Treatment Of Severe Refractory Hypoglycemia Due To Malignant Insulinoma With A Novel Anti-Insulin Receptor Antibody

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Abstract

- Severe hypoglycemia caused by malignant insulinoma is often resistant to medical therapy targeting both tumor burden and insulin secretion.
- We report a patient who developed severe, treatment-resistant hypoglycemia after receiving ^{177}lutetium-DOTATATE (Lu-177).
- Hypoglycemia was completely resolved after treatment with RZ358, a human monoclonal antibody that functions as a negative allosteric modulator of the insulin receptor, reducing insulin signaling and inducing whole-body insulin resistance..

Introduction

Malignant insulinoma can cause severe hypoglycemia, a highly challenging clinical condition which is often refractory to maximal medical therapies, including dietary modification, diazoxide, somatostatin receptor agonists, and everolimus.[1,2] In this setting, prolonged hospitalization for intravenous dextrose infusion may be required and the severe hypoglycemia may contribute to substantial morbidity and mortality.

Current chronic medical treatments for insulinoma-associated hypoglycemia act by:

(1) **Reduction of insulin secretion** via:
- activation of ATP-sensitive potassium (K_{ATP}) channels (e.g., diazoxide),
- inhibition of calcium channels,
- activation of somatostatin receptors (e.g., octreotide, pasireotide, lanreotide),
- inhibition of mTOR-dependent insulin secretion (e..g everolimus)

(2) **Induction of peripheral and hepatic insulin resistance**
e.g. glucocorticoids, mTOR inhibitors

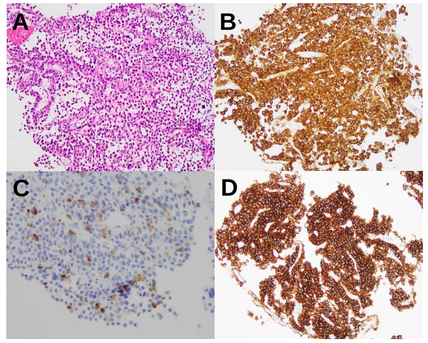
(3) **Anti-tumor therapy** e.g. ^{177}lutetium-DOTATATE

These strategies may be inadequate to control hypoglycemia in metastatic insulinoma due to high tumor burden, extreme hyperinsulinemia due to autonomous insulin secretion independent of physiologic control mechanisms, post-therapy tumor lysis, inadequate glycogen and/or gluconeogenic precursor availability, and limiting side effects.

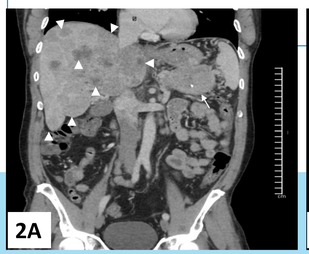
Patient Presentation

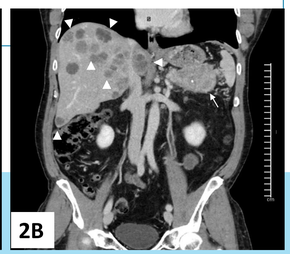
A 55 year old man presented with abdominal pain, fatigue, and weight loss; imaging showed a 1.8 cm pancreatic tail mass and numerous hepatic lesions. Liver biopsy demonstrated well-differentiated pancreatic neuroendocrine tumor, WHO Grade 2 (Figure 1) and pathogenic MEN1 mutation. Subsequent genomic MEN1 mutation analysis was negative.

Figure 1.A. H & E. Immunostains for: **B.** Chromogranin. **C.** Insulin. **D.** SSTR2.



Following one year of octreotide therapy, both pancreatic and hepatic tumors increased in size (Figure 2A), prompting Lu-177 therapy. Two days after the first dose, the patient became unresponsive, with capillary glucose 20 mg/dL. He developed recurrent neuroglycopenia on day 8, with venous glucose 41 mg/dL, insulin 45 μIU/mL, C-peptide 6.5 ng/mL and proinsulin 453 pmol/L, requiring intensive care unit admission for intravenous glucose. High-dose diazoxide, everolimus, dexamethasone, glucagon, pasireotide, or enteral feeding did not produce a response. Despite multiple therapies, neuroglycopenia required frequent dextrose boluses and continuous intravenous glucose (up to 30 g/hr of 50% dextrose); up to 58% of sensor glucose was below 70 mg/dL and 19% below 54 mg/dL over 24 hours. CT imaging 1 month after Lu-177 showed significant reduction in liver metastases size (Figure 2B).





