INTRODUCTION
Incretin (GLP-1) based therapies have ushered in a new paradigm in the treatment strategy of type 2 diabetes. They promise to address the treatment gaps in type 2 diabetes and have already consolidated their position in the therapeutic armamentarium. American Diabetes Association/European Association for the Study of Diabetes (ADA/ EASD) consensus statement 2012 and American Association of Clinical Endocrinologists (AACE) 2011 guidelines recommend use of incretin-based therapies in type 2 diabetes subjects failing on metformin.\textsuperscript{1,2} Currently available treatment modalities have several shortcomings including:
- Failure to address progressive decline in beta-cell function
- Unacceptable incidence of hypoglycemia
- Significant weight gain
- Cardiovascular safety issues
- Side effects related to individual drugs.

On the other hand, GLP-1 based therapies address majority of these concerns. Glucagon-like peptide-1 is an endogenous hormone secreted from L cells in the intestine in response to nutrient ingestion.\textsuperscript{3} They provide glucose-dependent insulin secretion from beta cells of pancreas; thus obviating the possibility of hypoglycemia. They also cause glucose-dependent suppression of glucagon secretion from alpha cells of pancreas; further preventing the possibility of hypoglycemia. Glucagon-like peptide-1 has a unique property of binding to G-protein-coupled receptors in the pancreas that increases the level of cyclic adenosine monophosphate (cAMP) augmenting glucose-stimulated insulin secretion.\textsuperscript{4} Agents that act by augmenting cAMP signaling in the islets tend to prevent beta-cell loss and may even promote beta-cell recovery.\textsuperscript{5} Pancreatic islet G-protein-coupled receptor is more selective with limited expression in other tissues.

Glucagon-like peptide-1 based therapies relieve endoplasmic reticulum stress, delay beta-cell apoptosis, decrease hepatic glucose production and increase insulin sensitivity. It is well-known that beta-cell exhaustion is partly due to excessive demand placed upon them resulting in endoplasmic reticulum stress.\textsuperscript{6} Studies conducted with human islets have shown preservation of beta-cell mass and function with these agents. This is primarily on account of reduced apoptosis.\textsuperscript{7} Significant improvements in the surrogate markers of beta-cell function like homeostatic model assessment (HOMA) beta and proinsulin: insulin ratio has been demonstrated in clinical trials in humans.\textsuperscript{8-10} Beta-cell assessment in humans is an extremely difficult proposition and therefore one has to use surrogate markers for their assessment. Sustainability of glycemic control over prolonged period however is a good indicator of beta-cell preservation.

ADVANTAGES OF INCRETIN-BASED THERAPIES
Incretin-based therapies have several advantages besides achieving excellent glycemic control. These include:
1. Near freedom from hypoglycemia. Incidence of hypoglycemia with incretin-based therapies has been reported to be as low as those caused by placebo.\textsuperscript{11-13} This has enormous impact on adherence to treatment and helps achieve glycemic targets in majority of these individuals. This has also been experienced in clinical practice.
2. Beta-cell preservation, both due to reduced apoptosis and increased neogenesis and replication of pancreatic beta cells. This is likely to provide sustained glycemic control over prolonged period of time.
3. Significant weight loss by reduced gastric emptying and appetite suppression through their action on area postrema in the hypothalamus. This is important as type 2 diabetes is invariably associated with obesity and majority of existing antidiabetic agents including insulin, sulfonylureas (SU) and thiazolidinedione’s cause weight gain.
4. Favorable action profile on cardiomyocytes and vascular endothelium promising favorable cardiovascular outcome. This is extremely important in subjects with type 2 diabetes, as majority of them have concomitant cardiovascular disorders.
5. Improved insulin sensitivity by their action on adipose tissue and skeletal muscles.
6. Reduction in hepatic glucose output through glucagon suppression.

