Hypoglycemia in Type 1 diabetes: Near-term challenges, long-term risks, and the need for new therapeutic options

Carmen Valcarce, Executive Vice President and Chief Scientific Officer at vTv Therapeutics, discusses the complex issues surrounding the treatment of Type 1 diabetes, looking in particular at hypoglycemia and the impact it has on both patients and researchers

Type 1 diabetes (T1D) is a serious life-threatening autoimmune disease that usually leads to absolute insulin deficiency. Multiple genetic predispositions and poorly defined environmental factors result in the destruction of pancreatic β-cells, the site of insulin secretion. T1D affects more than one million people in the US, and strikes both children and adults at any age. The primary health risk for patients with T1D is soaring blood glucose levels (hyperglycemia) that become fatal if not addressed. Perhaps ironically, the key challenge in optimising outcomes for patients with T1D is the risk of hypoglycemia, an acute, life-threatening condition resulting from a critical drop in blood glucose levels and one of the most feared complications of insulin therapy. Under normal physiologic conditions, blood glucose levels are maintained within a narrow range through a complex system that exogenous insulin cannot recapitulate on its own.

Recent advances in technology have enabled continuous glucose monitoring (CGM), and continuous subcutaneous insulin infusion (CSII) therapy, both of which are designed to minimise the wide swings in glucose levels that can occur when insulin is administered periodically in larger bolus doses. Despite these advances, only 20%-30% of patients with T1D achieve or maintain the tight glycemic control (<7% glycated hemoglobin [HbA1c]) that is critical for preventing long-term microvascular and macrovascular complications.[1] Suboptimal glycemic control is also associated with a higher risk of short-term complications, including diabetic ketoacidosis (DKA) and severe hypoglycemia.[2]

The perils of hypoglycemia in T1D

Hypoglycemia remains a leading cause of morbidity in T1D.[3] It is the main concern for patients and treating clinicians, and it is seen as inextricably tied to the challenge of achieving glycemic control. In fact, hypoglycemia is a key obstacle to achieving optimal glycemic control and a significant cause of disease-related morbidity in patients with T1D.[3] At its best, hypoglycemia interferes with patients' daily living due to the need to interrupt activities to treat low blood sugar. In its more pernicious forms, hypoglycemia can lead to coma, seizures, and death. In between these two extremes, a history of severe hypoglycemia is associated with negative changes in cardiac function, and is a risk factor for future cardiovascular complications in older patients with T1D.[4] In an effort to avoid hypoglycemia, patients with T1D may intentionally allow their blood glucose levels to remain above optimal levels, despite their knowledge of the long-term negative impacts of failing to achieve and sustain tight glycemic control.

Episodes of severe and non-severe hypoglycemia are associated with considerable costs, in terms of both medical resource consumption and productivity losses. Recognising the threat that hypoglycemia poses to human health and healthcare costs for patients with diabetes, the US Department of Health and Human Services included hypoglycemia associated with insulin administration as one of three initial targets in its National Action Plan for Adverse Drug Event Prevention.[5]

Although substantial declines in mortality rates have been reported with improvements in glycemic control and better treatment of cardiovascular disease (CVD) risk factors, recent reports describe greater excess mortality in T1D, even among those with a mean HbA1c of less than 7%.[6, 7, 8] A recent publication using data from the UK estimated that patients with T1D lose approximately 100 days of life for each year living with HbA1c >7%.[9]

With the incidence of T1D projected to grow by nearly 40% in the next 10 years, there is an increasingly urgent need for novel therapies that can provide effective glycemic control while minimising the frequency and severity of short-term complications such as hypoglycemia and DKA.[10]

Adjunctive therapies for T1D

The need for novel approaches that improve treatment outcomes of patients with T1D has long been known. A variety of therapies initially developed for the treatment of Type 2 diabetes (T2D), including metformin, GLP-1 agonists, and SGLT-2 inhibitors, have been evaluated as potential adjunctive therapy to improve glycemic control in patients with T1D. Unfortunately, while these therapies are effective in T2D, they either had no effect on T1D, or improved glycemic control, though at the risk of exacerbating short-term life-threatening complications such as DKA or hypoglycemia.

