PharmaNote®

Vol. 33, Issue 1 October 2017 Established 1985

Combination GLP-1 Agonist and Basal Insulin for the Management of Type 2 Diabetes Mellitus

Laira Chambers, PharmD Candidate

Diabetes mellitus, characterized by hyperglycemia, affects over 29 million Americans.[1] Hyperglycemia typically occurs as a result of defects in the secretion of insulin, the action of insulin, or both. Chronic uncontrolled diabetes can manifest into microvascular (i.e., nephropathy, neuropathy) or macrovascular complications (i.e., coronary artery disease, stroke). Therefore, glycemic control is essential to reduce the risk of complications. Achievement of appropriate glycemic control is often done through both lifestyle modification and pharmacological management. Metformin is generally the preferred initial pharmacologic agent for the treatment of type 2 diabetes mellitus; however, other options such as basal insulin and glucagon-like peptide 1 receptor (GLP-1) agonist may be considered in highly uncontrolled patients.

Insulin therapy should be considered, with or without additional agents, in patients with newly diagnosed type 2 diabetes, who are symptomatic and/or have an HbA1c of ≥10% and/or blood glucose levels ≥300 mg/dL.[2] Insulin has previously been found to be the most effective method of reducing blood glucose levels in patients with type 2 diabetes and is estimated to reduce HbA1c by 1.5 to 3.5%.[3,4] Basal insulin is slowly absorbed and long-acting, with a duration of action lasting between 10 and 24 hours. Another class of add-on agents to reduce blood glucose levels are the GLP-1 agonist. These agents have advantages over other agents as they tend to not cause hypoglycemia and are associated with weight loss. They are estimated to reduce HbA1c by 1.0 to 1.5%, which is about 0.5% more than other adjunct options.[5]

A fairly new group of combination injections for the management of type 2 diabetes are the combined basal insulin and GLP-1 agonist injections. Soliqua®, also called LixiLan in clinical trials, is a once daily combination pen of long-acting insulin glargine (100 units/mL) and GLP-1 agonist, lixisenatide (33 mcg/mL). Xultophy®, also called IDegLira in clinical trials, is a once daily combination pen of long-acting insulin degludec (100 units) and GLP-1 agonist, liraglutide (3.6 mg). This review summarizes the pharmacology of basal insulin and GLP-1 agonist, and discusses the supporting evidence for combined use of basal insulin/GLP-1 agonist in the management of type 2 diabetes mellitus.

In This Issue

Pharmacology

Mechanism of Action

Insulin is a hormone, which is secreted by the pancreatic beta cells of the islets of Langerhans and is essential for the metabolism of glucose. Endogenous insulin regulates carbohydrate, fat, and protein metabolism by promoting the uptake of glucose in both muscle and adipose tissue, as well as inhibiting the hepatic production of glucose. Both insulin glargine and insulin degludec are once-daily long-acting insulin analogs.

Incretins, such as GLP-1 and GIP (gastric inhibitory polypeptide), are endogenous compounds that increase glycemic control. GLP-1 is produced from the proglucagon gene in L-cells of the small intestine and is released in response to the ingestion of nutrients. GLP-1 exerts its main effects by stimulating glucose-dependent insulin release from the pancreatic islets. The GLP-1 agonists, lixisenatide and liraglutide, mimic the incretin effects in the body by binding to and activating GLP-1 receptors.[6]

Pharmacokinetics

Table 1 summarizes the pharmacokinetic properties for the individual components of Soliqua® and Xultophy®.[7-9] In general, basal insulins are long acting and have little to no peak in concentration. Insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain and forms two active metabolites. In contrast, insulin degludec is mostly metabolized by the liver and kidneys and does not form any active metabolites. GLP-1 agonist are either short or long acting, exhibiting varying peak concentrations and durations. Lixisenatide is presumably metabolized and eliminated through glomerular filtration, thus, caution should be used in patients with renal impairment. Liraglutide is metabolized by the liver and kidneys and is partly excreted as metabolites in the urine and feces, thus, caution should be used in patients with hepatic or renal impairment.

