OBSTETRICS

M281, an anti-FcRn antibody, inhibits IgG transfer in a human ex vivo placental perfusion model

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Background

The transfer of pathogenic immunoglobulin G antibodies from mother to fetus is a critical step in the pathophysiology of alloimmune and autoimmune diseases of the fetus and neonate. Immunoglobulin G transfer across the human placenta to the fetus is mediated by the neonatal Fc receptor, and blockade of the neonatal Fc receptor may provide a therapeutic strategy to prevent or minimize pathological events associated with immune-mediated diseases of pregnancy. M281 is a fully human, aglycosylated monoclonal immunoglobulin G1 antineonatal Fc receptor antibody that has been shown to block the neonatal Fc receptor with high affinity in nonclinical studies and in a phase 1 study in healthy volunteers.

Objective

The objective of the study was to determine the transplacental transfer of M281 and its potential to inhibit transfer of immunoglobulin G from maternal to fetal circulation.

Study Design

To determine the concentration of M281 required for rapid cellular uptake and complete saturation of the neonatal Fc receptor in placental trophoblasts, primary human villous trophoblasts were incubated with various concentrations of M281 in a receptor occupancy assay. The placental transfer of M281, immunoglobulin G, and immunoglobulin G in the presence of M281 was studied using the dually perfused human placental lobule model. Immunoglobulin G transfer was established using a representative immunoglobulin G molecule, adalimumab, a human immunoglobulin G1 monoclonal antibody, at a concentration of 270 μg/mL. Inhibition of immunoglobulin G transfer by M281 was determined by cotransfusing 270 μg/mL of adalimumab with 10 μg/mL or 300 μg/mL of M281. Concentrations of adalimumab and M281 in sample aliquots from maternal and fetal circuits were analyzed using a sandwich enzyme-linked immunosorbent assay and Meso Scale Discovery assay, respectively.

Results

In primary human villous trophoblasts, the saturation of the neonatal Fc receptor by M281 was observed within 30−60 minutes at 0.15−5.0 μg/mL, suggesting rapid blockade of neonatal Fc receptor in placental cells. The transfer rate of adalimumab (0.23% ± 0.21%) across dually perfused human placental lobule was significantly decreased by 10 μg/mL and 300 μg/mL of M281 to 0.07 ± 0.01% and 0.06 ± 0.01%, respectively. Furthermore, the transfer rate of M281 was 0.002% ± 0.02%, approximately 100-fold lower than that of adalimumab (Table).

Conclusion

The significant inhibition of immunoglobulin G transfer across the human placental lobule by M281 and the minimal transfer of M281 supports the development of M281 as a novel agent for the treatment of fetal and neonatal diseases caused by transplacental transfer of alloimmune and autoimmune pathogenic immunoglobulin G antibodies. ■

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Supporting material appears on the next page

TABLE
M281 inhibition of IgG transfer from maternal to fetal circulation

Maternal circuit M281, μg/mL[a]	Maternal circuit adalimumab, μg/mL[a]	Fetal circuit adalimumab at study end, mean (SD), μg/mL	Fetal transfer rate Adalimumab, mean (SD), %	*P* value[b]	Number of studies	Experimental period, hours
0	270	0.50 (0.5)	0.23 (0.21)	NA	8	6
10	270	0.12 (0.02)	0.07 (0.01)	< .001	3	6
300	270	0.12 (0.01)	0.06 (0.01)	< .001	5	6

Mean antipyrine fetal transfer rate for these studies was 41.7% ± 2.7% for adalimumab alone and 43.8% ± 4.2% for all adalimumab plus M281 studies. Fetal transfer rate = 100 × concentration of the test substance in the fetal circuit at the end of the experimental period/concentration of the test substance in the maternal circuit at the start of the experimental period.

NA, not applicable.

[a] Concentration of test compounds in the maternal perfusate at initiation of the experimental period; [b] *P* values were calculated compared with no M281 using a linear mixed-effects model with random slope and intercept.

Roy et al. M281 inhibits IgG transplacental transfer. Am J Obstet Gynecol 2019.

CORRECTIONS

September 2018 (vol. 219, no. 3, page 243)

Check for updates

Lu J, Cheng YKY, Ting YH, et al. Pitfalls in assessing chorioamnionicity: novel observations and literature review. Am J Obstet Gynecol 2018;219:242-54.

The legend for Figure 1 of the Expert Review article cited above should read as follows, reversing the identification of panels B and C as published in September 2018:

A and **C**: A pair of dichorionic diamniotic twins with λ sign under 2D and 3D ultrasound examination, respectively (arrows). **B** and **D**: A pair of monochorionic diamniotic twins with T sign under 2D ultrasound (arrow), but the inter-twin membrane is too thin to be clearly seen on 3D imaging.

September 2018 (vol. 219, no. 3, pages 303.e1 and 303.e6)

Check for updates

Gabbe SG, Vetter MH, Nguyen MC, et al. Changes in the burnout profile of chairs of academic departments of obstetrics and gynecology over the past 15 years. Am J Obstet Gynecol 2018;219:303.e1-6.

The "Cite this article as" section of an Original Research article published in September 2018 listed the second author incorrectly. As corrected above, the citation form for Monica Hagan Vetter should have appeared as Vetter MH—not, as published, as Hagan Vetter M.

The same correction applies to the "Author and article information" section that follows the reference list of the article.