patients who are not adequately controlled with basal insulin alone, advancing insulin therapy is crucial. Traditional methods of intensifying treatment include basal-bolus regimens, premixed insulins, and combinations of basal insulin with GLP-1 receptor agonists. However, these regimens can be complicated, requiring multiple daily injections, meticulous meal planning, and frequent glucose monitoring.[7,8] iGlarLixi provides a streamlined alternative by merging basal insulin with a GLP-1 receptor agonist, aiming to simplify therapy while addressing various pathophysiological targets of T2DM.[9]

Unmet needs with complex regimens in T2D management

Despite the availability of numerous glucose-lowering therapies, many patients struggle to achieve optimal glycemic control due to the complexities of traditional insulin regimens. These challenges include an increased risk of hypoglycemia, weight gain, reduced flexibility, and the burden of multiple daily injections.[10] Simplified regimens like iGlarLixi hold the potential to enhance adherence and improve patient outcomes by addressing these issues.

Combining basal insulin and GLP-1 RA

Combination therapies like iGlarLixi, which integrate basal insulin and GLP-1 receptor agonists, provide an effective strategy for managing T2DM. Basal insulin is primarily effective in lowering fasting blood glucose by reducing hepatic glucose production. In contrast, GLP-1 receptor agonists enhance post-meal glucose control through mechanisms such as promoting glucose-dependent insulin secretion, inhibiting glucagon release, and delaying stomach emptying. These combined actions address a wide range of T2DM pathophysiological issues, leading to better overall glycemic control and minimizing risks of hypoglycemia and weight gain.[11,12]

Mechanism of action

The mechanisms of insulin glargine and lixisenatide in iGlarLixi, work together to achieve effective glycemic management. Insulin glargine, a long-acting insulin analog, forms microprecipitates after

being injected subcutaneously, which allows for slow insulin release and maintains a steady basal insulin level. This process aids in lowering fasting glucose levels by inhibiting hepatic glucose output. On the other hand, lixisenatide, a GLP-1 receptor agonist, increases glucose-dependent insulin secretion, decreases glucagon secretion, slows gastric emptying, and lowers post-meal glucose levels. By combining these two agents, iGlarLixi effectively addresses seven out of eight key pathophysiological issues in T2DM, providing a comprehensive solution for managing blood sugar levels.[13]

Clinical evidence

SoliMix study

The SoliMix study, classified as Phase 3b, was a randomized controlled trial that assessed the efficacy and safety of once-daily iGlarLixi versus twice-daily biphasic insulin aspart 30 (BIAsp 30) in patients with T2DM who were inadequately controlled on basal insulin plus oral antidiabetic drugs (OADs). A total of 887 participants were randomized to either iGlarLixi or BIAsp 30. The primary outcome measured was the change in HbA1c levels from the baseline after 26 weeks.

Findings indicated that iGlarLixi achieved a greater reduction in HbA1c compared to BIAsp 30 (-1.6% vs. -1.3%). Additionally, patients receiving iGlarLixi showed a significant reduction in weight (-0.7 kg vs. +0.9 kg) and a lower rate of hypoglycemia (32% vs. 43%). These results underscore the effectiveness of iGlarLixi in enhancing glycemic control with fewer adverse effects compared to traditional premixed insulin treatments.[14]

LixiLan-O study

The LixiLan-O study evaluated the efficacy and safety of iGlarLixi in comparison to insulin glargine alone and lixisenatide alone in patients inadequately managed on oral antidiabetic drugs (OADs). This Phase 3 trial included 1170 patients who were randomized to receive either iGlarLixi, insulin glargine, or lixisenatide.

The results showed that iGlarLixi led to a more significant reduction in HbA1c (-1.6%) compared to both insulin glargine (-1.3%) and lixisenatide (-0.9%). Furthermore, iGlarLixi substantially improved post-meal glucose control and resulted in greater weight loss (-1.4 kg) compared to insulin glargine (-0.7 kg) and lixisenatide (-1.3 kg). The occurrence of gastrointestinal side effects was low and comparable across all treatment groups, confirming the favorable safety profile of iGlarLixi.[15]

LixiLan-L study

The LixiLan-L study evaluated the efficacy and safety of iGlarLixi in comparison to insulin glargine in patients with T2DM who were inadequately controlled on basal insulin. This Phase 3 trial involved 736 patients who were randomized to receive either iGlarLixi or insulin glargine.