Clinical Trials

Six phase III clinical trials have been completed evaluating the safety and efficacy of combined use insulin glargine and lixisenatide, while ten phase III clinical trials have been completed for combination insulin degludec and liraglutide. These trials evaluated the potential role of combination basal insulin and GLP-1 agonist in the management of type 2 diabetes. **Table 2** provides a summary of the relevant clinical trials for these combinations. These trials were selected due to their study design and generaliza-

Table 1 | Pharmacokinetic Properties of Select Long-Acting Insulins and GLP-1 Receptor Agonists[7-10]

	Basal Insulin		GLP-1 Receptor Agonist	
Drug	**Glargine**	**Degludec**	**Lixisenatide**	**Liraglutide**
C_{max}	18.9 mUnits/mL	4472 pmol/L	187.2 pg/mL	35 ng/mL
T_{max}	No pronounced peak	9—12 h	1—3.5 h	8—12 h
Onset	1.5 h	1 h	-	Within 4 weeks
Half-Life	24 h	25 h	3 h	13 h
V_d	4.41 L	-	100 L	13—25 L
Clearance	2.47 L/h	0.03 L/kg/h	35 L/h	0.9—1.4 L/h

C_{max} = maximum concentration; **h** = hour; **kg** = kilogram; **L** = liter; **mL** = milliliter; **ng** = nanogram; **pg** = picogram; **pmol** = picomole; **T_{max}** = time to maximum concentration; **Vd** = volume of distribution

bility to the overall patient population.

LixiLan-O

LixiLan-O (Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents) was an open-label, randomized, parallel-group, multinational, multicenter phase III clinical trial that included 1,170 patients with type 2 diabetes.[11] The purpose of this trial was to evaluate the safety and efficacy of combined insulin glargine and liraglutide compared with the individual components in patients with type 2 diabetes. Participants were inadequately controlled on metformin with or without a second oral glucose-lowering drug, and showed inadequate glycemic control despite being treated for at least 3 months. Inadequate glycemic control was defined as HbA1c ≥7.5% and ≤10.0% for patients treated with metformin alone. In contrast, inadequate control was defined as ≥7.0% and ≤9.0% for those previously treated with metformin and a second oral glucose-lowering agent. Eligible patients entered a 4-week run-in phase, where those receiving metformin plus a second oral agent were required to stop the additional oral agent. Additionally, during this phase, the dose of metformin was titrated to at least 2,000 mg/day or to the maximum tolerated dose, which had to be at least 1,500 mg/day. Participants were randomly assigned in a 2:2:1 ratio to receive insulin glargine/lixisenatide combination (iGlarLixi), insulin glargine (iGlar) or lixisenatide (Lixi), respectively, for 30 weeks. Patients assigned to receive once-daily iGlarLixi or iGlar were titrated to fasting plasma glucose of <100 mg/dL, up to a maximum insulin dose of 60 units/day. Patients assigned to receive once-daily Lixi received 20 mcg/day. The primary efficacy endpoint was change in HbA1c from baseline to 30 weeks. The safety endpoints assessed were symptomatic hypoglycemia and other adverse events, including allergic reaction, major cardiovascular events and pancreatic events. HbA1c at baseline was 8.1% ± 0.7 in all three treatment groups. Mean HbA1c levels achieved at week 30 were 6.5% for iGlarLixi (-1.6%), 6.8% for iGlar (-1.3%, p<0.0001) and 7.3% for Lixi (-0.9%, p<0.0001). The incidence of symptomatic documented hypoglycemia was 26% and 24% for iGlarLixi and iGlar, respectively. Overall, all treatments were well tolerated and the safety profile of iGlarLixi reflected the established safety profiles of its individual components, except for considerably fewer gastrointestinal (GI) adverse effects compared with Lixi (9.6% vs 24.0%, respectively). Nausea and diarrhea were the most frequent GI adverse effects associated with the iGlarLixi and Lixi groups. The study demonstrates that combination insulin glargine and lixisenatide is more effective in achieving meaningful improvements in glycemic control compared to both insulin glargine and lixisenatide alone.

