Observational Study

Basal insulin and glucagon-like peptide 1 receptor agonist (GLP1-RA) combination

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Diabetes mellitus is a chronic disease affecting more than 425 million people worldwide. Patients with type 2 diabetes frequently do not reach HbA1c targets. Historically insulin has been viewed as the most effective glucose-lowering agent in poorly controlled type 2 diabetes. When therapeutic intensification beyond basal insulin plus oral agents is required, adding a bolus, or prandial, rapid-acting insulin analog has been recommended either in a stepwise approach or as a full basal-bolus in¬sulin regimen. Adding a GLP-1 receptor agonist to basal insulin may be as effective as adding prandial insulin therapy. Two products, an insulin degludec/liraglutide combination (IDegLira) and an insulin glargine/lixisenatide combination (IGlarLixi), ARE approved for use in adults with T2DM. The efficacy and safety of these two basal insulin/GLP-1RA combination products have been studied in the DUAL program and Laxilan program. Clinical trial data has showed insulin/GLP-1RA fixed-ratio combinations are superior at reducing HbA1c with weight neutrality or weight loss rather than weight gain, as well as reduced hypoglycemia rates compared with basal insulin highlighting the great potential of these agents.

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Diabetes mellitus is a chronic disease affecting more than 425 million people worldwide. The International Diabetes Federation (IDF) has described diabetes as "one of the largest global health emergencies of the 21st century". If these trends continue, by 2045, 693 million people will have diabetes. There is an urgency for greater action to improve diabetes outcomes and reduce the global burden of Diabetes[1].

Improvement in our understanding of pathophysiology of diabetes over decades have recognized multiple pathophysiologic factors collectively named as the 'Ominous Octet', and as the 'Dirty Dozen' leading to diabetes[2]. Patients with type 2 diabetes frequently do not reach HbA1c targets, despite the growing arsenal of glucose lowering agents.In India, 70% of diagnosed diabetes cases remains uncontrolled (FCG = 126 mg/dL or PPCG/RCG = 200 mg/dL)[3]. Various professional society guidelines recommends health care professionals to consider dual or triple therapy if patients do not meet glycemic targets with lifestyle changes and metformin alone based on an assessment of efficacy, hypoglycemia risk, contraindications, cost, and preference. However, weight gain, hypoglycemia, and complex treatment regimens can make it difficult to intensify treatment in the real world. This review describes the use of a simple strategy to manage diabetes with injectable therapy.

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- **FRC of basal insulin and GLP-1 RA is superior in BbA1c reduction, glycemic control compared to basal-bolus therapy.**
- **This further minimizes hypoglycemia and also weight neutral.**
- **Titration algorithms are available based on FPG level.**
- **More study needed to establish long term safety and benefits.**

Basal Insulin :

Patients with persistent hyperglycemia despite oral hypoglycemic therapy may: Add insulin to oral medication or Stop the oral drug(s) and begin insulin

When insulin is combined with oral agents, a basal (long- or intermediate-acting) is a reasonable first choice. The rationale for combination oral hypoglycemic drug and insulin therapy is that, by suppressing hepatic glucose production, the patient can retain the convenience of oral agents while minimizing total insulin requirements and weight gain.

Compared with first generation insulin analogue newer analogues have longer duration of action beyond 24 hours without possessing an action peak allowing once daily use (Table 1). They have a lower intra-individual and inter-individual day-to-day variability of action and lower risk of hypoglycemia .These properties allow a greater flexibility in time of day dosing, easier to compensate for missed doses and also allow patient to stay on track with glycemic control strategies. However, not all patients respond to basal insulin[4,5].

Table 1 — *Pharmacological profile of basal insulins*[4]

Basal insulin	Peak	Duration	T ½ (h)	Variability (CV)%	Frequency of dosing
NPH	4-6	12-16	4	68	Twice daily
Glargine 100	Flat some peak at 4-12 hour	24	12	32-82	Once daily or (sometimes) twice daily
Detemir	Flat some peak at 7-14 hour	20-24	5-7	27	Once daily or (often) twice daily
Degludec	Flat, no peak	>24 hour (up to 48 hour)	25	20	Once daily
Glargine 300	Flat, no peak	>24 hour (up to 36 hour)	18	17-35	Once daily +/- 3 hour

Basal Insulin Inadequacy :

The 4 options for an uncontrolled patient on basal insulin are:

- Add rapid acting insulin
- Add a GLP-1 RA
- Use premixed insulin
- Add fixed ratio combination of Basal insulin and GLP-1 RA.