Glucagon-like peptide-1 and glucose-dependent insulinotropic peptide (GIP) are most important incretin hormones known to exert significant role in glucose homeostasis. However, it has been observed that only GLP-1 has the potential for therapeutic uses. Native GLP-1 has an extremely short half-life of less than 2 minutes. It is rapidly inactivated by the ubiquitous enzyme dipeptidyl peptidase IV (DPP-IV) after being secreted from the L cells of the ileum in small intestine. Considerable molecular alterations are desirable to realize the therapeutic potential of GLP-1 in clinical therapeutics. For optimum action GLP-1 ought to be present in therapeutic concentration for 24 hours. Two commonly employed approaches are inhibition of the enzyme DPP-IV by DPP-IV inhibitors and prolongation of the half-life by either GLP-1 analogs or incretin mimetics. The short half-life of native GLP-1 (1–2 minutes) has necessitated the development of long-acting GLP-1 receptor agonists for the management of type 2 diabetes.\textsuperscript{14-16} The short half-life is due to inactivation by cleavage by the enzyme DPP-IV at the alanine residue at position two of the molecule.\textsuperscript{14,16-18}
Dipeptidyl peptidase IV inhibitors have already been made available for therapeutic uses. They have several advantages and certain limitations. They reduce hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) by about 0.5–0.9% only, are weight neutral and fairly expensive.\textsuperscript{19} However, they have the advantage of being oral treatment and have excellent safety and tolerability profile. Hypoglycemia is almost nonexistent and barring very few gastrointestinal side effects and skin and nasobronchial allergies; they are extremely safe. Dipeptidyl peptidase IV inhibitors approved for therapeutic uses include vilodaglaptin, sitagliptin, saxagliptin, linagliptin and alogliptin.

**INCRETIN MIMETICS/ANALOGS**

Incretin mimetics or analogs in contrast to DPP-IV inhibitors provide pharmacological concentration of GLP-1 and thereby exert potent pleotropic effects of GLP-1.\textsuperscript{1,14,16} They help achieve effective glycemic control without hypoglycemia. Furthermore, they lead to sustained weight loss, reduction in systolic blood pressure, beta-cell protection and improvement in cardiovascular risk factors.\textsuperscript{20,21} The long-acting GLP-1 receptor agonists are attractive for the treatment of people with type 2 diabetes, as the regulation of both insulin and glucagon is glucose dependent. Therefore, there is a reduced risk of hypoglycemia.

Incretin mimetics or incretin analogs were the first amongst the incretins to be used in clinical practice. Exenatide was first incretin mimetic approved for therapeutic use. Its naturally active form exendin-4 is resistant to enzyme DPP-IV and was isolated from the saliva of a lizard Gila monster (heloderma suspectum).\textsuperscript{22} This had 53% homology to the native GLP-1 molecule and has a much longer half-life than GLP-1. It has a life of 2–3 hours and therefore has to be administered parenterally twice a day.\textsuperscript{23} Exenatide administration restores first phase insulin secretion in humans. Exenatide demonstrated reduction in HbA\textsubscript{1c} to the tune of 0.8–0.9% in phase 3 clinical trials at a dose of 5–10 µg bid and were approved for human use in 2005. It exerts its major effect on postprandial hyperglycemia. Glycemic control is sustained for pronged period of time reflecting its potential in protecting the beta-cell function. Exenatide has the potential to augment beat cell proliferation and islet neogenesis from precursor cells in different models of diabetes. Notwithstanding difficulties in assessing beta-cell mass and function in humans, several surrogate markers have been demonstrated to be favorably affected by exenatide.\textsuperscript{24} These include HOMA beta, proinsulin/insulin ratio and 30 minutes oral glucose test measuring area under curve for the glucose.