LixiLan-L

LixiLan-L (Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial) was an open-label, randomized, parallel-group, multinational, multicenter phase III clinical trial that included 736 patients with type 2 diabetes.[12] The purpose of this trial was to demonstrate the safety and efficacy of iGlarLixi compared with iGlar in patients with type 2 diabetes inadequately controlled on basal insulin with or without up to two oral glucose-lowering agents. Patients were eligible if they were ≥18 years of age and had been diagnosed with type 2 diabetes at least 1 year before screening. Additionally, patients were required to have been treated with basal insulin for at least 6 months before screening and have a stable regimen for at least 3 months. The dose of any oral glucose-lowering medications were also required to be stable for at least 3 months. Eligible patients entered a 6-week run-in phase, during which time oral glucose-lowering medications other than metformin were discontinued. Patients taking basal insulins other than glargine were switched to and titrated on insulin glargine.

Participants in LixiLan-L were randomized in a 1:1 ratio to receive either iGlarLixi or iGlar. The primary efficacy endpoint was change in HbA1c from baseline to week 30. Safety endpoints included symptomatic hypoglycemia, defined as hypoglycemia requiring another person's assistance to administer carbohydrates or glucagon, and other resuscitative needs. GI adverse effects are also assessed as a safety endpoint. Baseline HbA1c was 8.1% ± 0.7 in both groups. Mean HbA1c levels were reduced to 6.9% and 7.5% in the iGlarLixi and iGlar groups at week 30, respectively (-1.2% vs -0.6%, p<0.0001). Patients reporting symptomatic hypoglycemia were about 40% in the iGlarLixi group and comparatively about 42.5% in the iGlar group. Overall, both treatments were well tolerated, and the safety of iGlarLixi reflected the established safety profiles of its individual components. This study demonstrated that combination insulin glargine and lixisenatide was more effective at achieving meaningful improvements in glycemic control when compared to insulin glargine alone.

DUAL II

DUAL II (Contribution of Liraglutide in the Fixed-Ratio Combination of Insulin Degludec and Liraglutide) was a 26-week,

Table 2 | Summary of Clinical Trials[11-15]

Trial	Patient (n)	Intervention	Additional Treatment	Duration (weeks)	Baseline HbA1C (%)	Change in A1C (%)	A1C < 7% (%)	P-value[a]
LixiLan-O	1170	iGlarLixi iGlar Lixi	Metformin	30	8.1 8.1 8.1	-1.6 -1.3 -0.8	74 59 33	< 0.0001
LixiLan-L	736	iGlarLixi iGlar	± Metfor-min	30	8.1 8.1	-1.2 -0.6	55 30	< 0.0001
DUAL II	413	IDegLira IDeg	Metformin	26	8.7 8.8	-1.8 -0.8	60 23	< 0.0001
DUAL IIII	438	IDegLira GLP-1RA	± oral meds[b]	26	7.8 7.7	-1.4 -0.3	75 36	< 0.001
DUAL V	557	Degludec/ Liraglutide Insulin Glargine	———	26	8.4 8.2	-1.8 -1.1	———	< 0.001

[a] Change in A1c with intervention vs standard therapy
[b] Oral medications included metformin alone or in combination with pioglitazone and/or sulfonylurea
GLP-1RA = Glucagon-like peptide 1 receptor agonist (liraglutide or exenatide); **IDeg** = insulin degludec; **IDegLira** = inslin degludec and liraglutide; **iGlarLixi** = insulin glargine and lixisenatide; **Lixi** = lixisenatide

randomized, parallel, two-arm, double-blind phase III clinical trial that included 413 patients with type 2 diabetes on basal insulin and metformin with or without sulfonylurea or glinides.[13] This trial aimed to compare the efficacy and safety of combination insulin degludec/liraglutide (IDegLira) and metformin with insulin degludec (IDeg) in patients with type 2 diabetes inadequately controlled on basal insulin and metformin, with or without sulfonylureas or glinides. Patients were eligible if they were ≥18 years of age with inadequately controlled type 2 diabetes defined as HbA1c between 7.5 and 10.0%. Additionally, eligible patients had a BMI of ≥27 kg/m2 and treated for at least 90 days with basal insulin at a stable dose in combination with metformin, with or without sulfonylureas or glinides. Participants were randomly allocated in a 1:1 ratio to receive either once daily IDegLira or IDeg, and allocation was stratified with respect to pretrial treatment with or without sulfonylurea or glinides. At randomization, participants discontinued all glucose-lowering drugs other than metformin and transitioned from their current basal insulin to IDegLira or IDeg. Unlike the other trials reviewed in this article, this trial was blinded to both participants and investigators.