Primary care physicians (PCPs) don't initiate/postpone bolus insulin to maintain glycemic control frequently because they fear hypoglycemia. Addition of a GLP-1 RA to basal insulin may offer a safe and effective alternative to basal–bolus insulin because of the lower risk of hypoglycemia and weight gain.

Glucagon-like Peptide-1 (GLP 1) :

GLP-1 is secreted from L-cells of the small intestine in response to nutrients and exerts its main effect by stimulating glucose-dependent insulin release from the pancreatic islets and suppressing glucagon release, an action likely to be mediated through the local release of somatostatin from islet d cells. Additional effects of GLP 1 include retardation of gastric emptying, suppression of appetite and, potentially, inhibition of ß cell apoptosis. GLP-1 has a short half-life of one to two minutes due to N-terminal degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) Synthetic glucagon-like peptide-1 (GLP-1) receptor agonists are resistant to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) facilitating their clinical use.

Currently, six glucagon-like peptide-1 receptor agonists (GLP-1RAs) are FDA approved for type 2 diabetes. Thy can be classified into two categories based on their receptor activation: short-acting exenatide twice daily and lixisenatide once daily; and longer-acting liraglutide once daily, exenatide once weekly, albiglutide once weekly, dulaglutide once weekly and semaglutide once weekly. The phase III trial of a seventh GLP-1RA, taspoglutide once weekly, was stopped because of unacceptable adverse events (AEs)

The pharmacokinetic differences between these drugs is responsible for important differences in their pharmacodynamic profiles.GLP 1-induced reduction of fasting hyperglycemia seems to be mediated predominantly through their insulinotropic and glucagonostatic actions through its effects on the islet a cells and ß cells, whereas post-prandial glucose control seems to be largely mediated through the delaying effect of GLP 1 on gastric emptying. The short-acting GLP-1 receptor agonists primarily lower postprandial blood glucose levels, whereas the long-acting compounds have a stronger effect on fasting glucose levels enabling tailoring of incretin-based treatment to the needs of each patient. (Table 2)[6-9].

The Rationale of Combination :

The rationale for this combination is to exploit the advantages of each of the drugs while counterbalancing their side effects (Table 3). GLP-1 RAs have a complementary mechanism of action to basal insulin to decrease fasting blood glucose and decrease postprandial glucose excursions by inhibiting glucagon secretion, suppressing appetite and delaying gastric emptying. The GLP1RA-insulin combination therapy also helps reduce weight by the direct weight-reducing effect of GLP1RA along with contribution by the reduction in insulin dose made possible by the combination. GLP1RA addition to insulin allows for significant reduction in insulin dose[10-12].

Table 2 — *Comparison of short-acting versus long-acting GLP 1 receptor agonists*[6]

Parameters	Short acting GLP-1 RA	Long acting GLP-1 RA
Half life	2-5h	12h-several days
Effects		
Fasting glucose	Modest reduction	Strong reduction
Postprandial hyperglycemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	reduction
Heart rate	No effect or small increase (0-2bpm)	Moderate increase
Body weight reduction	1-5 kg	2-5kg
Induction of nausea	20-50%, attenuates slowly (weeks-many months)	20-40%, attenuates quickly (4-8weeks)

Table 3 — *Complementary action of basal insulin and glucagon like peptide 1 receptor agonists (GLP 1 RA)*[10]

	Basal insulin	GLP1 RA
Mode of administration	subcutaneous	subcutaneous
Frequency of dosage	Once/twice daily	Once /twice daily
Primary action	On fasting glucose	On post prandial Glucose
Effect on weight	Weight gain/weight loss	Weight loss
Hypoglycemia	Low risk	Very low risk
Effect synergistic	Beta cell sparing	Insulin sparing

Approved Fixed Ratio Combinations of Basal Insulin And GLP-1 RA :

In November 2016, the U.S. Food and Drug Administration approved two titratable fixed-ratio combinations (FRCs) of basal insulin and a GLP-1 receptor agonist: insulin glargine/lixisenatide 3:1 ratio (iGlarLixi [Soliqua]) and insulin degludec/liraglutide 1:0.036 ratio (IDegLira [Xultophy])[13-16].

