SAT 583

XOMA 129, a Novel Insulin Receptor Negative Modulator, Is Efficacious in Treating Insulin-Induced Hypoglycemia in Minipigs

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ABSTRACT

Hypoglycemia has become one of the most complicated challenges of diabetes management. These events can be acute (e.g. insulin overdose), prolonged (e.g. oral ingestion of a sulfonylurea drug), or even undetected (e.g. many nocturnal hypoglycemias). Severe hypoglycemia can lead to irreversible damage to vital organs, even death. There is a need for a safe and well-tolerated treatment for the different forms of hypoglycemia. XOMA 129 is a fully human, high affinity Fab antibody fragment that specifically targets the human insulin receptor. It binds to an allosteric site on the receptor, distinct from the insulin binding site, and dampens insulin signaling. Previously, we reported that XOMA 129 can promptly reverse hypoglycemia in rats. Here, we extend the characterization of XOMA 129 in minipigs. XOMA 129 — at ≤10 mg/kg — significantly modulates glucose levels for several hours via three administration routes (IV, IM and SC). When minipigs were challenged with insulin bolus, IV XOMA 129 at 2 mg/kg reversed hypoglycemia within 15 min without causing hyperglycemia. XOMA 129 at 5 mg/kg via intramuscular administration effectively blunt the glucose drop within 15 minutes. When given prophylactically, XOMA 129 via subcutaneous administration at 9 mg/kg was preventative in a model of nocturnal hypoglycemia. Thus, XOMA 129 has potential as a novel treatment for many hypoglycemic conditions.

SUMMARY

XOMA 129 is a fully human, high affinity Fab that specifically targets the human insulin receptor (InsR). As a negative allosteric modulator (NAM), it binds to a site distinct from insulin binding, with high affinity and dampens insulin signaling. Here we tested XOMA 129 in minipigs to understand its effects on hypoglycemia. Subcutaneous administration of Vetsulin induced rapid blood glucose drop within 20 minutes and the hypoglycemia lasted for over 8 hours. Hence, this response is suitable for us to test XOMA 129 onset, duration and potency. It also represents a model for nocturnal hypoglycemia. XOMA 129 — at doses of 2 and 10 mg/kg i.v. — elevated glucose levels rapidly and reach the maximal effect within 2 hours, and the effect of XOMA 129 lasted for about 8 hours. XOMA 129 — at dose of 5mg/kg i.m. — countered the blood glucose drop within 15 minute after injection and effectively normalized blood glucose. When given preventatively, XOMA 129 — at 9 mg/kg s.c. — prevented blood glucose decrease and the effect lasted the duration of the study.

Hence, we describe a novel antibody fragment (INSR NAM) that can not only promptly reverse hypoglycemia with a rapid onset and optimal duration, but also prevent nocturnal hypoglycemia without causing hyperglycemia. Thus, XOMA 129 has potential as a novel treatment for acute hypoglycemic conditions.

MATERIALS AND METHODS

Animal models

PK analysis in minipig: The PK of XOMA 129 was studied in normal male Gottingen minipigs, around 10 kg bodyweight. Minipigs were fed at 6:00 am, food was removed during the duration of the study. XOMA 129 was administered at 10 mg/kg intramuscularly. Blood samples were taken from the tail before and at 5, 10, 30, 60 minutes and 2, 4 and 8 hours after the administration of XOMA 129. A sandwich ELISA method was used to measure the concentrations of XOMA 129. Data were analyzed using WinNonlin. Blood glucose was detected using Abbott AlphaTRAK.

This experiment was performed at Charles River Laboratories, INC. (Spencerville, OH).

Hypoglycemia models in minipig: normal male Gottingen minipigs, around 10 kg bodyweight, were fasted to 2.5 hours prior. Vetsulin was administered subcutaneously in a dose of 0.5 IU/kg.

IV rescue model: 45 minutes post Vetsulin administration, XOMA 129 at either 10 or 2 mg/kg were administered intravenously. Blood samples were taken from the ear before and at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 420 min after the administration of XOMA 129 for determination of the blood glucose.

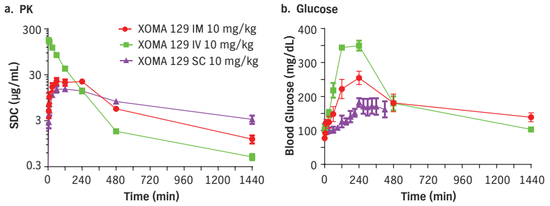
IM rescue model: 35 minutes post Vetsulin administration, XOMA 129 at 5 mg/kg were administered intramuscularly. Blood samples were taken from the ear before and 30 min post Vetsulin and at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 420 min after the administration of XOMA 129 for determination of the blood glucose.

SC prevention model: 90 minutes prior to Vetsulin administration, XOMA 129 at 9 mg/kg were administered subcutaneously. Blood samples were taken from the ear before, 30 and 60 min post XOMA 129 and at at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 420 min after the administration of Vetsulin for determination of the blood glucose

These experiments were performed at Charles River Laboratories, INC. (Spencerville, OH).

RESULTS

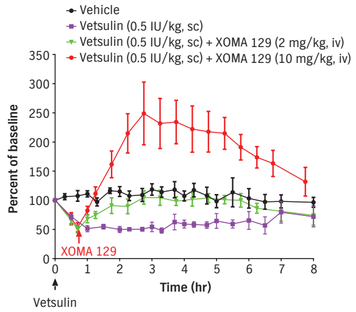
Figure 1: PK and PD profile of XOMA 129 in minipig via IV, IM and SC administration.