The primary endpoint of DUAL II was change in HbA1c from baseline to week 26. Safety assessment included adverse events related to drug therapy, as well as hypoglycemic episodes. Baseline HbA1c was 8.7% ± 0.7 and 8.8% ±0.7 in the IDegLira and IDeg groups respectively. Mean HbA1c levels achieved at week 26 were 6.9% for the IDegLira group and 8.0% for the IDeg group (-1.8% vs -0.8%, p<0.0001). The rate and severity of adverse effects were similar between both groups, 4.0 vs 3.6 events per patient years of exposure in the IDegLira and IDeg groups respectively. The rate of confirmed hypoglycemic episodes was also comparable and not statistically significant. Overall, the rate of GI adverse effects were higher in the IDegLira group; however, no participants discontinued the study due to GI side effects. The combination of insulin degludec and liraglutide was generally well tolerated, with safety profiles comparable to its individual components. This study demonstrated superiority of insulin degludec/liraglutide combination in reducing HbA1c compared to insulin degludec alone, with no noted increased rates of adverse events.

DUAL III

DUAL III (The Efficacy of IDegLira (Insulin Degludec/ Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial) was a multicenter, randomized, open-label, two-group parallel, phase III, treat-to-target trial that included 438 patients with type 2 diabetes.[14] This trial aimed to investigate the efficacy of combination insulin degludec and liraglutide in glycemic control of patients with type 2 diabetes inadequately controlled on a GLP-1 agonist and oral glucose-lowering agents. Patients were eligible if they were insulin-naive and had inadequately controlled HbA1c, between 7.0 and 9.0%, with a GLP-1 agonist and either metformin alone or in combination with pioglitazone and/or sulfonylurea. Included patients were ≥18 years of age and had a body mass index of ≤40 mg/m2. Patients were excluded if they had used any oral glucose lowering agents other than metformin, pioglitazone, and sulfonylurea within 90 days prior to screening. Eligible patients were treated with the maximum tolerated dose of liraglutide once daily or exenatide twice daily, and oral glucose-lowering agents (metformin alone or in combination with pioglitazone and/or sulfonylurea) at a stable dose for at least 90 days before screening. Patients were stratified according to which GLP-1 agonist they were on pre-trial and were randomized in a 2:1 ratio to IDegLira or continuation of pretrial dosing regimen (standard therapy). Patients previously taking metformin alone or in combination with pioglitazone and/or sulfonylurea, were continued on their pre-trial treatment schedule, in both treatment arms. The primary endpoint was change in HbA1c from baseline to 26 weeks. Primary safety endpoints included the number of treatment related adverse effects and confirmed episodes of hypoglycemia, which would be defined as blood glucose ≤56 mg/dL or hypoglycemia severe enough to require third-party assistance. Baseline HbA1c was 7.8% ± 0.6 for the IDegLira and 7.7 % ± 0.6 for the standard therapy group. Mean HbA1c levels achieved at week 26 were 6.4% and 7.4% in the IDegLira and standard therapy group, respectively (-1.4% vs -0.3%, p<0.001). Hypoglycemic episodes were summarized according to whether patients were receiving concomitant sulfonylurea therapy. In those receiving concomitant sulfonylurea therapy and IDegLira, the rate of confirmed hypoglycemia was 6.34 events per patient years of expo-

sure (PYE) and 0.51 events per PYE in the standard therapy group. For patients not treated with concomitant sulfonylurea, the rate of confirmed hypoglycemia was 1.75 events per PYE in the IDegLira group and 0 events per PYE in the standard therapy group. Overall, the rates of treatment related adverse effects are similar between the groups, and the safety and tolerability profile of IDegLira is consistent with the safety of its individual components. This study demonstrated that combination insulin degludec and liraglutide is a safe and efficacious approach to intensifying therapy in patients uncontrolled on a GLP-1 receptor agonist.

