Congenital Hyperinsulinism Treatment Gaps and a Potential Solution

Defining Rare Disease

Although rare diseases, by definition, affect fewer individuals than other diseases do, they tend to be particularly devastating: they are often debilitating or lethal. If fewer than 200,000 people in the United States (about 1 in 1655 people) are affected by a given disease, it is designated as rare; similarly, the European Union defines a rare disease as one that affects fewer than 1 in 2000.[1]

It is estimated that as many as 7000 rare diseases exist globally. While the number of individuals with a specific rare disease may be small, the total number of people with any rare disease is actually quite large.[1] A significant proportion of patients diagnosed with a rare disease have inherited it, but many others are due to other causes. For example, some infections and autoimmune diseases are considered to be rare diseases. Rare diseases may be diagnosed during childhood or later in adulthood.

Due to the paucity of information available about diseases that affect so few, people living with rare diseases can face long paths to correct diagnoses, several barriers to disease management and few to no therapeutic options. Additionally, it is often the case that fewer research and therapeutic development efforts are invested in each individual rare disease because of their low demographic impact.

In the US, federal efforts to counteract these trends were formalised through the Orphan Drug Act, which was created by Congress in 1983 in an effort to encourage drug developers to look into potential treatments for these rare or orphan diseases. The National Institutes of Health and one of its centres, the National Center for Advancing Translational Sciences, support research and the discovery and advancement of new potential treatments or cures for rare diseases. Efforts to bring these treatments to market are incentivised by the US Food and Drug Administration along with its Office of Orphan Products Development (OOPD).[1]

Since 1983, the OOPD has assisted the development and commercialisation of more than 400 drugs and biologic products for rare diseases,[1] but many are still left with little or no effective therapeutic options. Congenital hyperinsulinism is just one example of a rare disease and patient population with a significant unmet need for improved treatments.

Exploring Congenital Hyperinsulinism

Congenital hyperinsulinism (HI) is an ultra-rare paediatric genetic disorder characterised by excessive and dysregulated production and secretion of the hormone insulin, which plays a key role in blood sugar regulation. The condition affects roughly 1 in 25,000 to 1 in 50,000 newborns, but it is more common in certain populations.[2,3,4]

Although genetic mutations account for a significant number of cases, the specific underlying causes of roughly half of congenital HI cases remain unknown.[2] So far, more than ten single-gene mutations that account for congenital HI have been identified.[5]

Patients with congenital HI experience frequent episodes of hypoglycaemia, or low blood sugar, due to the effect of excess insulin in the body. When food is consumed, insulin is secreted by the pancreas to support the uptake, utilisation, and storage of glucose by peripheral target tissues, and to maintain normal blood glucose levels. When fasting, insulin secretion decreased, resulting in the release of glucose from peripheral target tissues such as the liver, into the bloodstream, to keep blood glucose normal. During periods of prolonged fasting, decreases in insulin and other metabolic countermeasures allow protein and fat stores to be used as sources of fuel in the body. This tight regulation enables a person without congenital HI to have normal blood glucose levels and sustained nutrition to the brain during both mealtime and fasting.[3]

In patients with congenital HI, excess amounts of insulin are produced by the pancreas regardless of blood glucose concentration, which can lead to profound hypoglycaemia that compromises processes in numerous organs and systems and especially threatens the brain. Glucose is the major source of energy for the brain, and when the brain does not receive enough glucose, it relies on alternative fuel sources, called ketone bodies, for its metabolism. However, in congenital HI, ketone body production is also suppressed by elevated insulin.[6] Thus, the brain is particularly vulnerable to HI-induced metabolic deprivation of its two fuel sources, which may lead to complications including developmental delays, learning disabilities, behavioural issues, seizures, coma or even death. As many as half of all congenital HI patients are believed to suffer from at least one of these outcomes.[7]

Albeit rare, congenital HI is the most common cause of persistent hypoglycaemia in children. Infants generally show symptoms in the first few days of life or during infancy, including poor feeding, seizures, unresponsiveness, irritability and increased sleepiness. In young children, symptoms of low blood sugar can be alarming and disruptive and include sweating, feelings of tiredness and shakiness and rapid heart rate.[3]

With early and aggressive intervention, brain damage can be prevented in patients with congenital HI, but diagnostic difficulties present a challenge and significant neurological consequences can occur if the condition is not recognised or if treatment is ineffective.[3]

Diagnosing Congenital HI

The diagnosis of congenital HI is relatively challenging to make – it is difficult to identify symptoms as such because they are

non-specific and may often be confused with typical newborn behaviours.

