Translating iGlarLixi Evidence for the Management of Frequent Clinical Scenarios in Type 2 Diabetes

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Introduction | Clinical profiles | Conclusions

Introduction

iGlarLixi is a once-daily titratable fixed-ratio combination (FRC) of basal insulin glargine 100 U/mL (iGlar) and the GLP-1 RA, Lixi (lixisenatide) for the treatment of people with type 2 diabetes (T2D)

iGlarLixi can provide improved glycemic control versus its individual components in a range of patients with T2D

iGlarLixi can be a first injectable as an adjunct to diet and exercise alongside metformin with or without SGLT2i

Or for advancing from basal insulin or GLP-1 RA therapy

While the cases presented here are fictional and not real case reviews, they are representative of typical clinical profiles of people with T2D

Objective

The purpose of this review is to help clinicians understand treatment intensification using **iGlarLixi** in people with T2D by presenting four fictional but typical clinical scenarios supported by research evidence

Clinical profiles

Michael

OAD — HbA_{1c} 8.5 %

Age: **60 years** | Diabetes duration: **12 years** | BMI: **32 kg/m²**

Case history

1. Michael has hypertension and dyslipidemia controlled with therapy
2. He has an HbA_{1c} of 8.5 % despite losing 3 kg through diet and exercise in the last 6 months
3. His therapy was intensified with a GLP-1 RA previously, but this was halted due to gastrointestinal adverse events (GI AEs)
4. Due to his elevated cardiovascular risk and renal impairment, Michael's clinician has started him on a fixed-dose combination of SGLT2i (empagliflozin) and DPP-4i (linagliptin), which has reduced his HbA_{1c}; however, it still fluctuates between 7.6 % and 7.9 %
5. He recognizes his HbA_{1c} is greater than his target of ≤7 %; however:
   - He is reluctant to start basal insulin due to concerns about weight gain
   - He is concerned about reinitiating a GLP-1 RA due to GI AEs he experienced previously

Research evidence

In the LixiLan-O trial, iGlarLixi provided improved HbA_{1c} reductions versus iGlar or Lixi alone in people with T2D previously treated with oral antihyperglycemic drugs (OADs) without weight gain or increased hypoglycemia compared with iGlar[1]

Post hoc analyses of the LixiLan-G trial also show that iGlarLixi provides comparable efficacy and safety regardless of SGLT2i use[2]

iGlarLixi, being an FRC, enables the Lixi dose to be gradually increased as the iGlar component is titrated, thus increasing gastrointestinal tolerance[1]

Case summary

Switching Michael to **iGlarLixi** may help improve glycemic control compared with initiating basal insulin alone, with efficacy and safety being unaffected by SGLT2i use

Michael's clinician can help allay Michael's concerns by using shared decision making to explain the reduced risk of weight gain and GI AEs associated with **iGlarLixi** versus basal insulin or GLP-1 RA, respectively

The cardiovascular and renal-protective benefits of SGLT2i therapy can be continued after initiating **iGlarLixi** by stopping his fixed-dose combination of SGLT2i and DPP-4i and switching him to a fixed-dose combination of metformin + SGLT2i

As Michael has no history of insulin therapy he should be initiated on the recommended starting dose for insulin-naïve individuals.[3,4] His dose should be titrated weekly to reach his individualized fasting SMPG while avoiding hypoglycemia

Thomas

OAD — HbA_{1c} 9.6 %

Age: **54 years** | Diabetes duration: **3 years** | BMI: **32 kg/m²**

Case history

1. Thomas has hypertension
2. Thomas is currently on metformin, an SGLT2i (empagliflozin), and an SU (glimepiride)
3. He has been unable to reach his target HbA_{1c} of <7 % with OADs alone
4. Thomas is aware his HbA_{1c} is >2 % above target and he will require treatment intensification

Research evidence

Few people (<25%) with HbA_{1c} ≥9 % reach HbA_{1c} <7 % within 12 months of initiating therapy with basal insulin or GLP-1 RA alone.[5] iGlarLixi may provide greater HbA_{1c} reductions and help more people to reach HbA_{1c} <7 % compared with iGlar or Lixi alone[6]

Initiating therapy with basal insulin and GLP-1 RA simultaneously increases the likelihood of reaching glycemic control compared with separate initiation[7]

Case summary

iGlarLixi could help Thomas reach his HbA_{1c} target more effectively than sequential addition of either GLP-1 RA or basal insulin, particularly given his high HbA_{1c}[1,6]

Faster achievement of his HbA_{1c} target would limit Thomas' cumulative glycemic exposure, potentially reducing cardiovascular disease complications[8]