DUAL V

DUAL V (Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes) was a multinational, multicenter, 26-week, open-label, two-group, randomized, phase III, treat-to-target trial that included 557 with type 2 diabetes.[15] The purpose of this trial was to determine whether combination insulin degludec and liraglutide was noninferior to continued titration of insulin glargine in patients with uncontrolled type 2 diabetes, previously treated with insulin glargine and metformin. Patients were eligible if they were at least 18 years of age with type 2 diabetes and an HbA1c between 7.0% and 10.0%. Patients were also required to be taking a stable dose of insulin glargine (total daily dose of 20-50 units), a stable daily dose of metformin (≥1500 mg or max tolerated dose), and have a BMI of 40 kg/m2 or lower. Patients were randomized in a 1:1 ratio to receive IDegLira or continued insulin glargine, with both treatment groups being titrated to the same fasting glucose targets of 72 to 90 mg/dL. The primary endpoint of this study was change in HbA1c from baseline to week 26. If noninferiority was achieved, endpoints were analyzed for statistical superiority. Safety endpoints included number of treatment related adverse events, as well as confirmed hypoglycemic episodes, defined as episodes where blood glucose ≤56 mg/dL, with or without symptoms. Baseline HbA1c were 8.4% ± 0.9 and 8.2% ± 0.9 for the IDegLira group and continued insulin glargine group respectively. Mean HbA1c levels achieved after 26 weeks of treatment were 6.6% and 7.1% with IDegLira and continued insulin glargine respectively (-1.8% vs -1.1%, p<0.001 for superiority). Fewer patients had a confirmed hypoglycemic episode in the IDegLira group (28.4%) than the continued insulin glargine group (49.1%). The overall rates of adverse events were 343.3 per 100 PYE for the IDegLira group and 286.4 per 100 PYE for the insulin glargine group. In general, adverse events were mild and the safety of IDegLira reflected the established safety profiles of its individual components. Primarily, this study demonstrated that in patients with type 2 diabetes previously taking insulin glargine and metformin combination, combination insulin degludec and liraglutide was superior to the continued titration of insulin glargine.

Adverse Effects

The most common adverse effects associated with Soliqua® and Xultophy® are the risk for hypoglycemia, as a result of the insulin component. Clinically significant hypoglycemia, defined as glucose <54 mg/dL[16], typically presents as diaphoresis, headache, blurred vision, shakiness and loss of consciousness. Minor episodes of hypoglycemia may be resolved by the ingestion of carbohydrates, such as high sugar drinks like orange juice or soda. In severe cases, hospitalization may be required. In addition, nausea and vomiting make the GLP-1 agonist component intolerable for some patients. Overall, the most common adverse effects associated with these agents are the risk of hypoglycemia and headache due to the insulin component, as well as, nausea and anorexia due to the GLP-1 agonist. Adverse effects of Soliqua® and Xultophy® observed in the clinical trials are summarized in **Table 3**.

Dosing and Administration

Soliqua® should be injected subcutaneously in doses ranging from 15-60 units.[17] In patients adequately controlled on either <30 units of basal insulin or lixisenatide, initiate with 15 units (15 units insulin glargine and 5 mcg lixisenatide) subcutaneously once daily within the hour prior to the first meal of the day. In patients inadequately controlled on either 30 to 60 units of basal insulin or lixisenatide, initiate with 30 units (30 units insulin glargine and 10 mcg lixisenatide) subcutaneously once daily within the hour prior to the first meal of the day. Titrate the dosage by 2 to 4 units every week based on the patient's blood glucose monitoring results, and glycemic control as tolerated.[7] The maximum dose of Soliqua® is 60 units (60 units insulin glargine and 20 mcg lixisenatide).[17]

Xultophy® should be injected subcutaneously in doses ranging from 10-50 units. It is recommended and supported by literature that patients starting a GLP-1 agonist should have their dose of basal insulin reduced, if their HbA1c is ≤8.0%, to avoid increasing the risk of hypoglycemia.[18] The recommended starting dose is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) subcutaneously once-daily at the same time each day, with or without food. The dosage should be titrated by 2 units (2 units of insulin degludec and 0.072 mg of liraglutide) every 3 to 4 days based on the patient's blood glucose monitoring results and glycemic control, as tolerated.[7] The maximum dose of Xultophy® is 50 units (50 units insulin degludec and 1.8 mg liraglutide).[19]