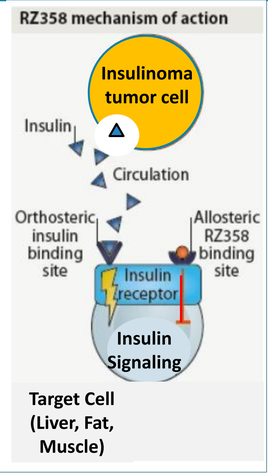
Novel Therapeutic Approach & Results

Given the severity of hypoglycemia despite tumor regression, we initiated treatment with RZ358, a human monoclonal antibody that acts as a negative allosteric modulator of the insulin receptor, inducing insulin resistance. We obtained emergency use authorization from the FDA, approval from the local Institutional Review Board, and written informed consent.

Following a 6 mg/kg dose of RZ358, there was transient worsening of hypoglycemia accompanied by an 8-fold increase in insulin, potentially due to reduced insulin clearance. After dose increase to 9 mg/kg weekly, glucose infusion was weaned. Metabolic stability was achieved after 6 doses, allowing a second dose of Lu-177 and eventual discharge. Diazoxide was discontinued, steroid doses were reduced, and RZ358 dosing was reduced to every 3-4 weeks. A third dose of Lu-177 was administered without complications. Despite elevated insulin (537 uIU/mL), C-peptide (10.1 ng/mL), and proinsulin (634.0 pmol/L), he remains free of level 3 hypoglycemia. No adverse effects have been observed. Please see right for clinical course (Figure 3).

Discussion

- ^{177}lutetium-DOTATATE can induce prolonged hypoglycemia.
- Inhibition of insulin receptor with RZ-358 can effectively rescue refractory hypoglycemia in insulinoma.
- Reduced insulin action ↓ insulin-stimulated glucose uptake and ↓ insulin clearance.
- Double inhibition within the insulin receptor-mTOR pathway was well-tolerated in this patient.



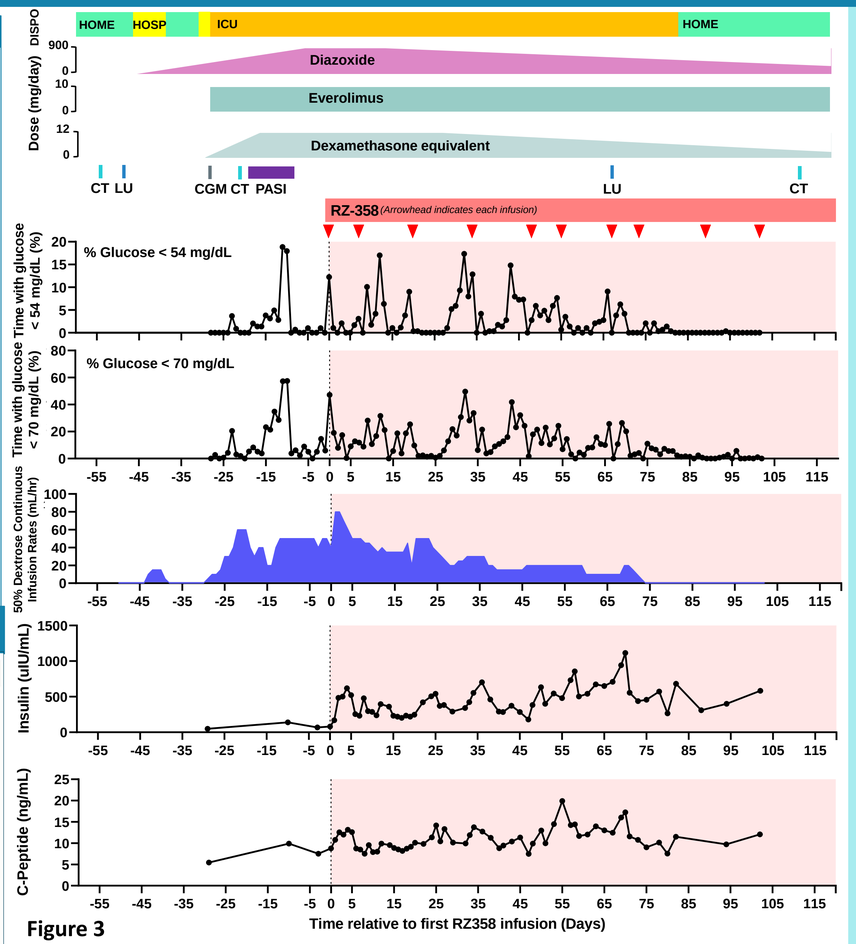


Figure 3

Conclusions

In summary, the anti-insulin receptor monoclonal antibody RZ358 effectively controlled hypoglycemia refractory to multiple other therapies, allowing restoration of normoglycemia and enabling additional successful cancer therapy.

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