The reduction in HbA\textsubscript{1c} with exenatide BID is about 0.5–1.0% in patients with a baseline HbA\textsubscript{1c} of 7.9–8.4%, whereas open-label comparator studies showed HbA\textsubscript{1c} reduction of 1.1–1.5% from baseline HbA\textsubscript{1c} values of 8.2–9.0%.\textsuperscript{20,24}

In addition to the glycemic benefits exenatide showed remarkable impact on weight reduction (1.6–2.8 kg) after 30 weeks of administration and modest impact on reduction in systolic blood pressure.\textsuperscript{24} Both these effects could have long-term impact in mitigating the cardiovascular complications in these subjects. Several studies in animals and humans clearly showed improvement in left ventricular function, reduction in infarct size and reduction of cardiac biomarkers.\textsuperscript{25}

Most important limiting factor with exenatide is moderate to severe nausea particularly in first 10–12 weeks. Persistent and prolonged nausea might be attributed to the fluctuating peaks and troughs of GLP-1 with twice daily administration of exenatide. However, it usually settles in 12–16 weeks-time, except in few cases where the drug has to be withdrawn permanently.

Acute pancreatitis was reported in excess during exenatide approval trials as compared to comparators.\textsuperscript{26} However, subsequent analysis failed to demonstrate increased hazard ratio with the use of exenatide as compared to comparators like metformin and sulfonylurea. Nevertheless, this prompted the regulatory agencies to issue warning to practicing physicians to stop the drug in subjects complaining with symptoms suggestive of pancreatitis unless excluded by further relevant investigations.

Exenatide has the potential of producing neutralizing antibodies on account of only 53% homology to the native GLP-1 molecule. Significance of these antibodies remains to be ascertained particularly with reference to their neutralizing properties. However, deposition of these antigen antibody complexes into glomerular basement membrane might explain the warning of restraining the use of exenatide in presence of renal dysfunction.\textsuperscript{23}

Exenatide can be used in combination with other oral anti-diabetic agents including metformin, SU, pioglitazone, alpha-glucosidase inhibitors (AGIs) and insulin. Exenatide and SU combination is likely to increase the risk of hypoglycemia. In combination with insulin it provides additional reduction in HbA\textsubscript{1c} without leading to any significant weight gain. Clinical experience has also shown a reduction in the dose of insulin by adding exenatide to existing insulin treatment.\textsuperscript{27} It has no significant drug interaction and therefore no adjustment is required when exenatide is co-administered with agents like angiotensin-converting enzyme (ACE) inhibitors, digoxin, 3-hydroxy-3-methyl-glutaryl-3-coenzyme A (HMG CoA) reductase inhibitors (statins), warfarin, etc. However, drugs requiring rapid gastrointestinal absorption should be used with caution along with exenatide as delayed gastric emptying might lead to loss of efficacy of the co-administered drug. They should either be administered an hour before the exenatide injection or should be taken with meals which are not preceded by exenatide administration.

**EXENATIDE QW (EXENATIDE LONG-ACTING RELEASE)**

Exenatide long-acting release (LAR) has been developed by incorporating exenatide into biodegradable polymeric microspheres. Once weekly administration of exenatide QW has been evaluated for its efficacy and safety against wide variety of anti-diabetic agents including incretin-based treatment in duration 1 to duration 6 studies.\textsuperscript{20,23} It has been found to be superior in achieving glycemic control as compared to twice daily exenatide and sitagliptin, but inferior to liiraglutide and pioglitazone. No difference was demonstrated between exenatide QW versus metformin and SU. Nausea was less than twice daily exenatide and weight reduction was more robust.

Weekly administration of exenatide QW has now been approved by several regulatory agencies. It offers the advantage of better glycemic control and greater weight loss than twice daily administration of exenatide. However, reconstitution before administration is quite cumbersome and antibody formation is even higher. Injection site nodules are also quite common with these agents.