Precautions and Contraindications

There are no dose adjustments for patients taking lixisenatide with hepatic or renal impairment; however, caution should be used in patients with renal impairment.[9,18] Soliqua® is absolutely contraindicated in patients with a history of angioedema or during an episode of hypoglycemia.[7,17]

There are no dose adjustments for patients taking liraglutide; however, caution should be used for patients with hepatic or renal

Table 3 | Adverse Effects of Soliqua® and Xultophy® Observed in Clinical Trials[11-15]

Adverse Effect	iGlar-Lixi	IDeg-Lira
Nausea	9.6—10.4%	3.1—9.4%
Vomiting	3.2—3.6%	——
Diarrhea	4.4—9.0%	6.5%
Symptomatic Hypoglycemia[a]	14.1—40%	24.1—28.4%
Severe Hypoglycemia[b]	0—1.1%	< 0.01%
Discontinuation due to AE	2.6—2.7%	0.3—3.2%

[a] Defined as glucose < 60 mg/dL requiring administration of glucose, carbohydrates or glucagon injection
[b] Hypoglycemia requiring another person's assistance to administer carbohydrates or glucagon, and other resuscitative needs
IDegLira = insulin degludec and liraglutide (Xultophy®); **iGlarLixi** = insulin glargine and lixisenatide (Soliqua®)

impairment.[8,18] Xultophy® is absolutely contraindicated in patients with a history of angioedema, medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, and during an episode of hypoglycemia.[7,19]

Drug Interactions

Due to the insulin component in these medications, taking other medications that can cause hypoglycemia should be avoided. Other medications that have a risk of hypoglycemia include, but are not limited to sulfonylureas. Alcohol should also be avoided in patients using insulin, as it may have effects on blood glucose levels.[20] Alcohol may worsen glycemic control as it is a source of additional calories, but it may also increase the risk of hypoglycemia due to decreases in endogenous glucose production.[7] GLP-1 agonists, due to their mechanism of action, tend to slow gastric emptying and medications that require certain concentrations to be maintained (ie. antibiotics or oral contraceptives) in order to be effective should be dosed prior to the GLP-1 agonist.

Monitoring

These combinations should be monitored for both efficacy, as well as safety and side effect profile. HbA1c should be monitored no more frequently than every three months to assess glycemic control. Insulin therapy is associated with a high risk of hypoglycemia, and patients should be educated on the warning signs in addition to being monitored. Home self-monitoring of blood glucose is especially important for those patients using insulin to prevent asymptomatic hypoglycemia and hyperglycemia.[16]

Cost

Cost is often a barrier when choosing appropriate pharmacotherapy for the management of any disease state, but especially type 2 diabetes. While there are many new drugs on the rise offering better glycemic control, they come at a significant cost. Soliqua® starts at around $650 (out-of-pocket), with a free coupon, for a carton of five 3 mL pens.[21] There is a savings card available through the manufacturer offering a $0 copay for the first 12 months for commercially-insured patients. Unfortunately, these savings do not apply to government-insured patients. Xultophy® starts at around $980 (out-of-pocket), with a free coupon, for one package of five 3 mL pens.[22] There is a savings card available through the manufacturer offering a copay of as little as $30 a month for the first 12 months for commercially-insured patients. These savings do not apply to government-insured patients.