In patients with hypoglycaemia, a thorough and detailed history should be obtained and include the timing and relation of episodes to mealtimes or fasting, along with birth weight, gestational age and family history. Physical examination should include looking for findings that may point a clinician toward a specific diagnosis or syndromic condition that may be associated with hypoglycaemia. Whenever possible and before treatment, a "critical sample" of blood should be obtained at time of presentation of hypoglycaemia, to confirm hypoglycaemia and support the diagnostic evaluation. In the absence of this, a provocative fasting test is the most informative method for identifying the underlying cause of hypoglycaemia disorders.[6]

Knowing which infants and children to evaluate diagnostically for hypoglycaemia is an important first step. For neonates suspected to be at high risk of having a persistent hypoglycaemia disorder, evaluation is recommended when the infant is at least 48 hours of age.[6] Delaying diagnostic evaluations until two to three days after birth is important because of the difficulty in distinguishing a suspected persistent hypoglycaemia disorder from what is called transitional neonatal glucose concentrations.

For safety, a fasting test should be completed with frequent monitoring of vital signs, plasma glucose and other concentrations of key laboratory values. A fasting study identifies if a child is able to fast appropriately for his or her age and confirms if he or she is making too much insulin or missing other hormones. The constellation of persistent hypoglycaemia, increased consumption of glucose, insulin greater than the lower limit of detection, low plasma ketones, decreased free fatty acids and a response to glucagon when hypoglycaemic are strongly suggestive of hyperinsulinism.[6]

Genetic testing is another diagnostic approach that physicians and geneticists may consider, which can be useful in certain cases, particularly if the hypoglycaemia persists, the patient has a form of HI that is non-responsive to diazoxide, and the case is de novo in the absence of a known family and genetic history, but otherwise is not necessarily part of standard prenatal or neonatal care. Once a diagnosis is made, treatment is the next step, but there is no satisfactory treatment or cure for congenital HI to date.

Treating Congenital HI

On a day-to-day basis, management of congenital HI requires promptly addressing acute low blood sugar episodes as they arise, both for immediate safety and to prevent the long-term complications associated with frequent, repeated episodes of low blood sugar. Patients must often receive extra sugar to offset the immediate effects of excess insulin until longer-term interventions can be made. Children may need an infusion of a dextrose-containing solution into their vein to relieve severe hypoglycaemia, until other measures can be implemented. Some children require a feeding tube that infuses a sugar solution into the gut overnight or during other extended periods of fasting to prevent severe hypoglycaemia. However, these short-term solutions do not address the underlying pathology of congenital HI and they introduce immense burdens to parents or caregivers since they require frequent, close monitoring.

One drug option is glucagon, prescribed for its opposition of insulin action. However, its use is not straightforward: glucagon formulations currently have a short half-life, so they can only correct hypoglycaemia for short periods of time. Long-term use of glucagon may diminish its efficacy and deplete stores of glucose in the liver, further compounding glucose dysregulation.[8]