Dulaglutide is another weekly injection of similar agents where the molecular structure is slightly altered by fusion of GLP-1 to a larger carrier moiety to reduce in vivo clearance. This molecule has GLP-1 fused to a modified immunoglobulin G4 (IgG4) FC fragment.\textsuperscript{34} This is suitable for once weekly administration. This is likely to reduce the antibody formation and reconstitution is not required. The molecule is in phase III development program. Phase 2 results are quite promising both for glycemic control and reduction in the body weight.\textsuperscript{35}

**Liraglutide**

Liraglutide is the first human GLP-1 analog and has been developed by addition of myristic acid at terminal 7 and switching the amino acid 1 to position 2. The half-life has been further protracted by albumin binding to 13 hours making it eminently suitable for once
daily administration. Liraglutide achieves steady state concentration within a week of initiating treatment and effectively restores beta-cell sensitivity to glucose with single administration. Phase III A and III B studies demonstrated approximately 1.1–1.6% reduction in HbA1c. Glycemic control with liraglutide was found to be superior to glimepiride, rosiglitazone, insulin glargine, exenatide, and sitagliptin. Weight loss was observed in three quarters of these subjects and was found to be greater in those with a higher baseline body mass index (BMI). Glycemic control was independent of weight loss as subjects with lowest and highest quartiles of weight loss demonstrated similar reductions in the HbA1c. Glycemic control has been found to be maintained for 3 years reflecting its potential to protect the beta-cell function.

Effect on surrogate markers of beta-cell function including HOMA-β and proinsulin/insulin ratio showed liraglutide to be superior to rosiglitazone, exenatide and sitagliptin.

Liraglutide causes reduction in systolic blood pressure by approximately 3–7 mm Hg. This could be important as systolic blood pressure is an important surrogate for cardiovascular complications. It also showed impressive reduction in cardiac biomarkers including brain natriuretic peptide (BNP), plasminogen activator inhibitor 1 (PAI-1) and high-sensitivity C-reactive protein (hsCRP). Like exenatide liraglutide also showed improved myocardial contraction, improved left ventricular function and reduced infarct size in animal models.

Nausea caused by liraglutide is self-limiting. However, it could be significant in first 8–12 weeks of treatment.

Albiglutide is another human GLP-1 analog in development. It has a plasma half-life of about 5 days, enabling once-weekly dosing. In a dose-response study, time to maximum plasma concentration was 2–5 days after a single injection and the mean half-life was in the range of 6–8 days. Albiglutide shows significant reduction in HbA1c and fasting blood glucose and blood pressure. The adverse effects seem to be the well-known of GLP-1 and were dose dependent. Albiglutide is being investigated in phase 3 HARMONY trials in a wide variety of clinical situations and is being compared with commonly used anti-diabetic agents.

CJC-1134-PC is another GLP-1 receptor agonist in a phase 3 program which consists of an exendin-4 molecule covalently linked to human recombinant albumin. Its half-life is similar to circulating human albumin, approximately about 8 days.

INCRETIN ANALOGS AND BODY WEIGHT

Incretin-based treatments are either weight neutral (DPP-IV inhibitors) or cause significant weight loss (incretin analogs). Incretin mimetics cause weight loss through various mechanisms. These include appetite suppression, improved satiety, delayed gastric emptying, etc. Trials with incretin mimetics, liraglutide and exenatide have documented impressive weight loss which is sustained for 2 years or more. Liraglutide has also shown great potential as an anti-obesity agent in a phase 2 study and is being investigated further in phase 3 study for approval as anti-obesity drug. Significant and sustained weight loss is extremely helpful in subjects with type 2 diabetes with obesity. This not only improves compliance with treatment but might also favorably influence cardiovascular outcomes. Primarily central regulation of appetite and satiety through its action on hypothalamus are profoundly influenced by liraglutide leading to consistent weight loss. Delayed gastric emptying may contribute to some extent. An altered preference for healthy food in place of candies has been demonstrated in rat model with the use of liraglutide. Nausea with liraglutide is very common. It is usually self-limiting within 10–12 weeks-time. It is interesting to note that nausea is not the main cause of weight loss with liraglutide. Exenatide and weekly exenatide are equally effective in causing weight loss with marginal differences.

INCRETIN ANALOGS AND CARDIOVASCULAR OUTCOMES

Glucagon-like peptide-1 receptors are present on vascular endothelium and on cardiomyocytes. Animal studies and clinical trials in humans have shown several beneficial effects with incretin-based treatment with respect to cardiovascular function. These include:

- Decreased size of myocardial damage following ischemic insult
- Improved left ventricular ejection fraction
- Reduction in systolic blood pressure
- Reduction in cardiac biomarkers including PAI-1, hsCRP and BNP.

These effects are likely to improve cardiovascular outcomes in type 2 diabetes subjects. Indeed major adverse cardiovascular events (MACE) were consistently less with incretin-based treatment as compared to conventional treatment modalities. Within the incretin family no major differences have been shown so far in terms of quantum of benefit with these agents with respect to cardiovascular benefits. Several long-term clinical trials are already underway to evaluate the impact of these agents on cardiovascular outcomes. This has now been mandated by regulatory agencies.

CONCERNS WITH INCRETIN-BASED THERAPIES

Pancreatitis

It is important to put into perspective certain issues of concern that rose with the use of incretin mimetics and DPP-IV inhibitors. Pancreatitis has been reported in number of subjects exposed to these agents in the clinical trials. However, the incidence of pancreatitis has not been found to be more than that in the background population of type 2 diabetics and compared to those who were treated with metformin sulfonylurea combination. Furthermore, several causative factors like associated gallstones disease, hypertriglyceridemia, obesity and many concomitant antihypertensive and other medications could account for the perceived excess incidence of pancreatitis in these patients. This issue along with the temporal relationship of drug exposure and development of pancreatitis negate a cause and effect relationship and most likely reflects a reporting bias. Certainly, this demands a diligent and continued surveillance of subjects taking incretin-based treatments to ensure that occurrence of pancreatitis is not in excess of what is expected in the background type 2 diabetic populations.

Risk of pancreatitis has been noted with the use of incretin-based therapies. However, a cause and effect relationship has not been established. C-cell hyperplasia and cancer with liraglutide has now been confirmed to be limited to rodents.

C-cell Hyperplasia and C-cell Cancer

Increased incidence of C-cell hyperplasia and C-cell cancer was noted in mice and rats during the clinical development program with liraglutide. This has now been confirmed as limited to rodents; as humans have extremely low numbers of C-cell receptors. Furthermore use of liraglutide in humans did not lead to activation of C-cell receptors as manifested by cAMP activation, nor did it lead to an increase in the serum calcitonin, which is the biomarker of C-cell activation.

Large numbers of clinical trials assessing long-term safety of different incretin-based therapies are being conducted across the world recruiting several thousands of type 2 diabetes subjects. Another flip side of incretin therapy is the cost of the medication. However, the cost saved in glucose monitoring and treatment of
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hypoglycemia could partially, if not totally compensate for the high cost. Moreover, cost is a factor of time and most of the medications become affordable after certain period of time.

CONCLUSION

Incretin-based treatment modalities address majority of the treatment gaps in type 2 diabetes. Dipeptidyl peptidase IV inhibitors are effective and safe and have been widely accepted in clinical practice. They are a little inferior in terms of glycemic control (0.5–0.9%). Nevertheless, they are weight neutral and cause no or minimal hypoglycemia. Incretin analogs/mimetics, particularly liraglutide causes superior glycemic control with additional advantages of weight loss, no or minimal hypoglycemia and beta-cell protection. Long acting exenatide, exenatide LAR has shown equally impressive effect on glycemic control. Significantly these agents demonstrate sustainability of glycemic control over a period of at least 2 years. This reflects their potential to preserve beta-cell function and mass which needs to be confirmed in humans.

American Diabetes Association/European Association for the Study of Diabetes guideline 2012 has promoted incretin-based treatment along with SU, pioglitazone and insulin in the therapy of type 2 diabetes in subjects failing on life style modification and metformin. Other guidelines have similarly modified their recommendations in their favor because of robust clinical data. Trials are underway to evaluate their effect on long-term cardiovascular safety and even cardiovascular benefits. Whether they can be used as first line treatment or can be used in pre-diabetes remains to be proven.

REFERENCES

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