Conclusion

Soliqua® is a once daily combination pen of long-acting insulin glargine (100 units/mL) and GLP-1 agonist, lixisenatide (33 mcg/mL). Xultophy® is another once daily combination pen of long-acting insulin degludec (100 units/mL) and GLP-1 agonist, liraglutide (3.6 mg/mL). There are numerous reasons to consider the combination of basal insulin and GLP-1 agonist in the management of type 2 diabetes. In the five landmark trials previously discussed, all found combination basal insulin and GLP-1 agonist to be very effective at reducing HbA1c and improving glycemic control. Across the trials mentioned, reductions in baseline HbA1c ranged from 1.2% to 1.8% and achievement of HbA1c <7% ranged from 55% to 75%. By comparison to current standard therapy, the results have validated the safety and efficacy of these combinations and helped define their place in the management of diabetes. Additionally, adverse effects of basal insulin therapy, particularly weight gain, may be offset by the addition of a GLP-1 agonist. Overall, there is substantial evidence and literature to support the combined use of basal insulin and GLP-1 receptor agonist as both safe and efficacious in patients with type 2 diabetes, who are inadequately controlled on other glucose lowering agents.

References

1. 2014 National Diabetes Statistics Report. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/data/statistics/2014statisticsreport.html. Published May 15, 2015. Accessed May 25, 2017.
2. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care. 2016;40 (Supplement 1). doi:10.2337/dc17-s011.
3. Dailey G, Admane K, Mercier F, Owens D. Relationship of Insulin Dose, A1c Lowering, and Weight in Type 2 Diabetes: Comparing Insulin Glargine and Insulin Detemir. Diabetes Technology & Therapeutics. 2010;12(12):1019-1027. doi:10.1089/dia.2010.0063.
4. Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Clinical Diabetes. 2009;27(1):4-16. doi:10.2337/diaclin.27.1.4.
5. Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-1379. Diabetes Care. 2013;36(2):490-490. doi:10.2337/dc13-er02
6. Lee S, Lee DY. Glucagon-like peptide-1 and glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes. Annals of Pediatric Endocrinology & Metabolism. 2017;22(1):15. doi:10.6065/apem.2017.22.1.15.
7. Clinical Pharmacology. Clinical Pharmacology. http://www.clinicalpharmacology.com/. Accessed May 11, 2017.
8. Victoza® [package insert]. Plainsboro, NJ. Novo-nordisk; 2013.
9. Adlyxin [package insert]. Ridgefield, NJ: Sanofi; 2016.
10. Tham LS, Schneck K, Ertekin A, Reviriego J. Modeling Pharmacokinetic Profiles of Insulin Regimens to Enhance Understanding of Subcutaneous Insulin Regimens. The Journal of Clinical Pharmacology. 2017. doi:10.1002/jcph.899.
11. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial. Diabetes Care. 2016;39(11):2026-2035. doi:10.2337/dc16-0917.
12. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial. Diabetes Care. 2016;39(11):1972-1980. doi:10.2337/dc16-1495.
13. Buse JB, Vilsbøll T, Thurman J, et al. Contribution of Liraglutide in the Fixed-Ratio Combination of Insulin Degludec

and Liraglutide (IDegLira). Diabetes Care. 2014;37(11):2926-2933. doi:10.2337/dc14-0785.
14. Linjawi S, Bode BW, Chaykin LB, et al. The Efficacy of IDegLira (Insulin Degludec/Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial. Diabetes Therapy. 2016;8(1):101-114. doi:10.1007/s13300-016-0218-3.
15. Lingvay I, Manghi FP, García-Hernández P, et al. Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes. Jama. 2016;315(9):898. doi:10.1001/jama.2016.1252.
16. Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. Diabetes. 2016;66(2):241-255. doi:10.2337/db16-0806.
17. Soliqua® [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2016
18. Carris NW, Taylor JR, Gums JG. Combining a GLP-1 Receptor Agonist and Basal Insulin: Study Evidence and Practical Considerations. Drugs. 2014;74(18):2141-2152. doi:10.1007/s40265-014-0325-2.
19. Xultophy® [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S; 2016.
20. Drug Interactions Checker - For Drugs, Food & Alcohol. Drugs.com. https://www.drugs.com/drug_interactions.html. Accessed May 26, 2017.
21. Prices and Coupons for Soliqua 100/33. Prices and Soliqua 100/33 Coupons - GoodRx. https://www.goodrx.com/soliqua-100-33. Accessed May 26, 2017.
22. Prices and Coupons for Xultophy. Prices and Xultophy Coupons - GoodRx. https://www.goodrx.com/xultophy. Accessed May 26, 2017.