Tight glycemic control suffers from the pervasive fear of both patient and provider of inducing hypoglycemia. As noted above, hypoglycemia is a key obstacle to achieving optimal glycemic control, and a significant cause of disease-related morbidity in patients with T1D. Ideally, a significant advance in the treatment of patients with T1D will come from an oral adjunctive therapy that reduces the risk of hypoglycemia while maintaining or improving glycemic control, and without increasing blood ketones.

Liver-specific glucokinase activators as potential adjunctive therapy in T1D

Glucokinase (GK), has long been a target of interest due to the observation that human mutations in GK lead to alterations of blood glucose. Under normal physiologic conditions, GK acts as a glucose sensor, and plays a key role in regulating blood glucose levels. This regulation is mediated through modulation of activity in the liver and pancreas to maintain blood glucose levels within the normal physiologic range. Targeting liver-specific GK may activate the body's innate glucose-sensing machinery: hepatocytes, which play a critical role in storing glucose as glycogen when glucose and insulin levels are high, and releasing glucose back into the blood stream as glucose levels fall. This approach may harness the body's ability to keep blood glucose levels within normal parameters, therefore reducing the risk of hypoglycemia.

Recently, vTv Therapeutics published promising results from a Phase Ib/II placebo-controlled clinical trial of an orally administered liver-specific GK agonist, TTP399, as an add-on to insulin therapy. The data show that the difference in the change in HbA1c from baseline to 12 weeks between the TTP399 and placebo groups was -0.21% in the Part II-Phase II portion of the study.[11] Importantly, this reduction in HbA1c was achieved without an increase in hypoglycemia or diabetic ketoacidosis. In fact, in the Part II-Phase II portion of the study, patients in the TTP399 group had a 40% reduction in the frequency of severe or symptomatic hypoglycemia relative to the placebo group. Moreover, the favourable safety profile of TTP399 stands in contrast to what has been observed in trials of other promising adjunctive agents – GLP-1

agonists and SGLT-2 inhibitors – that have been evaluated as potential adjunctive therapy to insulin in the treatment of T1D. Though both of these drug classes improve glycemic control while reducing insulin doses, SGLT-1 and -2 inhibitors are associated with increased rates of ketosis and DKA, and GLP-1 agonists are associated with increased rates of hypoglycemia and increased frequency of hyperglycemic episodes associated with ketosis.[12, 13, 14] The ability of TTP399 to lower HbA1c, improve time in range, and reduce hypoglycemia in the absence of an increase in blood ketones indicates the value of this agent as a potential adjunctive therapy to insulin in people with T1D.

vTv Therapeutics has also initiated a mechanistic study of ketoacidosis that is designed to assess the impact of TTP399 on ketone body formation, and to provide additional evidence to support the hypothesis and early clinical trial data suggesting that this novel agent may reduce the incidence of ketoacidosis in patients with T1D. Data from this trial are expected in the second or third quarter of 2021, and the company intends to initiate the first of two pivotal trials of TTP399 in patients with T1D in the second half of the year.

While a cure for T1D remains the long-term objective, novel adjunctive therapies such as TTP399 may have an important role to play in enabling patients with this disease to effectively achieve and maintain tight glycemic control without the fear or negative health effects of hypoglycemia. Patients with T1D face multiple daily challenges to adhering to therapy and optimising their long-term health outcomes; fear of inducing hypoglycemia should not be one of them. Innovative approaches to T1D that harness the body's existing glucose regulatory machinery may help replace that fear with hope.

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Carmen Valcarce, PhD, Executive Vice President, Chief Scientific Officer at **vTv Therapeutics,** has more than 30 years of pharmaceutical research and development experience focused in the metabolic space. During her career, Carmen has managed more than 12 INDs and has run numerous positive clinical studies. Carmen was a member of the vTv IPO team, having joined the company from Novo Nordisk as a result of vTv's former partnership with Novo. Carmen is an inventor on more than 20 patents and patent applications and an author on numerous peer-reviewed scientific publications. Carmen obtained her PhD at the Universidad Autonoma de Madrid, Spain, in 1988 under the direction of Professor Jose M Cuezva in the field of metabolic diseases.