The findings showed that iGlarLixi provided superior glycemic control with a more significant reduction in HbA1c (-1.1%) compared to insulin glargine (-0.6%). Additionally, iGlarLixi significantly lowered post-meal glucose levels and reduced body weight (-0.7 kg vs. +0.7 kg). The rate of hypoglycemia was similar between the groups, emphasizing the safety and effectiveness of iGlarLixi in improving glycemic control without increasing the risk of hypoglycemia.[16]

LixiLan-G extension study

The LixiLan-G extension study assessed the long-term efficacy and safety of iGlarLixi over a period of 52 weeks. This study included patients from both the LixiLan-O and LixiLan-L trials who continued their treatment with iGlarLixi for an additional 26 weeks.

The results indicated that the glycemic control achieved at 26 weeks was sustained at 52 weeks, with continued reductions in HbA1c, fasting plasma glucose, and post-meal glucose levels. The safety profile of iGlarLixi remained positive, with low rates of hypoglycemia and gastrointestinal side effects, confirming the long-term advantages of this therapy.[17]

Guideline recommendations

International guidelines, including those from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), advocate for the use of combination therapies such as iGlarLixi for patients with T2DM who do not achieve adequate control with oral antidiabetic drugs (OADs) or basal insulin alone. These guidelines highlight the advantages of enhanced glycemic control, a lower risk of hypoglycemia, and weight stability offered by these combination treatments.

ADA/EASD Recommendations: The joint ADA/EASD consensus emphasizes the use of combination therapy for T2DM patients who are unable to meet glycemic targets with basal insulin alone. They underscore the potential of therapies like iGlarLixi to simplify treatment regimens, boost adherence, and improve patient outcomes.[18,19]

Dosing and administration

iGlarLixi is provided in a prefilled pen, combining insulin glargine and lixisenatide in a fixed ratio. The initial dose is tailored to the patient's prior insulin regimen and adjusted based on fasting plasma glucose levels. The pen administers doses incrementally, facilitating gradual titration to achieve optimal blood glucose control.

Starting Dose: For patients new to basal insulin or GLP-1 receptor agonists, or those using less than 30 units of basal insulin, a starting dose of 15 units once daily is recommended. Patients with inadequate control on 30 to 60 units of basal insulin should start with a dose of 30 units once daily.[20]

Titration: The dose should be adjusted by 2 to 4 units each week according to the patient's metabolic requirements, blood glucose monitoring outcomes, and glycemic targets until the desired fasting plasma glucose level is attained.[21]

Administration: iGlarLixi is to be administered subcutaneously in the abdomen, thigh, or upper arm, with rotation of injection sites to minimize the risk of lipodystrophy. It should not be diluted or mixed with other insulin products or solutions.[22]

Usage in special populations

iGlarLixi is suitable for elderly patients and those with mild to moderate renal or hepatic impairment. However, it is not advised for patients with severe renal impairment or end-stage renal disease. The safety and effectiveness of iGlarLixi during pregnancy have not been established, and it should be discontinued if pregnancy is detected.

Elderly patients

Clinical trials observed no significant differences in effectiveness and safety in elderly patients (aged ≥65 years). Nonetheless, caution is advised due to the potential for age-related renal function decline.[23]

Renal impairment

Patients with renal impairment may require frequent glucose monitoring and dose adjustments. Those with mild to moderate renal

impairment do not need dose adjustments but should be closely monitored due to increased risks of hypoglycemia, nausea, and vomiting.

Hepatic impairment

The impact of hepatic impairment on the pharmacokinetics of iGlarLixi has not been studied. Frequent glucose monitoring and potential dose adjustments may be required.

Pregnancy and lactation

iGlarLixi should be administered during pregnancy only if the potential benefits outweigh the risks to the fetus. It is unclear if iGlarLixi is excreted in human milk, so caution is advised when used by breastfeeding women.[24]

Safety Profile and Adverse Reactions[25,26]

The safety profile of iGlarLixi has been assessed in various clinical trials. Common adverse reactions reported include hypoglycemia, nausea, nasopharyngitis, diarrhea, upper respiratory tract infection, and headache.