Route	n	C_{max} (µg/mL)	T_{max} (h)	AUC (µg*h/mL)	$t_{1/2}$ (h)	F%
IV	4	172.8	~0.1	280.3	3.3	n/a
IM	4	24.1	2	185.3	5.6	66.9
SC	3	15.9	1.7	183.3	10.5	65.6

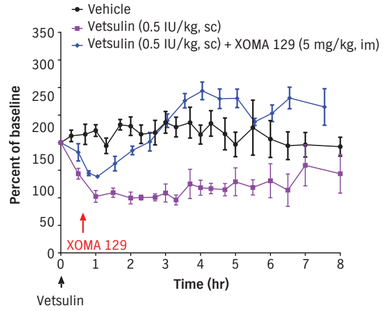
PK and PD profile of XOMA 129 in minipig via IV, IM and SC administration. *a. PK profile of XOMA 129 via three injection routes. Normal male Gottingen minipigs, administered as single dose bolus at 10 mg/kg either intravenously, intramuscularly or subcutaneously. Blood samples were taken from vena cava before and at 5, 10, 30 min 1, 2, 4, 8 and 24 hours after the administration of XOMA 129. A sandwich ELISA method was used to measure the concentrations of XOMA 129. Data were analyzed using WinNonlin. b. Glucose reading from normal Gottingen pigs post XOMA 129 administration. When XOMA 129 was administrated intravenously or intramuscularly, a drop of blood from the PK samples were tested via Abbott AlphaTRAK for glucose. When XOMA 129 was administrated via subcutaneous route, blood samples were collected from ear at before and at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 420 min after the administration of XOMA 129.*

Figure 2: Intravenous administration of XOMA 129 effectively rescued Vetsulin-induced hypoglycemia in minipigs.



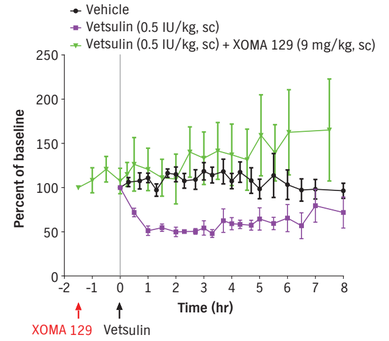
Intravenous administration of XOMA 129 effectively rescued Vetsulin-induced hypoglycemia in minipigs. *Normal male Gottingen minipigs were fasted for 2.5 hours. Vetsulin was administrated at 0.5 IU/kg subcutaneously to induce sustained hypoglycemia. XOMA 129 was administrated intravenously 45 minutes post Vetsulin administration at either 10 mg/kg or 2 mg/kg. blood samples were collected from ear at before, 30 and 45 minutes post Vetsulin administration and at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 420 min post XOMA 129 administration for glucose. Vehicle was used as normal glycemic control. Glucose readings at t0 min were defined as 100 and used as baseline, all subsequent glucose readings were calculated based on the baseline glucose reading. Each group has its own baseline.*

Figure 3: Intramuscular administration of XOMA 129 effectively rescued Vetsulin-induced hypoglycemia in minipigs.



Intramuscular administration of XOMA 129 effectively rescued Vetsulin-induced hypoglycemia in minipigs. *Normal male Gottingen minipigs were fasted for 2.5 hours. Vetsulin was administrated at 0.5 IU/kg subcutaneously to induce sustained hypoglycemia. XOMA 129 was administrated intramuscularly 35 minutes post Vetsulin administration at 5 mg/kg. blood samples were collected from ear at before and 30 minutes post Vetsulin administration and at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 420 min post XOMA 129 administration for glucose. Vehicle was used as control. Glucose readings at t0 min were defined as 100 and used as baseline, all subsequent glucose readings were calculated based on the baseline glucose reading. Each group has its own baseline.*

Figure 4: XOMA 129 effectively prevented nocturnal hypoglycemia in minipigs.



XOMA 129 effectively prevented nocturnal hypoglycemia in minipigs. *Normal male Gottingen minipigs were fasted for 2.5 hours. XOMA 129 was administrated subcutaneously 90 minutes (t-90 min) prior to Vetsulin administration at 9 mg/kg. Vetsulin was administrated at 0.5 IU/kg subcutaneously (t0 min) to induce sustained hypoglycemia. blood samples were collected from ear at before 30, 60 and 90 minutes post XOMA 129 administration and at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 420 min post Vetsulin administration for glucose. Vehicle was used as control. Glucose readings at t-90 min were defined as 100 and used as baseline, all subsequent glucose readings were calculated based on the baseline glucose reading. Each group has its own baseline.*

CONCLUSION

- XOMA 129 exhibits the pharmacokinetics and pharmacodynamics in minipigs to support continued development as a novel targeted pharmacotherapy for the treatment of acute and nocturnal hypoglycemic conditions.
- Intravenous administration of XOMA 129 effectively rescued Vetsulin-induced hypoglycemia at 2 mg/kg.
- Intramuscular administration of XOMA 129 effectively rescued Vetsulin-induced hypoglycemia
- XOMA 129 effectively prevented nocturnal hypoglycemia via subcutaneous route.
- XOMA 129 has potential as a novel treatment for many hypoglycemic conditions.