The Dual™ Program Trials :

IDegLira has been primarily investigated in seven pivotal 26-week randomized clinical trials (the DUAL™ program trials). Patient populations studied in each of the trials was different. DUAL I, III, and IV, VI trials were done on insulin naïve patients while patients were on insulin in DUAL II and V. VII; and GLP-1 receptor agonist–experienced in DUAL III.

In the DUAL-II trial, the relative contribution of the liraglutide component of IDegLira to glycemic control was evaluated by comparison with a group receiving a similar dose of insulin degludec. The HbA1c reduction from baseline was 1.1% greater, and the rate of confirmed hypoglycemia was lower, with IDegLira, as compared with insulin degludec alone. In addition, a significant reduction in body weight was reported with IDegLira, as compared with insulin degludec[17].

In DUAL III trial, 438 insulin-naïve patients, who were treated with a GLP-1RA and an OAD, were randomized to replacement of the GLP-1RA with IDegLira or a continuation of the pretrial GLP-1RA. IDegLira showed a statistically significant greater HbA1c reduction versus unchanged GLP-1RAs treatment, but at the cost of weight gain, and a higher risk of hypoglycemia. The study demonstrated that switching from a GLP-1RA to IDeglira is effective with regard to glycemic control, and safe[18].

In DUAL IV, enrolled insulin-naïve patients with an HbA1c between 7% and 9%and randomized them to either IDegLira or placebo group, added to SU with or without metformin. IDegLira led to superior HbA1c reduction compared with placebo, but with a higher risk of hypoglycemia[19].

In DUAL V, patients with suboptimal glycemic control on insulin glargine and metformin were randomized to intensified insulin glargine, or IDegLira treatment[14]. The IDegLira group achieved significant improvements in HbA1c, as compared with the insulin glargine group. IDegLira was also associated with both weight loss (as compared with the weight gain seen with insulin glargine), and a significantly lower rate of hypoglycemia[20].

In the DUAL trials, I–V IDegLira was titrated twice per week. In DUAL VI, insulin-naïve type 2 diabetic patients, were randomized to IDegLira titrated either once weekly based on the mean of two pre-breakfast PG readings or twice weekly based on the mean of three pre-breakfast readings. The DUAL-VI trial showed that a simple titration algorithm with once-weekly adjustment based on two readings resulted in a similar glycemic efficacy and safety profile compared with twice-weekly adjustments[21].

The DUAL VII trial[22] was a treat-to-target, and non-inferiority trial .Patients who were not controlled on basal insulin, were randomized to receive either basal –bolus regimen (insulin glargine U100 plus mealtime injections of short-acting insulin aspart) or iDegLira (a combination with liraglutide and degludec).After 26 weeks of treatment, HbA1c levels were comparable among both the groups. Average hemoglobin A1C levels drop was 1.48% with once-daily IDegLira vs 1.46% with basal-bolus regimen (P value less than .0001 for non-inferiority).

- One injection of iDegLira, which could be given at any time of day independent of meals, was able to compete with regards to efficacy with the full basal bolus (4-5 shots a day). The risk of hypoglycemia was lower in the iDegLira group. Just 20% of IDegLira patients had at least one confirmed event of hypoglycemia, compared with 53% of those on basal-bolus insulin. There was weight loss with IDegLira compared to weight gain with multiple daily injections.

At the end of the trial, the dose of the basal insulin with degludec in combination with liraglutide was around 40 units versus around 80 to 85 units with the combination of the bolus insulin and basal multiple daily injections. The total insulin dose was, again, about half suggesting reduction in total insulin requirement

Gastrointestinal side effects, were 11% in the iDegLira treatment arm experienced nausea as compared to 1.6% in the basal-bolus arm

Get Goal-L :

Lixisenatide may provide an alternative to rapid-acting insulin or other treatment options in patients inadequately controlled with basal insulin. Get Goal-M-Asia, Get Goal-Duo 1, Get Goal-L trials have evaluated lixisenatide for use in combination with basal insulin therapy. Get Goal-L was a, double-blind, placebo controlled trial which enrolled 495 patients with type 2 diabetes inadequately controlled with insulin glargine and metformin (mean A1C 8.4 percent. At 24 weeks the reduction in A1C was significantly greater in the lixisenatide group (-0.6 versus -0.3 percent)[23-25].