Hypoglycemia

Hypoglycemia is the most frequent adverse reaction linked with insulin-containing products, including iGlarLixi. Severe hypoglycemia can lead to seizures, be life-threatening, or cause death. Patients should be educated on identifying and managing hypoglycemia.

Gastrointestinal adverse reactions

Gastrointestinal side effects are common with lixisenatide and often occur more frequently at the start of therapy. These side effects include nausea, diarrhea, vomiting, and constipation.

Drug interactions[27]

Numerous medications can influence glucose metabolism and might necessitate dose adjustments of iGlarLixi. These include drugs that raise the risk of hypoglycemia (e.g., antidiabetic agents, ACE inhibitors) and those that reduce the blood glucose-lowering effect (e.g., corticosteroids, oral contraceptives). Lixisenatide, part of iGlarLixi, delays gastric emptying, potentially affecting the absorption of concurrently administered oral medications.

Prescribing information[28]

Indications and usage

iGlarLixi is prescribed alongside diet and exercise to enhance glycemic control in adults with type 2 diabetes mellitus. However, it has not been tested in individuals with a history of pancreatitis and is not advised for use with other GLP-1 receptor agonists, for managing type 1 diabetes or diabetic ketoacidosis, or in patients with gastroparesis.

Dosage and administration

iGlarLixi should be administered subcutaneously once daily within an hour before the first meal of the day. The pen delivers doses ranging from 15 units to 60 units, with a maximum daily dose of 60 units. For patients new to basal insulin or GLP-1 receptor agonists, or those using less than 30 units of basal insulin, the starting dose is 15 units. Patients with inadequate control on 30 to 60 units of basal insulin should begin with 30 units. Appropriate titration is crucial for optimal glycemic control.

Contraindications

iGlarLixi should not be used during hypoglycemic episodes or in patients who have hypersensitivity to insulin glargine, lixisenatide, or any of its ingredients.T2DM patients with family history of medullary thyroid carcinoma should not also be prescribed iGlarLixi.

Warnings and precautions

I. Anaphylaxis and Serious Hypersensitivity Reactions: Severe and life-threatening reactions can occur. Patients should discontinue use immediately if a reaction occurs.

II. Pancreatitis: Cease use immediately if pancreatitis is suspected.

III. Do Not Share iGlarLixi Prefilled Pen between Patients: Sharing can transmit blood-borne pathogens.

IV. Hyperglycaemia or Hypoglycemia with Regimen Changes: Requires close medical supervision.

V. Overdose Due to Medication Errors: Patients must verify the label before each injection.

VI. Hypoglycemia: Regularly monitor glucose levels, especially with changes in insulin dose, diet, or physical activity.

VII. Acute Kidney Injury: Renal function should be monitored in patients with kidney impairment.

VIII. Immunogenicity: Monitor for antibody development and consider alternative treatments if necessary.

IX. Hypokalemia: Monitor blood potassium levels.

X. Fluid Retention and Heart Failure with Thiazolidinediones (TZDs): Watch for signs of heart failure.

Evidence on long term effectiveness

An observational study evaluating effectiveness and safety of the drug over 24months in T2DM patients which included 1685 cases, reported that HbA1c target of <7% was achieved in around 22% cases at 24months. According to their observations, iGlarLixi use in therapy of diabetes was associated with better glycemic control without any change in body weight or increased hypoglycemia over 24 months.[29]

Conclusion

iGlarLixi marks a substantial advancement in T2DM management by offering a straightforward and effective method for glycemic control. The combination of basal insulin and GLP-1 receptor agonists tackles several pathophysiologic issues of T2DM, delivering significant benefits in HbA1c reduction, weight management, and lowering the risk of hypoglycemia. Clinical trials have shown its superiority over traditional insulin regimens, making it a valuable option for patients with complex treatment needs. With continuous endorsement from global guidelines for combination injectables, iGlarLixi is set to significantly improve management outcomes for T2DM patients.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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