When intensifying to **iGlarLixi**, Thomas' clinician should continue his metformin in addition to maintaining his SGLT2i therapy for cardiovascular and renal protection, but SU treatment should be discontinued[1]

As Thomas has no history of insulin therapy he should be initiated on the recommended starting dose for insulin-naïve individuals.[3,4] His dose should be titrated weekly to reach his individualized fasting SMPG while avoiding hypoglycemia

Jane

BI — HbA_{1c} 7.9 %

Age: **58 years** | Diabetes duration: **10 years** | BMI: **29 kg/m²**

Case history

1. Jane has hypertension, hypothyroidism, depression currently controlled on medications, and FPG levels of 100–130 mg/dL
2. Other than hypertension, Jane has no atherosclerotic cardiovascular or renal conditions and is currently taking an SGLT2i (dapagliflozin) to help provide continued cardiovascular and renal protection
3. Jane has been unable to reach an HbA_{1c} of <7 % despite being on iGlar therapy for 2.5 years
4. She wishes to avoid the increased self-monitoring, injection requirements, hypoglycemia risk, and weight gain associated with the addition of prandial insulin

Research evidence

In the LixiLan-L trial, iGlarLixi was shown to help people inadequately controlled on iGlar for over 6 months to reach their HbA_{1c} targets without increased risk of hypoglycemia and no increase in body weight[9]

Post hoc analyses of LixiLan-L suggest that iGlarLixi therapy can facilitate more individuals with residual hyperglycemia to reach HbA_{1c} <7 % than iGlar alone,[10] through combining the actions of Lixi (primarily targeting PPG)[11] and basal insulin (primarily targeting FPG)[12]

Case summary

FPG levels of 100–130 mg/dL despite an HbA_{1c} of 7.9 % suggest that Jane's elevated HbA_{1c} may be driven by increased PPG excursions, for which a once-daily **iGlarLixi** injection would provide a simpler therapy option with less treatment-related burden than a basal bolus regimen

Her SGLT2i therapy will be maintained to help provide continued cardiovascular and renal protection

As Jane is currently receiving 38 U of iGlar daily, her current therapy should be stopped and she should be initiated on 30 U of **iGlarLixi** using a pen containing 100 U iGlar and 33 µg Lixi.[3,4] This should be titrated to reach and maintain her individualized fasting SMPG while avoiding hypoglycemia

Betty

GLP-1 RA — HbA_{1c} 7.9 %

Age: **58 years** | Diabetes duration: **18.2 years** | BMI: **29.1 kg/m²**

Case history

1. Betty has hypertension
2. Betty's treatment was intensified from OADs alone to include a GLP-1 RA (liraglutide) following an HbA_{1c} reading of 9.2 %
3. Addition of liraglutide helped reduce her HbA_{1c} to 7.9 %, but did not enable her to reach her HbA_{1c} target of <7 %
4. Betty has an eGFR of 66 mL/min/1.73 m², indicating moderately impaired renal function. She has therefore been started on an SGLT2i (canagliflozin) for cardiovascular and renal protection

Research evidence

Results of the LixiLan-G study showed that switching to iGlarLixi can improve glycemic control compared with continuing previous GLP-1 RA therapy[13]; regardless of diabetes duration, baseline HbA_{1c}, or previous GLP-1 RA[14,15]

Incidence and rates of hypoglycemia and GI AEs are low with iGlarLixi but higher than with continued GLP-1 RA therapy[13]

Case summary

iGlarLixi may provide a more suitable therapy option for Betty than adding basal insulin separately

These benefits should be weighed against the increased potential for hypoglycemia and GI AEs compared with continuing GLP-1 RA therapy, particularly as these factors may adversely impact treatment adherence

Her SGLT2i use should be maintained for continued cardiovascular and renal protection

As Betty has no history of insulin therapy, she should be initiated on the dose recommended for insulin-naïve individuals, while stopping her current GLP-1 RA therapy.[3,4] Her dose should be titrated weekly to reach and maintain her individualized fasting SMPG while avoiding hypoglycemia

Conclusions

In patients with T2D, the FRC of iGlar and Lixi provides a patient-centric, easy to use treatment approach with robust glucose-lowering efficacy, a low incidence of hypoglycemia, and mitigation of weight gain and nausea compared with separate initiation of basal insulin or GLP-1 RA therapy, respectively

Abbreviations
BI, basal insulin; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomeruler filtration rate; FPG, fasting plasma glucose; FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; OAD, oral antihyperglycemic drug; PPG, postprandial plasma glucose; SGLT2i, sodium glucose-like cotransporter-2 inhibitor; SMPG, self-measured plasma glucose; SU, sulfonylurea; T2D, type 2 diabetes

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