Personalized Medicine Corner

Therapeutic Effects of CYP2C19 Pharmacogenetic Variability on Proton Pump Inhibitors

Up to a third of the population worldwide experience gastroesophageal reflux disease (GERD), with the majority of patients being treated with a proton pump inhibitor (PPI) for acid suppression.[1,2] PPIs are primarily metabolized by polymorphic cytochrome P450 2C19 (CYP2C19) enzyme to inactive metabolites that have no therapeutic activity. Genetic variation in CYP2C19 gene, which encodes the CYP2C19 enzyme, can lead to interindividual variability in therapeutic response to PPIs as a result of altered PPIs plasma levels. Approximately 30% of individuals of European or African ancestry and 3% of Asians carry a gene variant in CYP2C19 leading to increased CYP2C19 enzyme activity, and decreased PPI plasma levels as a result of enhanced clearance. Conversely, other common genetic variants can lead to decreased or absent CYP2C19 activity and increased PPI levels with usual recommended doses. The latter genetic variants are present in approximately 30% of individuals of European or African ancestry and up to 60% of Asians.[3,4]

Variability in PPIs related therapeutic effects due to CYP2C19 have been demonstrated. For example, higher H. pylori cure rates were observed in patients with treatment including a PPI and decreased CYP2C19 activity leading to higher plasma levels of PPIs, compared to similarly treated patients with normal or increased activity. On the other hand, patients with increased CYP2C19 activity were at a higher risk for lower GERD cure rates compared to patients with normal or decreased CYP2C19 activity.[1,4]

Although data are limited at this time, it is also theorized that adverse effects of PPIs with long term use (e.g., increased infection risk, hypomagnesemia, kidney disease, bone fractures, dementia) may be higher in patients with decreased CYP2C19 activity and resultant increased PPI levels.[5]

Guidelines are available from the Dutch Pharmacogenetics Working Group (DPWG) to provide recommendations on CYP2C19- genotype-guided dosing of PPIs. Depending on the PPI, the DPWG recommends a dose increase from 50-400% in patients with increased CYP2C19 activity.[6] In a recent review, Lima et al. recommended a dose increase of 50-100% in patients with an increased CYP2C19 activity and a dose decrease of 25-50% in patients with a decreased CYP2C19 activity.[7] Further studies on CYP2C19- genotype-guided dosing will refine recommendations for specific PPIs within this commonly used drug class.

For questions about these data, or how to order and interpret CYP2C19 or other pharmacogenetic tests, contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu).

References:

1. Ichikawa H et al. Rapid metabolizer genotype of CYP2C19 is a risk factor of being refractory to proton pump inhibitor therapy for reflux esophagitis. J Gastroenterol Hepatol. 2016;31:716-26.
2. Katz PO et al. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2013;108:308-328.
3. Furuta T et al. Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics of Proton Pump Inhibitors. In: Chiba T, Malfertheiner P, Satoh H, eds. Proton Pump Inhibitors: A Balanced View. Front Gastrointest Res. Basel, Switzerland: Karger Publishers; 2013.32:18-33.
4. Tang H et al. Effects of CYP2C19 Loss-of-Function Variants on the Eradication of H. pylori Infection in Patients Treated with Proton Pump Inhibitor-Based Triple Therapy Regimens: A Meta-Analysis of Randomized Clinical Trials. PLoS One. 2013;8:e62162.
5. Freedberg DE et al. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology. 2017;152:706-715.
6. Swen JJ et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. 2011;89:662-73.
7. Lima JJ et al. Pharmacogenomic testing: the case for CYP2C19 proton pump inhibitor gene-drug pairs. Pharmacogenomics 2014;15:1405-16.

Co-Editors: Larisa Cavallari, PharmD; Kristin Weitzel, PharmD;
Associate Editor: Siegfried O. Schmidt, MD, PhD;
Assistant Editor: Benjamin Quang Duong, PharmD

The Personalized Medicine Corner appears quarterly and is provided by the UF Health Personalized Medicine Program. To find out more or submit a question, email PMP-HELP@ctsi.ufl.edu.

Index of Volume 32 | Oct 2016 – Sept 2017

PharmaNote®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida