Exploring the Value and Costs of Incretin-Based Therapies

Written by Dennis Bittner

The development of incretin-based therapies over the past decade since the approval of exenatide has opened new possibilities for the treatment of type 2 diabetes mellitus (T2DM), which were discussed in a symposium on incretin-based therapies. Incretins are a group of gastrointestinal (GI) hormones that decrease blood glucose levels by increasing insulin release after a meal, reducing the rate of absorption of glucose from the GI tract into the bloodstream by slowing gastric emptying and inhibiting glucagon release. A decreased incretin effect is seen in T2DM [Holst JJ. *Physiol Rev*. 2007]. The 2 primary endogenous incretins—glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide—are both rapidly inactivated in vivo by the enzyme dipeptidyl peptidase 4 (DPP-4), making these native forms unsuitable for therapeutic use, thus leading to the commercial development of incretin analogs better able to persist in the bloodstream.

Leading off the session, Clifford J. Bailey, PhD, Aston University, Birmingham, United Kingdom, briefly described the various metabolic activities of endogenous GLP-1, as well as the activity of its antagonist, DPP-4. Moving on to recent studies involving injectable GLP-1 receptor agonists and orally administered DPP-4 inhibitors (gliptins), Prof Bailey addressed exenatide, a modification of a GLP-1 analog discovered in the saliva of *Heloderma suspectum* (Gila monster) that became the first incretin-based agent to be approved for treatment of T2DM. Other approved therapies were also listed, including liraglutide, lixisenatide, and albiglutide. In reviewing the amino acid sequences and structural details of these molecules, Prof Bailey paid particular attention to the different strategies employed for blocking cleavage by DPP-4, thereby increasing the half-life of these GLP1 agonists in the bloodstream. Prof Bailey showed a graph based on data from a number of phase 3 trials, thereby allowing visual comparison on the reductions in both HbA_{1c} and body weight afforded by the different incretin analogs.

A meta-analysis of incretin therapy showed that the effect on HbA_{1c} and body weight varies within the GLP-1 agonists and between the GLP-1 agonists and DPP-4 inhibitors [Aroda VR et al. *Clin Ther*. 2012]. Prof Bailey cautioned that there were subtle but important differences among the trials within the meta-analysis.

David M. Nathan, MD, Massachusetts General Hospital, Boston, Massachusetts, USA, stated that the pandemic of diabetes drives the need for new treatments. However, there are no outcomes studies with the GLP-1 agonists or the DPP-4 inhibitors that show that they reduce microvascular complications, an effect that has been shown with the established drugs used to treat T2DM. Furthermore, HbA_{1c} has been used as a surrogate for hard morbidity and mortality end points in the studies to date. The lack of comparative effectiveness data hampers the ability to choose wisely among the available drugs, and there are limited head-to-head comparisons of the agents. Finally, all of the trials have been short, only 26 weeks to 2 years, in the setting of a disease that lasts a lifetime, he stated.

The high cost of the GLP-1 agonists must be balanced against their modest lowering of HbA_{1c} levels and the documented added value with this class of drugs—that is, modest weight loss or weight neutrality and no risk of hypoglycemia. GLP-1 agonists cause frequent GI side effects. Along with the limited length of the studies, it is challenging to determine when it is best to use this class of drug. The first study that will examine the comparative effectiveness of this drug class over a clinically significant period is the ongoing GRADE study.

Dr Nathan emphasized that balancing effectiveness against side effects also applies to non-incretin-based therapies, noting that all diabetes drugs have side effects; however, the GI side effects with the incretin drugs should not be minimized—they led to considerable attrition in clinical studies (Table 1).

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Table 1. Side Effects of Therapies for Type 2 Diabetes

Class	Hypoglycemia	Weight Gain	GI	Other
Insulin	+	+		↑ Cancer risk (Lantus)
Sulfonylureas	+	+		↑ CVD risk
"Glinides"	+	+		
Biguanides		–	+	Rare lactic acidosis, ↓ CVD, cancer
Thiazolidinediones		+		CHF, fluid retention, ↑ CVD risk, bone loss, bladder cancer
α-Glucosidase inhibitors		0	+ +	Reduced CVD
GLP agonists		–	+ +	Pancreatitis, pancreas and medullary thyroid cancer, weight loss
DPP-4 inhibitors		0		URI, UTIs
SGLT-2 inhibitors		–		Lower BP, UTI, yeast infection, ↑ CVD

BP, blood pressure; CHF, chronic heart failure; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP, glucagon-like peptide; SGLT-2, sodium-glucose cotransporter 2; URI, upper respiratory infection; UTI, urinary tract infection.

In the final talk of the session, Baptist Gallwitz, MD, Eberhard-Karls University, Tuebingen, Germany, followed up on concerns raised by the previous speaker on side effects of incretin-based therapies, delving into issues of pancreatitis and the possible development of pancreatic cancer, as well as the potential association of GLP-1 receptor stimulation with hyperplasia of thyroid C cells leading to medullary thyroid carcinoma.

Several case reports exist of acute pancreatitis in obese patients on GLP-1 receptor agonist therapy, with 1 study group voicing concerns over risk for not only pancreatic neoplasms but also thyroid cancer and possibly neuroendocrine tumors [Butler AE et al. *Diabetes*. 2013]. After a review of the data, the European Medicines Agency and the US Food and Drug Administration decided to not make any substantive changes in clinical recommendations for the use of incretin-based therapies. A large meta-analysis found a slight but nonsignificant increase in incidence of pancreatitis associated with use of GLP-1 receptor agonists [Raz I et al. *Diabetes Care.* 2014; Meier J et al. *Diabetologia*. 2014].

Stimulation of GLP-1 receptors in rodents raises cAMP levels in thyroid C cells, initiating release of calcitonin. This rise in calcitonin is accompanied by C-cell proliferation when there is longer term exposure, potentially followed by formation of C-cell adenomas and medullary thyroid carcinomas. Because of these nonclinical results, it has been hypothesized that incretin-based therapy could lead to medullary thyroid carcinoma in humans [Gier B et al. *J Clin Endocrinol Metab*. 2012]. Subsequent research has demonstrated that expression levels of GLP-1 receptors in human C cells are very low, and no biological signal similar to cAMP production has been observed in C cells in human studies of GLP-1 receptor agonists [Nauck MA, Friedrich N. *Diabetes Care*. 2013].

Prof Gallwitz concluded his talk by saying that the benefits of incretin-based therapies far outweigh the potential risks, as these must be judged relative to adverse events associated with alternative treatment options. Results of ongoing safety studies are required to determine if benefits observed in preclinical studies and short-term clinical trials will translate into favorable long-term outcomes.