Other drug therapies may also be prescribed in an effort to control symptoms. Currently available pharmaceutical options, however, are co-opted from other indications and were not specifically developed or approved by the US Food and Drug Administration (FDA) for use in congenital HI. Standard-of-care medications include drugs that block insulin production or the effects of insulin, such as diazoxide, octreotide or lanreotide. Unfortunately, not all patients respond well to these options and they may lose efficacy over time or cause especially unwanted side-effects. For diazoxide, which doesn't work in the half or more of patients with severe KATP channel hyperinsulinemia, these include an FDA black box warning, the strongest warning that the FDA can apply, for pulmonary hypertension, a type of high blood pressure that affects the vessels in the lungs and the right side of the heart.[9] Other more common side-effects include excessive hair growth all over the body, altered, coarsened facial features, and fluid retention which requires co-administration with diuretics and may adversely affect the heart and lungs.[5] For the somatostatin analogs octreotide and lanreotide, side-effects include gastrointestinal symptoms and gallstones,[10] the potential to interfere with the pituitary thyroid and growth axes, as well as potentially increased risk of dangerous tissue death in the bowel in the newborn period, called necrotising enterocolitis.[11]

Surgical removal of the pancreas is sometimes an option, but this approach is usually not curative, so much as it simply trades excess insulin production for the absence of insulin production altogether. Removing the pancreas is also a relatively invasive intervention and even after surgery, many children still experience low blood sugar, requiring frequent meals and medications to counteract their persistent symptoms. Accordingly, removing the entire pancreas may cause the near converse of HI: lifelong insulin-dependent type 1 diabetes, as well as insufficiency in pancreatic digestive enzymes. On the other hand, in cases of congenital HI in which only a certain area or focal lesion of the pancreas over-secretes insulin, removal of the lesion is often curative.[5]

Currently available treatments for congenital HI leave gaping deficits in quality of life and daily independence for patients. Patients, their families and their caregivers shoulder profound, lifelong burdens. In the absence of a safer, truly restorative therapy, patients remain at risk of feeding problems, developmental delays, learning disabilities, and lifelong brain damage.

New Avenues of Treatment for Congenital HI

Drug developers are evaluating a purpose-built antibody as a potential treatment for congenital HI patients. The antibody, named RZ358, is an intravenously administered human monoclonal antibody that binds specifically but reversibly to a site on insulin receptors. Its effect is dependent on both insulin levels and blood sugar levels in a reversible and dose-dependent manner, which should enable patients to achieve and maintain safe blood sugar levels.

More specifically, RZ358 works by binding to an allosteric site on insulin receptors, which are present at high density in insulin's target tissues like muscle, fat and liver tissue. As an allosteric modulator, RZ358 reduces the ability of insulin to bind and signal through its receptor. This results in an effective decrease in insulin activity, correcting the body's misperception of a 'fed' state and thus increasing the blood levels of glucose and ketone bodies that the brain depends on. At the same time, RZ358 counteracts insulin only when and to the extent that insulin is elevated, still permitting insulin to continue to act at physiological levels. Importantly, because RZ358 acts at insulin-dependent target tissues downstream from the insulin over-producing beta cells, it may be more universally effective in addressing any of the underlying genetic defects that cause the disease. This combination of mechanistic features makes RZ358 ideally suited as a potential therapy for conditions associated with endogenous hyperinsulinemia, including congenital HI.

Clinical Development

RZ358 is currently being studied in clinical trials to determine if it is suitable as a treatment for patients with congenital HI. To date, RZ358 was safe and well-tolerated in healthy volunteers in a Phase I trial, as well as in adult and paediatric patients with congenital HI in a Phase IIa proof-of-concept trial.

Additionally, there was a durable dose- and disease-dependent normalisation of blood sugar in patients with congenital HI who had hypoglycaemia at baseline. Consistent with the premise that RZ358 self-regulates and thus precludes 'overshooting' by inhibiting insulin excessively, RZ358 did not increase blood sugar levels in a subset of patients with normal baseline blood sugar levels. Consistent with its mechanism of action, RZ358 appears to attenuate insulin activity only when insulin is present in excess, i.e. it works only when it needs to. Further modelling and analysis of the data suggest that RZ358 will likely be effective at relatively infrequent dosing intervals of weekly to monthly.

Currently, a multi-centre, open-label, Phase IIb study of longer treatment duration is in progress, with goals of evaluating safety, efficacy, and the most appropriate dosing regimen of RZ358 in patients with congenital HI. Additional data will be necessary to determine whether RZ358 may offer the targeted, restorative, and universal treatment option currently absent from the congenital HI treatment landscape.

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