RZ358 (Ersodetug) as a Novel Therapy for Hypoglycemia due to Tumor Hyperinsulinism: Outcomes from an Expanded Access Program for Compassionate Use

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I. BACKGROUND

Tumor hyperinsulinism (tumorHI) occurs when insulin or related paraneoplastic substances produced in excess by tumors stimulate the insulin receptor, leading to excessive signaling and hypoglycemia. TumorHI arises from two types of neoplasms: pancreatic neuroendocrine tumors (pNETs), i.e. insulinomas, and a variety of other tumors, which can oversecrete forms of IGF- 2. The associated hypoglycemia is often life-threatening and current means of managing hypoglycemia produces significant morbidity. Tumor-directed therapies are often ineffective at controlling severe hypoglycemia in advanced disease. Hence, there is a significant unmet medical need for better hypoglycemia-directed therapies for tumorHI.

Ersodetug, a fully human monoclonal antibody that allosterically binds the insulin receptor and negatively modulates signaling by insulin or related hormones, is a novel therapy with a mechanistic potential to treat any congenital and acquired forms of HI. It is currently being investigated in a global Phase 3 study (sunRIZE) for congenital HI, after favorable safety and efficacy outcomes were demonstrated in Phase 2 (RIZE study). This motivated development of an Expanded Access Program (EAP) that has included patients with severe hypoglycemia due to tumorHI.

II. OBJECTIVE

To report the case experiences from a cohort of patients who have received RZ358 to treat tumorHI.

III. METHODS

Five adult patients (2M/3F) with refractory hypoglycemia due to metastatic insulin producing tumors received treatment with ersodetug after FDA/IRB-approval. At program entry, all patients required continuous parenteral dextrose, including 4 in a prolonged hospital setting. Ersodetug was initiated at 6 or 9mg/kg every 1-2 weeks (by 30-min intravenous infusion), and titrated to response, at physician discretion.

IV. RESULTS

Ersodetug was generally safe and well-tolerated, and patients were able to stop or substantially reduce parenteral dextrose, enabling hospital discharge after initiating therapy. Four patients achieved complete discontinuation, and one achieved a 50% reduction in intravenous carbohydrate support after dose increase to 9mg/kg. Three patients achieved complete resolution of hypoglycemia within two weeks of starting treatment. More protracted responses occurred in patients who initially received ersodetug at a lower dose or frequency.

V. CONCLUSION

EAP for compassionate use provides real-world proof-of-concept for the use of ersodetug to treat hypoglycemia due to tumorHI . These observations are consistent with the known mechanism of action of ersodetug, pharmacology studies, and recent results from studies in congenitalHI.

A global, multi-center Phase 3 study in tumorHI patients is planned.

Patient	Gender	Age	NET Type
1	M	55	Metastatic Insulinoma
2	F	50	Metastatic Insulinoma
3	F	50	Metastatic Insulin-Secreting Tumor (Cervical Primary)
4	F	43	Metastatic Insulinoma
5	M	74	Metastatic Insulinoma

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