Advantages of Insulin-GLP1RA combination :

- Superior glycemic control as compared to insulin monotherapy at equitant insulin doses without higher risk of hypoglycemia and with benefit of weight loss[26].

Table 4 — *Clinical indication and rationale for basal and glp1ra combination*

Scenario	Potential role of fixed-dose combination basal insulin–GLP-1 RA therapy
(1) Basal insulin inadequacy	• Combination therapy may improve glycemic control • Single injection does not add complexity to regimen
(2) Hypoglycaemic events prevent patient from reaching glycemic target	Combination therapy associated with relatively low risk of hypoglycemia
(3) Target FPG achieved, but patient continues to experience postprandial hyperglycemia	Addition of GLP-1 RA may help control postprandial hyperglycemia • Single injection of fixed-dose combination therapy is less complex than basal–bolus approach (multiple daily injections)
(4) Persons with high entry level HbA1c, who may be not be able to reach target HbA1c with monotherapy	Single injection of fixed-dose combination therapy is less complex
(5) Persons with increased appetite or weight gain while on basal insulin therapy	Combination therapy may improve glycemic control in addition to control of weight gain and appetite
(6) Persons with adverse gastrointestinal symptoms on GLP1 RA, requesting reduction in dose of the drug	Combination therapy associated with less adverse effects

• as single daily injections of two glycemic control medications lead to regimen simplification promoting treatment adherence with less potential for clinical inertia.

• Titration algorithms are available

• As compared with twice-daily premixed or basal–bolus insulin therapy, the requirement for glucose monitoring is less, because combination treatment is titrated using only the FPG level.

Limitations of Insulin-GLP1RA Combination :

• Although these agents are titratable based on the basal insulin component, patients requiring less than the minimum starting doses (iGlarLixi, 15 units; IDegLira, 16 units) or more than the maximum doses (iGlarLixi, 60 units; IDegLira, 50 units) may not be good candidates for these agent

• For patients who struggle with compliance, reinitiating at the starting dose is recommended for IDegLira after missing 3 days, whereas no guidance is available for iGlarLixi (LaxiLan).

• Previous basal insulin therapy should be discontinued before initiation of an FRC

• A possible drawback of the combination therapy is the fixed-dose principle, which reduces the flexibility to adjust insulin and GLP-1RA treatment in an individualized manner.

• In patients where weight loss is the primary aim, a more optimal treatment may be to titrate liraglutide to the maximal dose of 1.8 mg and then add basal insulin

• Prandial insulin has not been studied with these agents.

• Antibody development has been noted for the individual components in both FRCs; exact clinical significance of it still unknown .(Attenuated glycemic response and a higher incidence of allergic reactions were seen in patients on lixisenatide with elevated antibody concentrations.

• No head-to-head trials comparing the efficacy of FRCs with that of sequential basal insulin with a GLP-1 receptor agonist have been conducted.

• The DUAL trials were underpowered to assess the cardiovascular safety of IDegLira

Summary :

In summary, basal insulin–GLP-1 RA combination therapy may be an option for patients with type 2 diabetes inadequately controlled with other treatments (Table 3, 4). The complementary effects of each class provide a rationale for combining these therapies. The available evidence supports the use of GLP-1 receptor agonists (RAs) for use with basal insulin over conventional basal-prandial insulin regimens. This strategy minimizes the risk of hypoglycemia and weight gain incurred by traditional basal-bolus insulin therapy

Fixed ratio combinations (FRCs) of basal insulin and a GLP-1 receptor agonist: insulin glargine/lixisenatide 3:1 ratio (iGlarLixi [Soliqua]) and insulin degludec/liraglutide 1:0.036 ratio (IDegLira [Xultophy are approved by FDA. Titration algorithms for initiating and modifying the dose based on FPG have been established.

Further research is needed to establish the long term safety and benefits of insulin plus incretin therapy.

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